Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Supplemental Screening as an Adjunct to Mammography for Breast Cancer Screening in People With Dense Breasts: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Screening for breast cancer is the process of looking for the disease before any symptoms appear, so that it can be caught and treated early. Many factors affect a person's risk for breast cancer, including age, a strong family history of the disease, and breast density. Variations in breast density are normal and common, but higher breast density increases the risk of cancer and makes it harder to see cancers on a mammogram (a 2-dimensional breast x-ray).

One way to improve cancer detection for people with dense breasts might be to use other types of imaging in addition to mammography (called *supplemental screening*). Types of breast imaging that could be added include contrast-enhanced mammography, ultrasound, digital breast tomosynthesis (3-dimensional breast x-ray), or magnetic resonance imaging (MRI).

This health technology assessment looked at how accurate, safe, effective, and cost-effective supplemental screening is for people with dense breasts. It also looked at the budget impact of publicly funding supplemental screening; the experiences, preferences, understandings, and values of people with dense breasts and their health care providers; and ethical issues related to supplemental screening for people with dense breasts.

What Did This Health Technology Assessment Find?

When ultrasound, digital breast tomosynthesis, or MRI were added to mammography for screening, they detected more cancers. Fewer interval cancers (cancers that occur between screenings) were seen after supplemental screening, but supplemental screening led to many more follow-ups, including for false-positive test results. The effect of supplemental screening on survival is unclear.

Supplemental screening with ultrasound, digital breast tomosynthesis, or MRI led to better outcomes for people with dense breasts, but it increased costs. We estimate that publicly funding supplemental screening as an adjunct to mammography in Ontario over the next 5 years would cost an additional $15 million to $41 million for people with dense breasts, and an additional $4 million to $10 million for people with extremely dense breasts.

The people with dense breasts we interviewed valued the potential clinical benefits of supplemental screening and emphasized that patient education and equitable access should be a requirement for implementation in Ontario. In the qualitative literature, people who had or may have had dense breasts and many health care providers had limited knowledge of the concept of breast density. Many people who had or may have had dense breasts wanted to engage in supplemental screening, even when they knew about its potential harms. The main harms of supplemental screening for people with dense breasts are false-positives and overdiagnosis. Existing inequities in access to breast screening and cancer treatment are likely to persist with supplemental screening.

Acknowledgements

This report was developed by a multidisciplinary team from Ontario Health and the Canadian Agency for Drugs and Technologies in Health (CADTH). From Ontario Health, the primary clinical epidemiologist was Alexis Schaink, the secondary clinical epidemiologist was Kristen McMartin, the primary medical librarian was Caroline Higgins, the secondary medical librarian was Corinne Holubowich, the primary health economist was Frances Simbulan, the secondary health economist was Olga Gajic-Veljanoski, the primary patient engagement analyst was David Wells, and the secondary patient engagement analysts were Isabelle Labeca and Jigna Mistry. From CADTH, the research information specialist was Melissa Walter, the qualitative research officer was Jamie Anne Bentz, and the ethics analyst was Katherine Duthie.

The medical editor was Jeanne McKane. Others from Ontario Health involved in the development and production of this report were Jamie Turnbull, Claude Soulodre, Susan Harrison, Sarah McDowell, Chunmei Li, David Wells, Andrée Mitchell, Charles de Mestral, and Nancy Sikich. Others from CADTH involved in the development of this report were Francesca Brundisini, Renata Axler, David Kaunelis, Andrea Smith, Pierre Martinelli, and Laura Weeks.

We would like to thank the following people and organizations for lending their expertise to the development of this report:

- Anna Chiarelli, Ontario Breast Screening Program, Ontario Health (Cancer Care Ontario)
- Andrea Eisen, Ontario Health (Cancer Care Ontario)
- Samantha Fienberg, Ontario Breast Screening Program, Ontario Health (Cancer Care Ontario)
- Aisha Lofters, Prevention and Cancer Control, Ontario Health (Cancer Care Ontario)
- Derek Muradali, St. Michael's Hospital, University of Toronto
- Jean Seely, The Ottawa Hospital, and the University of Ottawa
- William W.L. Wong, School of Pharmacy, University of Waterloo
- Ontario Breast Screening Program, Ontario Health (Cancer Care Ontario)

We also thank our lived experience participants who generously gave their time to share their stories with us for this report.

We are thankful to Alison Steeves and the late Heather Pullen for suggesting this topic to Ontario Health. We welcome topic suggestions from patients, caregivers, health care professionals, and organizations from across Ontario. Applications can be submitted on our website.

The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

A Note About Terminology

As a government agency, Ontario Health can play an active role in ensuring that people of all identities and expressions can recognize themselves in what they read and hear from us. The focus of this report is female breast cancer; therefore, unless otherwise specified, any reference to breasts or breast cancer in this report refers to this clinical context. We recognize that gender identities are individual and that some people who experience female breast cancer or breast cancer screening do not identify as women, despite being assigned female sex at birth. Thus, in this health technology assessment, we aim to use gender-neutral pronouns and terms as much as possible in accordance with Ontario Health's Gender-Inclusive Language Guidelines. However, when citing published literature or statistics that use the terms "woman" or "women" to refer to the people undergoing breast screening or participating in research studies, we also use these terms for clarity and consistency with the cited sources.

Disclaimer

The primary economic evaluation and budget impact analysis were conducted using OncoSim, an independent cancer simulation tool.

OncoSim is led and supported by the Canadian Partnership Against Cancer, with model development by Statistics Canada, and is made possible through funding by Health Canada. Many partners and stakeholders within the cancer control community have made substantial contributions that made the OncoSim model possible (detailed acknowledgements in partnershipagainstcancer.ca/tools/oncosim/acknowledgements/). Contributions include, but are not limited to, statistical analyses, model construction, scenario development, and expert advice.

The results presented in this report do not represent the views of the organizations (Canadian Partnership Against Cancer, Statistics Canada, or Health Canada).

Citation

Ontario Health. Supplemental screening as an adjunct to mammography for breast cancer screening in people with dense breasts: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2023 Dec;23(9):1–293. Available from: hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/supplemental-screening-as-an-adjunct-to-mammography-for-breast-cancer-screening-in-people-with-dense-breasts

Abstract

Background

Screening with mammography aims to detect breast cancer before clinical symptoms appear. Among people with dense breasts, some cancers may be missed using mammography alone. The addition of supplemental imaging as an adjunct to screening mammography has been suggested to detect breast cancers missed on mammography, potentially reducing the number of deaths associated with the disease. We conducted a health technology assessment of supplemental screening with contrast-enhanced mammography, ultrasound, digital breast tomosynthesis (DBT), or magnetic resonance imaging (MRI) as an adjunct to mammography for people with dense breasts, which included an evaluation of effectiveness, harms, cost-effectiveness, the budget impact of publicly funding supplemental screening, the preferences and values of patients and health care providers, and ethical issues.

Methods

We performed a systematic literature search of the clinical evidence published from January 2015 to October 2021. We assessed the risk of bias of each included study using the Cochrane Risk of Bias or RoBANS tools, and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature review and conducted cost-effectiveness analyses with a lifetime horizon from a public payer perspective. We also analyzed the budget impact of publicly funding supplemental screening as an adjunct to mammography for people with dense breasts in Ontario. To contextualize the potential value of supplemental screening for dense breasts, we spoke with people with dense breasts who had undergone supplemental screening; performed a rapid review of the qualitative literature; and conducted an ethical analysis of supplemental screening as an adjunct to mammography.

Results

We included eight primary studies in the clinical evidence review. No studies evaluated contrast-enhanced mammography. Nonrandomized and randomized evidence (GRADE: Very low to Moderate) suggests that mammography plus ultrasound was more sensitive and less specific, and detected more cancers compared to mammography alone. Fewer interval cancers occurred after mammography plus ultrasound (GRADE: Very low to Low), but recall rates were nearly double that of mammography alone (GRADE: Very low to Moderate). Evidence of Low to Very low quality suggested that compared with supplemental DBT, supplemental ultrasound was more sensitive, detected more cancers, and led to more recalls. Among people with extremely dense breasts, fewer interval cancers occurred after mammography plus supplemental MRI compared to mammography alone (GRADE: High). Supplemental MRI after negative mammography was highly accurate in people with extremely dense breasts and heterogeneously dense breasts in nonrandomized and randomized studies (GRADE: Very Low and Moderate). In people with extremely dense breasts, MRI after negative mammography detected 16.5 cancers per 1,000 screens (GRADE: Moderate), and up to 9.5% of all people screened were recalled (GRADE: Moderate). Contrast-related adverse events were infrequent (GRADE: Moderate). No study reported psychological impacts, breast cancer–specific mortality, or overall mortality.

We included nine studies in the economic evidence, but none of the study findings was directly applicable to the Ontario context. Our lifetime cost-effectiveness analyses showed that supplemental screening with ultrasound, MRI, or DBT found more screen-detected cancers, decreased the number of interval cancers, had small gains in life-years or quality-adjusted life-years (QALYs), and was associated

with savings in cancer management costs. However, supplemental screening also increased imaging costs and the number of false-positive cases. Compared to mammography alone, the incremental cost-effectiveness ratios (ICERs) for supplemental screening with handheld ultrasound, MRI, or DBT for people with dense breasts were $119,943, $314,170, and $212,707 per QALY gained, respectively. The ICERs for people with extremely dense breasts were $83,529, $101,813, and $142,730 per QALY gained, respectively. In sensitivity analyses, the diagnostic test sensitivity of mammography alone and of mammography plus supplemental screening had the greatest effect on ICER estimates. The total budget impact of publicly funding supplemental screening with handheld ultrasound, MRI, or DBT for people with dense breasts over the next 5 years is estimated at $15 million, $41 million, or $33 million, respectively. The corresponding total budget impact for people with extremely dense breasts is $4 million, $10 million, or $9 million.

We engaged directly with 70 people via interviews and an online survey. The participants provided diverse perspectives on broad access to supplemental screening for people with dense breasts in Ontario. Themes discussed in the interviews included self-advocacy, patient–doctor partnership, preventive care, and a shared preference for broad access to screening modalities that are clinically effective in detecting breast cancer in people with dense breasts.

We included 10 studies in the qualitative evidence rapid review. Thematic synthesis of these reports yielded three analytical themes: coming to know and understand breast density, which included introductions to and making sense of breast density; experiences of vulnerability, which influenced or were influenced by understandings and misunderstandings of breast density and responses to breast density; and choosing supplemental screening, which was influenced by knowledge and perception of the risks and benefits of supplemental screening, and the availability of resources.

The ethics review determined that the main harms of supplemental screening for people with dense breasts are false-positives and overdiagnosis, both of which lead to unnecessary and burdensome health care treatments. Screening programs raise inherent tensions between individual- and population-level interests; they may yield population-level benefit, but are statistically of very little benefit to individuals. Entrenched cultural beliefs about the value of breast cancer screening, combined with uncertainty about the effects of supplemental screening on some outcomes and the discomfort of many health care providers in discussing screening options for people with dense breasts suggest that it may be difficult to ensure that patients can provide informed consent to engage in supplemental screening. Funding supplemental screening for people with dense breasts may lead to improved equity in the effectiveness of identifying cancers in people with dense breasts (compared to mammography alone), but it is not clear whether it would lead to equity in terms of improved survival and decreased morbidity.

Conclusions

Supplemental screening with ultrasound, DBT, or MRI as an adjunct to mammography detected more cancers and increased the number of recalls and biopsies, including false-positive results. Fewer interval cancers tended to occur after supplemental screening compared to mammography alone. It is unclear whether supplemental screening as an adjunct to mammography would reduce breast cancer–related or overall mortality among people with dense breasts.

Supplemental screening with ultrasound, DBT, or MRI as an adjunct to mammography in people aged 50 to 74 years improved cancer detection but increased costs. Depending on the type of imaging modality, publicly funding supplemental screening in Ontario over the next 5 years would require

additional total costs between $15 million and $41 million for people with dense breasts, and between $4 million and $10 million for people with extremely dense breasts.

The people we engaged with directly valued the potential clinical benefits of supplemental screening and emphasized that patient education and equitable access should be a requirement for implementation in Ontario. Our review of the qualitative literature found that the concept of breast density is poorly understood, both by people with dense breasts and by some general practitioners. People with dense breasts who receive routine mammography (especially those who receive health care in their nonpreferred language or are perceived to have lower economic status or health literacy) and their general practitioners may not have the awareness or knowledge to make informed decisions about supplemental screening. Some people with dense breasts experienced emotional distress from barriers to accessing supplemental screening, and many wanted to engage in supplemental screening, even when educated about its potential harms, including false-positives and overdiagnosis.

Given an overall lack of robust evidence about morbidity and mortality associated with supplemental screening for people with dense breasts, it is not possible to determine whether funding supplemental screening for dense breasts delivers on the ethical duties to maximize benefits and minimize harms for populations and individuals. It is likely that existing inequities in access to breast screening and cancer treatment will persist, even if supplemental screening for dense breasts is funded. Continued efforts to address these inequities by removing barriers to screening might mitigate this concern. It will be important to identify and minimize sources of uncertainty related to benefits and risks of supplemental screening for dense breasts to optimize the capacity for everyone involved to live up to their ethical obligations. Some of these may be resolved with further evidence related to the outcomes of supplemental screening for dense breasts.

Table of Contents

List of Tables

List of Figures

Objective

This health technology assessment evaluates the accuracy, effectiveness, harms, and cost-effectiveness of supplemental screening (with contrast-enhanced mammography, ultrasound, digital breast tomosynthesis [DBT], and magnetic resonance imaging [MRI]) as an adjunct to mammography for breast cancer screening in people with dense breasts. It also evaluates the budget impact of publicly funding supplemental screening; the preferences and values of people with lived experience of dense breasts and breast screening, as well as their health care providers; and the ethical issues associated with supplemental screening.

Background

Health Condition

In Canada, breast cancer accounts for about one-quarter of female cancer cases each year.[1,2] In the general population, about 13% of women will develop breast cancer in their lifetime.[3] The Canadian Cancer Society's 2020 projected 5-year net survival rate for breast cancer was 88%.[1] In Ontario in 2020, it was expected that nearly 12,000 people would be diagnosed with breast cancer, and nearly 2,000 would die from the disease.[4] This includes cases of both invasive breast cancer and ductal carcinoma in situ (DCIS; abnormal cells confined to the lining of the breast duct), which can evolve into invasive breast cancer in some people, although the natural history is not fully understood.[5]

Factors that increase the risk of developing breast cancer include female sex, advanced age, nulliparity (never having completed a pregnancy of ≥ 20 weeks), alcohol consumption, family history, personal history, or history of biopsies for benign proliferative breast disease.[6] Inheritance of detrimental gene mutations (e.g., *BRCA1* and *BRCA2*) strongly increases breast cancer risk, as does exposure to ionizing radiation in adolescence and young adulthood; early menarche (first menstruation); late menopause; and the use of estrogen–progesterone after menopause.[6]

High breast tissue density is another important risk factor for breast cancer. Younger women tend to have more dense breasts, as do women whose first pregnancy occurs later in life, those who are nulliparous, those who consume alcohol, or those who use postmenopausal hormones.[6] The relative risk of breast cancer in people with the most dense breast tissue is estimated to be three to four times higher than those with the least dense tissue.[7,8] Although the density of breast tissue can change over time (especially after menopause), the increased risk may persist for up to a decade after the first mammogram on which the dense tissue was seen.[9]

Clinical Need and Target Population

Breasts consist of adipose (fatty), fibrous (connective), and glandular (milk ducts and lobules) tissue in varying proportions. Breast density can be classified in different ways for clinical use. The American College of Radiology classifies breast composition according to Breast Imaging Reporting and Data System (BI-RADS) categories based on density observed on mammography.[10] The BI-RADS classification system is widely used; its first iteration was implemented in 1993, and it has supported radiologists in implementing more standardized terminology and reporting of breast imaging findings.

The fifth (and current) edition of the BI-RADS atlas (Table 1) employs descriptors for visual assessment (density categories A, B, C, or D) that emphasize the masking effect of dense breast tissue, in addition to estimating the dense tissue content for each category. This represents a divergence from the fourth

edition, which reflected the percentage of dense tissue as determined by visual assessment.[10] Although descriptors for breast density have varied across editions of the BI-RADS atlases, the historical distribution of densities has remained relatively stable over more than two decades, with 45% to 50% falling into the dense breast categories (about 40% heterogeneously dense and 10% extremely dense).[10] Such stability of distribution suggests that although the focus of the BI-RADS categorization has changed over time and in the different editions (initially emphasizing volume of dense tissue rather than the visual masking effect), the 4th and 5th editions appear to be highly correlated in terms of the populations they capture (i.e., people in category D have > 75% dense tissue).

Table 1: BI-RADS Categorization of Breast Composition by Visual Estimation on Mammography

Breast density category and description, 5th edition	Breast density percentages, 4th edition[a]	Sensitivity of mammography and implications	Estimated prevalence in screening population
A: Breasts are almost entirely fatty	< 25%	81%–93%; highly sensitive	10%
B: Scattered areas of dense glandular tissue and fibrous connective tissue	25%–50%	84%–90%	40%
C: Breasts are heterogeneously dense	50%–75%	69%–81%; may obscure small masses	40%
D: Extremely dense breast tissue	> 75%	51%–74%; lowest sensitivity	10%

Abbreviation: BI-RADS, Breast Imaging Reporting and Data System.

[a] Density classified according to the percentage of glandular tissue observed.[11]

Sources: American College of Radiology[10]; Rao et al[11]; Seely et al[12]; Kerlikowske et al.[13]

A limitation of the BI-RADS density classification system is its subjectivity and documented variability between readers and even with the same reader.[14] Several methods have been explored for quantitative or automated breast density measurement using algorithms or other means (e.g., MRI 3-dimensional volumetric analysis) to overcome this limitation, but the extent of their use in breast density assessment as part of screening is unclear.[14]

Higher breast tissue density is both normal and common; about 43% of screening-eligible people (i.e., those aged 40 to 74 years) are classified as having dense breasts.[12] In general, more fibroglandular tissue yields greater breast density, which may obscure masses on mammography and make it more difficult to detect breast cancer lesions.[10] The denser the tissue, the larger the size of the masses that could be obscured. However, the potential for dense tissue to mask cancers on mammography does not fully account for the increased risk of cancer found in people with dense breasts.[9]

People with high breast density may experience a smaller reduction in breast cancer–specific mortality with regular screening mammography than people with non-dense breasts (13% vs. 41%).[15] A lower cancer detection rate, more interval cancers, and a greater proportion of aggressive interval or advanced-stage cancers have also been documented among people with dense or extremely dense breasts compared with those with less dense breasts.[12] As well, the mortality rate associated with interval cancers in people with dense breasts is 2- to 3-fold higher.[12]

Current Breast Screening Practices

Breast screening may be done opportunistically (e.g., via referral by a person's primary health care provider) or through public health programs. Many jurisdictions have organized breast screening programs for eligible asymptomatic people within defined age categories. The principle behind such programs is the detection of cancers at an earlier stage (when they are smaller and localized); screening is thought to facilitate effective or even curative intervention and yield superior survival compared to the treatment of symptomatic cancers.[16] Advances in treatment and earlier detection of cancers through screening are both credited for a substantive decline in breast cancer mortality since the mid-1980s in many countries, including Canada, the United States, the United Kingdom, and Australia.[17-19]

The origins of most organized breast screening programs date back to the 1980s or 1990s, and most feature film or digital mammography (low-dose breast x-ray) as the core screening modality.[16] Anatomic changes are detected on mammography based on the differential density of tissue,[20] and findings are assigned a numeric category according to the BI-RADS atlas for mammography (referred to as BI-RADS assessment categories).[10] The current BI-RADS assessment category definitions are as follows:

- 0: Incomplete assessment; additional imaging or review of prior images is needed
- 1: Negative
- 2: Benign finding
- 3: Probably benign finding; short-interval follow-up is suggested
- 4: Suspicious abnormality; biopsy should be considered
- 5: Highly suggestive of malignancy; appropriate action should be taken

Fibroglandular tissue attenuates x-rays (i.e., reduces their intensity as they pass through) to a greater extent than fatty tissue, and it appears white, potentially masking lesions.[9] In dense breast tissue, mammography is limited (with sensitivities as low as 50% to 60% in the most dense tissue[12,21-23]), and it may not be as accurate in detecting abnormalities.[20]

Over 80% of breast cancers develop in people over 50 years of age, and it is estimated that less than 1% of women are at high risk of developing breast cancer.[4] Over time, as research has further elucidated the risk factors for breast cancer, some organized screening programs have employed different recommendations for the age to start screening, imaging modality, and screening interval for people at high risk (e.g., 20% to 25% lifetime risk of breast cancer), higher-than-average risk (intermediate risk), and average risk (e.g., < 15% lifetime risk).[24-26]

On its own, high breast density does not confer high risk of breast cancer. Instead, it may confer higher-than-average risk. Those with high breast density and no additional high-risk factors tend to follow an average-risk screening pathway, or a modified version of it. In Canadian organized breast screening programs, this typically means screening mammography annually or biennially (i.e., every 1 or 2 years); in the United States screening typically occurs annually,[12] and in the United Kingdom, triennially (every 3 years).[27] A recent study analyzing data from Canadian breast screening programs suggested that annual screening mammography for people with dense breasts was a more effective strategy, with a lower annualized interval cancer rate than biennial screening.[12] However, the impact of more frequent (e.g., annual) screening mammography for people with dense breasts on mortality and the stage of cancers detected is unclear because of a lack of data.[12,28]

Breast cancer can occur in people born male (referred to separately as male breast cancer). Compared to men, women have approximately 100 times the lifetime risk of developing breast cancer,[6] and in Canada, cases of male breast cancer account for less than 1% of all breast cancer.[2] Because of the rarity of male breast cancer, male breast screening is not warranted or offered in Canada.[29] It is recommended that those who were born male and present clinically with symptoms undergo investigation with diagnostic imaging such as ultrasound or mammography.[27,30]

For transgender (trans) people, who comprise about 0.6% of the Canadian population or approximately 77,000 people living in Ontario,[31] there is limited evidence to inform the risk of breast cancer.[32,33] The Ontario Health (Cancer Care Ontario) guidelines for the Ontario Breast Screening Program (OBSP) recommend breast screening for trans (trans men and trans women who have used or are using cross-sex hormones for 5 or more consecutive years) and nonbinary people who meet the program criteria.[31] Similarly, it is recommended that trans and nonbinary people who meet the criteria for high-risk referrals and high-risk OBSP screening receive those services. In the United Kingdom, the National Health Service offers breast screening for trans and nonbinary people, either by invitation or at the person's request.[34]

Overview of Health Technologies of Interest

Supplemental breast screening (i.e., additive or adjunctive imaging) refers to the use of additional imaging in parallel with or sequential to screening mammography. This is distinct from *diagnostic imaging*, which is used to investigate a clinical finding (e.g., a palpable lump) or a suspicious finding on mammography. Several different technologies may be used for supplemental screening of people with dense breasts. Supplemental screening is thought to assist in the detection of cancers that are not visible on mammography because of high breast density, and it may have potential to be cost-effective depending upon the technology used (e.g., ultrasound) and the population screened.[25] The accuracy of each imaging modality reported in the literature varies, as does its risks or contraindications; all of these must be weighed against the potential benefit.

Ultrasound

Ultrasound (also called sonography or ultrasonography) uses high-frequency sound waves to create images of breast tissue.[25,35]

Handheld ultrasound involves the manual use of a small transducer and ultrasound gel placed directly on the skin; representative images are obtained by the operator. The quality of the images is dependent on the skill and experience of the operator, who may be a specialized breast radiologist, a general radiologist, or a medical radiation technologist.[25,35,36] The exam takes approximately 20 minutes to complete.[37]

Automated breast ultrasound systems (ABUSs)—also called whole-breast ultrasound—are not dependent on the operator for image selection, and they allow radiologists to review an entire data set for interpretation. All automated systems allow for the imaging of the whole breast; some systems provide both 2-dimensional and 3-dimensional images.[25] Image acquisition time is approximately 5 minutes—much less per image than with handheld ultrasound.[37] The total time to image both entire breasts (i.e., two to three images) is about 20 minutes per patient.

From available published studies, it is unclear whether the accuracy of ABUS for screening differs meaningfully from the accuracy of handheld ultrasound.[36] However, those screened with ABUS must undergo additional diagnostic handheld ultrasound to characterize any findings. An advantage of ultrasound is its lack of ionizing radiation, but ultrasound can yield a relatively high rate of false-positive results.[38] The estimated sensitivity and specificity of ultrasound in people at average risk are about 55% and 94%, respectively.[39]

Magnetic Resonance Imaging

Magnetic resonance imaging uses a strong magnetic field, radiofrequency waves, and computer processing to create images. Gadolinium-based contrast agents are administered, and the new blood vessels that lesions create (i.e., neovascularization) preferentially take up the contrast agent to provide better visualization.[40] MRI breast screening can be relatively time-intensive, although abbreviated protocols have been validated against full protocols for people with extremely dense breasts; the abbreviated protocols can be completed in as little as 3 to 10 minutes of magnet time.[41,42] According to several Ontario experts, contrast-enhanced MRI is the standard for breast cancer screening in those at high risk; techniques without contrast (such as diffusion imaging) are considered experimental.

With MRI there is no exposure to ionizing radiation, but certain metal implants (e.g., pacemakers), allergies to the contrast agent, or claustrophobia are contraindications for MRI.[24] Contrast agents may also be contraindicated for some people with acute kidney injury or chronic kidney disease, because of elevated risk of nephrogenic systemic fibrosis or nephrotoxicity.[43,44] MRI is widely considered to be the most accurate imaging modality for breast screening because its sensitivity is generally high in populations at high risk (i.e., at least 80%). In average-risk screening populations, its sensitivity and specificity are 100% and 97%, respectively.[40]

Contrast-Enhanced Mammography

Contrast-enhanced (spectral) mammography (also known as contrast-enhanced digital mammography or contrast-enhanced dual-energy mammography) is designed to produce contrast-enhanced images of the breast using an x-ray contrast agent (a non-ionic iodinated agent) and a dual-energy acquisition technique.[45] Low- and high-energy images are taken sequentially, a few minutes after intravenous administration of the contrast agent, and are digitally recombined via vendor-specific algorithms.[45,46] The low-energy and recombined images are read together. Masses can be detected because the neovascularization of lesions can be visualized, as well as density and morphological features.

For detecting masses in breast screening, the sensitivity of contrast-enhanced mammography has been reported to be approximately 97%, and the specificity is approximately 70%.[47] With the use of low-osmolar contrast media, there is a risk of a contrast reaction, but the incidence of such reactions is reported to be 0.2% to 3.1%, and most reactions are mild to moderate.[48] Additional precautions and considerations may be required for people who have kidney disease or other pre-existing conditions (e.g., asthma or diabetes), and for people who have had a previous contrast reaction.[48]

Digital Breast Tomosynthesis

Another mammography-based modality, DBT (3-D mammography), uses x-rays to collect images of the breast from several angles and compute a 3-dimensional image. This capability is built into many newer digital mammography machines.[38] With DBT, the exposure to ionizing radiation is similar to that of standard digital mammography, so a person receives twice the radiation dose if it is used as an

adjunct.[38,49] Some software packages can produce a synthetic 2-dimensional mammography view from the tomosynthesis images, reducing the radiation exposure.[38]

Regulatory Information

Some imaging systems used for breast screening, as well as their intended use as per Health Canada, are listed in Table 2.

Numerous handheld ultrasound systems have been licensed by Health Canada as Class II devices, and are not specifically indicated for breast screening or imaging.[25] Two ABUSs are listed in Health Canada's Medical Devices Active Licence Listing database; however, only two hold active licences for sale in Canada.

Similarly, most MRI scanners are general systems that can be used on the breast but are not specifically indicated for breast cancer screening. Several licensed MRI systems are available that include software packages and modules specific to breast imaging, and numerous MRI coils are approved for use specifically in breast imaging in conjunction with a general magnetic resonance scanner. These devices are regulated as Health Canada Class II medical devices, and several hold active licences.[24]

Table 2: Health Canada–Listed Breast Imaging Systems and Reported Intended Use

Device	Licence number (first issue date)	Manufacturer	Health Canada–intended use(s)
Somo-v ABUS	74905 (Sep. 21, 2007)	GE Medical Systems	As adjunct to mammography to provide physicians with an increase in the sensitivity of breast cancer detection in diagnosing symptomatic and screening asymptomatic people; the device is not intended to be used as a replacement for screening mammography
Invenia ABUS	74905 (Sep. 14, 2015)	GE Medical Systems	As adjunct to mammography for breast cancer screening in asymptomatic women for whom screening mammography findings are normal or benign (BI-RADS assessment category 1 or 2), with dense breast parenchyma (BI-RADS 1 composition/ density C or D), and have not had previous clinical breast intervention. The device is intended to increase breast cancer detection in the described patient population. The device may also be used for diagnostic ultrasound imaging of the breast in symptomatic women
SenoClaire breast tomosynthesis system	93289 (May 29, 2014)	GE Medical Systems	Acquires 2D images and also acquires multiple projection views to produce 3D DBT images suitable for screening and diagnosis of breast cancer. The device can be used for the same clinical applications as traditional mammographic systems for screening mammography

Device	Licence number (first issue date)	Manufacturer	Health Canada–intended use(s)
Selenia Dimensions 2D/3D mammography system	79158 (Mar. 3, 2009)	Hologic Inc.	Generates digital mammographic images that can be used for screening and diagnosis of breast cancer. The system is intended for use in the same clinical applications as a 2D mammography system for screening mammograms. Specifically, the Selenia Dimensions system can be used to generate 2D digital mammograms and 3D mammograms Contrast-enhanced digital mammography (CEDM) is an extension of the existing indication for diagnostic mammography with the Selenia Dimensions system. The CEDM application shall enable contrast-enhanced breast imaging using a dual-energy technique. This imaging technique can be used as an adjunct following mammography and/or ultrasound exams to localize a known or suspected lesion In Canada and Singapore, tomosynthesis is not approved for screening, and must be used in conjunction with a 2D image (either a full-field digital mammography image or 2D image generated from the 3D image set)
Mammomat Inspiration	76969 (Mar. 26, 2015)	Siemens Healthcare	Intended for mammography exams, screening, diagnosis, and stereotactic biopsies under the supervision of medical professionals. Mammographic images can be interpreted by either hard copy film or soft copy workstation The Mammomat Inspiration with tomosynthesis option is indicated for acquisition of 2D as well as 3D digital mammography images to be used in screening and diagnosis of breast cancer
Mammomat Revelation with 50° wide-angle tomosynthesis and titanium contrast-enhanced mammography—Aquapak	102147 (Dec. 10, 2018)	Siemens Healthcare	Is intended to be used for mammography exams, screening, diagnosis, biopsies, and dual-energy procedures under the supervision of medical professionals. Mammography images can be interpreted by either hard copy film or soft copy workstation The Mammomat Revelation with tomosynthesis option is indicated for acquisition of 2D as well as 3D digital mammography images to be used in screening and diagnosis of breast cancer
SenoBright HD, contrast-enhanced spectral mammography	100429 (Jan. 22, 2018)	GE Medical Systems	An extension of the existing indication for diagnostic mammography with Senographe Pristina, it is labelled CESM (for contrast-enhanced spectral mammography) in the user interface of Senographe Pristina system. The CESM application shall enable contrast-enhanced breast imaging using a dual-energy technique. This imaging technique can be used as an adjunct following mammography and ultrasound exams to help localize a known or suspected lesion
Sofia automated tomographic ultrasound device	79608 (no longer authorized for sale in Canada, as of Jul. 24, 2019)	IVU Imaging Corporation	As B-mode ultrasonic imaging system for imaging of a patient's breast when used with an automatic scanning linear array transducer
SonoCiné automated whole-breast acquisition screening system	87616 (no longer authorized for sale in Canada, as of Oct. 31, 2016)	SonoCiné Inc.	Adjunct to mammography for screening asymptomatic people for breast cancer

Abbreviations: 2D, 2-dimensional; 3D, 3-dimensional; ABUS, automated breast ultrasound system; BI-RADS, Breast Imaging Reporting and Data System; DBT, digital breast tomosynthesis.

Sources: Health Canada (email communication; Sept. 8, 2021) and Medical Devices Active Licence Listing database.[50]

Ontario, Canadian, and International Context

Ontario

As of June 2021, breast density information is available for health care providers[51] and participants in the OBSP; information can be found on a dedicated webpage (for health care providers: cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/breast-density-provider-information; for the public: cancercareontario.ca/en/types-of-cancer/breast-cancer/screening/breast-density). Breast density is reported on screening mammogram reports (as percent mammographic density and BI-RADS category) by the reading radiologist.[52] If at least one breast has 75% breast density or higher, the participant is considered to have high breast density and is placed on a 1-year recall for mammography (rather than the typical 2-year recall).[53] People with heterogeneously dense breasts (50% to < 75% breast density or BI-RADS C) undergo biennial mammography as per the average-risk screening pathway.[53] At present in Ontario, supplemental screening is not funded or provided through the OBSP for people with dense breasts and no high-risk factors. People may access supplemental breast screening (e.g., ultrasound) with a requisition from their primary care provider. However, the OBSP does not endorse supplemental screening for people at average risk, and, because of a lack of resources and alignment with OBSP recommendations, some screening sites in Ontario do not offer supplemental screening if requested by primary care. The Ontario *Schedule of Benefits–Physician Services* states that routine breast screening with MRI in people at average risk is not an insured service.[54]

Canada

All Canadian provinces and territories have organized breast screening programs for people at average risk of breast cancer, except Nunavut.[55] British Columbia began informing screening-program participants of their breast density in screening mammography letters in 2018, and it was the first program to do so.[56] However, the BC Cancer Breast Screening Program does not recommend supplemental or more frequent screening for people with high breast density because of a lack of evidence.[57] Increased frequency of mammography screening for people with high breast density (typically defined as BI-RADS C or D, or ≥ 50% or ≥ 75% breast density) is recommended by the organized screening programs in the Yukon, Northwest Territories, Saskatchewan, Newfoundland, and Ontario.[29] In New Brunswick and Nova Scotia, more frequent or supplemental screening for people with very dense breasts occurs only at the recommendation of the radiologist.[29] Nunavut recommends more frequent opportunistic screening for people with high breast density.[29]

In Prince Edward Island, ultrasound screening is not publicly funded for people with dense breasts. Like Ontario, in PEI people with breast density greater than or equal to 75% are screened annually for breast cancer with mammography only. Additional imaging is available for people with radiology requests, regardless of breast density. In Alberta, tomosynthesis is reportedly used for screening of people with dense breasts at some sites and for all screening at others.[29] Ultrasound is used at some Alberta screening program sites as a supplemental modality for people with dense breasts.[29] The Alberta program is the only Canadian screening program to report such use of ultrasound and DBT. We are unaware of any province that uses MRI as an adjunct to screening mammography for people with dense breasts who are not at high risk.

International

In the United States, breast screening is opportunistic. Beginning in 2009—and increasing in response to 2019 federal legislation requiring breast density notification—at least 36 states now inform those who

have been screened of their breast density and typically suggest that patients discuss the implications and the suitability of supplemental screening with their health care provider.[58]

Current guideline recommendations for screening people with dense breasts are inconsistent (Table 3). Some international practices are shown in Appendix 1, Table A1. The most recent recommendation from the Canadian Task Force on Preventive Health Care (2018)[59] is not specific to people with dense breasts, but it does recommend against the use of supplemental screening with MRI, DBT, or ultrasound in people who are not at high risk. In contrast, the 2019 Canadian Association of Radiologists and Canadian Society of Breast Imaging guidelines[60] suggest that supplemental ultrasound be considered for people with dense breasts in the context of other risk factors.

A systematic review of international breast screening guidelines found that of 23 guidelines, only two included recommendations for the screening of people with dense breasts who were at less than high risk: the National Cancer Council in China recommends routine supplemental ultrasound, and a Brazilian guideline recommends consideration of supplemental ultrasound.[61]

Since the above systematic review was conducted, the 2021 American College of Radiology Appropriateness Criteria have stated that supplemental DBT is usually appropriate for people with dense breasts who are at average or intermediate (i.e., < 20%) lifetime risk.[62] Similarly, an updated 2022 guideline from the European Society of Breast Imaging recommends supplemental or standalone screening breast MRI every 2 to 4 years for women with extremely dense breasts.[63] The U.S. Preventative Services Task Force could not make a recommendation in 2016 because of insufficient evidence; their update of the evidence is underway (research plan finalized in May 2021).

Table 3: Selected Guideline Recommendations for Supplemental Screening of Dense Breasts

Region	Recommendation(s)	Guideline (year)
Australia	Biennial mammography, no special guidelines for dense breasts. The treating physician may order supplemental tomosynthesis, ultrasound, or MRI but will not be reimbursed	BreastScreen Australia—Breast Cancer Network Australia[64]
Brazil	Ultrasound should be considered as an adjunct to mammography in women with dense breasts[a]	Brazilian College of Radiology and Diagnostic Imaging, Brazilian Breast Disease Society, and Brazilian Federation of Gynecological and Obstetrical Associations (2017)[65]
Canada	Supplemental screening breast ultrasound may be considered for patients with dense breast tissue (ACR density categories C and D) When considering supplemental screening breast ultrasound, breast density should be placed in context with other risk factors and risk-reduction strategies	Canadian Association of Radiologists, Canadian Society of Breast Imaging (2019)[60]
Canada	The task force did not specifically review evidence on supplemental screening for women with dense breast tissue Recommends not using MRI, tomosynthesis, or ultrasound to screen for breast cancer in women who are not at increased risk (strong recommendation; no evidence)	Canadian Task Force on Preventive Health Care (2018)[59]
China	Annual screening with mammography and ultrasound for women with dense breasts	China National Cancer Centre (2020)[61,b]

Region	Recommendation(s)	Guideline (year)
Europe	Supplemental screening for women with extremely dense breasts using MRI at least every 4 years (ideally every 2–3 years) between the ages of 50 and 70 years. MRI can be used without mammography Where MRI is not available, ultrasound as an adjunct to mammography may be used as an alternative, provided that women are adequately informed about the different performance of various non-mammography modalities Quality-assurance systems and benchmarks must be established for non-mammography screening methods, because of underdiagnosis in extremely dense breasts	European Society of Breast Imaging (2022)[63]
Europe	In organized screening programs, for people with high breast density, screening with DBT or digital mammography is recommended Screening with MRI, DBT, or ultrasound (handheld or automated) are not recommended in addition to digital mammography	European Commission Initiative for Breast Cancer Screening and Diagnosis guidelines (2021)[66]
United Kingdom	Additional screening with ultrasound after negative mammography screening in women with dense breasts is not recommended, based on a 2019 review	UK National Screening Committee (2019)[67,68]
United States	For women with dense breasts, current evidence is insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer following a negative mammogram using breast ultrasonography, MRI, DBT, or other methods in women identified to have dense breasts on an otherwise negative screening mammogram (I statement[a])	U.S. Preventative Services Task Force (2016)[69,70] Update in progress, 2021
United States	Women with dense breasts at average risk (< 15% lifetime risk): • DBT screening is usually appropriate[c] as supplemental breast cancer screening • Supplemental imaging with breast ultrasound is controversial but may be appropriate. There is insufficient medical literature to conclude whether or not patients would benefit • Contrast-enhanced mammography, MRI (with and without intravenous contrast, regular or abbreviated) may be appropriate[d] Women with dense breasts at intermediate risk (15%–20% lifetime risk): • DBT screening is usually appropriate for supplemental breast cancer screening • Supplemental ultrasound, contrast-enhanced mammography, MRI (with and without intravenous contrast, regular or abbreviated) may be appropriate	American College of Radiology Appropriateness Criteria Supplemental Breast Cancer Screening Based on Breast Density (2021)[62]

Abbreviations: ACR, American College of Radiology; DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging.

[a] Category B recommendation, based on reasonable scientific evidence and consistent consensus to strongly support the recommendation.

[b] Guideline published in Chinese only; translation taken from systematic review of guidelines by Ren et al.[61]

[c] Favourable risk–benefit ratio for patients in this clinical scenario.[62]

[d] May be an alternative to preferred imaging that has a better risk–benefit ratio in specific clinical scenarios, or the risk–benefit is equivocal.[62]

Equity Considerations

We considered potential equity issues across the factors outlined in PROGRESS-Plus.[71] Dense breasts are more common in people in their 40s than in people aged 50 or older. Mammographic densities (and therefore the accuracy of screening mammography) also may differ by race or ethnicity.[72] East Asian women tend to have denser breasts than White women, and the onset of breast cancer tends to occur about a decade earlier (i.e., age 40 to 50 years).[73-76] A 2020 systematic review by Wang et al[76] investigated ultrasound as a replacement primary imaging modality for population breast screening in some Asian countries by comparing the test accuracy of ultrasound in East Asian women with that of mammography. Their meta-analysis of six studies found that although there was no significant difference in pooled specificity between ultrasound and mammography for population breast screening, the pooled sensitivity of mammography was significantly higher in the U.S. population.[76] The pooled sensitivity of mammography in the East Asian population was 0.81 (95% confidence interval 0.71–0.88) in one meta-analysis, whereas in other studies in the U.S. population it was about 0.87.

Disparities in breast screening have been noted for certain populations in Ontario, which can lead to delays in cancer diagnosis and poorer outcomes.[77] In the literature, it has been recognized that immigrant women,[78] Black Canadian women,[79] people of lower socioeconomic status,[80] and Indigenous peoples[81] are underscreened, and these disparities would likely remain relevant in the context of supplemental breast screening in people with dense breasts.

Harms Considerations

No test is perfect; all supplemental screening modalities have the potential to yield inaccurate (false) test results—false-positives and false-negatives. False-positive test results will lead to a person being recalled for additional unnecessary testing or procedures to reach a diagnosis. These investigations may include diagnostic mammography, ultrasound, and biopsy (percutaneous, or surgical if necessary), each of which is associated with its own risks and potential complications. False-negative test results may delay necessary treatment.[24,82] Inaccurate test results can also lead to substantial psychological distress and anxiety for those who are screened.[82,83] Both false-positive and false-negative results tend to prompt people who have had false test results to want more screening or more types of imaging when they are being screened.[83]

Other potential risks in breast cancer screening include overdiagnosis and overtreatment. Some cancers detected by screening may never lead to symptoms or become life-threatening. At present, there is no conclusive way to determine at diagnosis if a screen-detected cancer will progress, meaning that some may undergo unnecessary treatment with surgery, radiation therapy, or chemotherapy.[24,84]

Any x-ray-based imaging modality—including mammography, DBT, or contrast-enhanced mammography—involve exposure to ionizing radiation. The radiation dose to the breast with standard 2-dimensional mammography is about 4 milliSieverts on average, but it varies with the number of views required, based on factors such as breast size and density.[5,85] Although the projected incidence of radiation-induced cancers from cumulative breast screening is low, minimizing unnecessary exposure to radiation-sensitive breast tissue is prudent.[86]

Expert Consultation

We engaged with clinical and research experts, radiologists, oncologists, family physicians, and other clinicians with expertise in breast imaging and breast cancer screening, to help inform the refinement of

the research questions and to contextualize the evidence on adjunct imaging modalities for screening people with dense breasts in Ontario.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD #42022311789), available at www.crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Questions

- What are the sensitivity and specificity of supplemental breast screening with ultrasound, digital breast tomosynthesis (DBT), magnetic resonance imaging (MRI), or contrast-enhanced mammography, as an adjunct to mammography for breast cancer screening in people with dense breasts?
- What are the comparative sensitivity and specificity of supplemental breast screening with ultrasound, DBT, MRI, or contrast-enhanced mammography, as an adjunct to mammography compared to mammography alone for breast cancer screening in people with dense breasts?
- What are the effectiveness and harms of supplemental breast screening with ultrasound, DBT, MRI, or contrast-enhanced mammography as an adjunct to mammography compared to mammography alone for breast cancer screening in people with dense breasts?

Methods

Clinical Literature Search

We performed a clinical literature search on October 29, 2021, to retrieve studies published from January 1, 2015, until the search date. Several systematic reviews and health technology assessments related to this topic had been published around 2016, including previous work by Health Quality Ontario[24,25] and the synthesis that informed the current recommendations of the U.S. Preventive Services Task Force.[69] These reviews found few, if any, studies focused on the dense breast population. Therefore, we searched for publications from 2015 to the present. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED). We also searched the International Network of Agencies for Health Technology Assessment (INAHTA) database of health technology assessments.

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[87]

We created database auto-alerts in MEDLINE and Embase and monitored them until May 16, 2022. We also performed a targeted grey literature search of health technology assessment agency websites and clinical trial and systematic review registries following a standard list of sites developed internally. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published since January 1, 2015
- Study designs (hierarchical eligibility):

- Systematic reviews (including meta-analyses and health technology assessments that included a systematic review) of comparative studies (randomized controlled trials and nonrandomized studies) that matched our research question and population, intervention, comparator, and outcomes. We also considered systematic reviews with a broader scope than our review to be eligible, provided that they included results for our specific question. Systematic reviews had to have clearly reported literature search methods, including (at a minimum) information about the databases searched, search terms, and search dates; they also had to provide explicit prespecified eligibility criteria
- Primary studies: prospective comparative studies (randomized controlled trials and nonrandomized studies); if none, retrospective nonrandomized comparative studies:
  - Comparative test accuracy studies (primary cohort or cross-sectional studies; paired or randomized designs) in which all study participants received both mammography and the index test (i.e., supplemental imaging modality), followed by verification of disease by the reference standard
  - Single-test accuracy studies (i.e., primary cohort or cross-sectional studies where the reference standard was histological confirmation of cancer) with either false-positive/false-negative rates or sufficient information to construct a 2 × 2 table (true positives, true negatives, false-positives, false-negatives) to calculate sensitivity and specificity

Exclusion Criteria

- Noncomparative case–control/two-gate diagnostic studies
- Modelling, reader, or simulation studies
- Technical validation, laboratory, animal, or in vitro studies
- Narrative or nonsystematic reviews, editorials, commentaries, case reports, conferences abstracts and posters, letters

PARTICIPANTS

Inclusion Criteria

- Asymptomatic people 40 years of age or older with negative or benign breast screening mammography results (i.e., Breast Imaging Reporting and Data System [BI-RADS] assessment category 1 or 2), no high-risk factors, and dense breasts (defined as > 50% or ≥ 75% dense tissue, BI-RADS composition categories C and/or D or equivalent, regardless of method of density determination [e.g., visual, quantitative, or automated software/artificial intelligence])

Exclusion Criteria

- Participants with high-risk factors (i.e., known high-risk genetic mutations; a family history of high-risk genetic mutations or cancer; a ≥ 25% lifetime risk of breast cancer based on IBIS [International Breast Cancer Intervention Study breast cancer risk prediction tool], BOADICEA [Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm], or a similar tool; or a history of chest irradiation) or defined as high-risk in research articles; participants with male breast cancer; participants younger than age 40 years

- Population in which breast density was not specified, or that included those with and without high breast density, and the characteristics of the target population (and their results) could not be extracted

INTERVENTIONS

Inclusion Criteria

- Supplemental screening after 2-dimensional digital or film mammography with one of:
  - Contrast-enhanced (spectral) mammography
  - Ultrasound: including handheld ultrasound or automated breast ultrasound (ABUS)
  - Digital breast tomosynthesis (DBT)
  - MRI with or without contrast

Exclusion Criteria

- Imaging for surveillance (i.e., recurrence or progression), diagnosis, staging, prognosis, risk stratification, and other purposes not related to screening

COMPARATORS

Inclusion Criteria

- For sensitivity and specificity: comparator test (screening mammography alone) or clinical reference standard (histopathological confirmation of cancer)
- For effectiveness: screening mammography alone or comparisons between eligible supplemental imaging modalities

Exclusion Criteria

- Imaging modalities for primary screening (i.e., compared to mammography as a replacement)

OUTCOME MEASURES

- Sensitivity
- Specificity
- Interval cancer rate
- Incremental cancer detection rate of supplemental screening
- Prognostic features of cancers detected by supplemental screening (e.g., invasive, ductal carcinoma in situ [DCIS], nodal status, tumour size, stage)
- Abnormal recall rate
- Adverse reactions to contrast media
- Psychological impact, distress, anxiety
- Overall or breast cancer–specific mortality or survival

Literature Screening

Two reviewers (AS and KM) conducted an initial screening of titles and abstracts using Covidence[88] and then obtained the full texts of studies that appeared eligible for review according to Cochrane rapid review methods.[89] One reviewer (AS) then examined the full-text articles and selected studies eligible for inclusion. The second reviewer (KM) screened all excluded full-text articles. During screening, any disagreements between reviewers were resolved by consensus. One reviewer (AS) also examined the reference lists of included studies for any additional relevant studies not identified through the search. Citation flow and reasons for exclusion of full-text articles are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[90]

Data Extraction

One reviewer (AS) extracted relevant data on study design and characteristics, risk-of-bias items, results, and PICOTS (population, intervention, comparator, outcome, time, and setting). The second reviewer (KM) independently validated the data extraction. The reviewer (AS) extracted relevant data using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

When multiple publications reported on the same study, we used the most recent publication or the publication reporting the outcomes of interest most clearly. When multiple publications were available for a single study but reporting different outcomes of interest, we extracted relevant data from those publications.

In the interest of comprehensiveness and capturing the best available evidence, we included two studies with broader age eligibility than our target population, because the mean or median age of study participants was 40 years of age or greater.[91,92] We also included one study that reported that only a very small proportion of its population had high-risk factors (i.e., ≤ 5% with a family history of breast cancer).[93] We included studies that met all other eligibility criteria and did not report participant risk factors, provided that they did not permit people with one or more high-risk factors to enrol in the study.

Statistical Analysis

Owing to heterogeneity in populations, imaging, and methods (i.e., in population characteristics, number of readers and process for reading, screening frequency, and test-positive threshold) meta-analysis was not appropriate. Therefore, we have provided a narrative summary of results by modality, comparison, and outcome.

A summary of the definitions and formulas we used to calculate diagnostic performance is provided in Appendix 3. Given that sensitivity and specificity depend on the threshold used to define a positive test, we accepted and reported the categories for positive and negative tests as defined in the studies, based on the study's assignment of BI-RADS assessment categories, as defined by the American College of Radiology (ACR).[10] The general BI-RADS assessment category definitions (0 to 5) are described in the Background.

Distinct and separate from the numeric BI-RADS assessment categories used for imaging findings, BI-RADS breast composition categories (defined in two editions of the ACR atlas) are most frequently used in the literature. The breast composition categories of *heterogeneously dense* and *extremely dense* are referred to in studies as BI-RADS C or D, ACR C or D, or ACR 3 or 4, respectively. For accuracy, we report the density categorization terminology used in each study.

SUBGROUP ANALYSES

We addressed the comparison of ABUS with handheld ultrasound using data from one study designed to compare the two types of ultrasound.

We planned the following subgroup analyses but were unable to conduct them because of a lack of available data:

- Heterogeneously dense (BI-RADS C or 51%–75% density) versus extremely dense (BI-RADS D or > 75% density)
- Age (e.g., < 50 years vs. ≥ 50 years)
- Frequency of screening (e.g., annual vs. biennial)
- Ethnicity
- People with a personal history of breast cancer
- People with breast implants
- Nonbinary people with hormone use
- Body mass index

Critical Appraisal of Evidence

We assessed risk of bias using the Cochrane risk-of-bias tool for randomized controlled trials[94] or the Risk of Bias Assessment Tool for Nonrandomized Studies (ROBANS[95]; Appendix 4).

One reviewer (AS) evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[96] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The database search of the clinical literature yielded 3,252 citations published between January 1, 2015, and October 29, 2021. We identified 21 additional studies through grey literature searches, for a total of 2,176 after duplicates were removed. We also screened an additional 738 results from database alerts during the assessment period (monitored until May 16, 2022).

We identified 12 systematic reviews that reported outcomes of adjunctive breast screening with various modalities for people with dense breasts (three on multiple modalities,[21,69,97] one on contrast-enhanced mammography,[98] six on ultrasound[68,99-103] and two on DBT[104,105]). Upon further examination of the more than 180 primary studies included in those 12 systematic reviews, we identified no primary studies that met our predefined eligibility criteria, apart from those we screened in our literature search. The primary studies included in the systematic reviews had one or more ineligible feature, including the following: imaging in a mixed diagnostic or preoperative setting; inclusion (exclusively or in large part) of participants at high risk for breast cancer; publication date prior to 2015; or did not examine the imaging modalities as adjuncts to mammography (e.g., they were examined as replacements instead). Therefore, we excluded the systematic reviews (see Appendix 5 for a list of reviews excluded).

We excluded primary studies conducted in a general breast screening population in which only a subset of participants had dense breasts, either because they reported insufficient information about the baseline characteristics of the participants with dense breasts (to determine eligibility) or because of a lack of detail about analyses or outcomes for participants with dense breasts. Furthermore, because randomized controlled trials and prospective studies were available, we excluded studies with retrospective study designs in accordance with our predefined hierarchical eligibility criteria for study design (see Appendix 5 for a list of selected studies excluded after full-text review).

In total, we identified eight primary studies reported in 10 publications that met our inclusion criteria (two randomized controlled trials[93,106-108] and six prospective studies[36,41,91,92,109,110]). Figure 1 presents the PRISMA flow diagram for the clinical literature search.

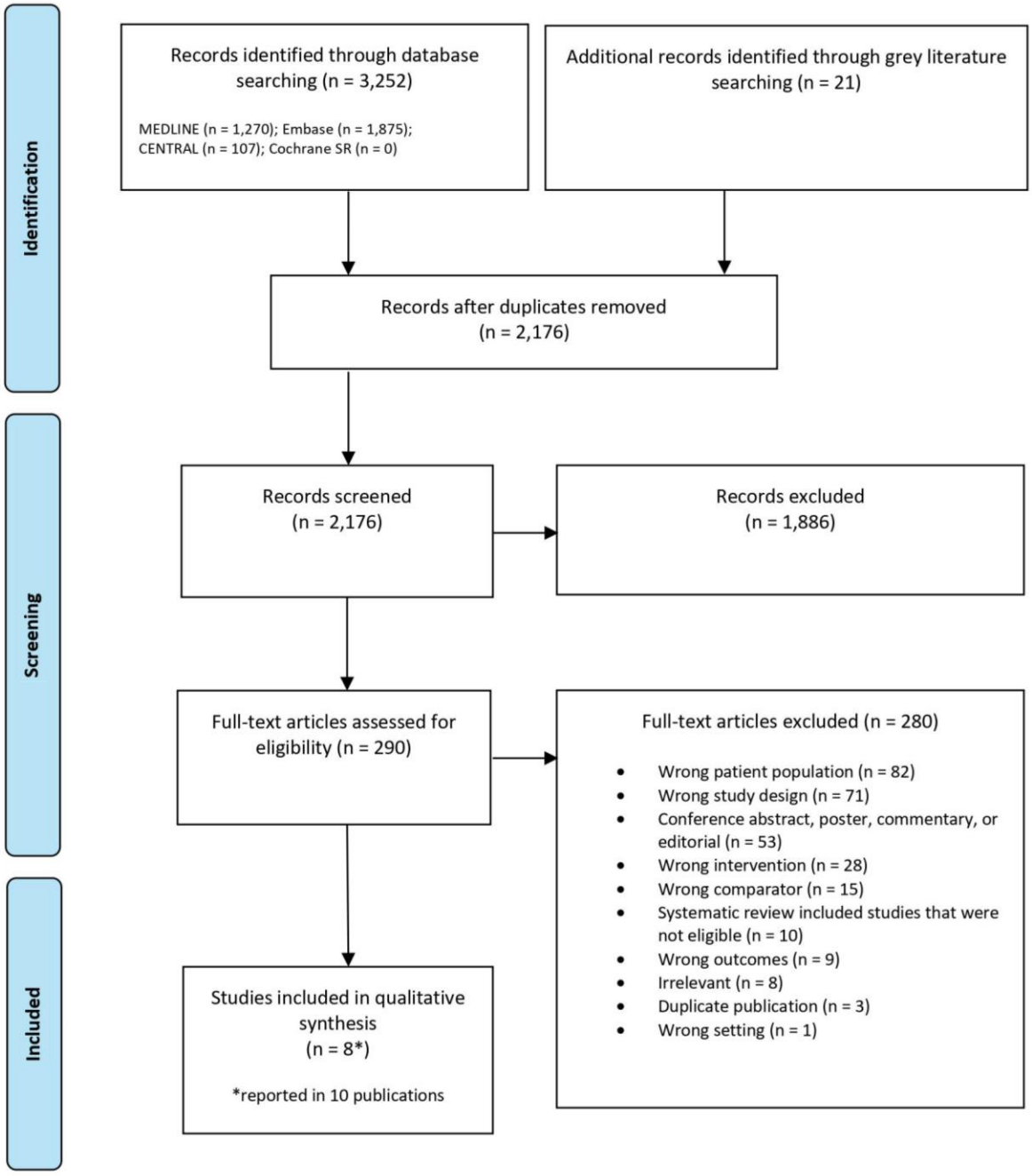


Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 3,252 citations published between January 1, 2015, and October 29, 2021. We identified 21 additional eligible studies from the grey literature search. After removing duplicates, we screened the abstracts of 2,176 studies and excluded 1,886. We assessed the full text of 290 articles and excluded a further 280. In the end, we included eight studies (reported in 10 articles) in the qualitative synthesis.[36,41,91-93,106-110]

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SR, systematic review.

Source: Adapted from Page et al.[90]

Overview of Included Studies

As shown in Table 4, three studies assessed supplemental ultrasound[93,109,110] and two assessed supplemental MRI.[41,106] Two prospective studies compared supplemental DBT and ultrasound,[91,92] and one prospective study compared handheld ultrasound and ABUS.[36] No studies on supplemental contrast-enhanced mammography or on supplemental DBT plus mammography versus mammography alone met our inclusion criteria.

The included studies assessed participants with heterogeneously or extremely dense breasts, except for the DENSE trial,[106] which was limited to people with extremely dense breasts only. The full characteristics of the included studies are presented in the section for each modality.

Table 4: Overview of Included Studies

Supplemental modality	Study ID	Country	Study design	Participants
Handheld ultrasound	J-START trial[93]	Japan	Randomized controlled trial	Heterogeneously and extremely dense breasts (approximately 5% had a first-degree relative with breast cancer)
ABUS	Gatta et al, 2021[109]	Italy	Prospective study	Heterogeneously and extremely dense breasts
ABUS	Wilczek et al, 2016[110]	Sweden	Prospective study	Heterogeneously and extremely dense breasts
Handheld ultrasound vs. ABUS	Philadelpho et al, 2021[36]	Brazil	Prospective study	Heterogeneously and extremely dense breasts
Handheld ultrasound vs. DBT	ASTOUND-2 trial[92]	Italy	Prospective study	Heterogeneously and extremely dense breasts
Handheld ultrasound vs. DBT	ASTOUND trial[91]	Italy	Prospective study	Heterogeneously and extremely dense breasts
MRI	DENSE trial[106,107,108]	Netherlands	Randomized controlled trial	Extremely dense breasts
MRI	Chen et al, 2017[41]	China	Prospective study	Heterogeneously and extremely dense breasts[a]

Abbreviations: ABUS, automated breast ultrasound; BI-RADS, Breast Imaging Reporting and Data System; DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging.

[a] Authors reported the inclusion of people with dense breasts as classified by the American College of Radiology (i.e., BI-RADS density categories), for which the two categories of highest density (heterogeneously dense and extremely dense) are typically considered "dense."[41]

Supplemental Ultrasound

CHARACTERISTICS OF INCLUDED STUDIES—SUPPLEMENTAL ULTRASOUND

We included three primary studies (one randomized controlled trial[93] and two nonrandomized studies[109,110]) on supplemental ultrasound screening (Table 5). The studies were conducted in Japan,[93] Italy,[109] and Sweden.[110] The randomized controlled trial[93] involved the use of handheld ultrasound for supplemental breast screening as an adjunct to mammography, and the other two used ABUS systems.[109,110] All of the studies categorized breast density in accordance with the ACR BI-RADS system (4th or 5th edition) and included people with heterogeneously dense and extremely dense breasts. Two studies had a higher proportion of participants with heterogeneously dense breasts,[93,109] and one study included predominantly participants with extremely dense breasts.[110]

The Japan Strategic Anti-cancer Randomized Trial (J-START)[93] was a large, multicentre, randomized controlled trial designed to assess the value of supplemental ultrasound as an adjunct to mammography. The research protocol included a separate planned compound study that compared outcomes between and within density groups (dense and non-dense; supplemental section 6.1 in the published article).[93] The details and results presented here are from the density substudy only. Participants underwent randomization to annual mammography or annual mammography with supplemental handheld ultrasound, and 95% also underwent a clinical breast examination, For the density substudy, the data from only one of the 42 trial sites (Miyagi prefecture; N = 19,213) were analyzed because of the availability of breast density information (participants with dense breasts = 11,390; intervention arm = 5,797; control arm = 5,593). Study participants had a mean age of 44.5 years (SD 2.9 years), and the overwhelming majority of participants (95%) had no family history of breast cancer (i.e., 1 or more first-degree relatives).

Two prospective studies evaluated supplemental ABUS, which produces 3-dimensional images of the whole breast. The study by Gatta et al[109] used an ABUS system in which participants lay in a prone position (Arietta/Sofia, Hitachi; Tokyo, Japan). The study by Wilczek et al[110] used an ABUS system in which participants lay in a supine position (U-Systems Inc; Sunnyvale, California, USA). In the study by Gatta et al,[109] participants were 47 to 50 years of age on average, and none had breast implants, breast biopsy or surgery in the previous year, or a personal or family history of cancer (the latter two characteristics were part of the study's eligibility criteria). Similarly, women with a history of cancer or breast cancer treatment or surgery in the preceding year were not eligible for the study by Wilczek et al.[110] The women in that study had a mean age of 48.5 years (SD 7.9 years); 0.2% had a personal history of breast cancer and 3.5% had a family history of breast cancer.

Pregnant or breastfeeding women were excluded from all studies. None of the studies reported participants' ethnicity, body mass index, gender identity, socioeconomic status, geographical considerations, or other demographic information.

Table 5: Characteristics of Included Studies—Supplemental Ultrasound

Study ID	Country Funding	Study design No. of centres	Participants Total, n Subgroup(s), n	Age	Characteristics	Density assessment	Screening frequency Rounds Reading	Breast imaging device and brand Protocol (timing, readers) Mammography	Ultrasound	Threshold for positive test Reference standard
J-START[93]	Japan Supported by research grant from Japanese ministry of health, labour, and welfare	Randomized controlled trial (ITT analysis for all outcomes; protocol published 2010) 1 centre[a]	11,390 BI-RADS C or D BI-RADS C: 10,019 BI-RADS D: 1,371 Intervention: 5,797 Control: 5,593	*Participants with dense breasts only* Mean age: 44.5 y (SD 2.9 y) Eligible: 40–49 y	Japanese	Visual judgment BI-RADS 5th edition (hetero-geneously and extremely dense)	Annual; FFDM 2-y follow-up Double reading (2 physicians)	Various, but all met protocol requirements Interpreted independent of ultrasound; performed simultaneously with ultrasound	Handheld ultrasound devices that met protocol requirements Interpreted independent of mammography; performed simultaneously with FFDM Performed by technician or physician	BI-RADS 3, 4, 5 Breast cancers from registry (cytology/ pathology)
Gatta et al, 2021[109]	Italy Funded by Italian ministry of health (Ricerca Finalizata 2018)	Prospective cohort (single-arm) 1 centre	1,165 Density 3: 729 Density 4: 436	*Mean age*[b] Density 3: 47 y Density 4: 50 y *Age breakdown* 40–50 y: 68% 50–60 y: 25% 60–75 y: 7%	Those with implants or a family or personal history of cancer were ineligible	BI-RADS 4th edition Density 3 or 4 (hetero-geneously or extremely dense breasts)	Biennial[c]; FFDM 2-y follow-up Independent reading by 2 radiologists	Mammomat Inspiration (Siemens) First exam: 6 images (CC, MLO, ML) Second exam: 2 images (MLO, CC); interpreted independent of ABUS	Arietta/Sofia (Hitachi Tokyo) Supine ABUS Interpreted after mammography; final assessment based on mammography + ABUS by consensus	BI-RADS 4 or 5 positive (BI-RADS 1 or 3, further imaging to determine final BI-RADS) Biopsy/ pathology

Study ID	Country Funding	Study design No. of centres	Participants Total, n Subgroup(s), n	Age	Characteristics	Density assessment	Screening frequency Rounds Reading	Breast imaging device and brand Protocol (timing, readers) Mammography	 Ultrasound	Threshold for positive test Reference standard
Wilczek et al, 2016[110]	Sweden Funded by U-Systems, a GE Healthcare Company (no role in collection, analysis, interpretation, writing, or decision to submit for publication)	Prospective cohort 1 centre	1,668 ACR 3: 999 ACR 4: 669	*Mean age* Overall: 49.5 y (SD 7.9 y) ACR 3: 49.9 y (SD 7.9 y) ACR 4: 49.0 y (SD 7.8 y) *Median age* 48 y (overall and each ACR group) *Age range* 40–69 y	3.8% had a history of breast biopsy 0.2% had a personal history of breast cancer 3.5% had a family history of breast cancer	ACR density 3 or 4 assessed by screening radiographer	All women invited for routine biennial[d] FFDM 2-y follow-up	FFDM Microdose Senographe (Philips Solna) or Senographe DS (GE Healthcare) 2 views (MLO and CC) Dedicated breast radiologists experienced with handheld ultrasound read ABUS; two independent readers	3D-ABUS equipment (U-Systems Inc) Immediately after FFDM Image acquisition in transverse plane perpendicular to chest wall; reconstructed in sagittal and coronal planes	BI-RADS 3–5 underwent fine-needle biopsy or core biopsy Pathology

Abbreviations: 3D, 3-dimensional; ABUS, automated breast ultrasound; ACR, American College of Radiology; BI-RADS, Breast Imaging Reporting and Data System; CC, craniocaudal view; FFDM, full-field digital mammography; ITT, intention-to-treat; J-START, Japan Strategic Anti-cancer Randomized Trial; ML, mediolateral view; MLO, mediolateral oblique view; SD, standard deviation.

[a] The J-START included 42 sites, but only the participants screened at the site in Miyagi prefecture had breast density information available and could be analyzed for the density compound study.[93]

[b] Derived from data in Table 1 of the published study.[109]

[c] Implied based on 24-month follow-up.[109]

[d] Biennial routine screening inferred, given that authors noted interval cancers happened within 24 months after last screening.[110]

RISK OF BIAS IN INCLUDED STUDIES—SUPPLEMENTAL ULTRASOUND

The J-START trial[93] was determined to have some risk-of-bias concerns related to deviations from group assignment, mainly because of lack of blinding of the participants to their assignment group. Overall, it was judged to be at low risk of bias with respect to randomization, missing outcome data, outcome measurement, and reported results (Appendix 4, Table A4).

The risk-of-bias assessment for the nonrandomized studies is shown in Appendix 4, Table A5. The study by Gatta et al[109] was determined to be at low risk of bias on all dimensions. Wilczek et al[110] was determined to be at low risk of bias on all dimensions except blinding of outcome assessments, because of unclear reporting of the reading procedure.

SENSITIVITY AND SPECIFICITY—SUPPLEMENTAL ULTRASOUND

The studies used different thresholds (i.e., BI-RADS assessment category findings) for a positive test when calculating measures of test performance and cancer detection (Table 6).

Table 6: Sensitivity and Specificity—Supplemental Ultrasound

Study ID		Mammography alone		Mammography + ultrasound	
Ultrasound type	**Study design (N)**	**Sensitivity, % (95% CI)**	**Specificity, % (95% CI)**	**Sensitivity, % (95% CI)**	**Specificity, % (95% CI)**
Positive Test: BI-RADS 3, 4, 5					
J-START[93] Handheld ultrasound	Randomized controlled trial (11,390)	70.6[a] (55.3–85.9)	91.7[b] (91.0–92.4)	93.2[a,c] (85.7–100)	85.4[b] (84.5–86.3)
Wilczek et al, 2016[110] ABUS	Prospective cohort (1,668)	63.6 (33.3–90.9) Δ Mammography + ultrasound vs. mammography alone: 36.4 (9.1–66.7; $P < .001$) Including interval cancers: 43.8 (20.0–69.2) Δ Mammography + ultrasound vs. mammography alone, including interval cancers: 25 (5.6–50.0; $P < .001$)	99.0 (98.5–99.4) Δ Mammography + ultrasound vs. mammography alone: −0.7 (−1.2 to −0.01; $P = .018$)	100 (NR) Including interval cancers: 68.8 (43.3–92.3)	98.4 (97.8–98.9)
Positive Test: BI-RADS 4, 5					
Gatta et al, 2021[109] 3D prone ABUS	Prospective cohort (1,165)	58.8[d] (30.9–78.3) Including interval cancers: 35.2[e] (17.3–58.7)	94[f] (73.0–98.0)	93.5[d] (79.2–98.2) Including interval cancers: 67.0[e] (50.0–81.4)	87.0[f] (71.0–94.8)

Abbreviations: 3D, 3-dimensional; ABUS, automated breast ultrasound; BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; J-START, Japan Strategic Anti-cancer Randomized Trial; NR, not reported.

[a] Significant difference in sensitivity between mammography alone (control) and mammography + handheld ultrasound ($P < .001$).[93]

[b] Significant difference in specificity between mammography alone (control) and mammography + handheld ultrasound ($P < .001$).[93]

[c] Authors noted that the sensitivity of mammography alone in this group was 54.6% (95% CI 39.8%–69.3%).[93]

[d] Significant difference in sensitivity between mammography alone and mammography plus ABUS (34.7% [95% CI 16.3%–61.2%]; $P < .001$).[109]

[e] Significant difference in sensitivity (including interval cancers) between mammography alone and mammography plus ABUS (31.8% [95% CI 11.7–54.6]; $P < .001$).[109]

[f] Significant difference in specificity between mammography alone and mammography plus ABUS (7% [95% CI 4.3%–8.8%]; $P < .001$).[109]

We rated the certainty of the body of evidence of both the randomized controlled trial and nonrandomized studies as Very low to Low, downgrading for indirectness and imprecision (Appendix 4, Table A6).

Positive Test: BI-RADS 3, 4, 5

In the J-START trial[93] the sensitivity of mammography alone was significantly lower than mammography plus ultrasound: 70.6% (95% confidence interval [CI] 55.3%–85.9%) vs. 93.2% (95% CI 85.7%–100%), *P* < .001. Specificity also differed significantly between groups in this randomized controlled trial, with a higher specificity for mammography alone (91.7% [95% CI 91.0%–92.4%]) than for mammography plus ultrasound (85.4% [95% CI 84.5%–86.3%]; *P* < .001).

In the study by Wilczek et al,[110]supine ABUS supplemental to mammography yielded significantly higher sensitivity (100%) for screen-detected cancers only, an increase of 34.6% (95% CI 9.1%–66.7%; *P* < .001) compared to mammography alone (63.6% [95% CI 33.3%–90.9%]). A similar difference was observed when interval cancers were included in sensitivity calculations (mammography plus ABUS 68.8% [95% CI 43.3%–93.3%] vs. mammography alone 43.8% [95% CI 20.0%–69.2%]; difference of 25% [5.6%–50.0%]; *P* < .001). The specificity of mammography plus ABUS was slightly lower (98.4% [95% CI 97.8%–98.9%]) than that of mammography alone (99.0% [95% CI 98.5%–99.4%]; difference of −0.07 [−1.2 to −0.01]; *P* = .018).

Positive Test: BI-RADS 4, 5

In the study by Gatta et al,[109] the addition of prone ABUS to mammography yielded significantly higher sensitivity and slightly lower specificity compared to mammography alone. The sensitivity of mammography alone was 58.8% (95% CI 30.9%–78.3%), compared to 93.5% (95% CI 79.2%–98.2%) for mammography plus prone ABUS (difference of 34.7% [95% CI 16.3%–61.2%]; *P* < .001). A similar magnitude of increase in sensitivity was seen when interval cancers were included in the calculation of sensitivity (Table 6, footnote e). Specificity decreased from 94% (95% CI 73.0%–98.0%) for mammography alone to 87% (95% CI 71.0%–94.8%) with mammography plus prone ABUS (difference of 7% [95% CI 4.3%–8.8%]; *P* < .001).

CANCER DETECTION RATE—SUPPLEMENTAL ULTRASOUND

More cancers were detected with screening mammography and supplemental ultrasound combined, than with screening mammography alone (Table 7). In the J-START randomized controlled trial, the cancer detection rate was 7.1 per 1,000 screenings (95% CI 4.9–9.2) for mammography plus handheld ultrasound versus 4.3 per 1,000 screenings (95% CI 2.6–6.0) for mammography alone; the difference was significant (*P* = .04).[93] Two cancers were detected with only clinical breast examination in the control group, and none in the intervention group.

The addition of prone ABUS led to a significant four additional cancers detected (95% CI 1.09–10.24; *P* <.001) compared to mammography alone.[109] This translates to double the cancer detection rate for mammography plus ultrasound (6.8 per 1,000 women [95% CI 5.0–8.1]) versus mammography alone (3.4 per 1,000 women [95% CI 1.3–5.8]). The between-group difference in cancer detection rate was 3.4 per 1,000 women (95% CI 1.6–6.1; *P* < .001).

Supplemental supine ABUS added to mammography resulted in a 57% relative increase in cancer detection. Mammography alone detected 4.2 cancers per 1,000 women screened (95% CI 1.2–7.2),

versus 6.6 cancers detected per 1,000 women screened (95% CI 3.0–10.2) for mammography plus ultrasound. The additional 2.4 cancers detected per 1,000 women screened was significant ($P < .001$).[110]

Table 7: Cancer Detection Rate—Supplemental Ultrasound

Study ID Ultrasound type	Study design (N)	Cancer detection rate (95% CI) Mammography	 Mammography + ultrasound	Incremental cancer detection rate (95% CI)	*P* value
J-START[93] Handheld ultrasound	Randomized controlled trial (11,390)	4.3/1,000 screenings (2.6–6.0)	7.1/1,000 screenings (4.9–9.2)	NR	.04
		24/5,593	41/5,797	17	
Gatta et al, 2021[109] 3D prone ABUS	Prospective cohort (1,165)	3.4/1,000 women screened (1.7–5.8)	6.8/1,000 women screened (5.0–8.1)	3.4/1,000 women screened (1.6–6.1)	< .001[b]
		4 cancers detected[a] (1.09–10.24)	8 cancers detected[a] (3.45–15.76)	4 cancers detected[a] (1.09–10.24)	< .001
		ACR 3: 3	ACR 3: 4	ACR 3: 1	NR
		ACR 4: 1	ACR 4: 4	ACR 4: 3	NR
Wilczek et al 2016[110] ABUS	Prospective cohort (1,668)	4.2/1,000 women screened (1.2–7.2)	6.6/1,000 women screened (3.1–10.2)	2.4/1,000 women screened (0.6–4.8)	< .001

Abbreviations: ABUS, automated breast ultrasound; ACR, American College of Radiology; CI, confidence interval; J-START, Japan Strategic Anti-cancer Randomized Trial; NR, not reported.

[a] We assume that the unit of measure here is count, although this is unclear given that authors reported the difference as "out of 1,000 women" in section 3.2 of the article.[109]

[b] For statistical comparison of cancer detection of mammography plus prone ABUS versus mammography alone.[109]

We rated the certainty of the evidence as Very low to Moderate, downgrading for indirectness, imprecision, and inconsistency (Appendix 4, Table A6)

CHARACTERISTICS OF CANCERS DETECTED—SUPPLEMENTAL ULTRASOUND

In the J-START trial, 41 cancers were detected with mammography plus handheld ultrasound; 85.4% of those were stage 0 or I (Table 8).[93] In the mammography-only group, 24 cancers were detected; 79.2% of those were stage 0 or I. The proportion of invasive cancers detected by mammography (75%) was higher than the proportion detected with mammography plus handheld ultrasound (68.3%). In both groups, a small proportion of cancers were node-positive (mammography, 11%; mammography plus handheld ultrasound, 12%), and most of the invasive tumours were less than 20 mm in size.

The cancers detected by mammography alone in the study by Gatta et al[109] were mostly grade II or III, with a median size of 17.85 mm. Of the four cancers detected by prone ABUS as an adjunct to mammography but not mammography alone, most (three of four) were in people with extremely dense breasts and were histologic grade I.[109] The median size of these four additional tumours was 17.52 mm (range 12–20.04 mm, data not in Table 8).

A total of 11 cases (13 cancers in 11 women) were detected in the study by Wilczek et al.[110] The four that were not seen on mammography and detected only with supine ABUS were all invasive and human

epidermal growth factor receptor 2 (HER2) negative. Half (two of four) were stage I, and the others were stage II or III, with a median tumour size of 17 mm (range 13–40 mm).

Table 8: Characteristics of Cancers Detected—Supplemental Ultrasound

Study ID Ultrasound type	Screen-detected cancers	Types	Stage and grade	Other
J-START[93] Handheld ultrasound	Mammography + handheld ultrasound: 41/5,797	13/41 (31.7%) noninvasive (DCIS and LCIS) 28/41 (68.3%) invasive (invasive ductal carcinoma and special type)	35/41 (85.4%) stage 0 and I 6/41 (14.6%) stage II or higher	*Node status of invasive cancers* Negative: 23/28 (82.1%) Positive: 5/28 (17.9%) *Tumour size of invasive cancers* < 10 mm: 11/28 (39.3%) 11–20 mm: 15/28 (53.6%) > 20 mm 2/28 (7.1%)
	Mammography alone: 24/5,593	6/24 (25%) noninvasive 18/24 (75%) invasive	19/24 (79.2%) stage 0 or I 5/24 (20.8%) stage II or higher	*Node status of invasive cancers* Negative: 15/18 (83.3%) Positive: 2/18 (11.1%) Missing: 1/18 (5.6%) *Tumour size of invasive cancers* < 10 mm: 9/18 (50%) 11–20 mm: 4/18 (22.2%) > 20 mm: 4/18 (22.2%) Missing: 1/18 (5.6%)
Gatta et al, 2021[109] 3D prone ABUS	3D prone ABUS: 8	7/8 (87.5%) ductal carcinoma not otherwise specified[a] 1/8 (12.5%) mucinous carcinoma[a]	Stage NR *Histological grade* G1: 4/8 G2: 3/8 G3: 1/8	*Size of cancer, mm* Mean: 16.96 (SD 2.59) Median: 17.85 (quartile 1 16.4, quartile 3 19.65) Range: 12.6–20.04
	Mammography alone: 4	NR[a]	Stage NR *Histological grade* G1: 1/4 G2: 2/4 G3: 1/4	*Size of cancer, mm* Mean: 16.6 (SD 3.47) Median: 17.2 (quartile 1 16, quartile 3: 19.42) Range: 12–20
Wilczek et al, 2016[110] ABUS	ABUS only: 4	4/4 (100%) invasive ductal carcinoma[b]	Stage NR *Histological grade*[c] G1: 2/4 G2: 1/4 G3: 1/4	*Size of cancer, mm* Mean 21.8 (SD 12.6) Median 17 (quartile 1 13.5, quartile 3 30) Range 13–40 4/4 HER2 negative[c]
	ABUS or mammography: 11 cases[d]	8/11 (72.7%) invasive ductal carcinoma 1/11 (9.1%) invasive ductal carcinoma and DCIS 1/11 (9.1%) DCIS 1/11 (9.1%) DCIS and LCIS	Stage NR *Histological grade*[c] I: 2/11 II: 6/11 III: 3/11	*Size of cancer, mm* Mean 22.2 (SD 10.4) Median 20 (quartile 1 14, quartile 3 24) Range 13–44 9/11 HER2 negative 1/11 HER2 positive 1/11 not applicable

Abbreviations: ABUS, automated breast ultrasound; DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2; J-START, Japan Strategic Anti-cancer Randomized Trial; LCIS, lobular carcinoma in situ; NR, not reported; SD, standard deviation.

[a] Reported as eight cancers detected by ABUS after mammography. Information on types of cancers not available for mammography (Table 4 in the published article).[109]

[b] Interpreted from the published article (text of the results, section 4.2, and Table 2b); cancers with tumour size of 0 mm on full-field digital mammography (patients 1, 2, 4, and 10).[110]

[c] Only available for invasive cancers.[110]

[d] 13 cancers were detected in 11 women, by both mammography and ABUS.[110]

INTERVAL CANCERS—SUPPLEMENTAL ULTRASOUND

Significantly more interval cancers occurred after mammography alone in the J-START trial (Table 9).[93] Ten interval cancers occurred in the mammography-alone group (1.8 cancers per 1,000 screenings [95% CI 0.7–2.9]), compared with three interval cancers in the mammography-plus-ultrasound group (0.5 cancers per 1,000 screenings [95% CI −0.1 to 1.1]; *P* = .04).

In the study by Gatta et al,[109] the authors reported that four interval cancers were detected during mammography (0.3% [95% CI 1.09–10.24]); three were in people with extremely dense breasts (ACR 4) and one was in a person with heterogeneously dense breasts (ACR 3). It is unclear from the published article whether these interval cancers all occurred in the mammography-only group, but this may be the case because they are described as occurring "during mammography screening" and a *P* value is reported (*P* < .001; Table 9, footnote a), although it is unclear what comparison the *P* value pertains to. It is unknown from the publication whether any interval cancers occurred after mammography plus prone ABUS.

Table 9: Interval Cancers—Supplemental Ultrasound

Study ID		Interval cancer rate (95% CI)		
Ultrasound type	Study design (N)	Mammography	Mammography plus ultrasound	*P* value
J-START[93] Handheld ultrasound	Randomized controlled trial (11,390)	10/5,593 1.8 cancers/1,000 screenings (0.7 to 2.9)	3/5,797 0.5 cancers/1,000 screenings (−0.1 to 1.1/1,000)	.04
Gatta et al, 2021[109] 3D prone ABUS	Prospective cohort (1,165)	4/1,165[a] (ACR 4, 3; ACR3, 1) 0.3% (1.09 to 10.24)	NR[a]	< .001[a]

Abbreviations: ABUS, automated breast ultrasound; ACR, American College of Radiology; CI, confidence interval; J-START, Japan Strategic Anti-cancer Randomized Trial.

[a] Unclear reporting, but interval cancers are described as occurring "during mammography screening" and a *P* value is reported.[109]

Across 1,668 study participants in the study by Wilczek et al,[110] five (0.3%) interval cancers occurred after screening with mammography alone or combined with supine ABUS. These data are not shown in Table 9 because the authors did not report the imaging modality after which the cancers occurred. They did report that, after a retrospective review, two of the five interval cancers diagnosed between routine screenings may have been misinterpreted on mammography (1 case) or on both mammography and ABUS (1 case). The authors considered the other three to be true interval cancers (i.e., not detectable on either full-field digital mammography or supine ABUS).

We rated the certainty of the body of evidence as Very low to low, downgrading for inconsistency, indirectness, and imprecision (Appendix 4, Table A6)

Characteristics of Interval Cancers

Interval cancer characteristics were reported only from the J-START study (Table 10).[93] More interval cancers occurred in the mammography group (control; n = 10) than in the mammography plus handheld ultrasound group (n = 3). In the mammography group, 70% (7/10) of the interval cancers were invasive, 90% were stage 0 or I, and about half were node-negative and 20 mm or less in size. In contrast, in the

mammography plus handheld ultrasound group, all the interval cancers were invasive, and two of three were stage II or higher, node-positive, and greater than 20 mm in size.

The five interval cancers that occurred after mammography plus supplemental supine ABUS in the study by Wilczek et al[110] were mostly grade 2 (4/5); all were estrogen and progesterone receptor–positive, and two were HER2-positive. The authors did not report the imaging modality after which the cancers occurred; therefore, these data are not shown in Table 10. We found no information on the characteristics of interval cancers in the other study.[109,110]

Table 10: Interval Cancers After Screening in the J-START Trial

Group (N)	Interval cancers, n	Type	Stage	Node status Tumour size[a]
Mammography (5,593)	10	3/10 (30%) noninvasive[b] 7/10 (70%) invasive[c]	9/10 (90%) stage 0 or I 1/10 (10%) stage II or higher	*Node status of invasive cancers* Negative: 6/7 (85.7%) Missing: 1/7 (14.3%) *Tumour size of invasive cancers* < 10 mm: 1/7 (14.3%) 11–20 mm: 4/7 (57.1%) Missing: 2/7 (28.6%)
Mammography + handheld ultrasound (5,797)	3	3/3 (100%) invasive[c]	1/3 (33.3%) stage 0 or I 2/3 (66.7%) stage II or higher	*Node status of invasive cancers* Negative: 1/3 (33.3%) Positive: 2/3 (66.7%) *Tumour size of invasive cancers* < 10 mm: 1/3 (33.3%) > 20 mm: 2/3 (66.7%)

Abbreviations: DCIS, ductal carcinoma in situ; J-START, Japan Strategic Anti-cancer Randomized Trial; LCIS, lobular carcinoma in situ.

[a] For invasive cancers only.

[b] Includes DCIS and LCIS.

[c] Includes invasive ductal carcinoma or special type.

Source: Harada-Shoji et al.[93]

RECALL RATE AND BIOPSY—SUPPLEMENTAL ULTRASOUND

The J-START trial[93] defined *recall* as the need for any additional diagnostic testing after screening, including imaging and/or biopsy. Both the recall and biopsy rates were higher in the mammography plus handheld ultrasound group (15.2% and 6.2%) compared to the mammography-only group (8.7% and 2.3%; Table 11). A challenge with interpreting these figures was that in addition to imaging, clinical breast examination was also performed on some participants, and a positive result on clinical breast examination also prompted recall and biopsy, but the data were not reported. In the control group, a positive result on mammography alone resulted in a 6.7% recall rate and a 1.4% biopsy rate. The authors did not report recall based on positive results from mammography or handheld ultrasound in the intervention group (Table 11, footnote d).

In the study by Gatta et al,[109] 12.1 additional recalls per 1,000 women (95% CI not reported) resulted from the addition of prone ABUS to mammography. The recall rate after mammography plus prone ABUS (26.6 per 1,000 women; [95% CI 16.2–30.0]) was significantly higher than with mammography alone (14.5 per 1,000 women [95% CI 9.0–19.8]; $P < .001$). The biopsy rate was also significantly higher after mammography plus prone ABUS (7 per 1,000 women [95% CI 4.3–8.8]; $P < .001$).

In the study by Wilczek et al,[110] supplemental supine ABUS plus mammography resulted in nine additional recalls per 1,000 women screened (95% CI 3.0–15). The recall rate for mammography plus ABUS was 22.8 per 1,000 women screened (95% CI 16.2–30.0), compared with 13.8 per 1,000 women screened (95% CI 9.0–19.8) for mammography alone (*P* = .004). Similarly, the biopsy rate was also significantly higher for ABUS plus mammography compared to mammography alone: 13.8 per 1,000 women screened (95% CI 8.4–19.8) versus 6.6 per 1,000 women screened (95% CI 3.0–10.8; *P* < .001).

Table 11: Abnormal Recall Rate and Biopsy—Supplemental Ultrasound

Study ID Ultrasound type	Study design (N)	Abnormal recall rate Mammography	Abnormal recall rate Mammography + ultrasound	Incremental recall rate	*P* value	Biopsies
J-START[93] Handheld ultrasound	Randomized controlled trial (11,390	8.7%[a] 485/5,593	15.2%[b] 880/5,797	NR	NR	Mammography alone: 2.3%[c] Mammography + ultrasound: 6.2%[d]
Gatta et al, 2021[109] 3D prone ABUS	Prospective cohort (1,165)	14.5/1,000 women (9.0–19.8)	26.6/1,000 women (16.2–30.0)	Additional recalls: 12.1/1,000 women (4.0–39.9)	< .001	Mammography + ABUS: 9/31 recalled Mammography: 4/17 recalled *Biopsy rate* Mammography + ABUS: 14/1,000 women (5.0–28) Mammography: 7/1,000 women (4.1–8.2)
Wilczek et al, 2016[110] ABUS	Prospective cohort (1,668)	13.8/1,000 women screened (9.0–19.8) 1.4%[e] (23/1,668)	22.8/1,000 women screened (16.2–30.0) 2.3% (38/1,668)	9.0/1,000 women screened (3.0–15.0) 0.9% (15/1,668)	0.004	*Biopsy rate* Mammography: 6.6/1,000 women screened (3.0–10.8) Mammography + ABUS: 13.8/1,000 women screened (8.4–19.8) Increase in biopsy rate with mammography + ABUS vs. mammography alone: 7.2/1,000 women screened (3.6–11.4; *P* < .001)

Abbreviations: ABUS, automated breast ultrasound; J-START, Japan Strategic Anti-cancer Randomized Trial.

[a] All recalls due to positivity on one or both of mammography or clinical breast examination. Recalls from mammography only among people with dense breasts in the control group were 6.7% (374/5,593).[93]

[b] All recalls due to positivity on one or more of mammography, handheld ultrasound, or clinical breast examination among people with dense breasts in the intervention group. Recalls for positivity on mammography only were 6.1% (356/5,797) and on ultrasound only were 7.0% (404/5,797).[93]

[c] All biopsies due to positivity on one or both of mammography or clinical breast examination. Biopsies after mammography-positive only among people with dense breasts in the control group were 1.4% (77/5,593), accounting for 77 of 127 biopsies done in this group on first-round screening.[93]

[d] All biopsies due to positivity on one or more of mammography, handheld ultrasound, or clinical breast examination among people with dense breasts in the intervention group. Biopsies after positivity on mammography only were 1.0% (56/5,797) and ultrasound only were 4.4% (255/5,797), together accounting for 311 of the 360 biopsies done in this group during first-round screening.[93]

[e] Authors stated that the recall rate in the "ordinary screening program" the year before the study (i.e., mammography alone) was 2.1% (data not presented).[110]

We rated the certainty of the evidence as Very low to Moderate, downgrading for inconsistency, indirectness, and imprecision (Appendix 4, Table A6)

OTHER OUTCOMES—SUPPLEMENTAL ULTRASOUND

No included studies reported the outcomes of interval cancers, psychological impact, or overall or breast cancer–specific mortality.

Supplemental Handheld Ultrasound Versus Supplemental ABUS

CHARACTERISTICS OF INCLUDED STUDY—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL ABUS

One cross-sectional study[36]—conducted at a single imaging centre in Brazil and comparing the performance of handheld ultrasound and ABUS as supplemental screening modalities—addressed our planned subgroup analysis (Table 12). Women with heterogeneously dense or extremely dense breasts (BI-RADS C or D) underwent both handheld ultrasound and ABUS after negative screening mammography. Those who had undergone breast surgery or radiation in the previous year, or who had breast implants, were excluded. The study enrolled 444 participants; most had heterogeneously dense breasts (95%), and the median age was 48 years (range 20 to 79 years). The authors provided no information on participants' body mass index, ethnicity, personal history of breast cancer, or gender identity.

Handheld ultrasound was performed by a breast radiologist or by a nonspecialist radiologist (the latter was the case for 77.5% of the exams), and ABUS was performed only by breast radiologists. Four exams (2.8%) were excluded from the analysis because of inadequate breast compression during ABUS. The primary outcome was cancer detection, although the study also sought to measure procedure-related outcomes for the two modalities (e.g., acquisition time).[36]

Table 12: Characteristics of Included Study—Supplemental Handheld Ultrasound Versus Supplemental ABUS

Study ID	Country Funding	Study design No. of centres	Participants Total, n	Age	Population	Density assessment	Screening frequency Rounds Reading	Breast imaging device and brand Protocol (timing, readers) Mammography	Ultrasound	Threshold for positive test Reference standard
Philadelphoet al, 2021[36]	Brazil Funded by Diagnosticos das Americas (DASA); device lent by GE Healthcare, support provided	Cross-sectional 1 centre	440	Median: 48 y (range 20–79 y)	NR	Heterogeneously or extremely dense breast tissue BI-RADS 5th edition, C or D	Routine screening Mammography + handheld ultrasound on same day ABUS Interpreted with access to mammography for density info; blind to handheld ultrasound or ABUS, during interpretation	FFDM to assess density Same day as ultrasound exams	*Handheld ultrasound (various systems)* Radiologist, some (13/30) specialized in breast imaging Performed on same day as mammography and ABUS *Invenia ABUS system (GE Healthcare)* Trained mammography technician with pre-established protocol Performed on same day as mammography and handheld ultrasound	BI-RADS 4 Diagnostic handheld ultrasound for suspicious findings (recall) Handheld ultrasound-guided percutaneous biopsy

Abbreviations: ABUS, automated breast ultrasound; BI-RADS, Breast Imaging Reporting and Data System; FFDM, full-field digital mammography; NR, not reported.

RISK OF BIAS IN INCLUDED STUDY—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL ABUS

The study by Philadelpho et al[36] was determined to be at low risk of bias for participant selection, measurement of exposure, and selective outcome reporting, and at unclear risk of bias because of confounding variables, blinding of outcome assessment, and incomplete outcome data (Appendix 4, Table A7).

CANCER DETECTION RATE—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL ABUS

In the study by Philadelpho et al,[36] the cancer detection rate from handheld ultrasound was 2.3 per 1,000 women, versus 4.5 per 1,000 women screened with ABUS (no statistical comparison; Table 13). The test positivity threshold was BI-RADS 4.

Table 13: Cancer Detection Rate—Supplemental Handheld Ultrasound Versus Supplemental ABUS

Study ID	Handheld ultrasound cancer detection rate[a]	ABUS cancer detection rate[b]
Philadelpho et al, 2021[36]	2.3/1,000 women	4.5/1,000 women

Abbreviations: ABUS, automated breast ultrasound.

[a] Performed by breast radiologists, or nonspecialist radiologists (77.5% of exams).

[b] Performed by breast radiologists.

Source: Philadelpho et al.[36]

We rated the certainty of the evidence as Very low, downgrading for imprecision (Appendix 4, Table A8).

CHARACTERISTICS OF CANCERS DETECTED—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL ABUS

The authors reported the number of lesions rated as BI-RADS 3 (recalls) or 4 (positive tests) by modality, outcome, and concordance between technologies (Table 14).[36] Handheld ultrasound and ABUS each detected six BI-RADS 4 lesions, of which three invasive ductal carcinomas were correctly described by both modalities. Handheld ultrasound detected three other lesions that turned out to be benign, returning 50% false-positives. ABUS detected one additional cancer (invasive lobular carcinoma) and two high-risk lesions (one papilloma and one radial scar) that were not detected by handheld ultrasound. The stages and histologic grades of the cancers detected were not reported.

The mean size of all lesions detected (benign and cancerous) was similar for handheld ultrasound and ABUS (1.17 cm vs. 1.14 cm; $P = 0.662$). The concordance for overall lesion detection between handheld ultrasound and ABUS was 80.9%.

Table 14: Characteristics of Cancers Detected—Supplemental Handheld Ultrasound Versus ABUS

Ultrasound modality	No. cancers detected from BI-RADS 4 lesions	Cancer types[a]	Mean lesion size, cm[b]
Handheld ultrasound	3[c]	3/3 (100%) invasive ductal carcinoma	1.17 cm
ABUS	6[d]	3/6 (50%) invasive ductal carcinoma 1/6 (16.7%) papilloma 1/6 (16.7%) invasive lobular carcinoma 1/6 (16.7%) radial scar	1.14 cm

Abbreviations: ABUS, automated breast ultrasound; BI-RADS, Breast Imaging Reporting and Diagnostic System.
[a] Percentages may not add up to exactly 100% due to rounding.
[b] Difference in means was not statistically significant (P = .662).
[c] Three additional benign lesions were identified as BI-RADS 4 with handheld ultrasound.
[d] Three of the BI-RADS 4 lesions detected with ABUS were not detected with handheld ultrasound.
Source: Philadelpho et al.[36]

OTHER OUTCOMES—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL ABUS

The included study did not report sensitivity, specificity, interval cancers, psychological impact, or overall or breast cancer–specific mortality.

Supplemental Handheld Ultrasound Versus Supplemental DBT

CHARACTERISTICS OF INCLUDED STUDIES—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL DBT

The Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts (ASTOUND) trial[91] was an Italian prospective, multicentre trial conducted at five dedicated breast imaging radiology services in public hospitals, comparing the incremental value of adjunctive DBT with adjunctive handheld ultrasound. ASTOUND-2[92] was a second phase of the trial, conducted in four new centres that did not participate in ASTOUND. Although both trials followed the same research protocol, we have reported them separately throughout because there was no overlap in the study cohorts (ASTOUND enrolled from December 2012 to March 2015, and ASTOUND-2 enrolled from April 2015 to September 2017) and only three centres participated in both phases (Table 15).

People whose screening mammography result was negative and who had heterogeneously or extremely dense breasts underwent both DBT and handheld ultrasound. In ASTOUND,[91] the supplemental imaging occurred in the same round, but ultrasound screens included both prevalence and incidence screens because of existing practices, whereas DBT was a prevalence screen only. In ASTOUND-2,[92] synthetic 2-dimensional mammographic images were reconstructed from DBT (instead of acquiring digital 2-dimensional mammography) whenever software was available to do so, in order to reduce radiation doses. Therefore, the cohort had either negative synthetic (21% or 1,104 participants) or acquired (the remainder) 2-dimensional mammography; the two types were considered equivalent. In the ASTOUND cohort, all participants had negative acquired 2-dimensional mammography.

People with a personal history of breast cancer, who had breast implants, or who were pregnant or breastfeeding were ineligible for the trials. ASTOUND included 3,231 participants (median age 51 y; interquartile range [IQR] 44–78 y).[91] ASTOUND-2 enrolled 5,300 participants (median age 50 y; IQR 43–79 y).[92] No information was reported about participants' ethnicity, body mass index, family history of cancer, or gender identity.

Table 15: Characteristics of Included Studies—Supplemental Handheld Ultrasound Versus Supplemental DBT

Study ID	Country Funder	Study design, No. centres	Participants N	Age	Charac-teristics	Density assessment	Screening frequency Rounds Reading	Breast imaging device and brand Protocol (timing, readers) DBT	Ultrasound	Threshold for positive test Reference standard
ASTOUND-2[92]	Italy NCT02066142 Coordinated by the University of Genoa	Prospective comparative cohort 7 centres (3 also participated in ASTOUND) April 2015 to September 2017	Eligible and participated: 5,300 Sample size calculation: 6,000 screens for cancer detection rate of 3/1,000; estimated 80% power to detect incremental cancer detection rate of > 2/1,000	Median 50 y (IQR 43–79 y)	NR	Visual determination Hetero-geneously or extremely dense	FFDM Selenia Dimensions (Hologic) Synthesized 2D images (software) used instead of 2D digital mammo-graphy when available Density checks immediate All readers experienced breast radiologists	DBT Selenia Dimensions (Hologic) Same radiologist reported 2D and DBT images Radiologist blinded to ultrasound findings	Handheld ultrasound (devices NR) Performed by radiologist blinded to DBT images and findings	BI-RADS 4 and 5 recalled for additional testing

Study ID	Country Funder	Study design, No. centres	Participants N	Age	Charac-teristics	Density assessment	Screening frequency Rounds Reading	Breast imaging device and brand Protocol (timing, readers) DBT	Ultrasound	Threshold for positive test Reference standard
ASTOUND[91]	Italy NCT02066142 Sponsored by the University of Genoa (responsible for governance of the 5 breast imaging centres)	Prospective comparative cohort 5 centres (public hospitals with dedicated breast imaging radiology services) December 2012 to March 2015	Invited: 3,295 Participated: 3,231	Median: 51 y (IQR 44–78 y; range 38–88 y)	NR	BI-RADS 4th edition Density 3 or 4 (hetero-geneously or extremely dense breasts)	Breast radiologists interpreted DBT and handheld ultrasound Readers blinded to sequential adjunct test results FFDM with Selenia Dimensions FFDM read by radiologist immediately to assess density	Selenia Dimensions (Hologic) Performed at same time as digital mammography, after density 3 or 4 was determined from mammography; same breast compression and 2 views (MLO and CC) Read with digital mammography by same radiologist	Handheld ultrasound (device NR) Performed by radiologist blinded to images from digital mammography and DBT (2 independent readers)	BI-RADS 4 and 5 on digital mammography DBT, or ultrasound were recalled for further investigation

Abbreviations: 2D, 2-dimensional; ABUS, automated breast ultrasound; ASTOUND, Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts; BI-RADS, Breast Imaging Reporting and Data System; CC, craniocaudal; DBT, digital breast tomosynthesis; FFDM, full-field digital mammography; IQR, interquartile range; MLO, mediolateral oblique; NR, not reported.

RISK OF BIAS OF INCLUDED STUDIES—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL DBT

The ASTOUND study[91] was determined to be at low risk of bias with respect to participant selection, intervention, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. It was unclear with respect to confounding variables, because of a lack of information in the eligibility or participant characteristics about family history of cancer or high-risk genetic mutations.

The ASTOUND-2 study[92] was determined to be at low risk of bias with respect to the intervention, blinding of outcome assessment, and selective outcome reporting. It was at unclear risk of bias with respect to participant selection and incomplete outcome data. This was mainly owing to the use of synthetic mammography in place of acquired 2-dimensional mammography for some participants, and the note that 1-year follow-up data were not available for all participants.

The full risk of bias assessment is in Appendix 4, Table A9.

SENSITIVITY AND SPECIFICITY—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL DBT

Both studies considered a positive test to be BI-RADS 4 or 5. We calculated the sensitivity and specificity of handheld ultrasound and DBT from data available in the ASTOUND and ASTOUND-2 reports (Table 16).[91,92] In both studies, the sensitivity of handheld ultrasound was quite high (ASTOUND 95.8% [95% CI 76.9%–99.8%] and ASTOUND-2 89.6% [95% CI 71.5%–97.3%]). The sensitivity of DBT was about 50% (ASTOUND 54.2% [95% CI 33.2%–73.8%] and ASTOUND-2 51.7% [95% CI 32.9%–70.1%]).

Specificity was very high for both modalities.[91,92] The specificity of handheld ultrasound was 98.0% (95% CI 97.4%–98.4%) in ASTOUND and 98.9% (95% CI 98.6%–99.2%) in ASTOUND-2. The specificity of DBT was 98.3% (95% CI 97.8%–98.7%) in ASTOUND and 99.7% (95% CI 99.5%–99.8%) in ASTOUND-2. No statistical comparisons of sensitivity or specificity were performed.

Table 16: Sensitivity and Specificity—Supplemental Handheld Ultrasound Versus Supplemental DBT

		Handheld Ultrasound		DBT	
Study ID	N	Sensitivity, % (95% CI)[a]	Specificity, % (95% CI)[a,b]	Sensitivity, % (95% CI)[a]	Specificity, % (95% CI)[a,b]
ASTOUND-2[92]	5,300	89.6 (71.5–97.3)	98.9 (98.6–99.2)	51.7 (32.9–70.1)	99.7 (99.5–99.8)
ASTOUND[91]	3,231	95.8 (76.9–99.8)	98.0 (97.4–98.4)	54.2 (33.2–73.8)	98.3 (97.8–98.7)

Abbreviations: ASTOUND, Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts; CI, confidence interval; DBT, digital breast tomosynthesis.

[a] Calculated by recreating a 2 × 2 table for DBT from summary data reported in Tables 1 and 3 in the published articles for ASTOUND-2[92] and ASTOUND.[91]

[b] Specificity calculation includes all false-positives (both those that did and did not lead to biopsy).

We rated the certainty of the evidence for sensitivity as Very low, downgrading for indirectness and imprecision. We rated the evidence for specificity as low (Appendix 4, Table A10).

CANCER DETECTION RATE—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL DBT

Supplemental handheld ultrasound had a significantly higher incremental cancer detection rate than supplemental DBT in both studies (Table 17). In the ASTOUND trial, the difference in incremental cancer detection rate between handheld ultrasound and DBT was 3.1 per 1,000 screens (95% CI 1.2–3.1). The incremental cancer detection rate for handheld ultrasound was 7.1 per 1,000 screens (95% CI 4.2–10.0) compared to DBT at 4.0 per 1,000 screens (95% CI 1.8–6.2; *P* =.006).[91]

The ASTOUND-2 trial had similar results: the incremental cancer detection rate for handheld ultrasound was 4.90 per 1,000 screens (95% CI 3.21–7.19) compared to 2.83 per 1,000 screens (95% CI 1.58–4.67) for DBT. This translated to a difference of 2.07 per 1,000 screens for handheld ultrasound versus DBT (*P* = .015).[92]

Table 17: Cancer Detection Rate—Supplemental Handheld Ultrasound Versus Supplemental DBT

Study ID	N	Incremental cancer detection rate (95% CI)		Δ Incremental cancer detection rate (95% CI)	*P* value
		Handheld ultrasound	DBT		
ASTOUND-2[92]	5,300	4.90/1,000 screens (3.21–7.19) N = 26	2.83/1,000 screens (1.58–4.67) N = 15	2.07/1,000 screens (1.81–2.32)	.015
ASTOUND[91]	3,231	7.1/1,000 screens (4.2–10.0) N = 23	4.0/1,000 screens (1.8–6.2) N = 13	3.1/1,000 screens (1.2–3.1)	.006

Abbreviations: ASTOUND, Adjunct Screening With Tomosynthesis or Ultrasound in Women with Mammography-Negative Dense Breasts; CI, confidence interval; DBT, digital breast tomosynthesis.

We rated the certainty of the evidence as Very low, downgrading for imprecision (Appendix 4, Table A10).

CHARACTERISTICS OF CANCERS DETECTED—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL DBT

In the ASTOUND-2 trial, 29 cancers were detected by supplemental handheld ultrasound or DBT.[92] Supplemental handheld ultrasound detected 26 invasive cancers, of which 69% (18/26) were grade 2 or 3, 77% (20/26) were node-negative and estrogen or progesterone receptor–positive, and mean tumour size was 14.9 mm (SD 7.9 mm). Supplemental DBT detected 15 cancers, of which 87% (13/15) were invasive, and two were DCIS. The cancers detected on DBT were predominantly node-negative and grade 1 or 2 (87%; 13/15), estrogen or progesterone receptor–positive (93%; 14/15), and with a mean size of 11.4 mm (SD 5.3 mm).[92]

A similar pattern was seen in the ASTOUND trial data. In this study, 24 cancers were detected by either handheld ultrasound (23 cancers detected) or DBT (13 cancers detected; Table 18).[91] All but one of the cancers seen on handheld ultrasound were invasive (96%; 22/23), with a mean tumour size of 15.1 mm (SD 4.8 mm). All seen by DBT were invasive, with a similar mean tumour size of 15.2 mm (SD 6.1 mm). A substantial amount of data on tumour grade, node status, and hormone receptor status were unavailable for both groups. To summarize the available data, in general the cancers detected by

handheld ultrasound or DBT were mostly grade 1 or 2 and estrogen or progesterone receptor–positive, and about half were node-negative.[91]

Table 18: Characteristics of Cancers Detected—Supplemental Handheld Ultrasound Versus Supplemental DBT[a]

Study ID	Screen-detected cancers	Types	Stage and grade	Other
ASTOUND-2[92]	Handheld ultrasound: 26	16/26 (61.5%) invasive ductal carcinoma 4/26 (15.4%) invasive lobular carcinoma 1/26 (3.8%) tubular 1/26 (3.8%) papillary ductal carcinoma 1/26 (3.8%) mucinous ductal carcinoma 3/26 (11.5%) mixed invasive	*Stage* NR *Grade* Grade 1: 8/26 Grade 2: 13/26 Grade 3: 5/26	*Node status* Positive: 6/26 (23.1%; 3/6 micrometastases) Negative: 20/26 (76.9%) *Estrogen or progesterone receptor status* Positive: 20 Negative: 4 NA: 2 *Mean tumour size* 14.9 mm (SD 7.9 mm) HER2 score 3+: 1 2+: 2 1+: 8 0: 14 NA: 1
	DBT: 15	10/15 (66.6%) invasive ductal carcinoma 1/15 (6.7%) tubular ductal carcinoma 1/15 (6.7%) mixed invasive 1/15 (6.7%) mucinous ductal carcinoma 2/15 (13.3%) DCIS	*Stage* NR *Grade* Grade 1: 6/15 Grade 2: 7/15 Grade 3: 2/15	*Node status* Positive: 2/15 (13.3%; 1/2 micrometastases) Negative: 13/15 (86.7%) *Estrogen or progesterone receptor status* Positive: 14/15 Negative: 1/15 *Mean tumour size* 11.4 mm (SD 5.3 mm) *HER2 score* 2+: 1/15 1+: 5/15 0: 9/15
ASTOUND[91]	Handheld ultrasound: 23	17/23 (74%) invasive ductal carcinoma 4/23 (17.4%) invasive lobular carcinoma 1/23 (4.3%) mixed invasive 1/23 (4.3%) DCIS	*Stage* NR *Grade* Grade 1: 3/23 Grade 2: 10/23 Grade 3: 5/23 NA: 4/23 DCIS: 1/23	*Node status* Positive, metastases: 7/23 (30.4%) Positive, micrometastases: 1/23 (4.3%) Negative: 13/23 (56.5%) NR: 2/23 (8.6%) *Estrogen or progesterone receptor status* Positive: 15/23 Negative: 2/23 NA: 6/23 *Mean tumour size* 15.1 mm (SD 4.8 mm) *HER2 score* 3+: 1/23 2+: 0/23 1+: 5/23 0: 9/23 NA: 8/23

Study ID	Screen-detected cancers	Types	Stage and grade	Other
	DBT: 13	11/13 (84.6%) invasive ductal carcinoma 2/13 (15.4%) invasive lobular carcinoma	*Stage* NR *Grade* Grade 1: 2/13 Grade 2: 5/13 Grade 3: 3/13 NA: 3/13	*Node status* Positive, metastases: 6/13 (46.2%) Negative: 6/13 (46.2%) NA: 1/13 (7.6%) *Estrogen or progesterone receptor status* Positive: 7/13 Negative: 2/13 NA: 4/13 *Mean tumour size* 15.2 mm (SD 6.1 mm) *HER2 score* 3+: 1/13 2+: 0/13 1+: 2/13 0: 4/13 NA: 6/13

Abbreviations: ASTOUND, Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts; DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor 2; G, grade; NA, not available; NR, not reported.

[a] All information on characteristics of cancers derived from Table 2 in the published report of ASTOUND-2[92] and Table 2 in the published report of ASTOUND.[91] Percentages may not add up to 100 due to rounding.

RECALL RATE AND FURTHER INVESTIGATIONS—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL DBT

In ASTOUND-2, the authors report that 1.22% (n = 64/5,300) of screens were recalled from either handheld ultrasound or DBT for further testing (95% CI 0.91%–1.49%) and that there were statistically more recalls for ultrasound than DBT ($P < 0.001$).[92] Of the women recalled who underwent needle biopsy (number unknown), two also underwent excisional biopsy.

In ASTOUND, the proportion of all screens recalled for further testing from either handheld ultrasound or DBT was 3.33% (95% CI 2.7%–3.96%; 107/3,231).[91] There were no significant differences in the number of recalls between the two adjunct modalities ($P = 0.26$). The authors report that 38 people (1.18% of screens) underwent biopsy and were classified as false-positive recalls, 24 by handheld ultrasound and 22 by DBT ($P = .86$).

These are the only data provided on recall. We rated the certainty of the evidence as Very low, downgrading for inconsistency (Appendix 4, Table A10)

OTHER OUTCOMES—SUPPLEMENTAL HANDHELD ULTRASOUND VERSUS SUPPLEMENTAL DBT

No included studies reported the outcomes of interval cancers, psychological impact, or overall or breast cancer–specific mortality.

Supplemental MRI

CHARACTERISTICS OF INCLUDED STUDIES—SUPPLEMENTAL MRI

Two studies assessed supplemental MRI after negative mammography (Table 19).

The Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial is a multicentre RCT at eight sites in the Netherlands undertaken within the national breast screening program.[106] Participation in the trial was limited to those with extremely dense breasts (ACR 4). After negative mammography, women were randomized 1:4 to undergo either regular biennial screening mammography (control arm; N = 32,312) or supplemental MRI as additive imaging (experimental arm; N = 4,783 of 8,061 who were invited to undergo MRI). Participants were followed for 6 years to compare the incidence of interval cancers between those who underwent supplemental MRI plus mammography versus mammography alone. The data from two completed screening rounds, each with 24 months follow-up, have been published.

The second study, by Chen et al,[41] was a prospective, single-arm cohort study in China of women with heterogeneously or extremely dense breasts (ACR dense) who underwent MRI after negative screening mammography. The objective was to assess the added value of MRI in the target population, and to assess the performance of an abbreviated MRI protocol in contrast to routine MRI imaging (full diagnostic protocol). A total of 444 women with negative mammography and dense breasts were enrolled in the study and underwent MRI. In accordance with our eligibility criteria, we extracted only sensitivity and specificity from this study because there was no comparator for effectiveness outcomes.

The age of participants was slightly younger in the Chen et al study (mean 49.3 years, range 30 to 71 years)[41] than in the DENSE trial (median: 54 years, IQR: 51 to 59 years).[106] In the DENSE trial, participants' socioeconomic status (quartiles) and urbanization levels were recorded ("not urban" to "extremely urban" based on the number of addresses per postal code). Approximately 30% of participants were "not urban" or "slightly urban"; 15% of participants fell into the lowest socioeconomic quartile, and 38.2% into the highest quartile.[106] Chen et al[41] did not report any information on participant characteristics.

Chen et al did not report explicit eligibility criteria beyond breast density and negative mammography results,[41] but the DENSE trial excluded people with relative or absolute contraindications to MRI (e.g., claustrophobia, metal implants) or contrast agent (e.g., impaired renal function or prior allergic reaction), and other practical contraindications (e.g., pregnancy, body weight > 150 kg).[106] Neither study reported information related to participants' body mass index, ethnicity, personal history of breast cancer, gender identity, or the presence of breast implants.

Both studies' MRI imaging protocols involved an initial dynamic scan followed by contrast-enhanced dynamic scans after administration of an intravenous gadolinium-based contrast agent. A 3.0 T magnet and dedicated breast coil were used. In the study by Chen et al,[41] the abbreviated protocol consisted of fewer images: the first post-contrast subtracted (FAST) and maximum intensity projection images.

Table 19: Characteristics of Included Studies—Supplemental MRI

Study ID	Country Funder	Study design No. centres	Participants N	Age	Characteristics	Density assessment	Screening frequency Rounds Reading	Breast imaging device and brand Protocol (timing, readers) Mammography	MRI	Threshold for positive test Reference standard
DENSE trial[106-108]	Netherlands Financially supported by University Medical Centre Utrecht, NL Organization for Health Research and Development, Dutch Cancer Society, Dutch Pink Ribbon-A Sister's Hope.org, Stichting Kankerpreventie Midden-West & Bayer Pharmaceuticals. Volpara Imaging Software (Matakina, NZ) provided for research purposes. No role of sponsors (except University Medical Centre Utrecht) in trial design, data collection/analysis, or manuscript writing	Randomized controlled trial 8 centres Randomization 1:4 to supplemental MRI (computer-generated, permuted blocks of random block size, stratified by hospital and regional screening organization) ITT (intention-to-screen) analysis	*First-round (prevalence) screening* FFDM: 32,312 Underwent MRI: 4,783 Invited non-participants: 3,278 Total invited to MRI: 8,061 *Second-round (incidence) screening* MRI: 3,346 72% of those had participated in round 1; 81% of those invited to round 2 participated	Mean: 54 y (IQR 51–61 y) Median age of MRI participants: 54 y (IQR 51–59 y)	Urbanization level Education Smoking status Exercise level	ACR 4 (extremely dense breasts) Volpara automated volumetric % density assessment (software version 1.5); Volpara Density Grade categories are correlated with BI-RADS (ACR) classification	Biennial 2 rounds	Bilateral CC and MLO views FFDM read independently by 2 dedicated screening radiologists (certified)	3 T system, dedicated bilateral breast coil Single reading by breast radiologists (experience 5–23 y) Gadovist (gadobutrol) contrast agent Performed after digital mammography read, density determined, and assessed as BI-RADS 1 or 2 Second screening round read by same group of radiologists	BI-RADS 4 or 5: recalled for additional workup BI-RADS 3: follow-up imaging after 6 mo (MRI)

Study ID	Country Funder	Study design No. centres	Participants N	Age	Characteristics	Density assessment	Screening frequency Rounds Reading	Breast imaging device and brand Protocol (timing, readers) Mammography	MRI	Threshold for positive test Reference standard
Chen et al, 2017[41]	China Funder/conflicts of interest NR	Prospective cohort	478	Mean: 49.3 y (range 30-71 y)	Chinese	Dense (ACR density classification)[a]	NR	Double reading	Performed after digital mammography 3 T magnet, dedicated breast coil (prone position) Gd-DTPA contrast agent Axial and sagittal scans Full diagnostic protocol: "routine breast MRI" Abbreviated protocol 2 radiologists with 10+ y experience independently read MRI first abbreviated protocol, then full diagnostic protocol Cases randomized and images read 1 mo apart to reduce bias	NR

Abbreviations: ACR, American College of Radiology; BI-RADS, Breast Imaging Reporting and Data System; CC, craniocaudal; DENSE, Dense Tissue and Early Breast Neoplasm Screening; FFDM, full-field digital mammography; Gd-DPTA; gadolinium-diethylene triamine penta-acetic acid; ITT, intention-to-treat; MLO, mediolateral oblique; MRI, magnetic resonance imaging; NR, not reported.

[a] Authors reported inclusion of people with dense breasts classified by ACR rubric, of which the two categories (heterogeneously dense and extremely dense) of highest density are typically considered "dense."[41]

RISK OF BIAS IN THE INCLUDED STUDIES—SUPPLEMENTAL MRI

The DENSE trial[106] was determined to be at low risk of bias for all dimensions apart from deviations from intended interventions (Appendix 4, Table A11). This was owing to the lack of blinding of participants to their study group allocation; however, an ITT analysis was used to appropriately consider deviations in the statistical analysis.

The study by Chen et al[41] was judged to be at low risk of bias with respect to incomplete outcome data and selective outcome reporting. Risk of bias was rated as unclear with respect to participant selection, adequate consideration of confounding variables, use of temporal spacing instead of blinding during outcome assessment, and measurement of the intervention (Appendix 4, Table A12).

SENSITIVITY AND SPECIFICITY—SUPPLEMENTAL MRI

The studies used different thresholds (i.e., BI-RADS assessment category findings) for a positive test when calculating measures of test performance and cancer detection (Table 20).

Table 20: Sensitivity and Specificity—Supplemental MRI After Negative Mammography

Study ID	Study design (N)	Population	MRI after negative mammography	
			Sensitivity, % (95% CI)	Specificity, % (95% CI)
DENSE trial[106] First screening round	Randomized controlled trial (4,783)	Extremely dense breasts (BI-RADS D)	95.2 (88.1–98.7)[a]	92.0 (NC)[b]
DENSE trial[107] Second screening round	Randomized controlled trial (3,346)	Extremely dense breasts (BI-RADS D)	NR	97.2 (NC)
Chen et al, 2017[41]	Prospective cohort; abbreviated MRI protocol vs. full diagnostic protocol (478)	Dense breasts (ACR standards)	*Full diagnostic protocol* 100 (75.5–100)[d] *Abbreviated protocol* 93.8 (67.7–99.7)[d] *P* = .623	*Full diagnostic protocol* 94.6 (92–96.4)[d] *Abbreviated protocol* 88.3 (84.9–91.0)[d] *P* = .036

Abbreviations: ACR, American College of Radiology; BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; DENSE, Dense Tissue and Early Breast Neoplasm Screening; MRI, magnetic resonance imaging; NC, not calculable; NR, not reported.

[a] Program sensitivity included screen-detected and interval cancers.[106]

[b] We calculated specificity at 1 − false-positive rate from data in Table 3 of the published article; we could not calculate 95% Cis from available data.[106]

[c] We calculated specificity at 1 − false-positive rate from data in Table 2 of the published article; we could not calculate 95% Cis from available data.[107]

[d] Calculated by recreating 2 × 2 table for the abbreviated and full diagnostic protocols from summary data (Table 2 of the published article).[41]

We rated the certainty of the evidence as Very low to Moderate, downgrading because of imprecision and indirectness (Appendix 4, Table A13).

Positive Test: BI-RADS 4

The threshold for test positivity in the DENSE trial was BI-RADS 4.[106] Considering both screen-detected cancers and interval cancers, the sensitivity and specificity of adjunct MRI in people with extremely dense breasts after negative mammography in the DENSE trial in the first (prevalence) round of screening were 95.2% (95% CI 88.1%–98.7%) and 92% (95% CI not calculable), respectively (Table 20).[106] Sensitivity for the second (incidence) screening round of the trial was not estimated, but specificity was

97.2% (95% CI not calculable).[107] Sensitivity and specificity were reported only for those who underwent supplemental MRI.

Other Threshold for Positive Test

The test positivity threshold used by Chen et al was not reported.[41] In their study population (people with dense breasts; see Table 19, footnote a), the sensitivity and specificity of supplemental (full diagnostic protocol) MRI imaging were 100% (95% CI 75.5%–100%) and 94.6% (95% CI 92%–96.4%), respectively.[41] The abbreviated protocol had slightly lower sensitivity and specificity than the full diagnostic protocol, and the difference in specificity reached statistical significance (*P* = .036).

CANCER DETECTION RATE—SUPPLEMENTAL MRI

More cancers were detected with MRI after negative mammography. In the first screening round of the DENSE trial,[111] MRI detected 79 additional cancers (64 invasive, 15 DCIS) for an overall cancer detection rate of 16.5 per 1,000 screens (95% CI 13.3–20.5; Table 21). The cancer detection rate for invasive cancers and DCIS in the first screening round were 13.4 per 1,000 screens (95% CI 10.5–17.1) and 3.1 per 1,000 screens (95% CI 1.9–5.2).

In the second screening round, 20 cancers were detected, for a cancer detection rate of 5.8 per 1,000 screens.[107] The proportion of DCIS detected was numerically but not significantly higher in the second screening round compared with the first (30% vs. 19%, *P* = .36).

Table 21: Cancer Detection Rate—Supplemental MRI After Negative Mammography

	Incremental cancer detection rate (95% CI)		
Study ID	**All cancers**	**Invasive cancers**	**DCIS**
DENSE trial[106]	79/4,783 (1.7%)	64/4,783 (1.34%)[a]	15/4,783 (0.33%)[a]
First screening round	16.5/1,000 screens (13.3–20.5)	13.4/1,000 screens (10.5–17.1)	3.1/1,000 screens (1.9–5.2)
DENSE trial[107]	N = 20/3,436 (0.58%)	N = 14/3,436 (0.41%)[b]	N = 6/3,436 (0.17%)[b]
Second screening round	5.8/1,000 screens (3.8–9.0)	4.1/1,000 screens (2.4–6.8)	1.7/1,000 screens (0.8–3.8)

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; DENSE, Dense Tissue and Early Breast Neoplasm Screening; MRI, magnetic resonance imaging.

[a] Calculated from data in Table 3 of Bakker et al[106] ; numbers may differ slightly due to rounding.

[b] Calculated from data in Table 2 of Veenhuizen et al[107]; numbers may differ slightly due to rounding.

We rated the certainty of the evidence as High (Appendix 4, Table A13).

CHARACTERISTICS OF CANCERS DETECTED—SUPPLEMENTAL MRI

The majority of cancers detected by MRI in the first screening round of the DENSE trial were invasive (81%), stage 0 or I (91%), grade 1 or 2 (85%), and node-negative (89%; Table 22).[106] The cancer detection rate for node-positive cancers was 1.9 per 1,000 screens (95% CI 1.0–3.6), and for late-stage (II–IV) cancers was 1.5 per 1,000 screens (95% CI 0.8–30). Of the invasive cancers, the most frequent types were invasive DCIS (55%), invasive lobular carcinoma (14%), mixed invasive ductal/lobular carcinoma

(12.5%), and tubular carcinoma (11%). Approximately 88% of the invasive cancers detected were receptor-positive (estrogen receptor, progesterone receptor, or both).

Similarly, in the second screening round of the DENSE trial, 70% of screen-detected cancers were invasive, and all were stage 0 or I and node-negative.[107] Most cancers (90%) were grade 1 or 2, and 70% were estrogen- and/or progesterone receptor–positive. The proportion of DCIS was numerically but not significantly higher in the first round (30%) compared to the second (19%; $P = 0.36$).

Table 22: Characteristics of Cancers Detected—Supplemental MRI, DENSE Trial

Screening round	No. screen-detected cancers	Types, n (%; no./1,000 screens)	Stage and grade	Node and receptor status
First round[106]	79/4,783	DCIS: 15/79 (19%; 3.1/1,000) Invasive cancers: 64/79 (81%) • Invasive ductal carcinoma: 35/64 • Invasive lobular carcinoma: 9/64 • Mixed invasive ductal/lobular carcinoma: 8/64 • Tubular carcinoma: 7/64 • Other invasive carcinoma: 5/64	*Stage* 0 or I: 72/79 (91.1%) II, III, or IV: 7/79 (8.9%) *Grade* DCIS Grade 1: 6/15 well differentiated Grade 2: 6/15 moderately differentiated Grade 3: 3/15 poorly differentiated Invasive cancers Grade 1: 31/64 Grade 2: 24/64 (G2) Grade 3: 4/64 (G3) Missing data/could not be assessed: 5/64	*Node status* Negative: 70/79 (88.6%) Positive: 9/79 (11.4%) *Median invasive tumour size* 9.5 mm (IQR 6.8–12.0 mm) *Invasive cancer receptor status* Positive for estrogen receptor, progesterone receptor, or both: 56/64 HER2-enriched: 2/64 Triple-negative: 4/64 Missing data: 2/64
Second round[107]	20/3,436	DCIS: 6/20 (30%; 1.7/1,000, 95% CI 0.8–3.8) Invasive cancer: 14/20 (70%) • Invasive ductal carcinoma: 8/14 • Invasive lobular carcinoma: 3/14 • Mixed invasive ductal/lobular carcinoma: 2/14 • Tubular carcinoma: 1/14	*Stage* Stage 0 or I: 20/20 (100%) Stage II–IV: 0/20 late-stage (95% CI 0–16.1) *Tumour grade* DCIS Grade 2: 5/6 Grade 3: 1/6 Invasive cancers Grade 1: 6/14 Grade 2: 7/14 Grade 3: 1/14	*Node status* Negative: 20/20 (100%) Positive: 0/20 (95% CI 0–16.1) *Median invasive tumour size* 7.0 mm (IQR 6.0–10.0 mm) *Invasive cancer receptor status* Estrogen receptor-positive: 12/14 Progesterone receptor–positive: 11/14 Estrogen receptor and/or progesterone receptor–positive: 14/14 HER2-enriched: 0/14 Triple-negative: 0/14 Missing data: 0/14

Abbreviations: DCIS, ductal carcinoma in situ; DENSE, Dense Tissue and Early Breast Neoplasm Screening; HER2, human epidermal growth factor 2; NA, data not available; NR, not reported.

Sources: Bakker et al,[106] Veenhuizen et al.[107]

INTERVAL CANCERS—SUPPLEMENTAL MRI

The primary outcome investigated in the DENSE trial was the incidence of interval cancers in the supplemental MRI group compared to mammography alone.[106]

An interval cancer was defined as a cancer diagnosed in the 24 months following negative mammography. According to the intention-to-screen analysis of all individuals invited to undergo supplemental MRI (both participants and nonparticipants, N = 8,061), 20 interval cancers occurred, for an interval cancer rate of 2.5 per 1,000 screens (95% CI 1.6–3.8).[106] In the mammography-only group (N = 32,312), 161 interval cancers occurred (5.0 per 1,000 screens [95% CI 4.3–5.8]), translating to a rate difference between groups of 2.5 per 1,000 screens (95% CI 1.0–3.7). The rate difference expressed per 1,000 person-years was 1.2 (95% CI 0.4–1.9).

Among the MRI participants (N = 4,783 of 8,061 invited women; 59%), in the 24 months following the first screening round, four interval cancers occurred (interval cancer rate 0.8 per 1,000 screens, 95% CI not reported).[106] The interval cancer rate was 4.9 per 1,000 screens in those who did not accept the MRI invitation (N = 3,278 of 8,016 invited women; Table 23).

Interval cancers were not assessed in the second screening round of the DENSE trial because these outcomes were not yet available from the cancer registry.[107]

Table 23: Interval Cancer Rate from the Intention-to-Screen Analysis in the First Screening Round of Supplemental MRI Versus Mammography Alone

Study group (N)	Interval cancer rate (95% CI)	Rate difference (95% CI)
Mammography only (32,312)	5.0/1,000 screens (4.3–5.8)	2.5/1,000 screens (1.0–3.7)
MRI invitation (8,061)	2.5/1,000 screens (1.6–3.8)	
MRI participants (4,783)	0.8/1,000 screens (NR)	–
MRI nonparticipants (3,278)[a]	4.9/1,000 screens (NR)	–

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging; NR, not reported.

[a] Refers to people who were invited to participate in the trial and undergo supplemental MRI but declined. Participant characteristics were comparable to the MRI participants group.

Source: Bakker et al.[106]

We rated the certainty of the evidence as High (Appendix 4, Table A13).

Characteristics of Interval Cancers

The majority of interval cancers were invasive in all groups (mammography-only, MRI participants, and MRI nonparticipants; Table 24).[106] In the mammography-only group, just over 58% of the cancers were late-stage (i.e., stage II, III, or IV), nearly 45% were node-positive, and about 70% of invasive cancers were intermediate- or high-grade (grade 2 or grade 3). There were nine cases of DCIS (5.6%) among all interval cancers in the mammography-only group. The occurrence and types of interval cancers in the MRI nonparticipants was similar to those of the mammography-only group.

In the MRI participants group, four interval cancers occurred. All interval cancers were invasive, half were node-positive, and three with available data were intermediate- or high-grade (grade 2 or grade 3).[106]

Table 24: Interval Cancers After the First Screening Round of the DENSE Trial

Group (N)	No. interval cancers	Types	Stage and grade	Node and receptor status[a]
Mammography only (32, 312)	161	DCIS: 9/161 (5.6%) Invasive ductal carcinoma: 113/161 (70.2%) Invasive lobular carcinoma: 20/161 (12.4%) Mixed invasive ductal/lobular carcinoma: 3/161 (1.9%) Tubular carcinoma: 2/161 (1.2%) Other invasive carcinoma: 14/161 (8.7%)	*Stage* Stage 0 or I: 67/161 (41.6%) Stage II, III, or IV: 94/161 (58.4%) *Tumour grade* DCIS Grade 1: 3/9 Grade 2: 1/9 Grade 3: 4/9 Missing data: 1/9 Invasive Grade 1: 29/152 Grade 2: 70/152 Grade 3: 39/152 Missing data: 14/152	*Node status* Negative: 89/161 (55.3%) Positive: 72/161 (44.7%) *Median invasive tumour size* 17.0 mm (IQR 12.0–23.0 mm) *Receptor status* Positive for estrogen receptor, progesterone receptor, or both: 119/152 HER2-enriched: 15/152 Triple-negative: 16/152 Missing data: 2/152
MRI participants (4,783)	4	Invasive ductal carcinoma: 2/4 (50%) Invasive lobular carcinoma: 2/4 (50%)	*Stage* Stage 0 or I: 2/4 (50%) Stage II, III, or IV: 2/4 (50%) *Tumour grade* Grade 2: 2/4 moderately differentiated Grade 3: 1/4 poorly differentiated Missing data: 1/4	*Node status* Negative: 2/4 (50%) Positive: 2/4 (50%) *Median invasive tumour size* 13.0 mm (IQR 10.5–17.0 mm) *Receptor status* Positive for estrogen receptor, progesterone receptor, or both: 3/4 HER2 enriched: 1/4
MRI nonparticipants[b] (3,278)	16	DCIS: 2/16 (12.5%) Invasive ductal carcinoma: 10/16 (62.5%) Invasive lobular carcinoma: 4/16 (25%)	*Stage* Stage 0 or I: 8/16 (50%) Stage II, III, or IV: 8/16 (50%) *Tumour grade* DCIS Grade 2: 1/2 Grade 3: 1/2 Invasive Grade 2: 7/14 Grade 3: 4/14 Missing: 3/14	*Node status* Negative: 9/16 (56.3%) Positive: 7/16 (43.7%) *Median invasive tumour size* 15.0 mm (IQR 12.0–31.0 mm) *Receptor status* Positive for estrogen receptor, progesterone receptor, or both: 10/14 HER2-enriched: 2/14 Triple-negative: 1/14 Missing data: 1/14

Abbreviations: DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor 2; MRI, magnetic resonance imaging; NA, data not available; NR, not reported.

[a] Receptor status reported only for invasive cancers.

[b] Refers to people who were invited to participate in the trial and undergo supplemental MRI but declined. Participant characteristics were comparable to the MRI participants group.

Source: Bakker et al, 2019.[106]

RECALL RATE AND BIOPSY/FOLLOW-UP PROCEDURES—SUPPLEMENTAL MRI

Participants whose MRI result was positive were recalled for additional investigations (Table 25). The recall rate after the first screening round was 9.5% (94.9 per 1,000 screens, 95% CI 86.9–103.6). Just over 6% of MRI participants underwent biopsy, representing about two-thirds of those recalled (300/454).[106]

In the second screening round, the recall rate was 3.2% (32 per 1,000 screens, 95% CI 26.6–38.4).[107] Of the 110 individuals recalled, 84 underwent biopsy (76.4%; 2.4% of all those screened with MRI in the second round). As noted in the section on cancer detection above, 79 cancers were detected in the first screening round; therefore, 375 of the 454 recalls were false-positives. In the second screening round, 20 cancers were detected; therefore, 90 of the 110 recalls were false-positives (81.8%). The false-positive rate (per 1,000 screens) was notably lower in the second screening round (26.3 [95% CI 21.5–32.3]) compared to the first (79.8 [95% CI 72.4–87.9]).[107]

Table 25: Abnormal Recall Rate—Supplemental MRI After Negative Mammography

Screening round	Recall rate[a]	Biopsy rate and other sequelae
First round[106]	9.5% (454/4,783) 94.9/1,000 screens (95% CI 86.9–103.6)	*Biopsy* 6.3% (300/4,783)[b] 62.7/1,000 screens (95% CI 56.2–70.0) *False-positives among those recalled* 82.6% (375/454)[b]
Second round[107]	3.2% (110/3,436) 32.0/1,000 screens (95% CI 26.6–38.4)	*Biopsy* 2.4% (84/3,436)[c] 24.4/1,000 screens (95% CI 19.8–30.2) *False-positives among those recalled* 81.8% (90/110)[c]

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; MRI, magnetic resonance imaging.

[a] Defined as the number of MRI participants who had a positive MRI result (i.e., BI-RADS 3, 4, or 5) divided by the total number of participants who underwent MRI imaging in the screening round.

[b] Calculated from data available in Table 3 of the published article.[106]

[c] Calculated from data available in Table 2 of the published article.[107]

We rated the certainty of the evidence as High (Appendix 4, Table A13)

ADVERSE REACTIONS TO CONTRAST MEDIA AND OTHER ADVERSE EVENTS—SUPPLEMENTAL MRI

During or immediately after the first supplemental MRI, 0.1% of participants (5/4,783) experienced a serious adverse event (an adverse event requiring emergency department visit or unplanned hospitalization): three allergic reactions to the contrast agent and two vasovagal reactions.[106] An additional three participants (0.06%) experienced an adverse event of either extravasation of the contrast agent (n = 2) or shoulder subluxation (n = 1) during or immediately after imaging.[106]

Twenty-seven (0.6%) participants reported a health problem qualifying as a serious adverse event, and 1,233 (25.7%) reported any adverse event on a questionnaire sent to participants to gather information on any health problems within 30 days after the exam, related or unrelated to supplemental MRI.[106] During the second screening round, one serious adverse event occurred (0.03%, vasovagal reaction) and extravasation of the contrast agent in two other participants (0.06%).[107]

We rated the certainty of the evidence as Moderate, downgrading for imprecision (Appendix 4, Table A13).

OTHER OUTCOMES—SUPPLEMENTAL MRI

The included study did not report the outcomes of psychological impact or overall or breast cancer–specific mortality.

Ongoing Studies

The DENSE trial is ongoing and plans to complete three full screening rounds, concluding in April 2023. Further results from this study of supplemental MRI as adjunct to mammography for people with extremely dense breasts may be published in the future (NCT01315015).

We are aware of several ongoing systematic reviews that may be relevant to this topic (Table 26).

Table 26: Ongoing Systematic Reviews

Title	Trial number (registry)	Status
U.S. Preventative Services Task Force Recommendation: Screening for Breast Cancer	Not available	Final research plan (last update May 6, 2021)[a,b]
Role of breast magnetic resonance imaging in screening women with mammographically dense breasts for breast cancer: a systematic review	CRD42021230277 (PROSPERO)	In progress (last update Nov. 19, 2021)[a]
Supplemental screening modality in patients with intermediate risk of breast cancer based on breast density with negative mammogram—what is the most effective modality? Systematic review, meta-analysis and cost-effectiveness analysis	CRD42018080402 (PROSPERO)	In progress (last update Sept. 21, 2021)[a]
Adjunctive ultrasonography for breast cancer screening in women with a mammography-negative dense breast: a systematic review and meta-analysis	CRD42017067425 (PROSPERO)	Review ongoing (last update May 19, 2017)[a]
Umbrella review and meta-analysis of the screening performance of imaging modalities to detect breast cancer in women with dense breasts	CRD42022293560 (PROSPERO)	Review ongoing[a]

[a] As posted on website.

[b] Per organizational correspondence, updating a recommendation takes approximately 3 years.

Discussion

We found that adding supplemental ultrasound, DBT, or MRI to screening mammography generally increased the sensitivity and decreased the specificity of breast screening. The definition of a positive test varied; however, with limited evidence we are unable to quantify the effect on the measures of test performance. The cancer detection rate was higher with supplemental screening. The interval cancer rate was lower after supplemental screening, but absolute numbers were small and therefore challenging to interpret. Information about the characteristics of cancers were inconsistently available and inconsistently reported. In general, screen-detected cancers tended to be mostly invasive and node-negative, although not in all cases. Interval cancers tended to be more invasive tumours of varied stage, size, and nodal status after mammography alone or with supplemental imaging. Although some information was available about the receptor status of cancers, it was complicated to interpret (i.e.,

with appropriate treatment, HER2-positive tumours do better than HER2-negative tumours; without appropriate treatment, they do worse). Our review also found more abnormal recalls after supplemental screening, reflecting more false-positive results. We did not find any evidence on supplemental contrast-enhanced mammography as an adjunct to mammography for breast cancer screening in people with dense breasts, or evidence comparing screening mammography plus DBT with mammography alone.

Our systematic review found no evidence on the patient-important outcome and ultimate objective of supplemental breast cancer screening: survival. This outcome requires decades of time to assess, whereas most studies followed participants for 1 or 2 years; the longest duration of follow-up in the included studies was 4 years (the DENSE trial). Without this ultimate clinical outcome, it is unclear the extent to which the additional cancers detected by supplemental screening did or did not represent overdiagnosis and overtreatment, or whether there would or would not be a reduction in disease progression and improved survival (i.e., potential lead-time bias). Furthermore, in most studies we could not separate out the proportion of cancers that were DCIS (stage 0) because DCIS was most often grouped with stage I cancers (considered together as "early stage") in studies. These are challenges routinely noted in prior systematic reviews, and the timeline when mortality data may become available is unknown.[24,25] In the absence of mortality data, interval cancers may provide some insight into the impact of supplemental screening on overall prognosis. However, interval cancers remain a surrogate outcome for mortality, and it is impossible to determine which develop between screening and which were present but missed.[112] We found no evidence in the studies about the psychological impact of screening and false results in the context of supplemental screening in people with dense breasts; however, this outcome has been documented in general terms in the literature.[83]

Comparing and generalizing from the included studies requires acknowledgement of the many factors that may influence the results. The included studies varied considerably with respect to the populations included (e.g., density, age, ethnicities represented), imaging protocols (e.g., views, technologist- versus physician-performed exams, single versus double-reading), and other screening factors (e.g., screening interval, definition of test positivity). The imaging procedures used in the studies may not reflect routine practice in screening programs, such as the experience level or expertise of readers, double-reading, or independent review of images from multiple modalities. Furthermore, some studies included clinical breast examination as part of screening, which added potential confounding and is not reflective of practice in other jurisdictions.

Our results were not dissimilar to those of previously published systematic reviews, such as those we excluded (Appendix 4), despite our stricter focus and eligibility criteria. Previous systematic reviews reflect a broader view of data on supplemental imaging for people with dense breasts; most included data on a subset of the general population, higher or mixed-risk screening participants, or from various comparisons. The published studies on contrast-enhanced mammography did not meet our eligibility criteria for similar reasons (i.e., various mixed populations and indications), but a similar trend toward additional cancer detection and increased recall has been noted.[22,113] Although it was informative, the added heterogeneity and potential additional confounding conferred by the inclusion of data from different settings and groups of participants warrants acknowledgement. We are aware of several ongoing systematic reviews that may provide additional insights when completed.

Strengths and Limitations

This systematic review provides an update on the available evidence since previous, seminal evidence syntheses. We sought to draw conclusions specifically about supplemental breast screening in people with dense breasts and no high-risk factors, largely aligned with current eligibility in the Ontario Breast Screening Program.[53] We considered evidence from highly controlled randomized trials and from systematic reviews and nonrandomized studies (in most cases conducted in real-world screening settings) to identify the best available evidence. Most published studies included participants with heterogeneously or extremely dense breasts, and assessment of study eligibility was challenged by unclear and inconsistent reporting of participant risk factors and characteristics. We erred on the side of inclusiveness when there was inadequate information to exclude. This provided as broad a view of the available literature as possible, while remaining focused.

When only a subset of study participants had dense breasts, insufficient information was reported about the characteristics of the participants with dense breasts and the presence of risk factors, and a lack of detail was available about the analysis or outcomes of participants with dense breasts. Given that our research question was not the primary objective of the studies, we did not include data from studies on a general screening population that stratified participants by density in subgroup analyses—because of feasibility and to avoid potential bias and possible issues with statistical power. We encountered several studies like this, and most aimed to compare people with high and low breast density. Other published systematic reviews provide insight into this evidence, having included a wider range of settings, population characteristics, and density definitions.

Because of a lack of data, we could not undertake most of our planned subgroup analyses. An exception was the comparison of handheld ultrasound and ABUS, which Philadelpho et al[36] investigated as their primary objective. Very few studies provided information on the characteristics of participants (e.g., ethnicity) and the limited amount available was uninformative. Therefore, we are unable to comment specifically on outcomes for people with dense breasts by age group, density category C versus D, screening interval, ethnicity, personal history of breast cancer, the presence of breast implants, gender identity, or body mass index.

We assessed multiple imaging modalities, but others were out of scope for this review, including positron emission tomography, elastography, computed tomography, and molecular breast imaging. We were limited in the conclusions we could draw in comparing modalities and could not ascertain which modality is the best for supplemental screening as an adjunct to mammography for people with dense breasts. As noted in several international guidelines (Table 3), the implementation of supplemental screening requires consideration not only of test performance and outcomes, but also an informed decision-making approach between individuals and health care providers, and feasibility in terms of availability and resource investment.

Conclusions

Our systematic review found no eligible studies on supplemental contrast-enhanced mammography as adjunct to mammography for breast cancer screening in people with dense breasts.

Supplemental Ultrasound

Among people with heterogeneously or extremely dense breasts, the evidence from both randomized controlled trials and nonrandomized studies suggests that mammography plus supplemental ultrasound (handheld ultrasound or ABUS) compared with mammography alone:

- Probably increases sensitivity by up to 30% (GRADE: Very low to Low)
- May decrease specificity by about 7% (GRADE: Very low to Moderate)
- Detects more cancers (30% to 100% more; GRADE: Very low to Moderate)
- Leads to approximately twice the recall rate and number of biopsies (GRADE: Very low to Moderate), although data were lacking about the proportion of recalls that were false-positives

Fewer interval cancers may be associated with mammography plus supplemental handheld ultrasound (GRADE: Low) or mammography plus supplemental ABUS (GRADE: Very low)

Supplemental Handheld Ultrasound Versus Supplemental ABUS

Based on one comparative study, the evidence suggests that in people with heterogeneously or extremely dense breasts and negative screening mammography, the cancer detection rate may be higher with supplemental ABUS versus supplemental handheld ultrasound (GRADE: Very low).

Supplemental Handheld Ultrasound Versus Supplemental DBT

Comparing supplemental DBT with supplemental handheld ultrasound among people with heterogeneously or extremely dense breasts who had negative screening mammography, the evidence suggests that:

- Supplemental handheld ultrasound may be more sensitive (range 90%–95%) than supplemental DBT (50%–54%, GRADE; Very low), but the modalities may have similar specificity (range 98%–100%; GRADE: Low)
- Cancer detection rates may be higher with supplemental handheld ultrasound than with supplemental DBT (GRADE: Very low); the incremental cancer detection rate for handheld ultrasound versus DBT was 2 to 3 per 1,000 screens ($P < .05$)
- It was unclear whether more recalls arose from supplemental handheld ultrasound versus supplemental DBT (GRADE: Very low). Up to 3.3% of all screens were recalled following supplemental handheld ultrasound or DBT, but available data state that 1.2% of all screens were false-positives

Supplemental MRI

Fewer interval cancers were observed among people with extremely dense breasts who underwent mammography plus supplemental MRI versus mammography alone (4 vs. 161 interval cancers over a 24-month screening interval; GRADE: High). The evidence also suggests that:

- Supplemental MRI has high sensitivity and specificity in extremely dense (GRADE: Moderate) and extremely and heterogeneously dense breasts (GRADE: Very low) after negative screening mammography
- In people with extremely dense breasts, supplemental MRI detected 16.5 cancers per 1,000 screens after negative screening mammography (GRADE: Moderate). The invasive cancer detection rate was 13.4 per 1,000

- Approximately 3% to 9.5% of people with extremely dense breasts who had supplemental MRI after negative screening mammography were recalled, and approximately 3 to 6% were biopsied (GRADE: Moderate). Available data reported that approximately 82% of MRI recalls were false-positives
- The frequency of contrast-related adverse events among people with extremely dense breasts undergoing supplemental MRI was low (i.e., approximately 0.1%; GRADE: Moderate)

None of the included studies reported on the outcomes of psychological impact, overall or breast cancer–specific mortality, or survival.

Economic Evidence

Research Question

What is the cost-effectiveness of supplemental screening with contrast-enhanced mammography, ultrasound, digital breast tomosynthesis (DBT), or magnetic resonance imaging (MRI) as an adjunct to mammography compared to mammography alone for breast cancer screening in people with dense breasts?

Methods

Economic Literature Search

We performed an economic literature search on November 1, 2021, to retrieve studies published from January 1, 2015, until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them until October 31, 2022. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published since January 1, 2015
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Narrative reviews, editorials, case reports, commentaries, abstracts, and protocols

POPULATION

Inclusion Criteria

- Asymptomatic people 40 years of age or older with negative or benign breast screening mammography results (i.e., Breast Imaging Reporting and Data System [BI-RADS] assessment category 1 or 2), no high-risk factors, and dense breasts (defined as >50% dense tissue; i.e., BI-RADS composition categories C [heterogeneously dense breasts, 50%–75% breast dense tissue] or D [extremely dense breasts, ≥ 75% breast dense tissue] or equivalent, regardless of method of density determination [e.g., visual, quantitative, or automated software/artificial intelligence])

Exclusion Criteria

- Participants with high-risk factors (i.e., known high-risk genetic mutations; a family history of high-risk genetic mutations or cancer; a ≥ 25% lifetime risk of breast cancer based on IBIS [International Breast Cancer Intervention Study breast cancer risk prediction tool], BOADICEA [Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm], or a similar tool; or a history of chest irradiation) or defined as high-risk in research articles; breast cancer survivors; participants with male breast cancer; participants younger than age 40 years

INTERVENTIONS

Inclusion Criteria

- Supplemental screening after 2-dimensional digital or film mammography with one of:
  - Contrast-enhanced (spectral) mammography
  - Ultrasound: including handheld ultrasound and automated breast ultrasound (ABUS)
  - DBT
  - MRI with or without contrast
- Comparator: breast screening with mammography alone or comparisons between eligible supplemental imaging modalities

Exclusion Criteria

- No comparator
- Diagnostic imaging (i.e., investigation of a detected or suspected lesion)
- Supplemental modality used for primary screening (i.e., to replace mammography)
- OctavaPink blood test (EventusDx), breast thermography, contrast-enhanced ultrasound, elastography, molecular breast imaging such as scintimammography, breast-specific gamma camera (e.g., Dilon 6800 gamma camera by Dilon Technologies Inc.), LumaGEM Molecular Breast Imaging System (with nucleotide tracers), etc.

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs], life-years, breast cancer mortality, cancer detection rate, abnormal recall rate, interval cancer rate, prognostic features of cancer detected [e.g., invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ (DCIS)], cancer stage)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICERs)

TIMING

- Subsequent to breast screening with mammography BI-RADS category 1 negative or category 2 benign, and breast density assessment or simultaneous screening with mammography, supplemental modality, and breast density assessment

SETTING

Inclusion Criteria

- Breast screening via opportunistic screening or an organized screening program

Exclusion Criteria

- Imaging for other purposes, such as surveillance (i.e., recurrence or progression), diagnosis, staging, prognosis, risk stratification, etc.

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[26] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, ICERs)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[114] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly applicable.

Results

Economic Literature Search

The database search of the economic literature yielded 214 citations published between January 1, 2015, and November 1, 2021, including grey literature searches and after duplicates were removed. We identified one additional eligible study from other sources, including database alerts (monitored

until September 30, 2022). In total, we identified nine studies (eight cost–utility analyses and one cost-effectiveness analysis) that met our inclusion criteria. See Appendix 6 for a list of selected studies excluded after full-text review. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

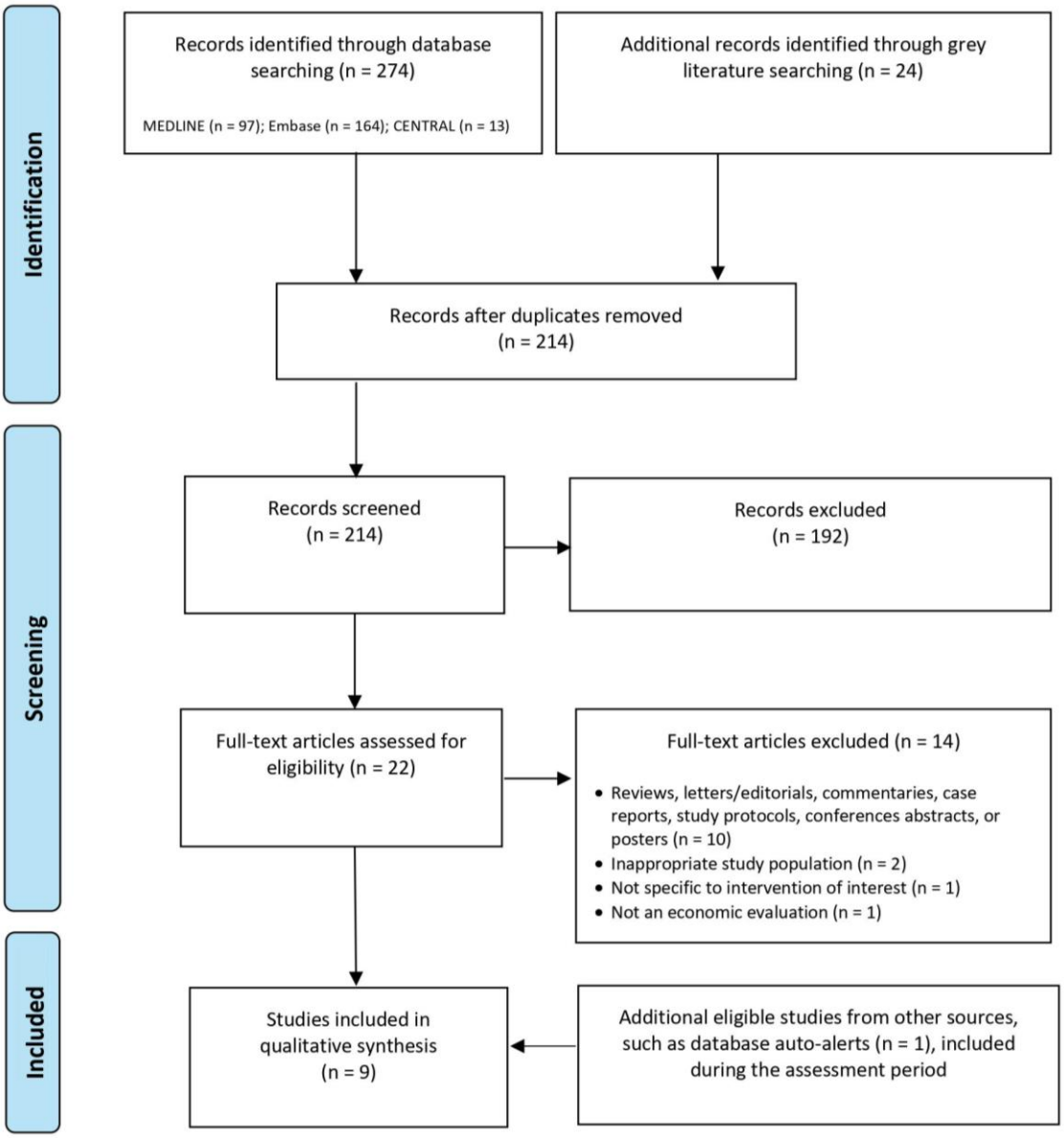


Figure 2: PRISMA Flow Diagram—Economic Search Strategy

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 274 citations published between January 1, 2015, and November 1, 2021. We identified 24 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 214 studies and excluded 192. We assessed the full text of 22 articles and excluded a further 14. In the end, we included nine articles in the qualitative synthesis, including one additional eligible study from database auto-alerts during the assessment period.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[90]

Overview of Included Economic Studies

STUDY CHARACTERISTICS

Our systematic review identified 214 deduplicated records, of which nine studies met our eligibility criteria: eight cost–utility analyses and one cost-effectiveness analysis of supplemental screening with ultrasound, DBT, or MRI as an adjunct to mammography compared to mammography alone for breast cancer screening in people with dense breasts (Table 27). The studies were conducted in the Netherlands,[115] Germany,[116-118] the United Kingdom,[119] Norway,[120] and the United States.[39,121,122]

Three studies evaluated mammography screening supplemented with MRI,[115-117] two studies with supplemental ultrasound,[39,119] one study with supplemental ultrasound or MRI,[122] two studies with supplemental DBT,[120,121] and one study with supplemental MRI or DBT.[118] No study evaluated contrast-enhanced mammography as a supplemental modality for breast cancer screening. In all studies, costs included were from the health care payer perspective. Eight studies used a lifetime horizon (20 to 30 years), [39,115-121] and one study used a 1-year time horizon.[122] Eight of the nine included studies conducted a cost–utility analysis using QALYs as the primary health outcome,[39,115-117,119-121] but three of these evaluated additional health outcomes expressed in natural units, such as life-years, number of breast cancers detected, number of interval cancers, number of false-positive findings, and breast cancer–related mortality.[39,120,121] The remaining study was a cost-effectiveness analysis, which included multiple health outcomes expressed in natural units, such as number of biopsies performed, number of cancers detected, number of false-positive findings, and number of interval cancers detected.[122]

All of the economic evaluations included people who were eligible for population-based breast cancer screening. In these studies, breast density was defined using the BI-RADS breast composition classification (as percentages in the BI-RADS atlas, 4th edition, or as categories A to D in the BI-RADS atlas 5th edition) or the Volpara Density Grade.

Four studies included only those with extremely dense breasts (BI-RADS D or ≥ 75% dense breast tissue).[39,115-117] One study by Sprague et al[39] assessed supplemental screening in women aged 50 to 74 years in two analyses: one in a subpopulation of those with extremely dense breasts, and another in the entire population of women with dense breasts (heterogeneously or extremely dense breasts). In the second analysis, the model parameters used were specific to women with either heterogeneously or extremely dense breasts (e.g., cancer detection rates in women with heterogeneously dense breasts were different from those in women with extremely dense breasts). However, the results were not stratified by breast density; they were reported for a single combined population. The study conducted an additional analysis that included women aged 40 to 74 years with annual breast screening.

Five studies included participants with heterogeneously dense breasts (BI-RADS C or 50%–75% dense breast tissue) and extremely dense breasts (BI-RADS D or ≥ 75% dense breast tissue) as a single (combined) population.[118-122] Three studies[119,121,122] used model parameters (e.g., sensitivity and specificity, breast cancer patient outcomes) specific to those with either heterogeneously and extremely dense breasts (two distinct populations). However, results were not stratified; they were reported for a single population. In two studies,[119,122] participants were stratified by breast cancer risk (e.g., age, breast density, and family and personal history). In two studies,[118,120] the study population was described as women with dense breasts, but “dense breasts” was not defined using BI-RADS or Volpara Density Grade classification. Therefore, we assumed that the study population included women with heterogeneously *or* extremely dense breasts (combined).

COST-EFFECTIVENESS OF SUPPLEMENTAL MODALITIES BY BREAST SCREENING FREQUENCY AND BREAST DENSITY CLASSIFICATION

Extremely Dense Breasts Only (BI-RADS D)

Three studies[115-117] evaluated supplemental screening with MRI as an adjunct to mammography compared to mammography alone in women with extremely dense breasts (BI-RADS D or ≥ 75% dense breast dense tissue).

In two cost–utility analyses,[116,117] biennial supplemental screening with MRI as an adjunct to mammography was cost-effective compared to mammography alone (ICERs $13,493 USD/QALY and $8,797 USD/QALY, respectively [2021 USD, discount rate 3%]), at a commonly accepted willingness-to-pay (WTP) value of $100,000 USD/QALY. However, in both studies, the costs related to MRI screening were the only costs captured (i.e., the costs of MRI plus mammography were not considered). The authors did not consider mammography costs in their analysis, given that the study population reflected the Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial, in which women were required to have a negative mammography screening result prior to the trial.[106,107] Therefore, the costs of the intervention strategy (i.e., mammography plus supplemental screening with MRI) and the ICER may have been underestimated.

Geuzinge et al[115] conducted a cost–utility analysis of supplemental screening with MRI as an adjunct to mammography (intervention arm), using various screening frequencies (every 2 to every 6 years) compared to mammography alone (usual care) in women with extremely dense breasts. The study also evaluated intervention strategies with MRI alone (every 2 to every 6 years) or alternating mammography and MRI every 2 years. In contrast to findings from the two studies above,[116,117] supplemental screening with MRI across all screening intervals resulted in lower QALYs and higher costs.

A study by Sprague et al[39] evaluated the cost utility of biennial supplemental screening with ultrasound as an adjunct to mammography versus mammography alone in women with extremely dense breasts, and in women with heterogeneously and extremely dense breasts (a single population). The authors found that supplemental screening with ultrasound was not cost-effective at a commonly accepted WTP value of $100,000 USD/QALY. The estimated ICERs were high, at $246,000 USD/QALY for women with extremely dense breasts, and $325,000 USD/QALY for women with heterogeneously and extremely dense breasts (2013 USD, discount rate 3%). A secondary analysis evaluating annual breast screening in women aged 40 to 74 years (supplemental screening with ultrasound after mammography vs. mammography alone) also resulted in high ICERs: $553,000 USD/QALY in women with extremely dense breasts, and $728,000 USD/QALY in women with heterogeneously or extremely dense breasts.

Heterogeneously Dense Breasts (BI-RADS C) and Extremely Dense Breasts (BI-RADS D)

Five studies[118-122] evaluated supplemental screening as an adjunct to mammography in women with heterogeneously and extremely dense breasts as a single population. Three of the five studies[119,121,122] used model parameters (e.g., sensitivity and specificity, breast cancer patient outcomes) specific to women with heterogeneously or extremely dense breasts. However, findings were not stratified by breast density; they were reported for a single combined population.

In the cost–utility analysis of supplemental screening with ultrasound as an adjunct to mammography (no screening interval indicated) by Gray et al,[119] women were stratified by breast cancer risk (Table 27), which included high breast density (defined as Volpara Density Grades 3 and 4). Similar to the findings of Sprague et al,[39] supplemental screening with ultrasound for women with dense breasts resulted in

higher costs and lower QALYs. Therefore, compared to mammography alone (every 3 years), supplemental screening with ultrasound was not cost-effective at a commonly accepted WTP value of £20,000 GBP/QALY, with an estimated ICER of £212,947 GBP/QALY (2015 GBP, discount rate 3.5%). Compared to no screening supplemental screening with ultrasound was also not cost-effective.

Ollendorf et al[122] conducted a cost-effectiveness analysis of supplemental screening with ultrasound (handheld ultrasound and ABUS) or with MRI as an adjunct to mammography in a cohort stratified by breast cancer risk based on age, family history (first-degree relative), and breast density (BI-RADS 4th edition, 50%–75% dense breast tissue and ≥ 75% dense breast tissue). The cost-effectiveness analysis used a 1-year time horizon, so outcomes estimated were from a 1-year screening interval. For women with moderate breast cancer risk (aged 40–49 years, with dense breasts and a family history of breast cancer; or aged 50–74 years, with dense breasts and no family history of breast cancer), supplemental screening with ultrasound or MRI increased the number of screen-detected breast cancers and decreased the number of interval cancers compared to mammography alone. However, supplemental screening also increased false-positive results, the number of recalls and biopsies performed, and health care costs. The ICERs for mammography plus handheld ultrasound or ABUS were $37,955 USD or $57,046 USD per cancer detected, and for mammography plus MRI was $93,077 USD per cancer detected (2014 USD, undiscounted). Findings for women at low, high, and all risk (combined low, moderate, and high) are summarized in Table 27.

Movik et al[120] evaluated the costs and QALYs of biennial supplemental screening with DBT after mammography compared to biennial mammography alone in women with dense breasts. The study population included women with dense breasts, but the authors did not define dense breasts based on BI-RADS categories or Volpara Density Grade classification. Compared to mammography alone, supplemental screening with DBT as an adjunct to mammography slightly increased QALYs (0.007) and life-years (0.005), as well as health care costs (Norwegian krone [NOK] 1,008), resulting in an ICER of 143,966 NOK/QALY (2017 NOK, discount rate 3%), which was cost-effective based on a Norwegian WTP value. The study did not indicate the commonly accepted WTP value, but previous studies have cited that the Norwegian Ministry of Health and Care Services compare estimated ICERs to a commonly accepted WTP value of 275,000 to 500,000 NOK ($33,805 to $61,464 USD).[123-125]

Lee et al[121] evaluated the cost utility of biennial supplemental screening with DBT as an adjunct to mammography compared to biennial mammography alone in women with heterogeneously and extremely dense breasts. Similar to the study by Movik et al,[120] the authors found that compared to mammography alone, biennial supplemental screening with DBT after mammography slightly increased QALYs and life-years (0.007), as well as health care costs ($349 USD) with ICERs of $53,893 USD/QALY and $70,500 USD/life-year gained (2013 USD, discount rate 3%), which was cost-effective at a commonly accepted WTP value of $100,000 USD/QALY. In a scenario analysis, biennial supplemental screening with DBT as an adjunct to mammography resulted in an additional six breast cancers, fewer breast cancer deaths (0.5 averted) and fewer false-positive results (405 averted), compared to annual mammography alone. Incremental QALYs, costs, and ICERs were not calculated for this scenario.

Tollens et al, published in 2022,[118] conducted a cost–utility analysis of biennial supplemental screening with DBT, abbreviated breast MRI, and full-protocol breast MRI compared to biennial mammography alone in women with dense breasts. The authors also evaluated the cost utility of abbreviated breast MRI at different cost values, from $200 USD to $314 USD (2022 USD). Compared to mammography alone, supplemental screening with DBT slightly increased the total cost by $97 USD and increased QALYs by 0.005, resulting an estimated ICER of $19,785 USD/QALY (discount rate 3%). Supplemental

screening with abbreviated breast MRI resulted in an increase of 0.037 QALYs, with incremental costs ranging from $155 USD to $1,062 USD compared to mammography alone and estimated ICERs of $4,163 USD/QALY to $28,458 USD/QALY. At screening cost of $200 USD, abbreviated breast MRI dominated mammography alone because of cost savings (savings of $38 USD) and increased effectiveness (0.037 QALYs). Supplemental screening with full-protocol breast MRI resulted in an ICER of $15,018 USD/QALY. At the commonly accepted WTP value of $100,000 USD/QALY, DBT, abbreviated breast MRI, and full-protocol breast MRI were cost-effective compared to mammography alone. However, similar to the studies by Kaiser et al[116] and Tollens et al,[117] the cost related to MRI screening was the only cost captured in the analysis (i.e., the cost of MRI plus mammography was not considered). Therefore, the costs of the intervention strategy (mammography plus supplemental screening with MRI) and ICERs may have been underestimated.

Table 27: Results of Economic Literature Review—Summary

Author, year, country	Analytic technique Study design Perspective Time horizon	Population	Intervention(s) and comparator(s)	Results[a]		
				Health outcomes	Costs	Cost-effectiveness
Tollens et al, 2022,[118] Germany	Cost–utility analysis Decision tree and Markov model US health care perspective Commonly accepted WTP value: $100,000 USD/QALY Lifetime horizon, 30 y	Women with dense breasts and negative/normal mammography result, 55 y on average *Density* Indicated "dense breasts" but did not provide a definition based on BI-RADS or VDG classification	*Interventions* Biennial mammography alone Biennial DBT Biennial AB-MRI (varying costs from $200 USD to $314 USD) Biennial FB-MRI	*QALYs* Mammography alone: 19.22 DBT: 19.22 AB-MRI: 19.25 FB-MRI: 19.26 *Incremental QALYs* DBT vs. mammography: 0.005 AB-MRI vs. mammography: 0.037 FB-MRI vs. mammography: 0.038 Discount rate: 3%	*Total direct health care costs (per person) in 2022 USD* Mammography alone: $8,718 USD DBT: $8,815 USD AB-MRI: $8,680 USD to $9,779 USD FB-MRI: $9,283 USD *Incremental costs* DBT vs. mammography): $97 USD AB-MRI vs. mammography: −$38 USD to $1,062 USD FB-MRI vs. mammography: $565 USD Discount rate: 3%	*ICERs* DBT vs. mammography alone: $19,785 USD/QALY AB-MRI ($220 USD to $314 USD) vs. mammography alone: $4,163 USD/QALY to $28,458 USD/QALY AB-MRI ($200 USD) vs. mammography alone: AB-MRI dominated mammography alone (lower cost, more effective) FB-MRI vs. mammography alone: $15,018 USD/QALY DBT, AB-MRI and FB-MRI were cost-effective at commonly accepted WTP values of $100,000 USD/QALY *Probabilistic sensitivity analysis* Not conducted *2-way sensitivity analysis of varying specificity of cost and specificity of AB-MRI* Decreased cost and higher specificity of AB-MRI was preferred compared to FB-MRI. At high costs and lower specificity of AB-MRI, FB-MRI was preferred *Cost threshold analysis for varying specificity of AB-MRI and FB-MRI* At a specificity of 95% for FB-MRI and 87% for AB-MRI, the cumulative costs of both strategies were equal when the cost per examination of AB-MRI was $260 USD (83% of the cost of a FB-MRI examination) Below costs per examination of $253 USD (81%), FB-MRI was no longer a cost-effective alternative based on a WTP threshold of $100,000 USD/QALY

Author, year, country	Analytic technique Study design Perspective Time horizon	Population	Intervention(s) and comparator(s)	Results[a]		
				Health outcomes	Costs	Cost-effectiveness
Geuzinge et al, 2021,[115] Netherlands	Cost–utility analysis Individual-level microsimulation decision analytic model Netherlands health care payer perspective Commonly accepted WTP value: €22,000 EUR (£20,000 GBP)/QALY based on the lower bound of the NICE threshold range Lifetime horizon (simulated women starting at 25 y old until death)	Women, aged 50−75 y Density: extremely dense breasts[b] and negative/normal mammography result Effectiveness from the DENSE trial[106] (embedded in the Dutch biennial mammography screening program)	*Interventions* No screening Mammography and MRI, biennial (2Mx_2MRI) Alternating mammography and MRI, biennial (2Mx/MRI) Mammography biennial and MRI every 4 y (2Mx_4MRI) Mammography every 4 y and MRI biennial (4Mx_2MRI) Mammography every 6 y and MRI biennial (6Mx_2MRI) MRI alone: biennial (2MRI), 3 y (3MRI), 4 y (4MRI) or 5 y (5MRI) *Comparator* Mammography alone, biennial (2Mx)	*QALYs (arranged based on increasing cost, sequential analysis)* No screening: 49.473 2Mx: 49.520 5MRI: 49.560 4MRI: 49.569 2Mx/MRI: 49.566 3MRI: 49.573 2Mx_4MRI: 49.565 6Mx_2MRI: 49.577 2MRI: 49.581 4Mx_2MRI: 49.581 2Mx_2MRI: 49.576 Discount rate: 3%	*Total direct health care costs (per person) in 2018 EUR (arranged increasing cost)* No screening: €10,029 EUR 2Mx: €10,682 EUR 5MRI: €11,111 EUR 4MRI: €11,246 EUR 2Mx/MRI: €11,331 EUR 3MRI: €11,412 EUR 2Mx_4MRI: €11,431 EUR 6Mx_2MRI: €11,763 EUR 2MRI: €11,806 EUR 4Mx_2MRI: €11,904 EUR 2Mx_2MRI: €11,944 EUR Discount rate: 3%	*ICER, per QALY, sequential analysis* 2Mx and 6Mx_2MRI resulted in more costs and fewer QALYs compared to interventions with MRI alone 2Mx_2MRI, 2Mx/MRI, 2Mx_4MRI, and 4Mx_2MRI resulted in more costs and fewer QALYs compared to interventions with MRI alone MRI every 2–5 y: €12,410 EUR to €46,971 EUR MRI every 4 y had the highest acceptable ICER: €15,620 EUR at commonly accepted WTP value When interventions that included supplemental screening with MRI as an adjunct to mammography were considered (i.e., MRI-only interventions not included), mammography every 2 y with MRI every 4 y had the highest acceptable ICER: €16,652 EUR/QALY *Probabilistic sensitivity analysis* Not conducted *1-way sensitivity analyses* MRI screening every 4 y remained cost-effective, with the highest acceptable ICER. The unit price of MRI had the greatest impact on the ICER (reference case €91.97 EUR [range ± 25%])

Author, year, country	Analytic technique Study design Perspective Time horizon	Population	Intervention(s) and comparator(s)	Results[a]		
				Health outcomes	Costs	Cost-effectiveness
Kaiser et al, 2021,[116] Germany	Cost–utility analysis Decision tree and Markov model US health care perspective Commonly accepted WTP value: $100,000 USD/QALY Lifetime horizon, 30 y (based on Dutch population-based screening program)	Women, mean age 55 y Density: intermediate risk of breast cancer, defined as high breast tissue density[b] Effectiveness from the DENSE trial included only the first round of screening[106]	*Intervention* MRI,[c] biennial *Comparator* Mammography alone, biennial	*QALYs* MRI: 18.92 Mammography: 18.87 *Incremental QALYs* MRI vs. mammography: 0.05 Discount rate: 3%	*Total direct health care costs (per person) in 2021 USD* MRI: $5,877 USD Mammography: $5,493 USD *Incremental cost* MRI vs. mammography: $384 USD Discount rate: 3%	*ICER* $8,797 USD/QALY, cost-effective at commonly accepted WTP value of $100,000 USD/QALY *1-way sensitivity analyses* Cost of MRI ($200 USD–$450 USD) and mammography ($50 USD–$200 USD) and annual probability of interval cancer in mammography screening (0.2%–0.3%) had the greatest impact on the ICER *Probabilistic sensitivity analyses* In most of the iterations, MRI was highly likely to be cost-effective
Tollens et al, 2021,[117] Germany	Cost–utility analysis Decision tree and Markov model US health care perspective Commonly accepted WTP value: $100,000 USD/QALY Lifetime horizon, 20 y (based on Dutch population-based screening program)	Women, mean age 55 y Density: intermediate risk of breast cancer, defined as high breast tissue density[b] Effectiveness from the DENSE trial, including findings from the second screening interval[107]	*Intervention* MRI,[c] biennial *Comparator* Mammography alone, biennial	*QALYs* MRI: 15.12 Mammography: 15.099 *Incremental QALYs* MRI vs. mammography: 0.02 Discount rate: 3%	*Total direct health care costs (per person) in 2021 USD* MRI: $6,081 USD Mammography: $5,810 USD *Incremental cost* MRI vs. mammography: $271 USD Discount rate: 3%	*ICER* $13,493 USD/QALY, cost-effective at commonly accepted WTP value of $100,000 USD/QALY *1-way sensitivity analysis* Cost of MRI ($250 USD–$450 USD), specificity of mammography (0.85–0.95) and MRI (0.90–0.99) had the most impact on the ICER *Probabilistic sensitivity analysis* Supplemental screening with MRI was highly likely to be cost-effective at a commonly accepted WTP value, where 86% of the iterations were cost-effective

Author, year, country	Analytic technique Study design Perspective Time horizon	Population	Intervention(s) and comparator(s)	Results[a]		
				Health outcomes	Costs	Cost-effectiveness
Gray et al, 2017,[119] United Kingdom	Cost–utility analysis Individual-level discrete event simulation model UK national health care perspective Commonly accepted WTP value: £20,000 GBP/QALY Lifetime horizon	Women, mean age 49 y, eligible for the NBSP stratified by breast cancer risk[d] *Density* High breast density defined as VDG 3 and 4	*Interventions*[d] Risk stratification 1 Risk stratification 2 Masking (mammography + ultrasound) Masking and risk stratification 1 *Comparators* UK NBSP: mammography every 3 y No screening	*QALYs* Risk stratification 1: 17.7119 Risk stratification 2: 17.7181 Masking (mammography + ultrasound): 17.7102 Masking and risk stratification 1: 17.7124 UK NBSP: 17.7095 No screening: 17.6919 *Incremental QALYs* Masking vs. UK NBSP: 0.0007 Masking vs. no screening: 0.0183 Discount rate: 3.5%	*Total direct health care costs (per person) in 2015 GBP* Risk stratification 1: £694 GBP Risk stratification 2: £858 GBP Masking (mammography + ultrasound): £809 GBP Masking and risk stratification 1: £870 GBP UK NBSP: £654 GBP No screening: £246 GBP *Incremental costs* Masking vs. UK NBSP: £155 GBP Masking vs. no screening: £563 GBP Discount rate: 3.5%	*ICER, intervention vs. UK NBSP* Risk stratification 1: £16,689 GBP/QALY Risk stratification 2: £23,924 GBP/QALY Masking (mammography + ultrasound): £212,947 GBP/QALY, not cost-effective at commonly accepted WTP value; fewer QALYs and more costs compared to UK NBSP Masking and risk stratification 1: £75,254 GBP/QALY *ICER, intervention vs. no screening* Risk stratification 1: £22,413 GBP/QALY Risk stratification 2: £23,435 GBP/QALY Masking (mammography + ultrasound): £30,772 GBP/QALY Masking and risk stratification 1: £30,532 GBP/QALY *Probabilistic sensitivity analyses* In the majority of the iterations, mammography + ultrasound was not cost-effective *1-way sensitivity analyses* Natural history parameter values and screening performance of mammography (range ± 20% from base case value) had the biggest impact on the ICERs

Author, year, country	Analytic technique Study design Perspective Time horizon	Population	Intervention(s) and comparator(s)	Results[a]		
				Health outcomes	Costs	Cost-effectiveness
Movik et al, 2017,[120] Norway	Cost–utility and cost-effectiveness analyses Individual-level discrete event simulation model Norwegian health care perspective Lifetime horizon, 20 y	Women, aged 50–70 y, eligible for the Norwegian breast cancer screening program *Density* Indicated "dense breasts" but did not define dense breasts based on BI-RADS or VDG classification	*Intervention* Digital mammography (synthetic 2-dimensional) supplemented with DBT (Hologic), biennial *Usual care* Digital mammography alone, biennial Effectiveness data from Oslo Tomosynthesis Screening Trial[126]	*QALYs* Mammography + DBT: 16.814 Mammography alone: 16.807 *Incremental QALYs* Mammography + DBT vs. mammography alone: 0.007 *Life-years* Mammography + DBT: 20.652 Mammography alone: 20.647 *Incremental life-years gained* Mammography + DBT vs. mammography alone: 0.005 Discount rate: 3%	*Total direct health care costs (per person) in 2017 NOK* Digital mammography + DBT: 28,979 NOK Digital mammography alone: 27,971 NOK *Incremental cost* Mammography + DBT vs. mammography alone: 1,008 NOK Discount rate: 3%	*ICER, per QALY* Mammography + DBT vs. mammography alone: 143,966 NOK/QALY, cost-effective at commonly accepted WTP values[e] *ICER, per life-year gained* 201,600 NOK/life-year gained *Probabilistic sensitivity analysis* Not conducted *1-way sensitivity analyses* Cost of DBT (base case value 300 NOK; range ± 200 NOK) had the greatest impact on the ICER. In all sensitivity analyses, DBT remained cost-effective (ICERs of 97,252 NOK to 210,552 NOK), except for upper bound cost of DBT (ICER 365,515 NOK)

Author, year, country	Analytic technique Study design Perspective Time horizon	Population	Intervention(s) and comparator(s)	Results[a]		
				Health outcomes	Costs	Cost-effectiveness
Lee et al, 2015,[121] United States	Cost–utility and cost-effectiveness analyses Discrete event simulation model US health care perspective Commonly accepted WTP value: $100,000 USD/QALY Lifetime horizon	Women, aged 50–74 y *Density* Heterogeneously and extremely dense breasts[f] determined at baseline mammogram screen at age 50 y	*Intervention* Digital mammography supplemented with DBT, biennial *Comparator* Digital mammography alone, biennial Effectiveness data from Oslo Tomosynthesis Screening Trial[126] *Scenario analysis* Intervention: digital mammography supplemented with DBT, biennial Comparator: digital mammography alone, annual	*QALYs* Mammography + DBT: 16.814 Mammography alone: 16.807 *Incremental QALYs* Mammography + DBT vs. mammography alone: 0.007 *Life-years* Mammography + DBT: 20.652 Mammography alone: 20.647 *Incremental QALYs* Mammography + DBT vs. mammography alone: 0.007 Discount rate: 3%	*Total direct health care costs (per person) in 2013 USD* Mammography + DBT: $4,440 USD Mammography alone: $4,091 USD *Incremental cost* $349 USD Discount rate: 3%	*ICER, per QALY* Mammography + DBT vs. mammography alone: $53,893 USD *ICER, per life-year gained* Mammography + DBT vs. mammography alone: $70,500 USD *Probabilistic sensitivity analysis* Not conducted *1-way sensitivity analyses* Cost of DBT (base case value $50 USD [range $0 USD–$139 USD]) had the greatest impact on the ICER, followed by sensitivity (base case value 0.8 [range 0.77–0.83]) and specificity (base case value 0.92 [range 0.88–0.95]) of mammography combined with supplemental DBT, and disutility from diagnostic workup following positive findings (base case value 0.105 [range 0–0.105]) *Scenario analysis* Biennial mammography + DBT vs. annual mammography alone Supplemental screening with DBT as an adjunct to mammography resulted in an additional 6 breast cancers detected, decreased breast cancer deaths by 0.5 and averted 405 false-positive results compared to annual mammography alone

Author, year, country	Analytic technique Study design Perspective Time horizon	Population	Intervention(s) and comparator(s)	Results[a]		
				Health outcomes	Costs	Cost-effectiveness
Sprague et al, 2015,[39] United States	Cost–utility and cost-effectiveness analyses Individual-level microsimulation model[g] United States health care perspective Commonly accepted WTP value: $100,000/QALY Lifetime horizon	Women, aged 50–74 y[h] with dense breasts eligible for biennial breast cancer screening *Density* Extremely dense breasts, and heterogeneously plus extremely dense breasts as a single population[f] *Secondary analyses* Included women aged 40–49 y at an annual screening interval	*Intervention* Digital mammography supplemented with ultrasound (after negative mammography) for women with extremely dense breasts,[f] biennial Digital mammography supplemented with ultrasound (after a negative mammography) for women with heterogeneously OR extremely dense breasts,[f] biennial No screening *Comparator* Digital mammography alone, biennial	*Women 50–74 y, biennial screening; 40–74 y annual screening* *QALYs* Mammography + ultrasound for extremely dense breasts: 19.0608; 19.0984 Mammography + ultrasound for heterogeneously and extremely dense breasts: 19.0599; 19.0969 Mammography alone: 19.0598; 19.0965 No screening: 19.0249 *Life-years* Mammography + ultrasound for extremely dense breasts: 23.1098; 23.1538 Mammography + ultrasound for heterogeneously and extremely dense breasts: 23.1087; 23.1520 Mammography alone: 23.1085; 23.1538 No screening: 23.0655 Discount rate: 3%	*Women 50–74 y, biennial screening; 40–74 y annual screening* *Total direct health care costs (per person) in 2013 USD* Mammography + ultrasound for extremely dense breasts: $3,390 USD; $6,580 USD Mammography + ultrasound for heterogeneously and extremely dense breasts: $3,080 USD; $5,420 USD Mammography alone: $3,020 USD; $5,150 USD No screening: $2,020 USD Discount rate: 3%	*Women 50–74 y, biennial screening; 40–74 y annual screening* *ICER, per QALY* Mammography + ultrasound for extremely dense breasts vs. mammography alone: $246,000 USD; $553,000 USD Mammography + ultrasound for heterogeneously and extremely dense breasts vs. mammography alone: $325,000 USD; $728,000 USD *ICER, per life-year gained* Mammography + ultrasound for extremely dense breasts vs. mammography alone: $239,167 USD; $470,278 USD Mammography + ultrasound for heterogeneously and extremely dense breasts vs. mammography alone: $266,667 USD; $597,297 USD *Probabilistic sensitivity analysis* Not conducted *1-way sensitivity analysis* Increasing ultrasound sensitivity and sensitivity, increasing cost of ultrasound, and capturing disutility for diagnostic workup had the biggest impact on ICERs. Supplemental screening with ultrasound remained not cost-effective; ICERs were > $100,000 USD/QALY

Author, year, country	Analytic technique Study design Perspective Time horizon	Population	Intervention(s) and comparator(s)	Results[a]		
				Health outcomes	Costs	Cost-effectiveness
Ollendorf et al, 2014,[122] United States	Cost-effectiveness analysis Cohort model (type of model not indicated) State of Washington health care perspective 1-year time horizon	Women aged 40–74 y with no high-risk factors (genetic susceptibility, personal history of breast cancer, or prior chest radiation) *Density* BI-RADS density category C and D, with an initial negative mammogram Cohort was stratified into three levels of underlying breast cancer risk[i]	*Intervention* Digital mammography supplemented with ultrasound (handheld ultrasound/ABUS) Digital mammography supplemented with MRI *Comparator* Digital mammography alone Note: No screening interval; time horizon was 1 y	*Incremental health outcomes for moderate risk[j] (low risk, high risk, all risk) per 1,000 women screened* *Biopsy performed* Mammography + ultrasound vs. mammography alone: 51.3 (25.1, 71.8, 45.0) Mammography + MRI vs. mammography alone: 32.6 (22.5, 42.6, 30.4) *Cancer detected* Mammography + ultrasound vs. mammography alone: 4.4 (1.8, 6.8, 3.8) Mammography + MRI vs. mammography alone: 6.5 (3.4, 10.6, 6.0) *Interval cancers averted* Mammography + ultrasound vs. mammography alone: 0.9 (0.3, 1.8, 0.7) Mammography + MRI vs. mammography alone: 1.0 (0.3, 2.1, 0.8) No discount rate applied; time horizon was 1 year	*Incremental direct health care cost in 2014 USD for moderate risk[j] (low risk, high risk, all risk) per 1,000 women screened)* Mammography + handheld ultrasound vs. mammography alone: $167 USD ($133 USD, $194 USD, $159 USD) Mammography + ABUS vs. mammography alone: $251 USD ($217 USD, $278 USD, $243 USD) Mammography + MRI vs. mammography alone: $605 USD ($591 USD, $618 USD, $602 USD) No discount rate applied; time horizon was 1 y	*ICER, per cancer detected for moderate risk[j] (low risk, high risk, all risk)* Mammography + handheld ultrasound vs. mammography alone: $37,955 USD ($443.33 USD; $107.70 USD; $227.14 USD) Mammography + ABUS vs. mammography alone: $57,046 USD ($723.33 USD; $154.44 USD; $347.14 USD) Mammography + MRI vs. mammography alone: $93,077 USD ($1,970 USD; $294.30 USD; $752.5 USD) Compared to mammography alone, all supplemental modalities improved cancer detection and decreased interval cancers but they increased false-positives, recalls, biopsies performed, and costs

Abbreviations: AB-MRI, abbreviated breast MRI; ABUS, automated breast ultrasound; DENSE trial, Dense Tissue and Early Breast Neoplasm Screening trial; FB-MRI full-protocol breast MRI; ICER, incremental cost-effectiveness ratio; NBSP, National Breast Screening Program; QALY, quality-adjusted life-year; VDG, Volpara Density Grade; WTP, willingness-to-pay.

[a] Analysis evaluating more than two interventions; the expected costs and outcomes of the interventions and the relevant incremental rations were calculated sequentially. Sequential analysis estimated the ICER for a less costly comparator compared to the next most costly comparator, excluding all comparators that dominated or were subject to extended dominance.

[b] Intervention with fewer QALYs and more costs than the previous strategy (strongly dominated).

[c] Although the analysis was a direct head-to-head comparison of the intervention, MRI, and mammography alone (usual care), clinical parameters were obtained from the DENSE trial, which included trial participants who had a negative or normal mammographic screening.[106]

Footnotes continued on the following page.

Continued from the previous page.

[d] Breast cancer risk: Risk 1—risk algorithm using a study by Evans et al,[127] enhanced with breast density and texture measures following the method of Brentnall et al.[128] Three strata, with associated screening intervals, were defined by 10-y risks of breast cancer of: a) < 3.5%, screening every 3 y; b) 3.5%–8%, every 2 y; and c) > 8%, every year. Risk 2—risk-based stratification defined by the same algorithm as risk 1 but with strata defined by dividing the population into thirds on the basis of 10-y risk: a) lowest-risk tertile, every 3 y; b) middle tertile, every 2- y; and c) highest-risk tertile, every year. Masking: mammography supplemented with ultrasound for women with high breast density, defined as VDG3 and VDG4. Women with both high breast density and high risk of breast cancer (i.e., 8% 10-y risk of breast cancer) were offered mammography supplemented with MRI. Risk 1 + masking: risk 1 stratification approach plus the strategy described in the masking approach.

[e] Commonly accepted WTP value was not indicated in the study. However, previous studies have cited WTP values of 275,000 NOK to 500,000 NOK ($33,805 USD to $61,464 USD)[123-125]

[f] Dense breasts were defined as breasts with high mammographic density; BI-RADS C and/or D; or 50%–75% dense breast tissue and/or ≥ 75% dense breast tissue.

[g] Findings from this study used the median value (range) of three microsimulation models that were developed independently by the National Cancer Institute-funded Cancer Intervention and Surveillance Modeling Network consortium (CISNET): Model E, Erasmus University Medical Center, Rotterdam, Netherlands; Model G-E, Georgetown University Medical Center, Washington, DC, and Albert Einstein College of Medicine, New York, NY; and Model W, University of Wisconsin, Madison, WI, and Harvard Medical School, Boston, MA.

[h] At age 40 y, simulated cohort were assigned an initial breast density based on the overall distribution of BI-RADS density categories. At age 50 y, women were assigned to the same breast density category, or to the next lower category calibrated to the prevalence observed for postmenopausal women by the Breast Cancer Surveillance Consortium.

[i] A hypothetical cohort of women was stratified to three levels of underlying breast cancer risk based on age, breast density, and family history of breast cancer (first-degree relative)—factors that would be indicated in a primary care setting: (i) low: age 40–49 y, 50%–75% or ≥ 75% dense breast tissue, no family history; (ii) moderate: age 40–49 y, 50%–75% or ≥75% dense breast tissue, with a family history OR age 50–74 y, 50%–75% or ≥ 75% dense breast tissue, no family history; or (iii) high: age 50–75 y, 50%–75% or ≥ 75% dense breast tissue, with a family history.

[i] Model results were reported for all risk groups combined and by risk group (low, moderate, and high); the table prioritizes findings for women at moderate risk because it was the most applicable population.

Applicability and Limitations of the Included Studies

Appendix 7 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies.

APPLICABILITY OF THE INCLUDED STUDIES

No study was deemed directly applicable to the research question because no study conducted a comparative assessment of all four supplemental modalities (ultrasound, contrast-enhanced mammography, DBT, MRI); evaluated annual screening for people with extremely dense breasts; or evaluated people with heterogeneously or extremely dense breasts alone (most studies captured a combined population of women with heterogeneously or extremely dense breasts). Three studies provided no rationale for why cost-effectiveness results were not stratified between the two dense breast populations.[119,120,122] Two studies indicated that breast density reporting legislation set by the American College of Radiology did not distinguish between the two BI-RADS density categories, and the objective of their analysis was to inform breast screening practice that was current at the time of the study.[10,129]

Seven studies were partially applicable to the research question;[39,115-117,119-121] they had minor differences in study population (age eligible for screening, breast density), breast cancer screening frequency, and estimated health outcomes and costs. However, they were conducted in a non-Canadian setting.

Two studies[118,122] were not applicable to our research question because of major differences in the target population assessed (e.g., age eligible for screening, family history, combined population of heterogeneously and extremely dense breasts); health effects expressed in terms of QALYs; a short 1-year time horizon (undiscounted ICERs), which may not have captured all of the significant differences in screening and patient outcomes; and health care costs associated with the supplemental modality were not fully considered.

LIMITATIONS OF THE INCLUDED STUDIES

Three studies[115,119,121] had minor limitations that were unlikely to change the conclusions about the cost-effectiveness of the supplemental modalities. Five studies[39,116-118,122] had potentially serious limitations, in which more than two criteria were partially fulfilled. Of these, four studies[39,116-118] provided insufficient information on costs related to further imaging and diagnostic assessment and made several assumptions in the utilities and the natural history of breast cancer, although some of these parameters were assessed in sensitivity analyses. One study[120] had very serious limitations because of insufficient information about health states and the structure of the discrete event simulation model, the definition of dense breasts (heterogeneously or extremely dense breasts, or both), the sources of the clinical and cost parameters, and the limited sensitivity analysis of uncertain parameters used in the model (e.g., diagnostic accuracy of the imaging modalities).

One of the common limitations across all nine studies was related to the sensitivity and specificity of the supplemental modality across screening intervals.[39,115-122] All studies assumed that the diagnostic accuracy of both mammography and the supplemental modality remained constant from the first screening interval to the last screening interval. This is because clinical evidence for supplemental screening as an adjunct to mammography is limited, and previous clinical trials and observational studies have had short-term follow-up to measure long-term diagnostic accuracy and patient-reported

outcomes.[107,130] As well, it was unclear in all but two studies[39,115] whether the breast density indicated at the first screening interval remained constant across screening intervals for the entire time horizon.

Discussion

We reviewed nine model-based economic evaluations (eight cost–utility analyses,[39,115-121] and one cost-effectiveness analysis[122]) that met our eligibility criteria. These studies assessed the health, cost, and economic impact of supplemental modalities as adjuncts to mammography for breast cancer screening in people with dense breasts compared to mammography alone (Appendix 8). However, no study was directly applicable to the research question given that all studies were conducted in non-Canadian settings with varied cost-effectiveness thresholds; differed according to population characteristics (e.g., age eligible for screening, breast cancer risk and breast density) and expected changes in breast density over time; captured biennial screening frequency, which would not be applicable to those with extremely dense breasts; and aimed to evaluate only one[39,115-117,119-121] or two[118,122] supplemental modalities. No study evaluated contrast-enhanced mammography.

The cost-effectiveness of supplemental screening as an adjunct to mammography was dependent on population characteristics (i.e., dense breast population, eligibility age of the screening cohort, breast cancer risks), the type of modality assessed, and the screening frequency.

Conclusions were conflicting as to the cost-effectiveness of MRI as a supplemental modality as an adjunct to mammography, as evaluated by four studies (Appendix 8). Three cost–utility analyses[116,117,118] found that biennial supplemental screening with MRI as an adjunct to mammography in people with extremely dense breasts was cost-effective compared to mammography alone. However, one cost–utility analysis[115] found that supplemental screening with MRI was not cost-effective at a commonly accepted WTP value of $100,000 USD/QALY. Two cost–utility analyses[39,119] found that compared to mammography alone, biennial supplemental screening with ultrasound as an adjunct to mammography was not cost-effective (at commonly accepted WTP values of £20,000 GBP/QALY and $100,000 USD/QALY, respectively) in people with extremely dense breasts, and in people with heterogeneously and extremely dense breasts. One cost-effectiveness analysis[122] that evaluated biennial supplemental screening with ultrasound found improved screening and patient-important outcomes but increased health care costs for both ultrasound and MRI in people with heterogeneously and extremely dense breasts (1-year time horizon). Finally, three cost–utility analyses[118,120,121] found that supplemental screening with DBT as an adjunct to mammography was cost-effective compared to mammography alone in women with heterogeneously and extremely dense breasts.

All studies evaluated eligible women for breast cancer screening; they did not provide information on the characteristics of the study population (e.g., the inclusion of trans people). As discussed in the Background of this health technology assessment, male breast cancer accounts for less than 1% of all breast cancers and, organized breast screening for men is not warranted or offered in Canada.[2,29] Limited evidence is available to inform the risk of breast cancer for transgender people, but the Ontario Health guidelines for the Ontario Breast Screening Program recommend breast screening for trans women and nonbinary people who meet program criteria and have a history of 5 or more consecutive years of cross-sex hormone use.[31-33] In addition, equity considerations relating to ethnicity and disparities in breast screening (e.g., immigrant women,[78] Black Canadian women,[79] people of lower socioeconomic status,[80] and Indigenous people[81] are reported to be under-screened) were not reported in the identified studies.

Conclusions

Our economic evidence review found nine studies that evaluated the cost–utility[39,115-121] and cost-effectiveness[122] of supplemental screening (MRI, ultrasound, and DBT) as an adjunct to mammography in people with dense breasts in the United States and Europe. The studies varied in scope (population, intervention, and comparator), and had conflicting results about the cost-effectiveness of supplemental modalities. We found no published economic studies on contrast-enhanced mammography. It remained uncertain whether supplemental screening as an adjunct to mammography is cost-effective compared to mammography alone for people with dense breasts in the Ontario or Canadian setting.

Primary Economic Evaluation

The published economic evaluations identified in the economic literature review assessed supplemental screening with ultrasound, magnetic resonance imaging (MRI) or digital breast tomosynthesis (DBT), but none took a Canadian or Ontario perspective or was applicable to our research question. Owing to these limitations, we conducted a primary economic evaluation to assess the cost-effectiveness of supplemental screening with ultrasound, MRI, or DBT as an adjunct to mammography. We did not conduct an evaluation of supplemental screening with contrast-enhanced mammography because no clinical evidence is available to date.

Research Question

What is the cost-effectiveness of supplemental screening with ultrasound, MRI, or DBT as an adjunct to mammography compared to mammography alone for breast cancer screening in people with dense breasts from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[131] The content of this report is based on a previously developed economic project plan dated May 10, 2022.

Type of Analysis

We conducted a cost–utility analysis, because it is the recommended reference case approach in the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluation.[132] Health outcomes are expressed in quality-adjusted life-years (QALYs), which consider both the length and quality of life (e.g., 1 QALY is equal to 1 year of life in perfect health).[133] The use of a generic outcome such as the QALY allows decision-makers to make comparisons across different conditions and interventions.

We also estimated clinically relevant outcomes, including the following:

- Life-years
- Number of breast cancer deaths
- Number of screen-detected cancers
- Number of interval cancers (i.e., cancers detected during the interval after a normal screening episode [includes screening and assessment, if required] and before the next screening interval)
- Number of false-positive results

Target Population

Our target population was asymptomatic people aged 50 to 74 years with dense breasts and no high-risk factors for breast cancer.

BREAST DENSITY

We estimated the cost-effectiveness of supplemental screening as an adjunct to mammography for people with dense breasts, which included both heterogeneously dense breasts and extremely dense breasts (categories C and D from the American College of Radiology [ACR] Breast Imaging Reporting and Data System [BI-RADS] atlas, 5th edition; categories are based on the effect of masking by dense breast tissue).[10] We also estimated the cost-effectiveness of supplemental screening as an adjunct to mammography for people with extremely dense breasts (BI-RADS D).

SCREEN-ELIGIBLE POPULATION AT AVERAGE RISK: ONTARIO BREAST SCREENING PROGRAM

Although the clinical evidence review included people aged 40 years or older in the target population, we followed the Ontario Breast Screening Program (OBSP) recommendations for screening people at average risk, including people aged 50 to 74 years as eligible for breast cancer screening.[134] We did not include people aged 40 to 49 years, because people in this age group are not eligible for average-risk breast screening through the OBSP. A study by Sprague et al[39] identified in the economic evidence showed that annual screening of people 40 to 74 years old with mammography and supplemental ultrasound resulted in high ICERs: $553,000 USD/QALY for people with extremely dense breasts and $728,000 USD/QALY for people with dense breasts (both heterogeneously and extremely dense breasts). In 2018, the Canadian Task Force on Preventative Health Care recommended that women aged 40 to 49 years should not be screened, based on low certainty of the evidence for benefits and harms from breast cancer screening and variability in patient preferences.[59] We also did not include people with high-risk factors, including the following: known carrier of high-risk genetic mutations (e.g., *BRCA1, BRCA2*); a family history of high-risk genetic mutations; a personal or family history of breast cancer; a history of chest irradiation; or personal lifetime risk of breast cancer of 25% or higher (based on IBIS, CanRisk, or a similar tool). It is recommended that these people follow the OBSP high-risk screening pathway.[53,134] As part of our target population, people screened in the average-risk screening program and found to have high breast density (e.g., ≥ 75% dense breast tissue) at the time of mammography may be at increased risk (i.e., higher-than-average risk).[7,8,12]

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

We conducted evaluations for supplemental screening with ultrasound, MRI, or DBT as an adjunct to mammography, compared to mammography alone. We assumed that screening with mammography and a supplemental modality would be conducted in the same screening interval. Table 28 summarizes the interventions evaluated in the economic model. We did not conduct a primary economic evaluation of supplemental screening with contrast-enhanced mammography because no clinical evidence is available to date.

Table 28: Disease Interventions and Comparators Evaluated in the Primary Economic Model

Interventions[a]	Comparator[a]	Population	Outcomes
Mammography screening with supplemental ultrasound[b] Mammography screening with supplemental MRI Mammography screening with supplemental DBT	Mammography alone	Individuals aged 50–74 y with dense breasts: heterogeneously dense (BI-RADS C) or extremely dense (BI-RADS D) Individuals aged 50–74 y with extremely dense breasts (BI-RADS D)	Clinical outcomes (number): screen-detected cancers, interval cancers, false-positive results, breast cancer–related deaths, life-years, and QALYS Direct health care costs: total and disaggregated costs (e.g., screening, diagnostic imaging and assessment, and breast cancer management)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.
[a] Screening (intervention and comparator) was conducted every year for people notified to have extremely dense breasts (BI-RADS D) and every 2 years for people notified to have heterogeneously dense breasts (BI-RADS C).
[b] Handheld ultrasound was assumed for the reference case; automated breast ultrasound (ABUS) was used in a scenario analysis.

FREQUENCY OF SUPPLEMENTAL SCREENING

The economic evidence showed that the frequency of breast screening varied in the literature: screening every 2 years in most studies,[39,115-117,120-122] or every 3 years in one study.[119] The OBSP guidelines recommend that people be recalled in 1 year if they are notified that they have 75% or more dense breast tissue at the time of mammography screening; people with less than 75% dense breast tissue are recalled in 2 years.[51-53,134] Therefore, our reference case analysis evaluated annual (every year) screening for people with extremely dense breasts (BI-RADS D), and biennial (every 2 years) screening for people with heterogeneously dense breasts (BI-RADS C). However, there may be overlap between the definition of dense breasts classified by the OBSP recommendations and the BI-RADS categories. For example, people with heterogeneously dense breasts (BI-RADS C) may be categorized as having ≥ 75% or more dense breast tissue based on the OBSP classification and would be recalled annually.

Time Horizon and Discounting

We used a lifetime horizon in our reference case analysis to capture the long-term impact of supplemental screening on clinical outcomes (e.g., breast cancer–related deaths, life-years, and QALYs) and health care costs. In accordance with the CADTH guidelines,[132] we applied an annual discount rate of 1.5% to costs and QALYs incurred after the first year.

Model Structure

We used the OncoSim-Breast microsimulation model (version 3.5.0.90) to estimate the cost-effectiveness of supplemental screening for each modality. The OncoSim-Breast model is a web-based deterministic microsimulation model of breast cancer led and supported by the Canadian Partnership Against Cancer and developed by Statistics Canada.[135-137] The development, application, and validation of the OncoSim-Breast model have been extensively described by Yong et al.[136] Microsimulation modelling allows for individual-level simulation to capture heterogeneity in population health and demographic history over time, including age, breast density, breast cancer risk, and mortality.

Using a large representative sample of the Ontario population, the model simulates the natural history and progression of breast cancer, as well as competing-cause mortality. It captures screening, diagnostic, and clinical treatment pathways based on current knowledge and evidence-based practice for breast

cancer in the Ontario setting. The OncoSim model captures health states, including the absence of breast cancer; stage-specific breast cancer DCIS, stages I to IV) accounting for varied treatment phases; and death. The model simulates the natural history of tumour onset (oncogenesis), the growth and spread of cancer, and DCIS and invasive cancers as previously described by Yong et al[136] and summarized in Appendix 9 Table A17.

Cancer detection (e.g., clinical or screen) depends on tumour size and spread. The probability of detecting breast cancer clinically (i.e., presentation of signs or symptoms) varies by tumour size and time. Breast cancer stage at detection is classified using the American Joint Committee on Cancer system of tumour size, nodal status, and metastasis and is generated by the model using the natural history component and age. Once the cancer is detected, the model simulates disease progression (recurrence and breast cancer death) based on stage, tumour biology, age at diagnosis, and whether the cancer was detected clinically or by screening.

The OncoSim-Breast model incorporates a screening program that includes different screening modalities and allows for the detection of early tumours that would not otherwise be detected clinically; this may lead to a stage shift and result in a survival benefit. The probability of screen detection for a given modality (e.g., mammography, mammography plus a supplemental modality), as well as diagnostic accuracy (sensitivity and specificity), is based on tumour size, the age of the person, and screen sequence.

The OncoSim-Breast model includes survival models that simulate survival from time of screen detection to breast cancer death using observed data from British Columbia. The model estimates breast cancer costs based on three phases of care (first 18 months after diagnosis, continuing care, and terminal care) and projects lifetime stage-specific breast cancer costs (Appendix 9, Table A18). Costs for the first 18 months after diagnosis are specific to breast cancer treatment (i.e., surgery, radiation, chemotherapy, hormonal treatments, imaging tests, and oncology and physician fees) which varies by stage, age at diagnosis, molecular subtype, and grade. Stage II, III, and IV breast cancers are estimated to have higher costs than stage 0 and I breast cancers. Similarly, the model estimates that continuing care costs vary by age, stage, molecular subtype, grade, and time after diagnosis.

The model estimates QALYs by multiplying the time an individual is occupying a health state by the utility that reflects the health-related quality of life in that health state and aggregated over the various health states for a lifetime horizon. The OncoSim model also captures breast cancer–specific utilities by stage and treatment phase. It combines relevant input parameters to estimate population-level outcomes such as breast cancer incidence, mortality, screening outcomes, life-years, QALYs, and lifetime health care costs (screening, follow-up imaging and diagnostic assessment, and cancer management).

In collaboration with the Canadian Partnership Against Cancer–OncoSim team and Statistics Canada, we adapted the OncoSim-Breast model by modifying the following components:

- Ontario screening participation rate using administrative data from the Ontario Cancer Screening Performance Report 2020[138] and the 2021 Cancer System Quality Index (CSQI) Report 2021[139]
- Developed additional screening scenarios for each supplemental modality (ultrasound, MRI, and DBT)
- Applied a relative risk of developing breast cancer for people with extremely dense breasts (BI-RADS D) and heterogeneously dense breasts (BI-RADS C) using the overall baseline tumour incidence rates populated in the OncoSim model

- Modified screening frequency to capture annual screening for people with extremely dense breasts (BI-RADS D) and biennial screening for people with heterogeneously dense breasts (BI-RADS C)[51-53,134]
- Modified sensitivity and specificity input parameters of mammography alone and mammography plus supplemental modality for people with dense breasts
- Modified costs related to screening with mammography, mammography plus a supplemental screening modality, and diagnostic assessment, using Ontario-specific costs whenever possible

Main Assumptions

The model's main assumptions were as follows:

- Supplemental screening would be conducted after mammography screening and before the next screening interval. We assumed that all people screened with mammography underwent supplemental screening (i.e., no loss to follow-up after mammography screening)
- Given that limited studies were available investigating annual breast screening frequency, we assumed that the sensitivity and specificity of mammography and supplemental modalities for annual screening for people with extremely dense breasts (BI-RADS D) were the same as those for biennial screening derived from the clinical evidence review
- Supplemental screening with ultrasound would be conducted using handheld ultrasound in the reference case analysis, because handheld ultrasound is in predominant use in Ontario (Samantha Fienberg, MD. email communication, September 16, 2022; Derek Muradali, MD, email communication, October 11, 2022). We conducted a scenario analysis using automated breast ultrasound (ABUS) as a supplemental modality
- Limited clinical evidence was available for the sensitivity and specificity of supplemental screening with ultrasound as an adjunct to mammography stratified by breast density. We assumed the same sensitivity and specificity for people with heterogeneously dense breasts (BI-RADS C) and extremely dense breasts (BI-RADS D). We conducted sensitivity analyses using the upper and lower bounds of the 95% confidence interval to assess this uncertainty
- False-negative cases would be identified in subsequent screens or detected clinically (i.e., presentation of symptoms)
- We did not consider adverse reactions from contrast media or radiation-induced outcomes from additional screening, given that these events are rare and limited information about estimated preference values and costs associated with these health states is available in the literature

Clinical Outcomes and Utility Parameters

We used input parameters related to demography, the natural history of tumour development and progression, screening, breast cancer costs, and quality of life as populated in the OncoSim-Breast model. Input parameters in the OncoSim-Breast model were obtained from Canadian data, whenever applicable, using the Canadian Cancer Registry, Canadian vital statistics, and Canadian Community Health Surveys (Yong et al, supplemental sections 2 to 4).[136,140,141] We modified several model input parameters related to the following:

- Breast cancer risk for people with dense breasts
- Screening participation rates (to match Ontario screening data)
- Annual screening frequency for people with extremely dense breasts (BI-RADS D)
- The sensitivity and specificity of mammography and mammography plus each supplemental screening modality for people with dense breasts (from the clinical evidence review)
- Screening costs for mammography and mammography plus each supplemental screening modality (including potential program costs estimated from the OBSP)
- Further imaging and diagnostic assessment for positive screen results (includes false- and true-positive screens)

DEMOGRAPHICS AND BREAST DENSITY

The OncoSim-Breast model simulates the Canadian population from 1872 to 2051 according to observed and projected demographic data. We selected Ontario as the province of interest to simulate a cohort that represented the age and sex distributions and all-cause mortality of the Ontario population using data from Statistics Canada.[141] We restricted the simulated cohort to people born between 1949 and 1973 (aged 50 to 74 years old in 2023). Given that breast density may change over time, we followed approximately 2,504,360 individuals eligible for breast screening (BI-RADS A to D) throughout their lifetime.

We used a distribution of breast density based on the BI-RADS density classification system (5th edition) and stratified by age group in the OncoSim-Breast model (Table 29).[142] Supplemental screening was applied only to people with dense breasts; the remaining screen-eligible population (i.e., those without dense breasts) received biennial mammography as per current standard practice in Ontario. We estimated the distribution of breast density by age from a weighted average of two data sets from Canada and the United States.[142,143] We obtained the Canadian data from a study that evaluated the distribution of BI-RADS breast density categories for average-risk women aged 40 to 74 years, reported by the British Columbia Cancer Breast Screening Program.[142] We obtained the United States data from the Breast Cancer Surveillance Consortium and the National Health and Nutrition Examination Survey, which included women aged 40 years and older who obtained a mammogram at a Breast Cancer Surveillance Consortium facility from 2007 to 2010.[143]

Table 29: Distribution of Breast Density by Age Used in the OncoSim-Breast Model

BI-RADS breast composition category by age group	People screened, %[a]
BI-RADS A (almost entirely fatty)	
50–59 y	14.2
60–69 y	22.3
≥ 70 y	26.2
BI-RADS B (scattered areas of fibroglandular density)	
50–59 y	36.4
60–69 y	42.9
≥ 70 y	49.0
BI-RADS C (heterogeneously dense breasts)	
50–59 y	39.5
60–69 y	29.4
≥ 70 y	23.6
BI-RADS D (extremely dense breasts)	
50–59 y	9.9
60–69 y	5.4
≥ 70 y	4.2

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System.

Distribution of breast density, based on the BI-RADS density classification system (5th edition), by age group used in the OncoSim-Breast model. Breast density distribution by age outlined in this table was estimated from a weighted average of two data sets of Canadian and United States populations. The Canadian data were obtained from a study that evaluated the distribution of BI-RADS breast density categories for average-risk women, ages 40 to 74 years, reported by the British Columbia Breast Cancer Screening Program.[142] The distribution of breast density by age in the United States data was obtained from the Breast Cancer Surveillance Consortium and National Health and Nutrition Examination Survey, which included women 40 years and older who obtained a mammogram at a Breast Cancer Surveillance Consortium facility from 2007 to 2010.[143]

[a] Percentages do not equal 100 in each BI-RADS category because the remaining people screened were less than age 50 y (i.e., BI-RADS A 8.6%, BI-RADS B 27.7%, BI-RADS C 46.3% and BI-RADS D 17.4%).

NATURAL HISTORY

We calibrated natural history—as well as cancer detection, staging, and tumour biology model inputs—from the University of Wisconsin Breast Cancer Epidemiology Simulation Model (Wisconsin Breast model)[144] to match the incidence of cancer by age group and year in the National Cancer Incidence Reporting System, Canadian Cancer Registry, and Canadian Cancer Screening Database. We estimated disease progression (recurrence and breast cancer deaths) using data from the British Columbia Cancer Agency, where province-specific relative risks were estimated from the Canadian Cancer Registry and applied to capture provincial differences in stage-specific survival.

To capture the increased risk of breast cancer in people with dense breasts, we applied a relative risk (RR) of developing breast cancer for people with heterogeneously dense breasts (RR 1.62 [95% confidence interval (CI) 1.51–1.75]; reference group, scattered areas of fibroglandular density) and extremely dense breasts (RR 2.04 [95% CI 1.84–2.26]; reference group, scattered areas of fibroglandular density) to the

overall baseline tumour incidence rates populated in the OncoSim model.[145,146] We conducted sensitivity analyses of the RR of developing breast cancer for people with heterogeneously dense breasts and extremely dense breasts using the upper and lower bounds of the 95% CIs.

SCREENING

To evaluate supplemental screening as an adjunct to mammography, we created screening strategies for each modality (ultrasound, MRI, or DBT) and applied each screening strategy to two scenarios: people with dense breasts (extremely dense breasts [BI-RADS D] and heterogeneously dense breasts [BI-RADS C]); and people with extremely dense breasts only. We modified the screening frequency, making it annual for people with extremely dense breasts to align with the OBSP recommendations for people with breast density of 75% or higher. The remaining simulated screen-eligible people (i.e., those without dense breasts) received biennial mammography as per the OBSP recommendations for people at average risk. Then, we modified screening participation and retention rates (64.81% screened through the OBSP) obtained from the CSQI 2020 Ontario Cancer System Performance report.[139]

Using findings from the clinical evidence review, we applied sensitivity and specificity parameters for mammography alone, and for mammography plus supplemental screening for people with dense breasts (Clinical Evidence Review, Tables 6, 16, and 20). These sensitivity and specificity parameters were diagnostic accuracy estimates based on biennial screening; for people with extremely dense breasts who received annual screening, we assumed the same sensitivity and specificity estimates as for biennial screening. A retrospective cohort study by Chiarelli et al[147] evaluating the diagnostic accuracy of mammography of annual and biennial screening found no significant difference in the sensitivity of annual screening compared to biennial screening for people with extremely dense breasts or a mammographic density of 75% or greater. However, the study did find that specificity was lower for annual screening versus biennial screening for people with extremely dense breasts. We conducted a scenario analysis to assess the decrease in specificity of annual mammography screening for people with extremely dense breasts.

For supplemental screening with MRI and DBT, studies included screening participants who had negative mammography results and reported sensitivity and specificity estimates for the supplemental modality alone.[41,92,106] Therefore, we combined the sensitivity and specificity estimates for digital mammography for people with dense breasts derived from Wanders et al[23] with the sensitivity and specificity estimates for supplemental MRI and DBT (Table 30). For supplemental screening with ultrasound, we obtained combined sensitivity and specificity estimates for mammography and supplemental ultrasound and compared those to the sensitivity and specificity estimates for mammography alone reported in the same study (Table 31). However, information in the literature was limited about the sensitivity and specificity of ultrasound stratified by breast density category. Therefore, we assumed the same sensitivity and specificity for people with heterogeneously dense breasts (BI-RADS C) and extremely dense breasts (BI-RADS D). In the reference case analysis, we evaluated supplemental screening with handheld ultrasound and assessed ABUS in a scenario analysis.

The diagnostic sensitivity and specificity parameters populated in the OncoSim-Breast model varied by screen sequence, age group, tumour size, and type of screening modality. We applied a calibrated multiplicative odd factor for each modality using the sensitivity and specificity estimates in the clinical studies (Appendix 9, Figures A1 and A2).

Table 30: Sensitivity and Specificity of Supplemental Screening With MRI and DBT Used in the OncoSim-Breast Model

Modality	Parameter	Value, % (95% CI)	Combined value, %[a]	Source
Mammography alone (comparator for MRI and DBT)	Sensitivity			
	BI-RADS C	69.5 (64.0–74.4)	–	Wanders et al, 2017[23]
	BI-RADS D	61.0 (51.2–70.0)	–	
	Specificity			
	BI-RADS C	98.8 (98.0–98.3)	–	Wanders et al, 2017[23]
	BI-RADS D	97.6 (97.2–97.9)	–	
Supplemental screening with MRI[b]	Sensitivity			
	BI-RADS C	100 (75.5–100)	100	Chen et al, 2017[41]
	BI-RADS D	95.2 (88.1–98.7)	98.1	Bakker et al, 2019[106]
	Specificity			
	BI-RADS C	94.6 (92.0–96.4)	93	Chen et al, 2017[41]
	BI-RADS D	92 (NC)	90	Bakker et al, 2019[106]
Supplemental screening with DBT[b]	Sensitivity			
	BI-RADS C	51.7 (32.9–70.1)	85.3	Tagliafico et al, 2018[92]
	BI-RADS D	51.7 (32.9–70.1)	81.2	
	Specificity			
	BI-RADS C	99.7 (99.5–99.8)	98.5	Tagliafico et al, 2018[92]
	BI-RADS D	99.7 (99.5–99.8)	97.3	

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging; NC, not calculated (insufficient data).

[a] Estimated combined sensitivity and specificity for digital mammography and supplemental screening using the following equations:

- Combined sensitivity = SensitivitytestA + SensitivitytestB − (SensitivitytestA × SensitivitytestB)
- Combined specificity = SpecificitytestA × SpecificitytestB

[b] Study population included screening participants who had a previous negative mammography result.

Table 31: Sensitivity and Specificity of Supplemental Screening With Ultrasound Used in the OncoSim-Breast Model

Modality	Parameter	Value, % (95% CI)	Source
Mammography alone (comparator to handheld ultrasound)	Sensitivity		Harada-Shoji et al, 2021[93]
	BI-RADS C and D	70.6 (55.3–85.9)	
	Specificity		
	BI-RADS C and D	91.7 (91.0–92.4)	
Mammography plus handheld ultrasound	Sensitivity		Harada-Shoji et al, 2021[93]
	BI-RADS C and D	93.2 (85.7–100)	
	Specificity		
	BI-RADS C and D	85.4 (84.5–86.3)	
Mammography alone (comparator to ABUS)	Sensitivity		Wilczek et al, 2016[110]
	BI-RADS C and D	63.6 (33.3–90.9)	
	Specificity		
	BI-RADS C and D	99.0 (98.5–99.4)	
Mammography plus ABUS	Sensitivity		Wilczek et al, 2016[110]
	BI-RADS C and D	100 (NR)	
	Specificity		
	BI-RADS C and D	98.4 (97.8–98.9)	

Abbreviations: ABUS, automated breast ultrasound; BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; NR, not reported.

HEALTH STATE UTILITIES

A health state utility represents a person's preference for a certain health state or outcome, such as stage-specific breast cancer or terminal care. Utilities are often measured on a scale of 0 (death) to 1 (full health). We used health state utilities populated in the OncoSim-Breast model (Table 32).[136] For people with no breast cancer, the model used age-specific utility scores for the Canadian general population obtained from the 2013/14 Canadian Community Health Survey and measured by the Health Utilities Index Mark 3 (HUI3).[148]

For people diagnosed with breast cancer, the model applies a utility score specific to the breast cancer stage (accounting for the probability and duration of a treatment phase) and an age-specific utility score for the Canadian general population. We obtained the breast cancer utility scores from a study that elicited utility scores for each health state using the Classification and Measurement System of Functional Health tool.[149] The tool includes 11 health status attributes adapted from the HUI3,[150] the Medical Outcomes Study Short-Form 36 (SF-36),[151] and EQ-5D, a health-related quality-of-life instrument from EuroQol.[152,153] The OncoSim-Breast model uses a multiplicative approach to estimate utility scores for combined or joint health states.[132,154] For example, for an individual diagnosed with stage IV cancer and receiving chemotherapy, the health state utility is the product of the utility score for metastatic cancer and the utility score for chemotherapy of moderate toxicity.

Table 32: Utilities Used in the OncoSim-Breast Model

Health state or treatment state	Utility	Source
No breast cancer diagnosis (age-specific)	0.616–1	2013/14 Canadian Community Health Survey report, 2018[148]
Stage I-III breast cancer		Prepopulated utilities in the OncoSim-Breast model; Yong et al, 2022,[136] Boswell-Purdy et al, 2007[155] McIntosh et al, 2007[149]
Diagnosis	0.891	
Surgery and immediate follow-up	0.652	
Radiotherapy	0.696	
Chemotherapy	0.661	
Anti-HER2 treatment	0.668	
Hormonal therapy	0.798	
No active treatment	0.906	
Stage IV breast cancer		
Diagnosis	0.439	
Surgery and immediate follow-up	0.321	
Radiotherapy	0.343	
Chemotherapy	0.326	
Anti-HER2 treatment	0.329	
No active treatment	0.484	
Terminal care	0.179	

Abbreviation: HER2, human epidermal growth factor receptor 2.

Cost Parameters

The screening and diagnostic follow-up cost components that we captured in the OncoSim-Breast model are summarized in Table 33. We obtained screening costs for mammography, ultrasound, and MRI (including technical and professional components for performing breast screening), from the Ontario Health Insurance Plan (OHIP) Schedule of Benefits and Fees.[54] For supplemental screening with DBT, we obtained screening costs from the Alberta Health Care Insurance Plan (AHCIP) Schedule of Medical Benefits, which provides an additional cost modifier for supplemental DBT screening. We estimated the costs for supplemental screening with ultrasound, MRI, and DBT from diagnostic fee codes, because no fee codes have been established in the OHIP and AHCIP schedules for breast cancer screening. To estimate potential additional screening costs for each supplemental modality offered through an organized screening program such as the OBSP, we included an OBSP site fee and a program cost obtained from Ontario Health (OBSP) Program Delivery, Operations (email communication, March 24, 2022). We modified the follow-up cost of an abnormal mammography screen obtained from a study estimating the health system resources and costs associated with breast cancer screening in Ontario using provincial administrative databases.[156]

We used health care costs associated with breast cancer in the OncoSim-Breast model (Appendix 9, Breast Cancer Cost Parameters), including breast cancer surgery, radiation treatment, chemotherapy, imaging and oncology physician fees, acute hospitalizations, emergency department visits, home care, long-term care, and continuing care obtained from Ontario costing administrative data.[136] We estimated

all costs in 2022 Canadian dollars; any costs reported prior to 2022 were converted to 2022 Canadian dollars using the Consumer Price Index.[157]

Table 33: Screening and Diagnostic Follow-up Costs Used in the OncoSim-Breast Model

Variable	Unit cost, $[a]	Reference
OBSP site fee and program cost	35.39	Ontario Health (OBSP) Program Delivery, Operations
Mammography		OHIP Schedule of Benefits (code X178), 2021[54]
Technical	37.15	
Professional	27.00	
Ultrasound		OHIP Schedule of Benefits (code J127), 2021[54]
Technical	23.70	
Professional	13.10	
Total cost, including mammography and OBSP site fee and program cost	136.34	
MRI[b]	179.40	OHIP Schedule of Benefits, 2021[54]
Total cost, including mammography and OBSP site fee and program cost	278.94	
Digital breast tomosynthesis	43.99	AHCIP Schedule of Medical Benefits (code TOMO)[158]
Total cost, including mammography and OBSP site fee and program cost	143.54	
Follow-up assessment for abnormal screen (i.e., true- and false-positive results)[c]	252.00	Mittmann et al, 2021[156]

Abbreviations: AHCIP, Alberta Health Care Insurance Plan; MRI, magnetic resonance imaging; OHIP, Ontario Health Insurance Plan; OBSP, Ontario Breast Screening Program.

[a] Unit costs are in 2022 Canadian dollars.

[b] MRI cost components obtained from a clinical expert input include multi-slide sequence (code X446, $73.35), gadolinium contrast (code X487, $36.65), 3-dimensional MRI, including postprocessing (code X499, $32.70), and 3-repeat sequences (code X447, $36.70; Samantha Fienberg, MD, email communication, December 21, 2022).

[c] Costs related to follow-up assessment for abnormal screen, both true- and false-positive results, included the cost of diagnostic procedures based on the distribution of people receiving imaging alone (mammogram, ultrasound, computed tomography/MRI) or imaging with biopsy, and other costs associated with OBSP, overhead, and genetic testing.

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included checking for errors, checking the accuracy of parameter inputs that were varied during the adaptation of the model, and checking results.

The OncoSim model has also been extensively validated by the model developers by[136]:

- Comparison of the projected incidence and stage distribution of breast cancer in Canada with observed data from the Canadian Cancer Registry (1992–2017)[140]
- Comparison of projected breast cancer mortality in 2018 with the latest breast cancer mortality reported in Canadian vital statistics

- Analysis of the screening strategies of the UK Age trial[159,160] using the OncoSim model to compare the model's projected impact of breast cancer screening on incidence and mortality with the observed effects in the trial. The UK Age trial has been used by other established breast cancer simulation models to validate their model projections against the trial results[161]

Analysis

Our reference case and sensitivity analyses adhered to the CADTH guidelines[132] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions.

We estimated the reference case of this analysis deterministically and simulated the number of screen-eligible people in Ontario, one at a time, to capture demographic and individual characteristics (e.g., age, breast density). For each scenario (by supplemental modality and breast density), the model was simulated with 12 subvalues (i.e., subsamples), and estimated the lifetime mean costs and QALYs across 12 deterministic subanalyses. We calculated the incremental costs, incremental QALYs, and ICERs for mammography plus supplemental screening compared to mammography alone.

The OncoSim-Breast model does not have the computing capability to run the model simulation probabilistically. We did not consider probabilistic distributions (parameter uncertainty intervals) for the model input parameters, given the deterministic nature of the OncoSim-Breast model. The deterministic model calculated point estimates (e.g., ICERs) using one set of input parameters and varied them individually to assess parameter uncertainty (deterministic sensitivity analyses).

ONE-WAY SENSITIVITY ANALYSES

We conducted one-way sensitivity analyses by varying specific model variables and examining the impact on the results. Table 34 presents the variables and ranges used. We used tornado diagrams to present the results.

Table 34: Variables Varied in One-Way Sensitivity Analyses

Parameter	Reference case[a]	Range (95% CI)[a]
Relative risk of breast cancer for people with heterogeneously dense breasts (BI-RADS C) compared to people with scattered areas of fibroglandular density (BI-RADS B)	1.62	1.51–1.75
Relative risk of breast cancer for people with extremely dense breasts (BI-RADS D) compared to people with scattered areas of fibroglandular density (BI-RADS B)	2.04	1.84–2.26
Screening participation and retention rate	64.8%	58.3%–71.3% (± 10% of reference case value)
Sensitivity for mammography alone (comparator for MRI and DBT)	BI-RADS C: 69.5% BI-RADS D: 61.0%	BI-RADS C: 64.0%–74.4% BI-RADS D: 51.2%–70.0%
Sensitivity for supplemental screening with MRI as an adjunct to mammography	BI-RADS C: 100.0% BI-RADS D: 95.2%	BI-RADS C: 75.5%–100.0% BI-RADS D: 88.1–98.7%
Sensitivity for supplemental screening with DBT as an adjunct to mammography	BI-RADS C and D: 51.7%	BI-RADS C and D: 32.9%–70.1%
Sensitivity for mammography alone (comparator for handheld ultrasound)	BI-RADS C and D: 70.6%	BI-RADS C and D: 55.3%–85.9%
Sensitivity for supplemental screening with handheld ultrasound as an adjunct to mammography	BI-RADS C and D: 93.2%	BI-RADS C and D: 85.7%–100.0%
Cost of ultrasound screening, including mammography and OBSP program costs	$136.34	$127.14–$145.54 (± 25% reference case value)
Cost of MRI screening, including mammography and OBSP program costs	$278.94	$234.09–$323.79 (± 25% reference case value)
Cost of DBT screening, including mammography and OBSP program costs	$143.53	$132.54–$154.53 (± 25% reference case value)
Cost of follow-up assessment for abnormal screen (i.e., false-positive and true-positive results)	$252.00	$189–$315 (± 25% reference case value)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging; OBSP, Ontario Breast Screening Program.

[a] Unit costs are in 2022 Canadian dollars.

SCENARIO ANALYSES

We conducted scenario analyses to evaluate the impact of using automated breast ultrasound as the modality for supplemental screening compared to handheld ultrasound in the reference case analysis; the specificity of mammography screening alone as a comparator for MRI and DBT; and increased treatment costs for stage III and IV breast cancers (Table 35).

Table 35: Variables Varied in Scenario Analyses

Parameter	Reference case	Scenario analysis
Intervention strategy	Supplemental screening with handheld ultrasound	Supplemental screening with ABUS[a]
	Sensitivity, BI-RADS C and D: 93.2% (85.7%–100%)	Sensitivity, BI-RADS C and D: 100% (NR)
	Specificity, BI-RADS C and D: 85.4% (84.5%–86.3%)	Specificity, BI-RADS C and D: 98.4% (97.8%–98.9%)
	Total screening costs: $136.34	Total screening costs: $284.15
Comparator strategy	Mammography screening alone (comparator for MRI and DBT)	Mammography screening alone (comparator for MRI and DBT)
	Specificity, BI-RADS C: 98.8%	Specificity, BI-RADS C and D: 88%[b]
	Specificity, BI-RADS D: 97.6%	
Treatment costs	Treatment costs for stage III and IV breast cancers using the populated costs from the OncoSim-Breast model[c]	Doubled treatment costs (100% increase) for stage III and IV cancers

Abbreviations: ABUS, automated breast ultrasound; BI-RADS, Breast Imaging Reporting and Data System; NR, not reported.
[a] We obtained the sensitivity and specificity of mammography plus supplemental screening with ABUS from Wilczek et al.[110] The total screening cost for ABUS included mammography costs ($64.15) and the estimated cost of ABUS screening ($220.00) obtained from the Toronto Centre for Medical Imaging.[162] We assumed that the cost of ABUS screening to be funded by the public payer would be the same cost indicated by the Toronto Centre for Medical Imaging, which is currently reimbursed through a private insurance company benefits plan.
[b] Source: Lee et al.[121]
[c] Appendix 9, Breast Cancer Cost Parameters.

Results

Reference Case Analysis

SUPPLEMENTAL SCREENING WITH HANDHELD ULTRASOUND AS AN ADJUNCT TO MAMMOGRAPHY

Results of the reference case analysis for supplemental screening with ultrasound as an adjunct to mammography are summarized in Table 36 for people with dense breasts (heterogeneously and extremely dense breasts) and Table 37 for people with extremely dense breasts.

Without supplemental screening, the model generated an expected total number of 102,577 screen-detected cancers out of 2,504,360 simulated people aged 50 to 74 years who were eligible for screening in Ontario over a lifetime horizon (Table 36). With supplemental screening using ultrasound as an adjunct to mammography in people with dense breasts (BI-RADS C and D), 111,865 screen-detected cancers were expected. We estimated that compared to mammography alone, supplemental screening with ultrasound led to an additional 9,288 screen-detected cancers, a reduction of interval breast cancers by 3,115 cases, and a reduction of breast cancer–related deaths by 867 cases.

Also compared to mammography alone, supplemental screening with ultrasound led to an increase in cases of stage 0 and I breast cancers, and a decrease in cases of stage II and III cancers (258 and 244 fewer, respectively), resulting in reductions in treatment costs for late-stage cancers of approximately $11 million and $14 million, respectively (Appendix 10, Table A19). However, it also increased the number of false-positive cases by 13,814. Supplemental screening with ultrasound decreased the cost of cancer management by approximately $19.8 million compared to mammography alone. However, it resulted in an increase in screening costs and costs related to diagnostic assessment for false-positive screens by an additional $223 million and $3.1 million, respectively.

Supplemental screening with ultrasound for people with dense breasts slightly increased life-years by an additional 0.004 years per person (1.5% discounted; 0.0063 undiscounted) and an additional 0.0007 QALYs per person (1.5% discounted). It increased total health care costs ($207 million, 1.5% discounted [$83 per person]), resulting in an ICER of $119,943/QALY gained compared to mammography alone.

Table 36: Reference Case Analysis—Cost-Effectiveness of Supplemental Screening With Handheld Ultrasound for People With Dense Breasts (Total Cohort)

Outcome[a]	Mammography alone	Supplemental screening with handheld ultrasound	Difference[b]
Clinical outcomes, total number			
Screen-detected cancers	102,577	111,865	9,288
Interval breast cancer within 1 y of previous screen	18,350	15,235	−3,115
False-positive cases	1,017,606	1,031,420	13,814
Breast cancer deaths	51,010	50,143	−867
Life-years,[c] 1.5% discounted (undiscounted) [per person (undiscounted)]	55,932,683 (70,478,047) [22.334 (28.142)]	55,942,672 (70,493,709) [22.338 (28.148)]	9,989 (15,662) [0.004 (0.006)]
QALYs, 1.5% discounted (per person)	42,263,280 (16.876)	42,265,010 (16.877)	1,730 (0.0007)
Cost outcomes, 1.5% discounted, $			
Total health care cost (per person)	8,433,906,319 (3,368)	8,641,407,682 (3,451)	207,501,363 (83)
Cost of screening	758,641,755	982,250,857	223,609,102
Cost of diagnostics for false-positive screen	156,450,201	159,517,911	3,067,710
Cost of diagnostics for true-positive screen	16,512,334	18,610,814	2,098,480
Cost of diagnostic clinical detection	30,541,037	29,041,138	−1,499,899
Cost of cancer management	7,471,760,993	7,451,986,963	−19,774,030
Cost-effectiveness[d]			
ICER, cost per QALY gained	–	–	119,943

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

[a] The OncoSim-Breast model simulated 2,504,360 people, aged 50 to 74 years, who were eligible for breast cancer screening in Ontario.

[b] Supplemental handheld ultrasound and mammography vs. mammography alone.

[c] Estimated life-years are additional life-years for people aged 50 to 74 years.

[d] Estimated by dividing the incremental total health care cost per person by the incremental QALYs or life-years per person (1.5% discounted).

We observed similar results for supplemental screening with ultrasound as an adjunct to mammography compared to mammography alone for people with extremely dense breasts (BI-RADS D only). The number of screen-detected cancers increased by an additional 1,826 cases, interval cancers decreased by 891 cases, and breast cancer–related deaths decreased by 226 cases (Table 37).

Compared to mammography alone, supplemental screening with ultrasound led to an increase in the number of stage 0 and I breast cancers, and a decrease in the number of stage II and III cancers (84 and

75 fewer, respectively), resulting in reductions in treatment costs for late-stage cancers of approximately $4 million and $175,095, respectively (Appendix 10, Table A19). However, it also increased the number of false-positive cases by 3,638, resulting in additional diagnostic costs of $0.81 million compared to mammography alone. Supplemental screening with ultrasound for people with extremely dense breasts resulted in a decrease of $7.3 million in total cancer management costs, but it also led to an additional $61.6 million in screening costs compared to mammography alone.

Supplemental screening with ultrasound for people with extremely dense breasts slightly increased life-years by an additional 0.00097 years per person (1.5% discounted; 0.0015 years undiscounted) and an additional 0.0003 QALYs per person (1.5% discounted). It increased total health care costs ($55.2 million for the total cohort [$22 per person]), resulting in an ICER of $83,529 per QALY gained compared to mammography alone.

Table 37: Reference Case Analysis—Cost-Effectiveness of Supplemental Screening With Handheld Ultrasound for People With Extremely Dense Breasts

Outcome[a]	Mammography alone	Supplemental screening with handheld ultrasound	Difference[b]
Clinical outcomes, total number			
Screen-detected cancers	102,577	104,403	1,826
Interval breast cancer within 1 y of previous screen	18,350	17,459	−891
False-positive cases	1,017,606	1,021,244	3,638
Breast cancer deaths	51,010	50,784	−226
Life-years,[c] 1.5% discounted (undiscounted) [per person (undiscounted)]	55,932,683 (70,478,047) [22.334 (28.142)]	55,935,106 (70,481,794) [22.335 (28.144)]	2,423 (3,747) [0.001 (0.002)]
QALYs, 1.5% discounted (per person)	42,263,280 (16.8759)	42,263,941 (16.8761)	661 (0.0003)
Cost outcomes, 1.5% discounted, $			
Total health care cost (per person)	8,433,906,319 (3,368)	8,489,119,057 (3,390)	55,212,738 (22)
Cost of screening	758,641,755	820,192,295	61,550,540
Cost of diagnostics for false-positive screen	156,450,201	157,258,110	807,909
Cost of diagnostics for true-positive screen	16,512,334	16,933,149	420,815
Cost of diagnostic clinical detection	30,541,037	30,249,345	−291,692
Cost of cancer management	7,471,760,993	7,464,486,159	−7,274,834
Cost-effectiveness[d]			
ICER, cost per QALY gained	–	–	83,529

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

[a] The OncoSim-Breast model simulated 2,504,360 people, aged 50 to 74 years, who were eligible for breast cancer screening in Ontario.

[b] Supplemental handheld ultrasound and mammography vs. mammography alone.

[c] Estimated life-years are additional life-years for people aged 50 to 74 years.

[d] Estimated by dividing the incremental total health care cost per person by the incremental QALYs or life-years per person (1.5% discounted).

SUPPLEMENTAL SCREENING WITH MRI AS AN ADJUNCT TO MAMMOGRAPHY

Results of the reference case analysis for supplemental screening with MRI as an adjunct to mammography are summarized in Table 38 for people with dense breasts (heterogeneously and extremely dense breasts) and Table 39 for people with extremely dense breasts.

Compared to mammography alone, supplemental screening with MRI as an adjunct to mammography for people with dense breasts led to an additional 16,070 screen-detected cancers, a reduction of interval breast cancers by 4,717 cases, and a reduction of breast cancer–related deaths by 1,556 cases (Table 38).

Also compared to mammography alone, supplemental screening with MRI led to an increase in cases of stage 0 and I breast cancers, and a decrease in cases of stage II and III cancers (798 and 412 fewer, respectively), resulting in reductions in treatment costs of approximately $34 million and $24 million, respectively (Appendix 10, Table A20). However, it also increased the number of false-positive cases by 11,105. Supplemental screening with MRI decreased the cost of cancer management by approximately $31.5 million compared to mammography alone. However, it resulted in an increase in screening costs and costs related to diagnostic assessment for false-positive screens by an additional $660 million and $2.5 million, respectively.

Supplemental screening with MRI for people with dense breasts slightly increased life-years by an additional 0.007 years per person (1.5% discounted; 0.01 undiscounted]) and an additional 0.0008 QALYs per person (1.5% discounted). It increased total health care costs ($632 million, 1.5% discounted [$252 per person]), resulting in a high ICER of $314,170 per QALY gained compared to mammography alone.

Table 38: Reference Case Analysis—Cost-Effectiveness of Supplemental Screening With MRI for People With Dense Breasts (Total Cohort)

Outcome[a]	Mammography alone	Supplemental screening with MRI	Difference[b]
Clinical outcomes, total number			
Screen-detected cancers	101,961	118,031	16,070
Interval breast cancer within 1 y of previous screen	18,660	13,943	–4,717
False-positive cases	1,006,089	1,017,194	11,105
Breast cancer deaths	51,056	49,500	–1,556
Life-years,[c] 1.5% discounted (undiscounted) [per person (undiscounted)]	55,932,017 (70,477,008) [22.334 (28.142)]	55,949,615 (70,504,416) [22.341 (28.153)]	17,598 (27,408) [0.007 (0.01)]
QALYs, 1.5% discounted (per person)	42,263,049 (16.8758)	42,265,060 (16.8766)	2,011 (0.0008)
Cost outcomes, 1.5% discounted, $			
Total health care cost (per person)	8,433,380,231 (3,367)	9,065,175,224 (3,620)	631,794,993 (252)
Cost of screening	758,217,323	1,417,882,325	659,665,002
Cost of diagnostics for false-positive screen	153,901,068	156,359,587	2,458,519
Cost of diagnostics for true-positive screen	16,375,404	20,057,813	3,682,409
Cost of diagnostic clinical detection	30,653,758	28,154,895	−2,498,863
Cost of cancer management	7,474,232,677	7,442,720,604	−31,512,073
Cost-effectiveness[d]			
ICER, cost per QALY gained	–	–	314,170

Abbreviations: ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-years.

[a] The OncoSim-Breast model simulated 2,504,360 people, aged 50 to 74 years, who were eligible for breast cancer screening in Ontario.

[b] Supplemental MRI and mammography vs. mammography alone.

[c] Estimated life-years are additional life-years for people aged 50 to 74 years.

[d] Estimated by dividing the incremental total health care cost per person by the incremental QALYs or life-years per person (1.5% discounted).

We observed similar results for supplemental screening with MRI as an adjunct to mammography compared to mammography alone for people with extremely dense breasts (BI-RADS D only). The number of screen-detected cancers increased by an additional 3,031 cases, interval cancers decreased by 1,535 cases, and breast cancer–related deaths decreased by 410 cases (Table 39).

Compared to mammography alone, supplemental screening with MRI led to an increase in the number of stage 0 and I breast cancers, and a decrease in the number of stage II and III cancers (205 and 114 fewer, respectively), resulting in reductions in treatment costs for late-stage cancers of approximately $8 million and $6 million, respectively (Appendix 10, Table A20). However, it also increased the number of false-positive cases by 3,893, resulting in additional diagnostic costs of $0.863 million compared to mammography alone. Supplemental screening with MRI for people with extremely dense breasts resulted in a decrease of $15 million in total cancer management costs, but it also led to an additional $182 million in screening costs compared to mammography alone.

Supplemental screening with MRI for people with extremely dense breasts slightly increased life-years by an additional 0.002 years per person (1.5% discounted; 0.003 years undiscounted) and an additional 0.0007 QALYs per person (1.5% discounted). It increased total health care costs ($168 million, 1.5% discounted [$67 per person]), resulting in an ICER of $101,813 per QALY gained compared to mammography alone.

Table 39: Reference Case Analysis—Cost-Effectiveness of Supplemental Screening With MRI for People With Extremely Dense Breasts

Outcome[a]	Mammography alone	Supplemental screening with MRI	Difference[b]
Clinical outcomes, total number			
Screen-detected cancers	101,961	104,992	3,031
Interval breast cancer within 1 y of previous screen	18,660	17,125	−1,535
False-positive cases	1,006,089	1,009,982	3,893
Breast cancer deaths	51,056	50,646	−410
Life-years,[c] 1.5% discounted (undiscounted) [per person (undiscounted)]	55,932,017 (70,477,008) [22.334 (28.142)]	55,936,990 (70,484,696) [22.336 (28.145)]	4,973 (7,688) [0.002 (0.003)]
QALYs, 1.5% discounted (per person)	42,263,049 (16.8758)	42,264,699 (16.8764)	1,650 (0.0007)
Cost outcomes, 1.5% discounted, $			
Total health care cost (per person)	8,433,380,231 (3,367)	8,601,371,371 (3,435)	167,991,140 (67)
Cost of screening	758,217,323	939,921,569	181,704,246
Cost of diagnostics for false-positive screen	153,901,068	154,763,908	862,840
Cost of diagnostics for true-positive screen	16,375,404	17,081,156	705,752
Cost of diagnostic clinical detection	30,653,758	30,158,516	−495,242
Cost of cancer management	7,474,232,677	7,459,446,223	−14,786,454
Cost-effectiveness[d]			
ICER, cost per QALY gained	–	–	101,813

Abbreviations: ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-years.

[a] The OncoSim-Breast model simulated 2,504,360 people, aged 50 to 74 years, who were eligible for breast cancer screening in Ontario.

[b] Supplemental MRI and mammography vs. mammography alone.

[c] Estimated life-years are additional life-years for people aged 50 to 74 years.

[d] Estimated by dividing the incremental total health care cost per person by the incremental QALYs or life-years per person (1.5% discounted).

SUPPLEMENTAL SCREENING WITH DBT AS AN ADJUNCT TO MAMMOGRAPHY

Results of the reference case analysis for supplemental screening with DBT as an adjunct to mammography are summarized in Table 40 for people with dense breasts (heterogeneously and extremely dense breasts) and Table 41 for people with extremely dense breasts.

Compared to mammography alone, supplemental screening with DBT as an adjunct to mammography for people with dense breasts led to an additional 4,205 screen-detected cancers, a reduction of interval breasts cancers by 1,750 cases, and a reduction of breast cancer–related deaths by 385 cases (Table 40).

Also compared to mammography alone, supplemental screening with DBT led to an increase in cases of stage 0 and I breast cancers, and a decreased in cases of stage II and III cancers (74 and 91 fewer, respectively), resulting in reductions in treatment costs of approximately $5.8 million and $6 million, respectively (Appendix 10, Table A21). However, it also resulted in a slight increase in the number of false-positive cases (an additional 441). Supplemental screening with DBT decreased the cost of cancer management by approximately $9.2 million compared to mammography alone. However, it resulted in an increase in screening costs and costs related to diagnostic assessment for false-positive screens by an additional $246 million and $98,074, respectively.

Supplemental screening with DBT for people with dense breasts slightly increased life-years by an additional 0.002 years per person (1.5% discounted; 0.003 undiscounted) and an additional 0.0004 QALYs per person (1.5% discounted). It increased total health care costs ($237 million, 1.5% discounted [$95 per person]), resulting in a high ICER of $212,707 per QALY gained compared to mammography alone.

Table 40: Reference Case Analysis—Cost-Effectiveness of Supplemental Screening With DBT for People With Dense Breasts (Total Cohort)

Outcome[a]	Mammography alone	Supplemental screening with DBT	Difference[b]
Clinical outcomes, total number			
Screen-detected cancers	101,961	106,166	4,205
Interval breast cancer within 1 y of previous screen	18,660	16,910	−1,750
False-positive cases	1,006,089	1,006,530	441
Breast cancer deaths	51,056	50,671	−385
Life-years,[c] 1.5% discounted (undiscounted) [per person (undiscounted)]	55,932,017 (70,477,008) [22.334 (28.142)]	55,936,392 (70,483,967) [22.336 (28.145)]	4,375 (6,959) [0.002 (0.003)]
QALYs, 1.5% discounted (per person)	42,263,049 (16.8758)	42,264,162 (16.8762)	1,113 (0.0004)
Cost outcomes, 1.5% discounted, $			
Total health care cost (per person)	8,433,380,231 (3,367)	8,670,123,261 (3,462)	236,743,030 (95)
Cost of screening	758,217,323	1,003,929,348	245,712,025
Cost of diagnostics for false-positive screen	153,901,068	153,999,142	98,074
Cost of diagnostics for true-positive screen	16,375,404	17,312,236	936,832
Cost of diagnostic clinical detection	30,653,758	29,923,855	−729,903
Cost of cancer management	7,474,232,677	7,464,958,680	−9,273,997
Cost-effectiveness[d]			
ICER, cost per QALY gained	–	–	212,707

Abbreviations: DBT, digital breast tomosynthesis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

[a] The OncoSim-Breast model simulated 2,504,360 people, aged 50 to 74 years, who were eligible for breast cancer screening in Ontario.

[b] Supplemental MRI and mammography vs. mammography alone.

[c] Estimated life-years are additional life-years for people aged 50 to 74 years.

[d] Estimated by dividing the incremental total health care cost per person by the incremental QALYs or life-years per person (1.5% discounted).

We observed similar results for supplemental screening with DBT as an adjunct to mammography compared to mammography alone for people with extremely dense breasts (BI-RADS D only). The number of screen-detected cancers increased by an additional 1,144 cases, interval cancers decreased by 681 cases, and breast cancer–related deaths decreased by 119 cases (Table 41).

Compared to mammography alone, supplemental screening with DBT led to an increase in the number of stage 0 and I breast cancers, and a decrease in the number of stage II and III cancers (30 and 30 fewer, respectively), resulting in reductions in treatment costs for late-stage cancers of approximately $1 million and $1.4 million, respectively (Appendix 10, Table A21). However, it also slightly increased the number of false-positive cases by 506, resulting in additional diagnostic costs of $0.113 million compared to mammography alone. Supplemental screening with DBT for people with extremely dense breasts resulted in a decrease in cancer management costs, but it also led to an additional $67.5 million in screening costs compared to mammography alone.

Supplemental screening with DBT for people with extremely dense breasts slightly increased life-years by an additional 0.0006 years per person (1.5% discounted; 0.001 years undiscounted) and an additional 0.0002 QALYs per person (1.5% discounted). It increased total health care costs ($63.8 million, 1.5% discounted [$25 per person]) resulting in an ICER of $142,730 per QALY gained compared to mammography alone.

Table 41: Reference Case Analysis—Cost-Effectiveness of Supplemental Screening With DBT for People With Extremely Dense Breasts

Outcome[a]	Mammography alone	Supplemental screening with DBT	Difference[b]
Clinical outcomes, total number			
Screen-detected cancers	101,961	103,105	1,144
Interval breast cancer within 1 y of previous screen	18,660	17,979	−681
False-positive cases	1,006,089	1,006,595	506
Breast cancer deaths	51,056	50,937	−119
Life-years,[c] 1.5% discounted (undiscounted) [per person (undiscounted)]	55,932,017 (70,477,008) [22.334 (28.142)]	55,933,412 (70,479,213) [22.3344 (28.143)]	1,395 (2,205) [0.0006 (0.001)]
QALYs, 1.5% discounted (per person)	42,263,049 (16.8758)	42,263,496 (16.8760)	447 (0.0002)
Cost outcomes, 1.5% discounted, $			
Total health care cost (per person)	8,433,380,231 (3,367)	8,497,180,443 (3,393)	63,800,212 (25)
Cost of screening	758,217,323	825,763,984	67,546,661
Cost of diagnostics for false-positive screen	153,901,068	154,013,886	112,818
Cost of diagnostics for true-positive screen	16,375,404	16,634,768	259,364
Cost of diagnostic clinical detection	30,653,758	30,452,529	−201,229
Cost of cancer management	7,474,232,677	7,470,315,275	−3,917,402
Cost-effectiveness[d]			
ICER, cost per QALY gained	–	–	142,730

Abbreviations: DBT, digital breast tomosynthesis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

[a] The OncoSim-Breast model simulated 2,504,360 people, aged 50 to 74 years, who were eligible for breast cancer screening in Ontario.

[b] Supplemental MRI and mammography vs. mammography alone.

[c] Estimated life-years are additional life-years for people aged 50 to 74 years.

[d] Estimated by dividing the incremental total health care cost per person by the incremental QALYs or life-years per person (1.5% discounted).

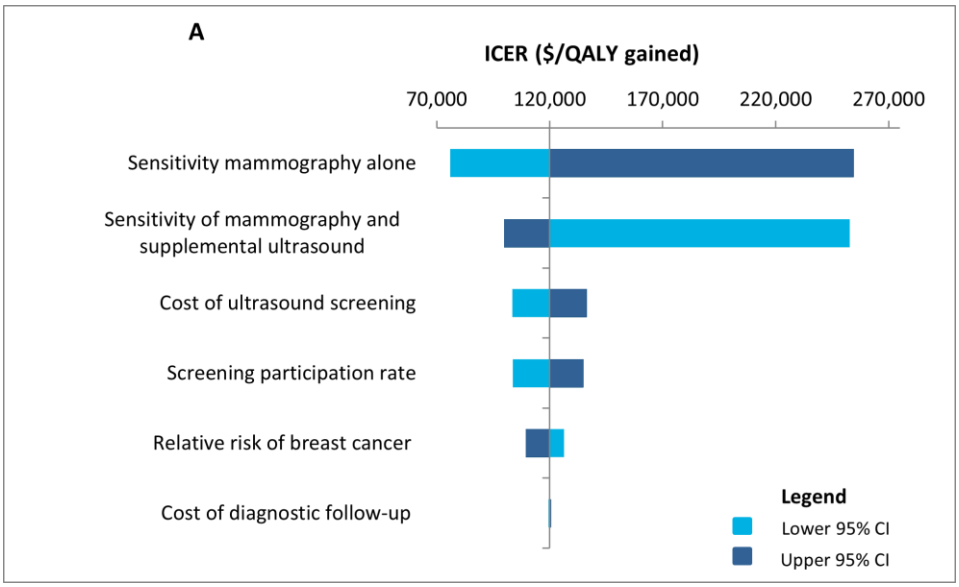
Sensitivity Analysis

In our sensitivity analysis (deterministic one-way sensitivity analyses and scenario analyses), we found that the sensitivity of mammography alone and the sensitivity of supplemental screening plus mammography for people with dense breasts were the model input parameters that most impacted total health care costs, QALYs, and estimated ICERs.

ONE-WAY SENSITIVITY ANALYSES

Supplemental Screening With Handheld Ultrasound as an Adjunct to Mammography

For supplemental screening with handheld ultrasound for people with dense breasts and extremely dense breasts, the estimated ICERs were impacted by changes to the sensitivity of mammography alone and the sensitivity of supplemental screening with ultrasound (Figure 3).



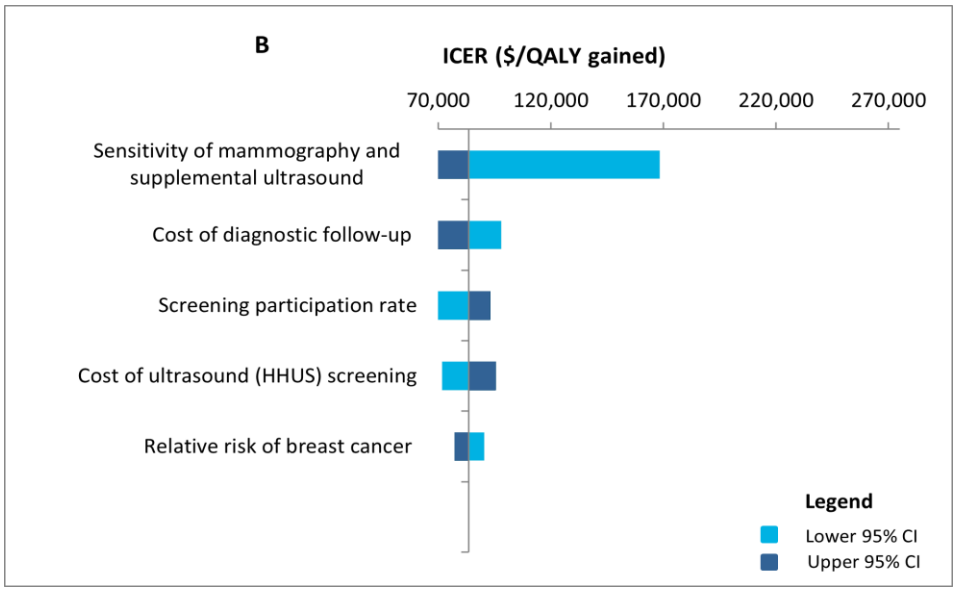


Figure 3: Tornado Diagram—Sensitivity Analysis, Supplemental Screening With Handheld Ultrasound for People With Dense Breasts and Extremely Dense Breasts

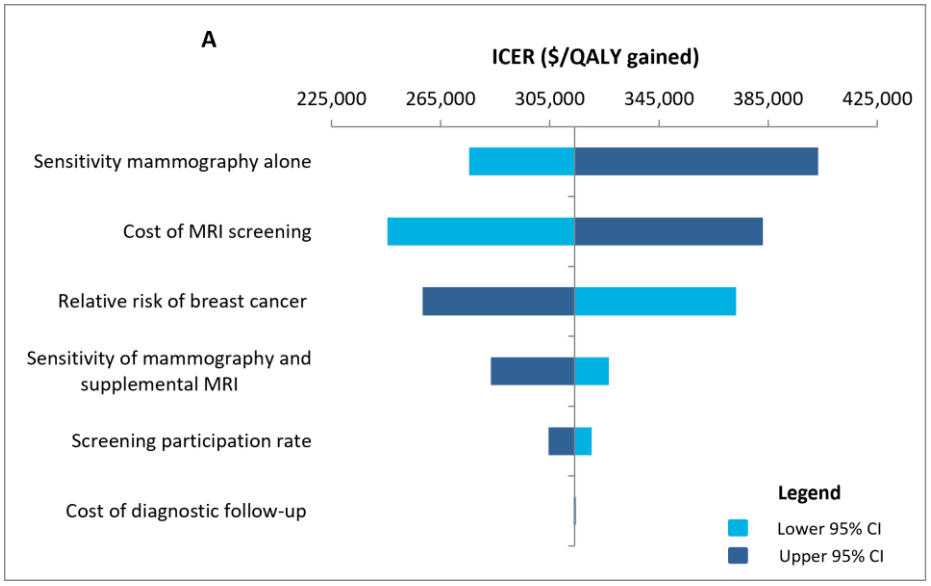
Abbreviations: CI, confidence interval; HHUS, handheld ultrasound; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.
Tornado diagram showing the sensitivity analysis for supplemental screening with handheld ultrasound. (A) For people with dense breasts, an increase in the sensitivity of mammography alone or a decrease in the sensitivity of supplemental ultrasound plus mammography decreased the incremental QALYs, resulting in an increase in estimated ICERs. In contrast, the ICERs were decreased when the sensitivity of mammography alone was decreased or the sensitivity of supplemental ultrasound plus mammography was increased. (B) For people with extremely dense breasts, increasing the sensitivity of mammography alone decreased the incremental QALYs, which led supplemental screening with ultrasound to be dominated (more costly, less effective) by mammography alone. A decrease in the sensitivity of supplemental ultrasound plus mammography decreased incremental QALYs and increased incremental costs, resulting in an increase in estimated ICERs.

For people with dense breasts, an increase in the sensitivity of mammography alone (i.e., 86% for the upper bound of the 95% CI vs. 71% for the reference case) or a decrease in the sensitivity of supplemental ultrasound plus mammography (i.e., 86% for the lower bound of the 95% CI vs. 93% for the reference case) decreased the incremental QALYs, resulting in an increase in estimated ICERs. In contrast, the ICERs were more favourable (i.e., decreased) when the sensitivity of mammography alone was decreased (i.e., 55% for the lower bound of the 95% CI vs. 71% for reference case) or the sensitivity of supplemental ultrasound plus mammography was increased (i.e., 100% for the upper bound of the 95% CI vs. 93% for the reference case).

For people with extremely dense breasts, increasing the sensitivity of mammography alone (i.e., 86% for the upper bound of the 95% CI vs. 71% for the reference case) decreased the incremental QALYs (resulted in negative QALYs), which led supplemental screening with ultrasound to be dominated (more costly, less effective) by mammography alone. In addition, a decrease in the sensitivity of supplemental ultrasound plus mammography (i.e., 86% for the lower bound of the 95% CI vs. 93% for the reference case) decreased incremental QALYs and increased incremental costs, resulting in an increase in estimated ICERs.

Supplemental Screening With MRI as an Adjunct to Mammography

For supplemental screening with MRI for people with dense breasts and extremely dense breasts, the estimated ICERs were impacted by changes to the sensitivity of mammography alone or of supplemental screening with MRI, the cost of MRI screening and the RR of breast cancer (Figure 4).



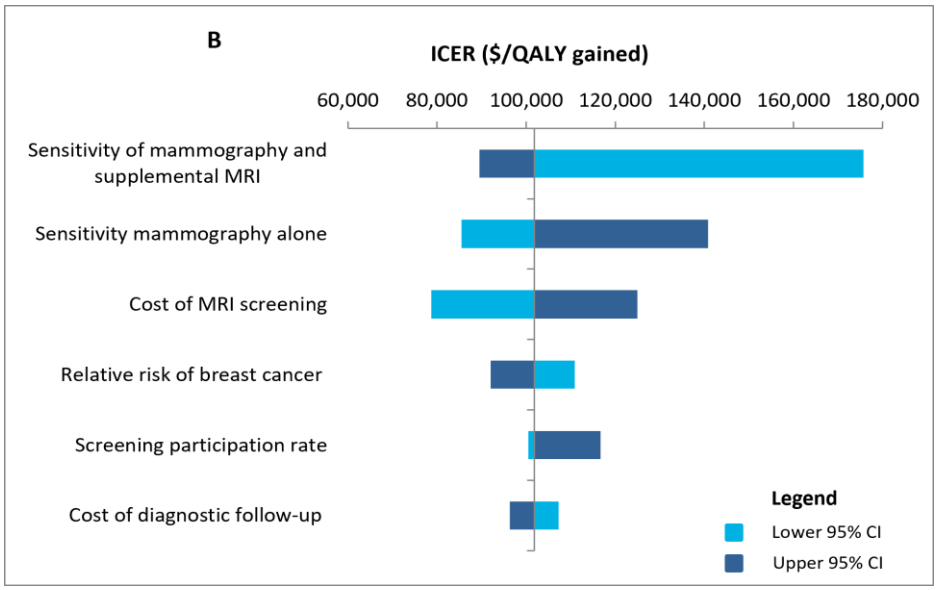


Figure 4: Tornado Diagram—Sensitivity Analysis, Supplemental Screening With MRI for People With Dense Breasts and Extremely Dense Breasts

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-years.

Tornado diagram showing the sensitivity analysis for supplemental screening with MRI. (A) For people with dense breasts, the estimated ICERs increased when the sensitivity of mammography alone increased and when the cost of MRI screening increased. Estimated ICERs were also impacted by the relative risk of breast cancer for people with heterogeneously dense breasts compared to people with scattered areas of fibroglandular density. (B) For people with extremely dense breasts, the ICERs were mostly impacted (increased) by a decrease in the sensitivity of mammography plus supplemental MRI and an increase in the sensitivity of mammography alone. and extremely dense breasts (i.e., 1.84 and 2.26 for the lower and upper bound of the 95% CI, respectively, vs. 2.04 for the reference case) compared to people with scattered areas of fibroglandular density (BI-RADS B; Figure 4A). Estimated ICERs were also impacted by the relative risk of breast cancer for people with extremely dense breasts compared to people with scattered areas of fibroglandular density.

The sensitivity analyses for supplemental screening with MRI for people with dense breasts showed that the estimated ICERs increased when the sensitivity of mammography alone increased (i.e., 74% and 70% for heterogeneously and extremely dense breasts, respectively, for the upper bound of the 95% CI vs. 70% and 61% for the reference case) and when the cost of MRI screening increased ($343.79, 25% increase vs. $278.94 reference cost).

Estimated ICERs were also impacted by the RR of breast cancer for people with heterogeneously dense breasts (i.e., 1.51 and 1.75 for the lower and upper bound of the 95% CI, respectively, vs. 1.62 for the reference case) and extremely dense breasts (i.e., 1.84 and 2.26 for the lower and upper bound of the 95% CI, respectively, vs. 2.04 for the reference case) compared to people with scattered areas of fibroglandular density (BI-RADS B; Figure 4A).

For people with extremely dense breasts, the ICERs were mostly impacted (increased) by a decrease in the sensitivity of mammography plus supplemental MRI (i.e., 88% for the lower bound of the 95% CI vs. 95% for the reference case), and an increase in the sensitivity of mammography alone (i.e., 70% for the upper bound of the 95% CI vs. 61% for the reference case; Figure 4B).

Supplemental Screening With DBT as an Adjunct to Mammography

For supplemental screening with DBT for people with dense breasts and extremely dense breasts, the estimated ICERs were impacted by changes to the sensitivity of mammography alone, the RR of breast cancer, and the sensitivity of supplemental screening with DBT (Figure 5).

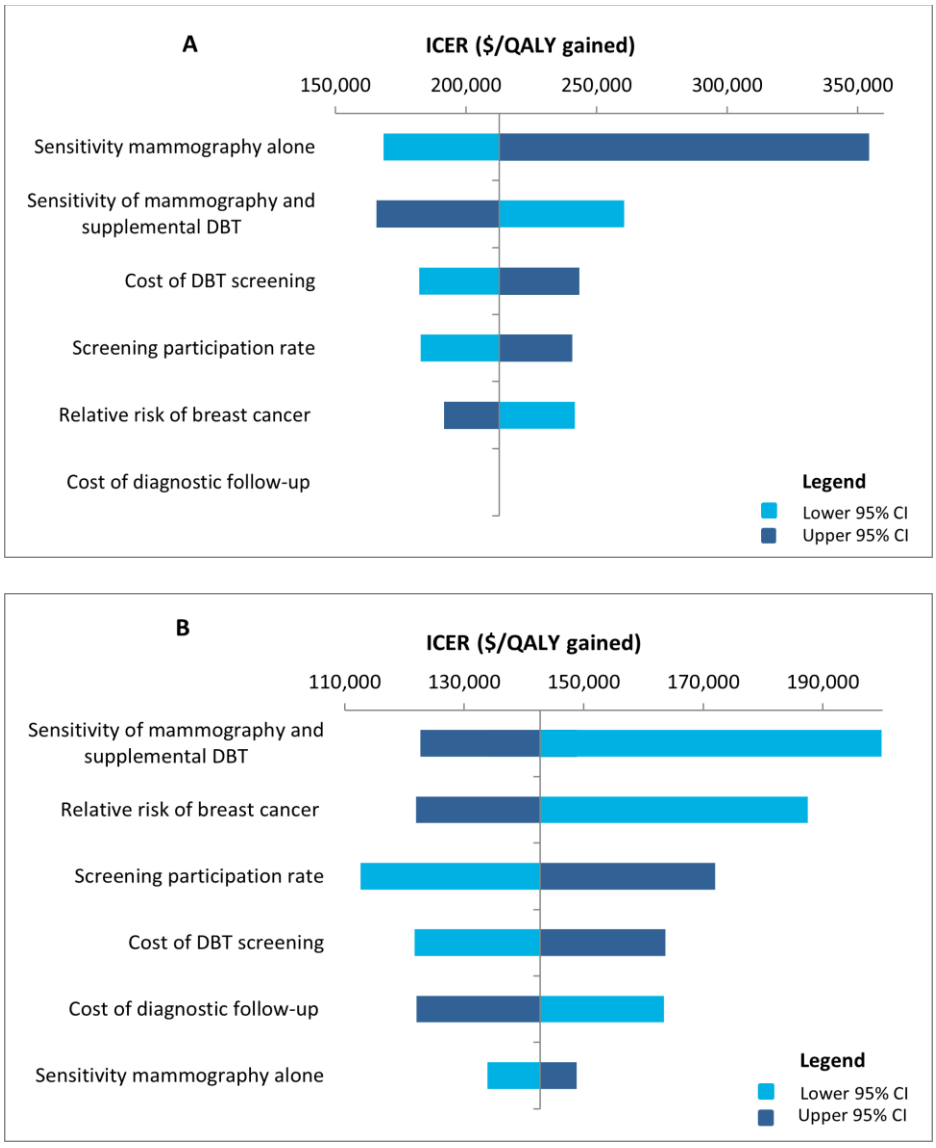


Figure 5: Tornado Diagram—Sensitivity Analysis, Supplemental Screening With DBT for People With Dense Breasts and Extremely Dense Breasts

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; DBT, digital breast tomosynthesis; QALY, quality-adjusted life-years.

Tornado diagram showing the sensitivity analysis for supplemental screening with DBT. (A) For people with dense breasts, increasing the diagnostic sensitivity of mammography alone had the biggest impact on ICERs. (B) For people with extremely dense breasts, a decrease in the relative risk of breast cancer compared to people with scattered areas of fibroglandular density and a decrease in the sensitivity of supplemental screening with increased estimated ICERs. Screening participation rate and the cost of DBT screening moderately affected estimated ICERs.

For supplemental screening with DBT in people with dense breasts, increasing the diagnostic sensitivity of mammography alone (i.e., 74% and 70% for heterogeneously and extremely dense breasts, respectively, for the upper bound of the 95% vs. 70% and 61% for the reference case) had the biggest impact on ICERs.

In people with extremely dense breasts, a decrease in the relative risk of breast cancer compared to people with scattered areas of fibroglandular density (BI-RADS B; i.e., 1.84 for the lower bound of the 95% CI vs. 2.04 for the reference case) and a decrease in the sensitivity of supplemental screening with DBT (i.e., 33% for the lower bound of the 95% CI vs. 52% for the reference case) increased estimated ICERs. Screening participation rate and the cost of DBT screening moderately affected estimated ICERs.

SCENARIO ANALYSES

Supplemental Screening With Ultrasound as an Adjunct to Mammography

The results of the scenario analyses for supplemental screening with ultrasound for people with dense breasts (heterogeneously dense breasts and extremely dense breasts) and for people with extremely dense breasts are presented in Table 42.

Compared to the reference case using handheld ultrasound as a supplemental modality (ICER $119,943/QALY), supplemental screening using ABUS for people with dense breasts increased the incremental QALYs and increased the incremental cost, resulting in an ICER of $270,304/QALY gained. For people with extremely dense breasts, supplemental screening with ABUS slightly increased the ICER to $89,635/QALY gained (compared to $83,529/QALY gained for handheld ultrasound).

Increasing the treatment cost of stage III and IV breast cancers by 100% reduced the ICERs from $119,943/QALY gained to $104,398/QALY gained for people with dense breasts, and from $83,529/QALY gained to $74,549/QALY gained for people with extremely dense breasts (assuming handheld ultrasound).

The ICER was also sensitive to the discount rate. Increasing the discount rate from 1.5% (reference case) to 3% led to a decrease in both incremental costs and QALYs, and an increase in ICER ($668,678/QALY gained; assuming handheld ultrasound). Similarly, a decrease in the discount rate from 1.5% to 0% resulted in an increase of incremental cost and QALYs, and a decrease in ICER ($50,451/QALY gained).

Table 42: Scenario Analysis—Supplemental Screening With Ultrasound for People With Dense Breasts and Extremely Dense Breasts

Scenario[a]	Total cost per person, $		Incremental cost, $[b,c]	Total effect per person, QALYs		Incremental effect, QALYs[c,d]	ICER, $/QALY
	Mammography	Mammography + supplemental ultrasound		Mammography	Mammography + supplemental ultrasound		
Dense breasts (heterogeneously dense breasts and extremely dense breasts)							
Reference case (handheld ultrasound)	3,368	3,451	83	16.8759	16.8766	0.00069	119,943
Scenario 1: Supplemental screening with ABUS	3,367	3,599	232	16.8758	16.8767	0.00086	270,304
Scenario 2: Doubled (100% increase) treatment cost for stage III and IV breast cancers	3,806	3,878	72	16.8759	16.8766	0.00069	104,398
Scenario 3: Discount rate 0%	4,163	4,248	86	20.9330	20.9347	0.00170	50,451
Scenario 4: Discount rate 3%	2,799	2,878	79	13.9784	13.9785	0.00012	668,678
Extremely dense breasts							
Reference case (handheld ultrasound)	3,368	3,390	22	16.8759	16.8761	0.00026	83,529
Scenario 1: Supplemental screening with ABUS	3,367	3,428	61	16.8758	16.8765	0.00068	89,635
Scenario 2: Doubled (100% increase) treatment cost for stage III and IV breast cancers	3,806	3,825	20	16.8759	16.8761	0.00026	74,549
Scenario 3: Discount rate 0%	4,163	4,186	23	20.9330	20.9335	0.00052	44,562
Scenario 4: Discount rate 3%	2,799	2,820	21	13.9784	13.9785	0.00011	189,175

Abbreviations: ABUS, automated breast ultrasound; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

[a] Scenarios 2,3, and 4 were evaluated using supplemental screening with handheld ultrasound.

[b] Incremental cost = average cost (strategy B) − average cost (strategy A).

[c] Results may appear inexact due to rounding.

[d] Incremental effect = average effect (strategy B) − average effect (strategy A).

Supplemental Screening With MRI as an Adjunct to Mammography

The results of the scenario analyses for supplemental screening with MRI for people with dense breasts (heterogeneously dense breasts and extremely dense breasts) and for people with extremely dense breasts are presented in Table 43.

We found that increasing the treatment cost of stage III and IV breast cancers by 100% reduced the ICERs from $314,170/QALY gained to $293,075/QALY gained for people with dense breasts, and from $101,813/QALY gained to $95,380/QALY gained for people with extremely dense breasts.

The ICER was also sensitive to the discount rate. A decrease from 1.5% (reference case) to 0% resulted in an increase of the incremental cost and QALYs, and a decrease in the ICER ($107,733/QALY gained). Similarly, an increase from 1.5% to 3% led to a decrease in incremental cost and QALYs, resulting in an increase in the ICER ($418,767/QALY gained).

We also assessed the impact of the specificity of mammography alone on the estimated ICERs (88% for both heterogeneously and extremely dense breasts in the scenario analysis vs. 98.8% and 97.6% for the reference case), which slightly decreased the estimated ICERs compared to the reference case analysis.

Table 43: Scenario Analysis—Supplemental Screening With MRI for People With Dense Breasts and Extremely Dense Breasts

Scenario	Total costs (per person), $		Incremental cost, $[a,b,c]	Total effects (per person), QALYs		Incremental effect, QALYs[c]	ICER ($/QALY)
	Mammography	Mammography + supplemental MRI		Mammography	Mammography + supplemental MRI		
Dense breasts—heterogeneously dense breasts and extremely dense breasts							
Reference case	3,367	3,620	252	16.8758	16.8766	0.0008	314,170
Scenario 1: Doubled (100% increase) treatment cost for stage III and IV breast cancers	3,806	4,042	235	16.8758	16.8766	0.0008	293,075
Scenario 2: Discount rate 0%	4,163	4,434	271	20.9328	20.9353	0.0025	107,733
Scenario 3: Discount rate 3%	2,799	3,033	234	13.9783	13.9789	0.0006	418,767
Scenario 4: Decreased specificity of mammography alone	3,369	3,620	250	16.8758	16.8766	0.0008	309,126
Extremely dense breasts							
Reference case	3,367	3,435	67	16.8758	16.8764	0.0007	101,813
Scenario 1: Doubled (100% increase) treatment cost for stage III and IV breast cancers	3,806	3,869	63	16.8758	16.8764	0.0007	95,380
Scenario 2: Discount rate 0%	4,163	4,236	73	20.9328	20.9340	0.0012	60,067
Scenario 3: Discount rate 3%	2,799	2,860	62	13.9783	13.9786	0.0003	190,224
Scenario 4: Decreased specificity of mammography alone	3,369	3,435	65	16.8758	16.8764	0.0007	97,843

Abbreviations: ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-years.

[a] Incremental cost = average cost (strategy B) − average cost (strategy A).

[b] Results may appear inexact due to rounding.

[c] Incremental effect = average effect (strategy B) − average effect (strategy A).

Supplemental Screening With DBT as an Adjunct to Mammography

The results of the scenario analyses for supplemental screening with DBT for people with dense breasts (heterogeneously dense breasts and extremely dense breasts) and for people with extremely dense breasts are presented in Table 44.

We found that increasing the treatment cost of stage III and IV breast cancers by 100% slightly reduced the ICERs from $212,707/QALY gained to $203,632/QALY gained for people with dense breasts, and from $142,730/QALY gained to $135,767/QALY gained for people with extremely dense breasts.

We also assessed the impact of the specificity of mammography alone on the estimated ICERs (88% for both heterogeneously and extremely dense breasts in the scenario analysis vs. 98.8% and 97.6% for the reference case), which slightly decreased the estimated ICERs compared to the reference case analysis.

Table 44: Scenario Analysis—Supplemental Screening With DBT for People With Dense Breasts and Extremely Dense Breasts

Scenario	Total costs (per person), $		Incremental cost, $[a,b,c]	Total effects (per person), QALYs		Incremental effect, QALYs[c]	ICER ($/QALY)
	Mammography	Mammography + supplemental DBT		Mammography	Mammography + supplemental DBT		
Dense breasts—heterogeneously dense breasts and extremely dense breasts							
Reference case	3,367	3,462	95	16.8758	16.8762	0.0004	212,707
Scenario 1: Doubled (100% increase) treatment cost for stage III and IV breast cancers	3,806	3,897	90	16.8758	16.8762	0.0004	203,632
Scenario 2: Discount rate 0%	4,163	4,267	104	20.9328	20.9337	0.0009	110,585
Scenario 3: Discount rate 3%	2,799	2,885	86	13.9783	13.9785	0.0002	537,976
Scenario 4: Decreased specificity of mammography alone	3,369	3,462	93	16.8758	16.8762	0.0005	205,182
Extremely dense breasts							
Reference case	3,367	3,393	25	16.8758	16.8760	0.0002	142,730
Scenario 1: Doubled (100% increase) treatment cost for stage III and IV breast cancers	3,806	3,831	24	16.8758	16.8760	0.0002	135,767
Scenario 2: Discount rate 0%	4,163	4,191	28	20.9328	20.9331	0.0003	82,470
Scenario 3: Discount rate 3%	2,799	2,822	23	13.9783	13.9784	0.0001	280,072
Scenario 4: Decreased specificity of mammography alone	3,369	3,393	24	16.8758	16.8760	0.0002	126,967

Abbreviations: DBT, digital breast tomosynthesis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

[a] Incremental cost = average cost (strategy B) − average cost (strategy A).

[b] Results may appear inexact due to rounding.

[c] Incremental effect = average effect (strategy B) − average effect (strategy A).

Discussion

The primary economic evaluation found that supplemental screening with handheld ultrasound, MRI, or DBT as an adjunct to mammography for people with dense breasts (heterogeneously and extremely dense breasts) improved the number of screen-detected cancers, decreased the number of interval cancers and breast cancer deaths, and led to small improvements in life-years (incremental difference of 0.003 to 0.01 life-years per person, undiscounted) and QALYs (incremental difference of 0.0004 to 0.0008 QALYs per person, 1.5% discount rate), but it also increased total health care costs. Although some cost savings were realized related to cancer management with supplemental screening compared to mammography alone, supplemental screening also increased the number of false-positive results because of decreased specificity, resulting in additional costs related to diagnostic assessment for false-positive screens. Supplemental screening also increased the cost of screening because more people were offered additional screening.

In people with dense breasts, supplemental ultrasound resulted in the highest number of false-positive screens, corresponding to a high cost of diagnostic assessment after screening because of its decreased specificity compared to mammography alone. Supplemental screening with ultrasound, MRI, and DBT resulted in additional health care costs of $207 million ($83 per person), $632 million ($252 per person), and $236 million ($95 per person), respectively. With small improvements in QALYs and increases in total health care costs, the ICERs for supplemental screening with ultrasound, MRI, and DBT compared to mammography alone were high, at $119,943/QALY gained, $314,170/QALY gained, and $212,707/QALY gained, respectively.

Similarly, providing supplemental screening only for people with extremely dense breasts increased the number of screen-detected cancers, decreased the number of interval breast cancers and breast cancer deaths, and led to small improvements in life-years (incremental difference of 0.001 to 0.003 years, undiscounted) and QALYs (incremental difference of 0.0003 to 0.001 QALYs, 1.5% discount rate). Given that the subset of people with extremely dense breasts is smaller than the total population with dense breasts (approximately 10% of the total screen-eligible population), the additional health care costs of supplemental screening were less than those of supplemental screening for all people with dense breasts. Supplemental screening with ultrasound, MRI, and DBT for people with extremely dense breasts resulted in an additional $55 million ($22 per person), $168 million ($67 per person), and $64 million ($25 per person) compared to mammography alone. However, with small improvements in QALYs and increases in total health care costs, the ICERs for supplemental screening with ultrasound, MRI, and DBT compared to mammography alone remained high, at $83,529/QALY gained, $101,813/QALY gained, and $142,730/QALY gained, respectively.

Our cost-effectiveness analysis was partially consistent with the economic literature. Similar to our analysis, Gray et al[119] and Sprague et al[39] found that supplemental screening with ultrasound for people with dense breasts and for people with extremely dense breasts resulted in small improvements in QALYs and increases in health care costs, for ICERs greater than $200,000 USD/QALY (2015/2017 USD). For supplemental screening with MRI, our findings were not consistent with previous economic evaluations in people with extremely dense breasts, which found supplemental screening to be cost-effective with low ICERs of about $9,000 to 20,000 USD/QALY gained.[115-118] However, these studies included only the cost of MRI alone and did not account for the cost of mammography in addition to MRI, possibly underestimating the total cost of supplemental screening with MRI as an adjunct to mammography, and therefore, leading to lower estimated ICERs. Our one-way sensitivity analysis showed that decreasing the cost of supplemental screening by 25% resulted in a lower estimated ICER compared to the reference

case analysis. In addition, the published studies used biennial supplemental screening rather than annual breast screening, which is currently recommended in Ontario for people with 75% dense breast tissue or more.

Our sensitivity analysis showed that the cost-effectiveness of supplemental screening was greatly influenced by the inputs related to the sensitivity of mammography screening alone and the sensitivity of mammography plus supplemental screening. Given that the confidence intervals from the clinical evidence were wide, decreased sensitivity of mammography alone (corresponding to the lower bound of the 95% CI) and increased sensitivity of mammography plus supplemental screening (corresponding to the upper bound of the 95% CI) for people with dense breasts resulted in lower ICERs ($75,000/QALY to $285,000/QALY) compared to the reference case analysis ($199,000/QALY to $314,000/QALY). However, supplemental screening would not be considered cost-effective at commonly used willingness-to-pay value of $50,000 per QALY.

Similarly for people with extremely dense breasts, decreased sensitivity of mammography alone and increased sensitivity of supplemental screening with MRI and DBT resulted in lower ICERs ($85,000/QALY to $133,000/QALY) compared to the reference case analysis ($101,000/QALY to $142,000/QALY). However, a decrease in the sensitivity of mammography alone as a comparator for supplemental screening with ultrasound decreased the estimated ICER to $30,841/QALY versus $83,529/QALY in the reference case analysis.

Strengths and Limitations

Our analysis had several strengths. We conducted the primary economic evaluation using a well validated individual-level OncoSim-Breast model, which used Ontario-specific demographic data (e.g., age and sex distribution, all-cause mortality), breast screening costs for ultrasound and MRI, and cancer-related costs.[135,136,163,164] The OncoSim-Breast model simulated a comprehensive component of the natural history and progression using input parameters calibrated to Canadian data. Given our ability to modify screening strategies in the OncoSim model, we were able to assign Ontario-recommended strategies based on the individual's breast density, in which supplemental screening was applied only for people with dense breasts or for people with extremely dense breasts (the remaining screen-eligible population continued to have biennial mammography screening). In addition, we used prepopulated input parameters that captured breast density changes using age-specific breast density distribution. This allowed us to capture population-level outcomes that best represented the impact of introducing supplemental screening in people with dense breasts in an established population-based screening program. Finally, although QALYs were the primary outcome of interest for economic evaluations, we reported additional clinically relevant outcomes, such as impact on cancer detection by screen, interval cancers, and false-positive rates. These outcomes can provide a better understanding of how supplemental screening can affect clinically meaningful outcomes that may not be captured by small improvements in outcomes such as life-years and QALYs.

Although our analysis had several strengths, it must be interpreted within the limitations of our model assumptions and input parameters:

- We were unable to run the analyses probabilistically, given computational and model constraints. Therefore, we could not evaluate the probability of supplemental screening being cost-effective across a wide range of commonly used cost-effectiveness (willingness-to-pay) values. To mitigate

this limitation of assessing parameter (second-order) uncertainty, we conducted several one-way sensitivity analyses to assess the impact of the main input parameters on the ICERs

- Because of limited comparative clinical evidence, we did not conduct a comparative cost-effectiveness analysis between the three supplemental modalities of interest; instead, we assessed the cost-effectiveness of each modality independently. We also did not conduct a cost-effectiveness analysis of supplemental contrast-enhanced mammography because we found no relevant clinical evidence on this modality as adjunct to mammography for breast cancer screening in people with dense breasts (clinical evidence review)
- Although we used the most recently published clinical evidence for the inputs for the sensitivity and specificity of mammography and supplemental modalities, the quality of the evidence was Low to Moderate for supplemental ultrasound and MRI, and Very low to Low for supplemental DBT. In addition, the sensitivity of mammography alone and of supplemental screening plus mammography for people with dense breasts obtained from the clinical studies had wide confidence intervals that highly influenced the estimated ICERs in our sensitivity analysis. Given that stratified data for people with heterogeneously and extremely dense breasts were also limited, we assumed that the sensitivity of supplemental ultrasound and DBT was the same for people with heterogeneously dense breasts and for people with extremely dense breasts. The sensitivity of supplemental ultrasound and DBT may be lower for people with extremely dense breasts than for people with heterogeneously dense breasts. Therefore, assuming that the sensitivity was the same for people with heterogeneously and extremely dense breasts in our reference case analysis may have overestimated the true sensitivity for people with extremely dense breasts. In our sensitivity analysis, a decrease in the sensitivity of supplemental screening plus mammography (corresponding to the lower bound of the 95% CI) for people with extremely dense breasts increased the estimated ICERs ($175,000/QALY to $268,000/QALY) compared to the reference case analysis ($83,000/QALY to $140,000/QALY)
- We did not evaluate the resource use or costs of new advanced breast cancer treatments, particularly for late-stage breast cancers (stages III and IV). We did conduct scenario analyses to assess the impact of increased treatment costs related to chemotherapy and anti-HER2 therapies for stage III and IV breast cancer,[165,166] but the cost-effectiveness results remained robust (i.e., they did not change drastically)
- Because of structure of the model related to combined mammography and supplemental screening, we were unable to evaluate the impact of potential loss of follow-up for supplemental screening after mammography screening
- We estimated the screening costs of ultrasound and MRI using billing codes from the OHIP Schedule of Benefits for Diagnostic Assessments[54] because no billing codes are currently available for supplemental screening. Therefore, we are uncertain about the additional screening costs that would be required for population-based supplemental screening. We mitigated this uncertainty in an estimate of the screening costs by adding a program (administrative) cost to the supplemental modality interventions, an estimated additional cost component that may be applied for a population-based screening intervention. As presented in the sensitivity analysis, the estimated ICERs increased slightly when the costs of supplemental screening were increased by 25% compared to the reference case analysis.

Conclusions

Our primary economic evaluation found that supplemental screening with ultrasound, MRI, or DBT as an adjunct to mammography for people with dense breasts and for people with extremely dense breasts increased screen-detected cancers and decreased interval cancers and breast cancer–related deaths compared to mammography alone. However, supplemental screening increased the costs of screening and the costs associated with false-positive screens. We found small improvements in life-years and QALYs with additional health care costs for supplemental screening compared to mammography alone, resulting in high ICERs. The estimated ICERs for supplemental screening with handheld ultrasound were $119,943/QALY for people with dense breasts and $83,529/QALY for people with extremely dense breasts. The estimated ICERs for supplemental screening with MRI were $314,170/QALY for people with dense breasts and $101,813/QALY for people with extremely dense breasts. The estimated ICERs for supplemental screening with DBT were $212,707/QALY for people with dense breasts and $142,730/QALY for people with extremely dense breasts.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding supplemental screening with ultrasound, magnetic resonance imaging (MRI), or digital breast tomosynthesis (DBT) as an adjunct to mammography for breast cancer screening in people with dense breasts?

Methods

Analytic Framework

We estimated the budget impact of publicly funding supplemental screening as an adjunct to mammography using the cost difference between two scenarios: (1) current clinical practice without public funding for supplemental screening as an adjunct to mammography (the current scenario), and (2) anticipated clinical practice with public funding for supplemental screening as an adjunct to mammography (the new scenario). Figure 6 presents the budget impact model schematic.

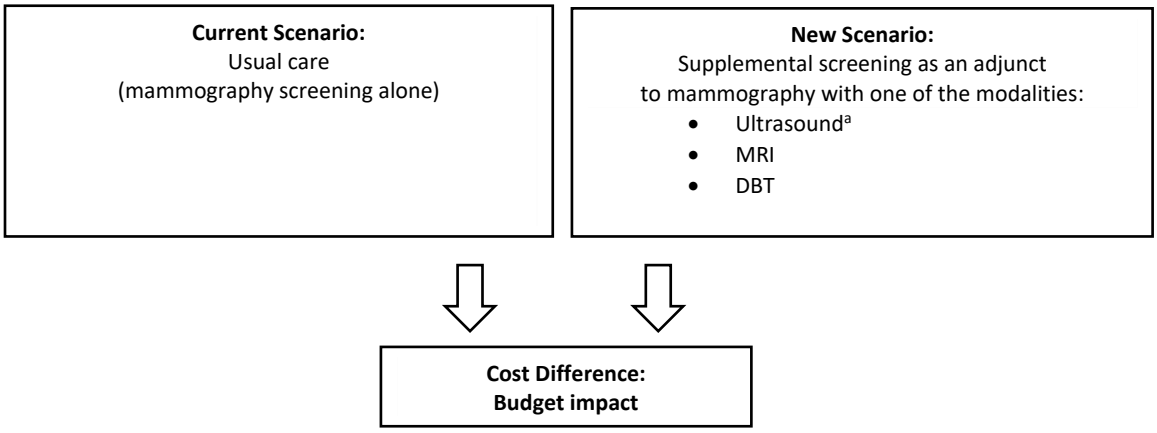


Figure 6: Schematic Model of Budget Impact

Abbreviations: DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging.

Flow chart describing the model for the budget impact analysis. The current scenario would explore resource use and total costs without public funding for supplemental screening as an adjunct to mammography. The new scenario would explore resource use and total costs *with* public funding for supplemental screening as an adjunct to mammography using ultrasound, MRI, or DBT. The budget impact would represent the difference in costs between the two scenarios.

[a] Handheld ultrasound used in all analyses except for the scenario analysis with automated breast ultrasound.

We estimated the budget impact for each supplemental modality for people with dense breasts (i.e., extremely dense breasts, or Breast Imaging Reporting and Data System [BI-RADS] D, and heterogeneously dense breasts, or BI-RADS C) and for people with extremely dense breasts (BI-RADS D only).

Key Assumptions

In addition to the assumptions made for the primary economic evaluation, we assumed the following for the budget impact analysis:

- There was no mix of supplemental imaging modalities, and the market shares of ultrasound, MRI, and DBT would be approximately equal
- Population growth of the number of individuals eligible for screening through the Ontario Breast Screening Program (OBSP) predicted by the OncoSim-Breast model using Ontario demographic data

Target Population

Our target population was asymptomatic people aged 50 to 74 years with dense breasts and no high-risk factors for breast cancer. We estimated the size of the target population from the number of people aged 50 to 74 years who were eligible for breast screening through the OBSP, using screening data from the 2021 Cancer System Quality Index (CSQI) report (Table 45).[139]

Table 45: People in Ontario Eligible for Screening Through the OBSP, 2012–2019

Population	2012–2013	2014–2015	2016–2017	2018–2019	Average (2012–2019)
Number of people eligible for screening	1,900,105	2,028,262	2,136,583	2,225,120	2,072,518
Number of people screened through the OBSP	931,051	1,074,979	1,217,852	1,246,067	1,117,487

Abbreviation: OBSP, Ontario Breast Screening Program.
Source: 2021 Cancer System Quality Index (CSQI) Report.[139]

From 2012 to 2019, an average of 2,072,518 people per year were eligible for breast screening in Ontario, and of those eligible, an average of 1,117,487 per year were screened through the OBSP. We estimated the volume of the target population that would be screened through the OBSP in year 1 by multiplying the average population growth from 2012 to 2019 (1.10) to the average number of people screened through the OBSP (1,117,487). Based on this calculation, approximately 1,233,208 individuals (BI-RADS A to D) would be screened through the OBSP in year 1 (2023). We calibrated the volume of the target population for years 2 to 5 by applying the predicted population growth from the OncoSim-Breast model to the CSQI screening data. We assumed a distribution of breast density by age group (as populated in the OncoSim-Breast model) for people who would receive supplemental screening as an adjunct to mammography.

Over 5 years, we estimated that of 6,626,507 people who would receive breast cancer screening, approximately 1,698,376 would have dense breasts (heterogeneously and extremely dense breasts) (Table 46). We estimated total health care costs for the total screening population; the additional costs related to supplemental screening were applied only to people with dense breasts.

Table 46: Estimated Number of People Screened in the Next 5 Years

Population[a]	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total number of people screened	1,233,208	1,328,819	1,326,991	1,369,316	1,368,172	6,626,507
Estimated number of people with dense breasts (heterogeneously and extremely dense breasts)	294,420	359,499	344,571	351,812	348,073	1,698,376
Estimated number of people with extremely dense breasts[b]	55,702	106,869	101,439	99,595	100,471	464,076
Estimated number of people without dense breasts	938,788	969,320	982,420	1,017,504	1,020,099	4,928,131

[a] We calibrated the volume of the target population, applying simulated population growth from the OncoSim-Breast model to Cancer System Quality Index (CSQI) screening data. Then, we applied the distribution of breast density by age group (populated in the OncoSim-Breast model) to the total eligible screening population, for which people with dense breasts (heterogeneously and extremely dense breasts) received supplemental screening as an adjunct to mammography. Estimated numbers are the average for each screening scenario (i.e., mammography alone and supplemental screening as an adjunct to mammography).

[b] These estimates represent a smaller subgroup of people with dense breasts and were used in analyses relevant to people with extremely dense breasts.

Current Intervention Mix

Currently, supplemental screening as an adjunct to mammography for breast cancer screening is not publicly funded in Ontario. We assumed that people with dense breasts who are eligible for screening in Ontario are receiving usual care. Asymptomatic people aged 50 to 74 years old who are eligible for average-risk breast screening through the OBSP receive biennial mammography screening. We assumed that people with extremely dense breasts (BI-RADS D) receive annual mammography screening, similar to people with 75% dense breast tissue or more, who are recalled by the OBSP for annual screening.[52,53,134]

Uptake of the New Intervention and New Intervention Mix

In the new scenario, people with dense breasts (heterogeneously dense breasts [BI-RADS C] and extremely dense breasts [BI-RADS D]) received mammography and supplemental screening with one of the three modalities: ultrasound, MRI, or DBT.

According to clinical experts, the uptake of supplemental screening is uncertain and would depend on the supplemental modality, the operational capacity at imaging sites (e.g., availability of modalities, human resource demands), and the implementation setting (e.g., organized screening programs such as the OBSP, opportunistic or central referral, high-risk centres; Samantha Fienberg, MD, email communication, September 23, 2022; Derek Muradali, MD, email communication, October 11, 2022). If supplemental screening with MRI were funded, uptake would be slow because of the limited number of MRI machines available in Ontario, long wait times, and limited numbers of personnel to conduct screening. Although supplemental screening with ultrasound is available at most OBSP sites (independent health facilities and hospital-based sites), it would also have slow uptake because ultrasound screening depends on skilled personnel (technologists) and resources that are currently too limited to provide supplemental screening to a broad population. Uptake of DBT would be moderate,

based on its availability across OBSP sites. Therefore, in the reference case analysis, we assumed that there would be no mix of interventions, and the estimated budget impact was based on slow uptake for ultrasound and MRI, and moderate uptake for DBT over the next 5 years:

- Slow uptake: 2.5%, 5.0%, 7.5%, 10.0%, and 12.5%
- Moderate uptake: 10%, 15%, 20%, 25%, and 30%

Resources and Costs

Using the OncoSim-Breast model, we estimated the annual undiscounted costs associated with supplemental screening as an adjunct to mammography and usual care (mammography alone). For the budget impact analysis, we used the same model inputs related to costs (e.g., screening, diagnostic assessment, and treatment) as in the primary economic evaluation. Costs estimated included breast screening with mammography and a supplemental modality, follow-up and diagnostic costs, and breast cancer management. All costs are reported in 2022 Canadian dollars.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results were affected by varying input parameters and model assumptions.

We conducted sensitivity and scenario analyses to assess the impact of varying parameters on the estimated budget impact:

- Screening with automated breast ultrasound (ABUS)
- The cost of screening for each modality (± 25% estimated cost)
- The cost of follow-up assessment for an abnormal screening result (i.e., false-positive and true-positive results; ± 25% estimated cost)
- Treatment costs for stage III and IV breast cancers (doubled; 100% increase)
- Uptake of supplemental screening in the next 5 years: moderate for supplemental screening with ultrasound and MRI, and slow for supplemental screening with DBT

Results

Reference Case

SUPPLEMENTAL SCREENING WITH HANDHELD ULTRASOUND AS AN ADJUNCT TO MAMMOGRAPHY

The budget impact of supplemental screening with ultrasound for people with dense breasts and extremely dense breasts is presented in Table 47 and Appendix 11, Table A22. In the current scenario, the average total health care cost (including breast screening, diagnostic assessment, and treatment) for

the total screening cohort (BI-RADS A to D) was approximately $794 million per year, for a total of $3.97 billion over 5 years. Of this, the total cost of breast screening with mammography was $425 million for approximately 6.6 million people screened over 5 years (Appendix 11, Table A22).

In the new scenario and assuming slow uptake (2.5% to 12.5% over the next 5 years), the average total health care cost for the total screening cohort (BI-RADS A to D) was approximately $797 million per year, for a total of $3.99 billion over 5 years. The total cost of breast screening alone, including supplemental screening with ultrasound for people with dense breasts, was $434.6 million over 5 years (Appendix 11, Table A22). Similarly, the total health care cost, including supplemental screening with ultrasound for people with extremely dense breasts, was $3.98 billion over 5 years (Table 47 and Appendix 11, Table A22). Breast screening alone (including supplemental screening with ultrasound) resulted in a total cost of $427.9 million over 5 years.

Assuming slow uptake, publicly funding supplemental screening with ultrasound as an adjunct to mammography for people with dense breasts and extremely dense breasts would result in an additional $14.9 million and $4.0 million, respectively, in total health care costs (including screening, diagnostic assessment, and treatment) over 5 years. The additional cost associated with breast screening alone for people with dense breasts and extremely dense breasts would be $9.4 million and $2.7 million, respectively, over 5 years (Appendix 11, Table A22).

Table 47: Budget Impact Analysis Results—Supplemental Screening With Handheld Ultrasound for People With Dense Breasts and Extremely Dense Breasts

	Budget impact, $[a,b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario (mammography screening alone)						
Total cost[c]	763,779,796	786,594,360	795,938,114	809,826,759	815,871,138	3,972,010,166
New scenario (supplemental screening with ultrasound for people with dense breasts)						
Total cost[c,d]	764,434,392	789,069,010	799,558,846	813,613,888	820,237,675	3,986,913,811
Budget impact	654,596	2,474,651	3,620,731	3,787,129	4,366,537	14,903,644
New scenario (supplemental screening with ultrasound for people with extremely dense breasts)						
Total cost[c,d]	763,904,317	787,326,672	796,950,687	810,872,466	816,959,060	3,976,013,202
Budget impact	124,521	732,312	1,012,573	1,045,706	1,087,923	4,003,035

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Total cost includes all health care costs related to breast screening, diagnostic assessment, and treatment for the total screening cohort (i.e., all people eligible for breast screening in Ontario).

[d] In the new scenario, the estimated cost corresponds to slow uptake of supplemental ultrasound from 2.5% to 12.5% for year 1 to year 5.

SUPPLEMENTAL SCREENING WITH MRI AS AN ADJUNCT TO MAMMOGRAPHY

The budget impact of supplemental screening with MRI for people with dense breasts and extremely dense breasts is presented in Table 48 and Appendix 11, Table A23. In the current scenario, the average total health care cost (including screening, diagnostic assessment, and treatment) for the total screening cohort (BI-RADS A to D) was approximately $793 million per year, for a total of $3.97 billion over 5 years.

Of this, the total cost of breast screening with mammography was $425 million for approximately 6.6 million people screened over 5 years (Appendix 11, Table A23).

In the new scenario and assuming slow uptake (2.5% to 12.5% over the next 5 years), the average total health care cost including supplemental screening with MRI for people with dense breasts was approximately $801 million per year, for a total of $4 billion over 5 years. Of this, the total cost of breast screening alone, including supplemental screening with MRI for people with dense breasts, was $453 million over 5 years (Appendix 11, Table A23). Similarly, the total health care cost, including supplemental screening with MRI for people with extremely dense breasts, was $3.98 billion over 5 years. Breast screening alone (including supplemental screening with MRI) resulted in a total cost of $433 million over 5 years.

Assuming slow uptake, publicly funding supplemental screening with MRI as an adjunct to mammography for people with dense breasts and extremely dense breasts would result in an additional $40.5 million and $9. 9 million, respectively, in total health care costs (including screening, diagnostic assessment, and treatment) over 5 years. The additional cost associated with breast screening alone for people with dense breasts and extremely dense breasts would be $27.7 million and $7.9 million, respectively, over 5 years (Appendix 11, Table A23).

Table 48: Budget Impact Analysis Results—Supplemental Screening With MRI for People With Dense Breasts and Extremely Dense Breasts

	Budget impact, $[a,b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario (mammography screening alone)						
Total cost[c]	763,429,716	784,878,348	794,249,919	809,498,356	815,003,627	3,967,059,966
New scenario (supplemental screening with MRI for people with dense breasts)						
Total cost[c,d]	765,263,392	791,346,973	804,131,000	820,093,759	826,689,599	4,007,524,723
Budget impact	1,833,676	6,468,625	9,881,081	10,595,403	11,685,972	40,464,757
New scenario (supplemental screening with MRI for people with extremely dense breasts)						
Total cost[c,d]	763,853,717	786,760,640	796,534,659	811,946,837	817,849,408	3,976,945,261
Budget impact	424,001	1,882,292	2,284,740	2,448,481	2,845,781	9,885,295

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Total cost includes all health care costs related to breast screening, diagnostic assessment, and treatment for the total screening cohort (i.e., all people eligible for breast screening in Ontario).

[d] In the new scenario, the estimated cost corresponds to slow uptake of supplemental MRI from 2.5% to 12.5% for year 1 to year 5.

SUPPLEMENTAL SCREENING WITH DBT AS AN ADJUNCT TO MAMMOGRAPHY

The budget impact of supplemental screening with DBT for people with dense breasts and extremely dense breasts is presented in Table 49 and Appendix 11, Table A24. In the current scenario, the average total health care cost (including screening, diagnostic assessment, and treatment) for the total screening cohort (BI-RADS A to D) was approximately $793 million per year, for a total of $3.97 billion over 5 years. Of this, the total cost of breast screening with mammography was $425 million for approximately 6.6 million people screened (Appendix 11 Table A24).

In the new scenario and assuming moderate uptake (10% to 30% in the next 5 years), the average total health care cost including supplemental screening with DBT for people with dense breasts was approximately $800 million per year, for a total of about $4 billion over 5 years. Of this, the total cost of breast screening alone, including supplemental screening with DBT for people with dense breasts, was about $453 million over 5 years (Appendix 11, Table A24). Similarly, the total health care cost, including supplemental screening with DBT for people with extremely dense breasts, was $3.98 billion over 5 years. Breast screening alone (including supplemental screening with DBT) resulted in a total cost of $433 million over 5 years.

Assuming moderate uptake, publicly funding supplemental screening with DBT as an adjunct to mammography for people with dense breasts and extremely dense breasts would result in an additional $32.8 million and $9.4 million, respectively, in total health care costs (including screening, diagnostic assessment, and treatment) over 5 years. The additional cost associated with breast screening alone for people with dense breasts and extremely dense breasts would be $27.4 million and $7.7 million, respectively, over 5 years (Appendix 11, Table A24).

Table 49: Budget Impact Analysis Results—Supplemental Screening With DBT for People With Dense Breasts and Extremely Dense Breasts

	Budget impact, $[a,b]					
Scenario	**Year 1**	**Year 1**	**Year 1**	**Year 1**	**Year 1**	**Year 1**
Current scenario (mammography screening alone)						
Total cost[c]	763,429,716	784,878,348	794,249,919	809,498,356	815,003,627	3,967,059,966
New scenario (supplemental screening with DBT for people with dense breasts)						
Total cost[c,d]	765,876,802	790,480,351	801,783,400	817,395,843	824,328,777	3,999,865,172
Budget impact	2,447,086	5,602,003	7,533,481	7,897,487	9,325,149	32,805,205
New scenario (supplemental screening with DBT for people with extremely dense breasts)						
Total cost[c,d]	763,910,042	786,633,079	796,621,490	811,620,564	817,674,411	3,976,459,587
Budget impact	480,326	1,754,731	2,371,572	2,122,208	2,670,784	9,399,621

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Total cost includes all health care costs related to breast screening, diagnostic assessment, and treatment for the total screening cohort (i.e., all people eligible for breast screening in Ontario).

[d] In the new scenario, the estimated cost corresponds to moderate uptake of supplemental DBT from 10% to 30% for year 1 to year 5.

Sensitivity Analysis

In our sensitivity analyses, uptake rate and supplemental screening with ABUS (for ultrasound) had the greatest impact on total health care costs, cost of screening, and budget impact.

SUPPLEMENTAL SCREENING WITH ULTRASOUND AS AN ADJUNCT TO MAMMOGRAPHY

The sensitivity analyses of supplemental screening with ultrasound for people with dense breasts and people with extremely dense breasts are presented in Table 50 and Table 51.

All analyses assumed the costs of handheld ultrasound, except for the scenario with ABUS. Supplemental screening with ABUS increased the budget impact from $15 million to $39 million for

people with dense breasts and from $4 million to about $10 million for people with extremely dense breasts. Assuming moderate uptake of supplemental screening (10% in year 1 to 30% in year 5) increased the budget impact from $15 million to $40 million for people with dense breasts, and from $4 million to $11 million for people with extremely dense breasts.

The budget impact decreased by 8% for people with dense breasts and 7% for people with extremely dense breasts when the cost of ultrasound screening was 25% less than its reference case value. Similarly, increasing the cost of ultrasound screening by 25% increased the budget impact by 8% for people with dense breasts and 10% for people with extremely dense breasts compared to the reference case value. Increased and decreased costs related to follow-up after an abnormal screen (± 25%) and increased treatment costs for stage III and IV breast cancers (doubled, or 100% increase) had minor effects on the estimated budget impact compared to the reference case.

Table 50: Sensitivity Analysis Results—Budget Impact of Supplemental Screening With Ultrasound for People With Dense Breasts

Scenario	Budget impact, $[a]						
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]	% Difference
Reference case[d]							
Total health care costs	654,596	2,474,651	3,620,731	3,787,129	4,366,537	14,903,644	–
Screening costs	531,387	1,298,453	1,863,481	2,530,854	3,131,653	9,355,828	–
Sensitivity analysis 1: ultrasound screening with ABUS							
Total health care costs	1,653,084	6,427,216	9,871,462	10,239,538	11,198,326	39,389,627	164%
Screening costs	1,472,030	3,594,399	5,143,687	6,963,403	8,598,352	25,771,871	175%
Sensitivity analysis 2: moderate uptake (10% to 30% in the next 5 years)							
Total health care costs	2,618,385	7,423,952	9,655,283	9,467,823	10,479,690	39,645,132	166%
Screening costs	2,125,548	3,895,360	4,969,283	6,327,134	7,515,968	24,833,293	165%
Sensitivity analysis 3A: cost of ultrasound, −25%							
Total health care costs	586,848	2,309,169	3,382,931	3,463,571	3,966,204	13,708,723	−8%
Screening costs	463,639	1,132,972	1,625,681	2,207,296	2,731,320	8,160,907	−13%
Sensitivity analysis 3B: cost of ultrasound, +25%							
Total health care costs	722,252	2,639,907	3,858,208	4,110,247	4,766,326	16,096,940	8%
Screening costs	599,043	1,463,709	2,100,958	2,853,971	3,531,442	10,549,124	13%
Sensitivity analysis 4A: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), −25%							
Total health care costs	652,225	2,464,864	3,609,286	3,774,949	4,351,017	14,852,341	−0.34%
Cost of follow-up for abnormal screens (true-and false-positive)	7,258	31,775	40,144	46,742	58,506	184,426	−25%
Sensitivity analysis 4B: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), +25%							
Total health care costs	656,967	2,484,437	3,632,177	3,799,309	4,382,058	14,954,948	0.34%
Cost of follow-up for abnormal screens (true- and false-positive)	12,097	52,960	66,909	77,905	97,513	307,385	25%
Sensitivity analysis 5: cost of treatment for stage III and IV breast cancers, doubled (100% increase)							
Total health care costs	660,553	2,510,388	3,684,381	3,691,146	4,242,552	14,789,021	−0.77%
Cost of cancer management	119,682	1,172,781	1,775,105	1,111,554	1,048,792	5,227,914	−2.15%

Abbreviation: ABUS, automated breast ultrasound.

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Negative costs indicate savings.

[d] Budget impact associated with total health care costs or with screening costs alone.

Table 51: Sensitivity Analysis Results—Budget Impact of Supplemental Screening With Ultrasound for People With Extremely Dense Breasts

Scenario	Budget impact, $[a]						
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]	% Difference
Reference case[d]							
Total health care costs	124,521	732,312	1,012,573	1,045,706	1,087,923	4,003,035	–
Screening costs	100,536	386,585	550,520	719,997	907,650	2,665,288	–
Sensitivity analysis 1: ultrasound screening with ABUS							
Total health care costs	327,007	1,949,435	2,418,399	2,324,036	2,670,882	9,689,759	142%
Screening costs	278,501	1,070,278	1,513,124	1,978,526	2,492,898	7,333,327	175%
Sensitivity analysis 2: moderate uptake (10% to 30% in the next 5 years)							
Total health care costs	498,084	2,196,937	2,700,194	2,614,266	2,611,015	10,620,496	165%
Screening costs	402,143	1,159,755	1,468,053	1,799,992	2,178,360	7,008,304	163%
Sensitivity analysis 3A: cost of ultrasound, −25%							
Total health care costs	111,703	688,786	950,885	965,275	986,426	3,703,075	−7%
Screening costs	87,718	337,947	481,070	629,097	792,990	2,328,821	−13%
Sensitivity analysis 3B: cost of ultrasound, +25%							
Total health care costs	137,321	787,338	1,091,692	1,149,695	1,219,020	4,385,067	10%
Screening costs	113,336	436,499	621,877	813,517	1,025,584	3,010,814	13%
Sensitivity analysis 4A: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), −25%							
Total health care costs	124,052	735,154	1,018,331	1,054,509	1,098,761	4,030,808	0.7%
Cost of follow-up for abnormal screens (true- and false-positive)	1,406	9,820	10,654	11,043	15,015	47,938	−24%
Sensitivity analysis 4B: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), +25%							
Total health care costs	124,990	741,037	1,024,342	1,060,587	1,106,843	4,057,799	1.4%
Cost of follow-up for abnormal screens (true- and false-positive)	2,344	16,366	17,757	18,406	25,026	79,900	27%
Sensitivity analysis 5: cost of treatment for stage III and IV breast cancers, doubled (100% increase)							
Total health care costs	124,796	747,470	1,031,570	1,033,726	1,075,570	4,013,132	0.3%
Cost of cancer management	22,385	348,438	468,012	300,178	150,015	1,289,027	0.3%

Abbreviation: ABUS, automated breast ultrasound.

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Negative costs indicate savings.

[d] Budget impact associated with total health care costs or with screening costs alone.

SUPPLEMENTAL SCREENING WITH MRI AS AN ADJUNCT TO MAMMOGRAPHY

The sensitivity analyses of supplemental screening with MRI for people with dense breasts and people with extremely dense breasts are presented in Table 52 and Table 53.

Assuming a moderate uptake of supplemental screening (10% in year 1 to 30% in year 5) increased the budget impact from $40.5 million to $107.7 million for people with dense breasts, and from $9.9 million to $26.4 million for people with extremely dense breasts.

The budget impact decreased by 14% for people with dense breasts and 16% for people with extremely dense breasts when the cost of MRI screening was 25% less than its reference case value. Similarly, increasing the cost of MRI screening by 25% increased the budget impact by 14% for people with dense breasts and 17% for people with extremely dense breasts compared to the reference case value. Increased and decreased costs related to follow-up after an abnormal screen (± 25%) and increased treatment costs for stage III and IV breast cancers (doubled, or 100% increase) had minor effects on the estimated budget impact compared to the reference case.

Table 52: Sensitivity Analysis Results—Budget Impact of Supplemental Screening With MRI for People With Dense Breasts

	Budget impact, $[a]						
Scenario	Year 1	Year 2	Year 1	Year 4	Year 1	Total[b,c]	% Difference
Reference case[d]							
Total health care costs	1,833,676	6,468,625	9,881,081	10,595,403	11,685,972	40,464,757	–
Screening costs	1,580,980	3,857,328	5,528,426	7,485,717	9,247,494	27,699,944	–
Sensitivity analysis 1: moderate uptake (10% to 30% in the next 5 years)							
Total health care costs	7,334,704	19,425,671	26,376,286	26,521,546	28,085,678	107,743,885	166%
Screening costs	6,323,920	11,575,500	14,747,055	18,720,166	22,200,994	73,567,635	166%
Sensitivity analysis 2A: cost of MRI, −25%							
Total health care costs	1,503,506	5,669,347	8,734,982	9,040,625	9,764,784	34,713,244	-14%
Screening costs	1,250,810	3,052,623	4,374,021	5,920,073	7,312,833	21,910,360	-21%
Sensitivity analysis 2B: cost of MRI, +25%							
Total health care costs	2,163,754	7,280,876	11,046,910	12,176,174	13,639,406	46,307,119	14%
Screening costs	1,911,057	4,664,152	6,685,948	9,055,622	11,187,455	33,504,234	21%
Sensitivity analysis 3A: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), −25%							
Total health care costs	1,830,965	6,458,841	9,870,204	10,593,788	11,685,472	40,439,270	−0.18%
Cost of follow-up for abnormal screens (true- and false-positive)	8,357	52,695	71,475	60,643	70,305	263,475	−25%
Sensitivity analysis 3B: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), +25%							
Total health care costs	1,836,387	6,491,606	9,912,010	10,623,449	11,719,260	40,582,712	0.17%
Cost of follow-up for abnormal screens (true- and false-positive)	13,930	87,827	119,128	101,075	117,178	439,136	25%
Sensitivity analysis 4: cost of treatment for stage III and IV breast cancers, doubled (100% increase)							
Total health care costs	1,839,071	6,531,867	10,013,169	10,504,153	11,520,223	40,408,482	−0.26%
Cost of cancer management	247,249	2,607,829	4,399,398	2,956,745	2,202,210	12,413,432	−0.84%

Abbreviation: MRI, magnetic resonance imaging.

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Negative costs indicate savings.

[d] Budget impact associated with total health care costs or with screening costs alone.

Table 53: Sensitivity Analysis Results—Budget Impact of Supplemental Screening With MRI for People With Extremely Dense Breasts

	Budget impact, $[a]						
Scenario	Year 1	Year 2	Year 1	Year 4	Year 1	Total[b,c]	% Difference
Reference case[d]							
Total health care costs	424,001	1,882,292	2,284,740	2,448,481	2,845,781	9,885,295	–
Screening costs	299,114	1,146,778	1,628,961	2,130,977	2,686,826	7,892,655	–
Sensitivity analysis 1: moderate uptake (10% to 30% in the next 5 years)							
Total health care costs	1,696,004	5,646,877	6,092,640	6,121,203	6,829,874	26,386,597	167%
Screening costs	1,196,455	3,440,333	4,343,896	5,327,443	6,448,382	20,756,509	163%
Sensitivity analysis 2A: cost of MRI, −25%							
Total health care costs	361,535	1,648,504	1,952,350	2,013,702	2,297,464	8,273,554	−16%
Screening costs	236,647	907,833	1,288,799	1,685,735	2,125,364	6,244,379	−21%
Sensitivity analysis 2B: cost of MRI, +25%							
Total health care costs	486,450	2,127,888	2,634,893	2,907,214	3,424,176	11,580,620	17%
Screening costs	361,563	1,387,217	1,971,342	2,579,247	3,252,076	9,551,445	21%
Sensitivity analysis 3A: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), −25%							
Total health care costs	422,977	1,883,596	2,289,775	2,457,482	2,857,209	9,911,040	0.3%
Cost of follow-up for abnormal screens (true- and false-positive)	3,185	15,670	14,483	12,463	16,224	62,025	−24%
Sensitivity analysis 3B: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), +25%							
Total health care costs	425,025	1,892,862	2,297,563	2,463,558	2,864,588	9,943,596	0.6%
Cost of follow-up for abnormal screens (true- and false-positive)	5,308	26,118	24,140	20,772	27,040	103,378	27%
Sensitivity analysis 4: cost of treatment for stage III and IV breast cancers, doubled (100% increase)							
Total health care costs	424,551	1,907,309	2,292,644	2,403,757	2,815,227	9,843,487	−0.4%
Cost of cancer management	121,342	741,208	646,936	259,029	111,645	1,880,159	−3%

Abbreviation: MRI, magnetic resonance imaging.

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Negative costs indicate savings.

[d] Budget impact associated with total health care costs or with screening costs alone.

SUPPLEMENTAL SCREENING WITH DBT AS AN ADJUNCT TO MAMMOGRAPHY

The sensitivity analyses of supplemental screening with DBT for people with dense breasts and for people with extremely dense breasts are presented in Table 54 and Table 55.

Assuming a slow uptake of supplemental screening (2.5% in year 1 to 12.5% in year 5) decreased the budget impact from $32.8 million to $12.4 million for people with dense breasts and from $9.4 million to $3.6 million for people with extremely dense breasts.

The budget impact decreased by 12% for people with dense breasts and 10% for people with extremely dense breasts when the cost of DBT screening was 25% less than its reference case value. Similarly, increasing the cost of DBT screening by 25% increased the budget impact by 11% for people with dense breasts and 13% for people with extremely dense breasts compared to the reference case value. Increased and decreased costs related to follow-up after an abnormal screen (± 25%) and increased treatment costs for stage III and IV breast cancers (doubled, or 100% increase) had minor effects on the estimated budget impact compared to the reference case.

Table 54: Sensitivity Analysis Results—Budget Impact of Supplemental Screening With DBT for People With Dense Breasts

Scenario	Budget impact, $[a]						
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]	% Difference
Reference case[d]							
Total health care costs	2,447,086	5,602,003	7,533,481	7,897,487	9,325,149	32,805,205	–
Screening costs	2,337,181	4,281,037	5,471,618	6,987,699	8,294,102	27,371,637	–
Sensitivity analysis 1: slow uptake (2.5% to 12.5% in the next 5 years)							
Total health care costs	611,771	1,873,269	2,834,063	3,171,137	3,900,747	12,390,986	−62%
Screening costs	584,295	1,427,834	2,053,075	2,796,752	3,457,960	10,319,916	−62%
Sensitivity analysis 2A: cost of DBT, −25%							
Total health care costs	2,123,369	5,026,742	6,799,171	6,958,955	8,211,589	29,119,826	−12%
Screening costs	2,013,464	3,690,436	4,716,538	6,022,994	7,148,900	23,592,332	−14%
Sensitivity analysis 2B: cost of DBT, +25%							
Total health care costs	2,770,804	6,212,872	8,315,829	8,896,728	10,511,995	36,708,227	11%
Screening costs	2,660,898	4,876,566	6,233,196	7,960,767	9,449,306	31,180,734	14%
Sensitivity analysis 3A: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), −25%							
Total health care costs	2,446,332	5,614,089	7,551,299	7,924,127	9,356,494	32,892,341	−0.10%
Cost of follow-up for abnormal screens (true- and false-positive)	2,522	20,334	26,205	24,206	31,564	104,831	−25.2%
Sensitivity analysis 3B: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), +25%							
Total health care costs	2,447,840	5,625,525	7,563,701	7,931,556	9,367,089	32,935,712	0.03%
Cost of follow-up for abnormal screens (true- and false-positive)	4,203	33,892	43,677	40,344	52,608	174,724	24.7%
Sensitivity analysis 4: cost of treatment for stage III and IV breast cancers, doubled (100% increase)							
Total health care costs	2,449,285	5,651,838	7,671,483	7,995,698	9,179,986	32,948,290	0.07%
Cost of cancer management	109,086	1,345,434	2,171,772	988,904	859,631	5,474,827	0.5%

Abbreviation: DBT, digital breast tomosynthesis.

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Negative costs indicate savings.

[d] Budget impact associated with total health care costs or with screening costs alone.

Table 55: Sensitivity Analysis Results—Budget Impact of Supplemental Screening With DBT for People With Extremely Dense Breasts

Scenario	Budget impact, $[a]						
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]	% Difference
Reference case[d]							
Total health care costs	480,326	1,754,731	2,371,572	2,122,208	2,670,784	9,399,621	–
Screening costs	442,183	1,275,632	1,622,647	1,994,177	2,413,046	7,747,685	–
Sensitivity analysis 1: slow uptake (2.5% to 12.5% in the next 5 years)							
Total health care costs	120,081	584,910	889,339	848,883	1,112,827	3,556,041	−62%
Screening costs	110,546	425,211	608,493	797,671	1,005,436	2,947,356	−62%
Sensitivity analysis 2A: Cost of DBT, −25%							
Total health care costs	419,080	1,595,243	2,169,760	1,875,009	2,371,490	8,430,582	−10%
Screening costs	380,938	1,100,925	1,400,255	1,720,917	2,082,222	6,685,257	−14%
Sensitivity analysis 2B: Cost of DBT, +25%							
Total health care costs	541,572	1,948,718	2,619,932	2,428,449	3,041,442	10,580,112	13%
Screening costs	503,429	1,454,400	1,850,426	2,274,357	2,752,174	8,834,787	14%
Sensitivity analysis 3A: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), −25%							
Total health care costs	479,916	1,769,108	2,392,396	2,150,008	2,703,885	9,495,314	1.0%
Cost of follow-up for abnormal screens (true- and false-positive)	1,228	9,955	10,685	9,978	13,715	45,561	−21%
Sensitivity analysis 3B: cost of follow-up assessment for abnormal screen (false-positive and true-positive screens), +25%							
Total health care costs	480,735	1,774,853	2,397,295	2,153,450	2,709,047	9,515,380	1.2%
Cost of follow-up for abnormal screens (true- and false-positive)	2,048	16,592	17,808	16,631	22,859	75,937	31%
Sensitivity analysis 4: cost of treatment for stage III and IV breast cancers, doubled (100% increase)							
Total health care costs	481,425	1,790,168	2,416,659	2,124,629	2,658,401	9,471,282	0.8%
Cost of cancer management	37,604	500,985	781,478	120,054	230,816	1,670,937	3%

Abbreviation: DBT, digital breast tomosynthesis.

[a] In 2022 Canadian dollars.

[b] Results may appear inexact due to rounding.

[c] Negative costs indicate savings.

[d] Budget impact associated with total health care costs or with screening costs alone.

Discussion

We conducted a budget impact analysis using the OncoSim-Breast model, which provided the annual undiscounted total health care costs for the next 5 years (2023–2027). The budget impact analysis showed that publicly funding supplemental screening as an adjunct to mammography for people with dense breasts would result in an additional cost over the next 5 years. Although supplemental screening decreased costs related to cancer management by improving the detection of early cancers, the increased budget impact was due largely to the additional cost of supplemental screening. Publicly funding supplemental screening with handheld ultrasound or MRI for people with dense breasts, assuming slow uptake over the next 5 years, would cost an additional $15 million or $40 million, respectively. Publicly funding supplemental screening with DBT for people with dense breasts, assuming moderate uptake over the next 5 years, would cost an additional $33 million. However, the budget impact would be much smaller if supplemental screening were publicly funded only for people with extremely dense breasts (smaller population); in this population, supplemental screening with ultrasound, MRI or DBT over the next 5 years, would cost an additional $4 million, $10 million or $9.4 million.

Given the uncertainty about the uptake of supplemental screening indicated by the clinical experts, we conducted sensitivity analyses to estimate the budget impact of moderate uptake for ultrasound and MRI, and of slow uptake for DBT. Assuming moderate uptake, the budget impact of publicly funding supplemental screening with ultrasound and MRI would increase by approximately 166% compared to the slow uptake we assumed in the reference case analysis. Assuming slow uptake of supplemental screening with DBT, the budget impact decreased by 62% compared to the moderate uptake we assumed in the reference case analysis.

Given that the budget impact of supplemental screening is due largely to the cost of screening, we also evaluated the estimated cost of supplemental screening for each modality. Across all three supplemental modalities, a 25% decrease or increase in the cost of screening compared to the value used in the reference case analysis resulted in an approximately 12% decrease or increase in budget impact.

Finally, although handheld ultrasound is often the ultrasound modality used for population-based screening, ABUS is available at private clinics, where patients pay for breast screening out of pocket or through their private insurance plan. Assuming the current costs at private clinics, publicly funding supplemental screening with ABUS would cost an additional $39 million for people with dense breasts or an additional $9 million for people with extremely dense breasts (compared to $14 million and $4 million, respectively, for supplemental handheld ultrasound).

Strengths and Limitations

One of the strengths of our budget impact analysis is that we estimated and calibrated the size of the target population using Ontario-specific screening data from the CSQI report.[139] We also evaluated additional cost components, such as diagnostic costs for true- and false-positive screens, diagnostic costs related to clinical detection, and costs of cancer management. However, this analysis also had several limitations. We considered people who were screened through the OBSP. In addition, we assumed no public funding of supplemental screening, capturing only mammography screening in the current scenario. However, clinical experts have suggested that patients may have access to supplemental screening at their physician's request. Therefore, our approach may underestimate the total cost in the current scenario and overestimate the budget impact of publicly funding supplemental

screening. As well, our analysis assumed that there was no mix of the supplemental modalities because of uncertainty related to capacity and the implementation of supplemental screening across OBSP sites that are modality dependent.

Conclusions

Publicly funding supplemental screening with handheld ultrasound, MRI, or DBT for people with dense breasts over the next 5 years would increase the total budget by $15 million, $40 million, or $33 million, respectively. However, publicly funding supplemental screening with handheld ultrasound, MRI, or DBT for people with extremely dense breasts (a smaller population) over the next 5 years would increase the total budget by $4 million, $10 million, or $9 million, respectively.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those with dense breasts who may undergo screening for breast cancer. We also looked to examine patient and family or caregiver perceptions of decision-making, as well as impacts, challenges, or barriers to accessing supplemental screening.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[111,167,168] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Since the needs, preferences, priorities, and values of those with lived experience in Ontario are important to understanding the impact of the technology on people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with dense breasts, as well as their family members and caregivers, in two ways:

- Direct engagement by Ontario Health with people with dense breasts through telephone interviews and online survey submissions
- A review by the Canadian Agency for Drugs and Technologies in Health (CADTH) of the published qualitative evidence

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with dense breasts and those of their families and caregivers. We engaged with participants via phone interviews and an online survey.

We conducted qualitative interviews, because this method of engagement allowed us to explore the meaning of central themes in the experiences of people with dense breasts, as well as those of their families and caregivers.[169] We also offered an online survey to reduce barriers to participation. The questions included in the survey were open-ended and reflected the central themes of the qualitative

interview. The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that supported our choice of methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[170-173] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of community and partner organizations to connect with and to contact people with dense breasts, family members, and caregivers, including those with experience of breast cancer screening.

Inclusion Criteria

We sought to speak with adults who had dense breasts and had undergone supplemental screening for breast cancer. We also invited family members and caregivers of those with dense breasts to participate. Participants did not have to have direct experience of supplemental screening after confirmation of their breast density status.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we engaged with 70 people, including 69 who reported having dense breasts and one family member. Fifty-five participated via phone interviews, and 15 completed an online survey.

Participants lived primarily in southern Ontario, and rural and urban settings were equally represented. Our engagement included those with dense breasts who had experience with supplemental screening for breast cancer and diagnostic imaging through provider referrals.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 12) if requested. We then obtained participants' verbal consent before starting the interview. With the participants' consent, we audiorecorded and then transcribed the interviews.

Interviews lasted approximately 45 minutes. The interview was semistructured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[174] The questions focused on the participants' journey to finding out their breast density status, the impacts of having dense breasts, and their perceptions of the benefits or limitations of broad access to supplemental screening in Ontario. To reduce barriers to participation, we made an online survey available via the Alchemer platform. Survey questions were open-ended and reflected the central themes of the qualitative interview. See Appendix 13 for our interview guide and Appendix 14 for our online survey.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts and survey results. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[175,176] We used the qualitative data analysis software program NVivo[32] to identify and interpret patterns in the data. The patterns we identified allowed us to describe the potential impact of having dense breasts and access to supplemental screening on patients as well as their family members and caregivers.

Results

CARE JOURNEY

Breast Density—Awareness and Prompting

Breast density awareness varied among those interviewed. However, the majority of participants reported first hearing about breast density through their health care provider during a routine mammogram or diagnostic test. Participants characterized their initial conversations about breast density as brief and indirect. Overall, when initially prompted, most participants felt that their general knowledge about breast density was limited, and its impact on their care was unclear:

> *When I would get the results from my mammogram, my doctor would say, "Oh yeah! You know, your breasts are quite dense," and I'd see it sometimes on the report. It was just kind of something in passing, you know? It was never really an in-depth thing.*
>
> *When I was in my 40s, it was just an off-hand comment from the mammography technician. Nothing was ever said directly to me.*
>
> *I had gone for a mammogram and there were suspicious findings, but because of the density, they couldn't get an accurate piece of information. And they wanted me to get an MRI—so it was only mentioned in the conversation of "Why is the mammogram not helpful?" and "Why do I need an MRI?"*
>
> *It was just a simple conversation of "Oh, you have dense breasts." No explanation that it puts you at increased risk, what does that mean other than you have it, or "We can't see anything on the mammogram so that was a bit of a waste of time and the MRI is a better diagnostic tool." So, there was really no education. And I think at that point, I was so overwhelmed by the amount of information coming at me for a whole bunch of content that it didn't occur to me to actually ask for more information.*

Other participants recalled receiving a notification letter from the provincial breast cancer screening program after a routine mammogram, and this letter confirmed their breast density status. Participants commented on the value of having access to this information, although they felt that they could have benefited from more personalized instruction. In many cases, they were not sure how to interpret the findings or what effect it would have on their personal risk for breast cancer:

> *In the follow-up letter that was sent out with routine mammogram results, there was passing mention that I had dense breasts, but no further information regarding the grading or any measures to take. It was never brought to my attention otherwise.*

In 2022, I got a letter saying, "You're going to get yearly screening because of dense tissue." I didn't know what was going on—screening seemed to come and go.

In the follow-up letter that gets sent out with routine mammogram results, there had been passing mention that I had dense breasts, but no further information regarding the grading or any measures to take. It was otherwise never brought to my attention. This lack of information had me relying solely on my routine annual mammogram to find any abnormalities, with no other type of screening, much to my detriment.

Factors that seemed to influence early awareness of breast tissue density and supplemental screening included a family history of breast cancer or lived experience as a caregiver. Participants who had cared for a friend or family member diagnosed with breast cancer were often prompted to seek out more information about dense breasts by those in their personal network. The people we interviewed shared how these prompts supported early health-seeking behaviour and reinforced their intent to complete routine and supplemental screening for breast cancer. Similarly, participants who had a professional medical background or knew someone with such a background often reported being aware of breast tissue density and knowing about its potential impact on breast cancer screening and personal risk:

My mom's a general practitioner and had breast cancer. So she was more aware of me and what my risks might be, and she said to me, "Don't worry about it. We'll get the information during your initial screening," which I did at 35.

My friends had told me that they knew people in their 40s who had developed breast cancer and had dense breasts, so they kept saying, "You really need to get screened. You really need to go."

Because my mother had breast cancer, I read up on it a lot. Then I read quite a lot about dense breasts being a risk factor for breast cancer. It made me even more eager to get tested.

My sister is a breast radiologist, and her forte is dense breasts. I've known about dense breasts way before I knew I had dense breasts—so when I went to start getting mammograms, I knew to ask if I had dense breasts, and I understood all the implications.

Breast Density—Access to Information

Participants emphasized the importance of having access to information about breast cancer prevention, and they valued shared decision-making. Many of those we interviewed described how knowing their breast density affected their decision-making and the barriers they encountered when trying to learn more about breast density or supplemental screening. Central themes from these discussions included the patient–doctor partnership and how communication with care providers can impact the patient experience:

The only way you can come to terms with your diagnosis is by finding out more about it and what you can do. Once you've taken charge of the situation, you feel like you have at least some control. I would rather know what's going on and be part of the decision-making—not that I'm going to question their medical ability or their care, but it would be nice to know what to expect, you know?

I was just so flabbergasted that my doctor just said no because I didn't have the other risk factors. And I had to go against everything I believed my whole life, which is that "the doctor

knows best." I now realize that doctors can't possibly know everything that's out there, but I was so uncomfortable. I thought, "Is she going to throw me out of her practice because I asked about supplemental screening?"

I like details—I need details. I'm one that wants follow-ups, that needs ultrasounds or any testing explained in detail. I mean, I do like a copy, but I also like a follow-up with the doctor to explain what it all means and why. I think that's fair as a patient to be able to understand the result and what the next steps are. I think it's very important.

Some participants also found it challenging to seek out information from their care team, and were not sure who should be their main point of contact. Participants had similar accounts related to navigating patient education programs at the community level. Overall, participants found it challenging to identify a point of contact and felt that more support could be offered to patients for accessing educational resources about breast tissue density:

When I went for those yearly mammograms, I would ask, "Do I have dense breasts?" and they would say "We have to ask your doctor." Then it went back and forth, and it felt like nobody could ever tell me what my body was doing.

I know they're busy and can't cover everything that you may need to know. But it just would have been good to be able to have access to someone to ask questions of at the time … That's why I think other types of resources are important.

The professionals I spoke with provided conflicting information. I did not get educational material on dense breasts through the hospital or my family doctor. It was only after extensive treatment for breast cancer and review of my own mammogram reports that I had definitive information on my own status.

What I'm learning in my own community is that there are a lot of resources! … I just heard about this new medical office that does screening on the fly the other day, and I was like, "Why isn't there a Facebook page or something that's on the news that says, 'Hey, here's this new program in town' or that type of thing?" I may not qualify for it, but at least it says what the resources are. I think something like that in this particular community would have been helpful for me.

To overcome these barriers, most participants opted to do their own research online. Through this search, participants often reported coming across online communities, and they reflected on how membership in these groups affected their care journey. Many appreciated the information offered by online communities about breast density as a risk factor, the different classifications of dense breast tissue, and options related to supplemental screening. Other participants mentioned the support they received from friends and family in navigating the health care system as someone with dense breasts:

I researched all over the internet. I looked at all of the medical reports they had, and the test studies they've done on breast density and the likelihood of cancer, and the treatments that were available, and the efficacy of all those treatments.

With COVID, you couldn't go in to talk to anybody, and everything was shut down. So I reached out to an online group for breast cancer—that's the comfort zone and a place where you feel understood.

I will be honest with you and say the best source of information and resources for me was a breast cancer support group that I found on Facebook in 2014. I belong to others as well, but this one in particular is for Canadian women, and just that connection with other women who have dealt with this thing made me feel a lot better.

Pretty much right after that mammogram I started looking into it, and I'm sure it was just a good old Google search, you know? And since then, I have talked with other friends—one friend in particular who is a breast cancer survivor and was diagnosed with dense breast tissue through supplemental screening that a mammogram had not picked up.

Access to Supplemental Screening and Self-Advocacy

Supplemental breast screening refers to additional imaging conducted at the same time as or after screening mammography. This is distinct from diagnostic imaging, which is typically used to follow a clinical or suspicious finding seen in mammography. The majority of the people we spoke with had experience with diagnostic imaging, but we were able to talk with participants who shared their experiences of supplemental screening through physician referral. These participants reported exposure to various imaging technologies, the most common being annual mammography and ultrasound imaging. They also commented on the importance of access to information and support from their care team in coordinating supplemental screening. In some cases, supplemental screening detected a breast tissue condition that had not been previously identified:

I was just sent for a breast MRI last month, and I didn't have to request this one. I can't stress this enough; I think the part that really helped me was that I had information in my back pocket! … I have been very fortunate to have family physicians that are willing to hear my points.

Once I knew I had D-density breasts, my goal was to get an ultrasound in addition to a mammogram. Not only that, it was suggested to me that my ultrasound not be at the same time as my mammogram, but they should both occur once a year. I truly think my doctor was an advocate and didn't question when I asked for support or didn't discourage me.

The radiologist was concerned about something that she saw in the ultrasound on my right breast. So she scheduled me for a contrast-enhanced mammogram and … it clearly showed up the tumour on my left side. She showed me the pictures and she showed me the right side, which was a tiny, tiny tumour that was hidden behind [my breast], and she said that shows that there was cancer on the right side as well.

When I asked my surgical oncologist if an MRI could be done to get a better picture of the extent of the disease given my dense breasts, and to determine if the mammogram had missed any area of concern in the other breast, I was told this was not standard practice in the province, that MRIs yielded more false-positives, which could increase my anxiety and delay treatment if more suspicious areas were identified. I finally managed to convince my family physician to put in the requisition for an MRI, which showed fibroadenoma in the other breast that needs to be monitored.

The participants who had access to supplemental screening also reflected on their experience navigating the health care system and detailed instances in which they had to self-advocate for continued access to screening. Participants who were breast cancer survivors often spoke about the challenges of supplemental screening with respect to continuity of care and systemic barriers. Others with

professional experience in the medical field expanded on the latter from both the patient and provider lenses:

> *Having cancer in my 30s meant I understood mammograms didn't work for me. But post–cancer treatment, the recommendation was to continue getting mammograms, so I did struggle a bit with, "So if they don't work and you can't see anything on them, why would you now be sending me for more mammograms? Is this a waste of taxpayer dollars?" So, again, helping me understand mammography as a diagnostic tool and then as a preventative tool.*
>
> *It was easy when I was getting cancer treatment—and then when you switch out of treatment to prevention, that's when the switch flipped. I was still going to the same hospital, but because I'm no longer an active patient, I don't qualify for the screening program.*
>
> *You would think they would be more in tune with women with breast cancer, but they're really not. You know, I get the mammogram done and usually I have to go back, and have it done again because of the scar tissue on the dense breasts—they can't see, and they want me back again for a second time. So, often that means a second day of missed work and an extended amount of time off.*
>
> *So, it's about equal access for all women—which means really a personalized approach. I think in order to get that, there have to be designated centres or at least education, so that when a family doctor is advising a patient, they can be more specific. There's a lot of hesitancy, though. I know from a professional perspective and from a system perspective, there's huge hesitancy to proceed with supplemental screening because it's a big workload, right? We've worked really hard to even get mammograms accepted and people are afraid of the work: "What if we drown?" Well, if we drown, it means we need more people.*

IMPACT OF FINDINGS ON PATIENTS AND CAREGIVERS

Physical Effects

Participants reported a broad range of health outcomes, some of which they perceived to be a consequence of lack of access to information about breast density or lack of access to routine supplemental screening. Many reflected on the physical effects and reaffirmed that they valued preventive care and patient education. A few of those we spoke to talked about how having access to information about breast density would have affected their decision-making throughout their care journey:

> *I mean in my mind, if I had known about the breast density, again going back to 2014, I am the sort of person who would have informed myself, would have insisted on getting an ultrasound, and maybe I wouldn't have had to have chemo and radiation and everything else. I might have been able to save that, but I'll never know.*
>
> *I just thought maybe I would have pushed for more, maybe I would have started my mammograms then, maybe I wouldn't have just sat for 5 years, and I wouldn't have had such a large area of cancer that had to be removed. Just all those what-ifs. So, for me, the knowledge didn't come at the right time.*

Now, had I known about my breast density and the scar tissue that was going to be a challenge with regard to screening, I think I would have decided to get both breasts removed … And that's a significant decision to make, but now that I've gone through everything that I've had to since 2013, I would have opted to get both removed. And I know that doesn't guarantee that your breast cancer or any kind of cancer won't return, but it's my understanding is that once you have your breasts removed, [recurrence] doesn't happen that often. It's rare.

Emotional Effects

Participants described the emotional effects of learning about their breast density status and how their ability to access to supplemental screening affected their mental wellness. Many reflected on the psychological burden of screening and spoke about how care coordination affected their perception of the quality of care they received. Overall, the majority of the participants said that poor communication and ambiguity around future screening increased feelings of anxiety and gave them a perception that their care was delayed and caused worse health outcomes:

What I know now about my breast density, I will not be able to relax and be at peace if I'm only offered a mammogram. My mental health will just be shot because I will just be constantly worrying that something has been missed … and I already feel like I already [had something missed]. And when something like this happens to you, you just you feel differently about everything.

I've definitely had some mental health challenges around it, but I also think I would much rather that and take the steps to be preventative versus finding out I have breast cancer in 4 years but I didn't know I was at risk.

I can't walk into a hospital without having a panic attack. Not only did I get breast cancer, I got PTSD [post-traumatic stress disorder] because I couldn't get the correct care throughout … I shouldn't have been put in this position, because if additional screening had been done earlier, I wouldn't have been in this situation.

My experience with screening for [breast cancer] is that the current process is inadequate, especially for women with dense breasts. I feel let down by the health care system, especially knowing that other technologies exist that could have been used to provide an earlier diagnosis.

Self-advocacy was also a prominent theme across all participants' lived experiences, and several perceived it to be a burden at certain points of their care journey. Those we spoke to described feelings of surprise and mistrust after learning about their breast density status. They felt that this knowledge challenged their perception of mammography and its effectiveness in detecting tumours in people with dense breasts:

I wish I had known. I wish someone had explained to me what dense breasts were, and I didn't have to resort to Google—that shouldn't be the way I get health care.

I was really shocked, because I thought, "Wow, all these years I've been having mammograms, they were pretty useless because they couldn't detect whether I had a tumour unless it was really big."

I was shocked, frustrated, and distressed when I was diagnosed with [breast cancer]. It was a large (T3) tumour, and I thought, "How is this possible?" I did exactly what I was told to do in terms of screening, and yet the tumour was not detected until it was very large and extensive. Who knows how long this had been growing? Perhaps it was even missed in the previous mammogram exam. No one has looked into that to see if it could have been an error. I felt angry and let down. I did not want to place blame; I just wanted to know why, and possibly prevent other women from not being diagnosed early.

SUPPLEMENTAL SCREENING AS AN ADJUNCT TO MAMMOGRAPHY FOR PEOPLE WITH DENSE BREASTS IN ONTARIO

All participants were asked to reflect on the potential of publicly funding supplemental screening for people with dense breasts in Ontario. Participants were encouraged to consider their preferences and values when it came to supplemental screening as someone with dense breasts and to explore what would be important to consider based on their experiences with additional screening, as well its overall effect on them and their family members or caregivers.

Preferences and Perceived Benefits

Participants expressed a strong preference for broad access to supplemental screening for people with dense breasts in Ontario. Key factors that informed this preference included the perceived clinical effectiveness of supplemental imaging technologies, such as ultrasound or tomosynthesis, and the potential for improved cancer detection for people with dense breasts. As well, those we spoke to were not concerned about false-positives or overmedicalization; they felt that these risks were outweighed by the potential medical benefits of preventive care:

There are many benefits of early diagnosis, and screening is a way to achieve them. Patients benefit from less invasive treatments, better quality of life and living longer. The health system can benefit from fewer cancers advancing to the point that treatments and care involve higher levels of care, more expensive treatments, and generally higher costs per patient over time. I'm not afraid of false-positives at all. I'd rather get a false-positive and get it investigated than not have it done at all.

If you want to screen properly, then you have to use the tools that are best; this thing about "we don't want to upset you, but we might miss a cancer," that makes no sense to me. If you have an early cancer and they miss it on a mammogram because they simply cannot see it, but they could pick it up in an ultrasound, isn't that a lot better? That's it. It's a "nothing treatment." It's very easy, it's very treatable. Whereas if you let someone go past stage III or IV, it's awful. Why do that?

To be honest with you, I know that false-positives and anxiety related to requiring an additional test have always been a focus in the literature—to me, that's garbage … I can tell you that there's far more anxiety related to a false-negative. "How come I didn't know? How come nobody told me? How did this happen versus a false-positive?" [Instead of] "I'm really sorry you came back for his test, but I don't see anything that looks like cancer. This is wonderful. We'll see you in a year." So, that short-term anxiety [from a] false-positive is far better tolerated than a false-negative. I think we should really change our focus and stop talking about false-positives and actually start to talk about false-negatives … You know, I think that would be a far more

proactive and beneficial approach than, "Oh, I don't want to cause you anxiety." It seems very paternalistic to me.

Moreover, the majority of the participants perceived supplemental screening as a means of improving care coordination and standardized risk assessment. For example, some participants felt that publicly funding supplemental screening for people with dense breasts could improve communication across care teams and support patient self-advocacy. Although participants had differing views on their preferred member of the care team for coordinating supplemental screening, they shared similar values around clinical expertise and continuity of care:

I think standardized follow-up is really important! What really helped me is I knew that my responsibility every year was … to advocate for a mammogram and an ultrasound.

Yeah, it would be easier if they all shared notes and knew why I was going to be there that day instead of "What can I do for you today?" And then I have to go over it all again.

I believe that the follow-up should be centralized in a specific breast centre and provide consistent follow-up so that everyone is getting the same feedback.

When reflecting on their lived experience, the participants who had experience with supplemental screening emphasized the importance of access to information that is contextualized to their care plan. Many of those we spoke with felt that publicly funding a supplemental screening program could be an opportunity to help inform Ontarians about breast tissue density and other breast cancer risk factors. Indeed, some participants went on to suggest potential strategies for knowledge dissemination. Overall, participants felt that broad access to supplemental screening for people with dense breasts aligned with their values, particularly in relation to preventive and patient-centred care:

For me, I think knowledge is power. I think that things like all women's care, menopause care, and things like that are not talked about, and it's not helping women.

If a screening program were established, it's about building awareness of it and providing the right level of information and access. And I know that this is impossible, but it would be great to have kind of a hotline where newly diagnosed patients could call and say, "Hey, I've just been diagnosed with cancer. I know that I have dense breasts. What are the implications for me? What should I do?"

I think that information that a man or woman should know about is [whether] you do have dense breasts and the category that they see you in. Because I think more information and education can cut a lot of worries and anxiety.

Even where you go and have your mammogram—even if they had pamphlets there about dense breasts—just make it that ladies know and are more aware, because I never heard anything about dense breasts until I was diagnosed, and then I was told had dense breasts.

Additional Considerations

Some participants also shared their views on supplemental screening for people with dense breasts from an equity perspective. Through their lived experiences, they explored themes related to gender

discrimination, ageism, paternalistic care models, and language barriers. Moreover, they considered how such barriers can affect decision-making and the overall patient experience navigating the health care system. Ultimately, participants agreed that equitable access should be a requirement of any supplemental screening program for people with dense breasts in Ontario:

> *I've read in the literature as well that we're not going to give women these [supplemental] tests because there might be false-positives. Are you kidding me?! … To me, that is gender discrimination.*
>
> *It's like, "Well, you've lived a good life. So, you get cancer? Big deal." Well, that's not fair—that's ageism and it's not okay for women to be expendable. Everything is connected to equity, and it's a big societal problem. I am for supplemental screening because it is advocating for your health.*
>
> *It's about equal access for all women—which really means a personalized approach. And I think in order to get that, there have to be designated centres or at least education so that when a family doctor is advising a patient, they can be more specific.*
>
> *[As caregiver,] you have to do the translation for them without having a background in medicine, and sometimes it's not really accurate … So that also creates another barrier.*

There was also a shared value among those interviewed around accessible care. A number of participants reflected on potential barriers to accessing supplemental screening as someone with dense breasts, and they emphasized that supplemental screening should be accessible through different health institutions (for example, walk-in-clinics, family doctor's clinics, and hospitals) across Ontario so that barriers are not introduced or worsened for those in underserved populations:

> *You can see how people at the periphery of the city don't have the same access. If there was a standard that was accessible to everyone regardless of their location … that would be awesome. It shouldn't be that we have to pull favours and have well-connected family, friends, or physicians to make sure that dense breasts don't turn into anything.*
>
> *Treatments at advanced stages are often only available in limited geographical areas, making accessibility an issue.*
>
> *Make it easy for women to follow up in whatever way is available in their community. I think it must be hard, like in northern communities, Indigenous communities, and other cultural groups where there are a lot more cultural issues around women's bodies and you can't even imagine how you navigate that.*
>
> *You see, we're in [town] and about 30 hours away—that's a $2,000 trip to Toronto [for screening]. So there's a time and travel barrier to overcome. And yes, the guidelines are set up as they should be—you know, you appeal to the middle and try to get the majority in the bell curve and I just happen fall outside that curve, as 10% to 15% of other women do too … But at some point, that's a lot of women.*

Discussion

Participants provided diverse perspectives on publicly funding supplemental screening for people with dense breasts in Ontario. Our direct engagement was conducted through phone interviews and online surveys to allow for a thorough examination of the health, emotional well-being, and decision-making processes of people with dense breasts and their family members as they engage in breast cancer screening.

All of the participants self-identified as having dense breasts, and the majority had access to routine screening via mammography through a provincial screening program or via physician referral. We also spoke with one family member, who shared their experience supporting a family member who had dense breasts and was subsequently diagnosed with breast cancer. Each participant shared a detailed account of their care journey, as well as the physical and emotional effects of having dense breasts. We explored themes around breast cancer risk appraisal and discussed the impact of supplemental screening for those with dense breasts in the context of participants' preferences and values. The resulting themes included self-advocacy, patient–doctor partnership, and preventive care; these informed a shared preference for access to supplemental screening modalities to detect breast cancer in people with dense breasts.

A potential limitation of our engagement is that few participants reported having access to supplemental screening when breast density was the sole risk factor. Moreover, because of our outreach methods, we were unable to speak with people who had experienced a false-positive as a result of supplemental screening. The people we spoke to perceived that the potential benefits of supplemental screening outweighed the consequences of a false-positive, but our analysis may have been limited because we were unable to appraise the emotional or physical effects of a false-positive test from people with that specific lived experience.

Despite this, all participants commented on the potential impact of supplemental screening from multiple perspectives (for example, individual, family member, and health care provider) using their lived experience as someone with or caring for someone with dense breasts. In this way, direct engagement through interviews generated a robust thematic analysis of diverse perspectives and values among people with dense breasts who are seeking breast cancer screening in Ontario.

Conclusions

Supplemental screening as an adjunct to mammography in people with dense breasts was viewed favourably by the people we interviewed. Participants perceived supplemental screening to be more effective than mammography alone and they felt that publicly funding supplemental screening aligned with their values related to preventive and patient-centred care. Participants also shared their experiences with navigating current barriers to supplemental screening for breast cancer and highlighted how the patient–doctor partnership and access to information about breast tissue density were key drivers in their ability to self-advocate. Overall, the people we spoke to valued the potential clinical benefits of supplemental screening and emphasized that patient education and equitable access should be considered for implementation in Ontario.

Qualitative Evidence Rapid Review

Research Question

- What are the experiences and understandings of breast density and supplemental screening as an adjunct to mammography among people who have or may have dense breasts, their family members, and their health care providers?

In addition to the primary research question, the reviewer paid particular attention to the following areas of interest when analyzing the data:

- The experiences and understandings of marginalized or racialized people with dense breasts
- How people giving and receiving breast density notifications understand and make sense of the concept of breast density and decide whether to proceed with supplemental screening
- The experiences of accessing, engaging with, or offering supplemental screening modalities (i.e., ultrasound, magnetic resonance imaging [MRI], contrast-enhanced mammography, and digital breast tomosynthesis), including the screening process and interpreting, communicating, and using results

Methods

STUDY DESIGN

A qualitative research officer and a research information specialist from the Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a rapid qualitative review and thematic synthesis[177] of primary qualitative studies that reported on the experiences and understandings of breast density and supplemental screening for breast cancer among people who have or may have dense breasts, their family members, and their health care providers.

QUALITATIVE LITERATURE SEARCH

The research information specialist performed a literature search on May 2, 2022. They used the Ovid and EBSCO interfaces to search the MEDLINE and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases, respectively.

The research information specialist developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The main search concept was breast density. They applied CADTH-developed search filters to limit retrieval to qualitative studies. They limited retrieval to English-language publications. They did not limit the search by publication date. They removed duplicates by manual deduplication in EndNote. The final search strategy was peer-reviewed using the PRESS Checklist.[87]

The research information specialist updated the search with regular database alerts in MEDLINE and CINAHL until August 3, 2022. They also performed a qualitative grey literature search of sources listed in relevant sections of *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* checklist,[178] which includes the websites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. They used Google to search for additional internet-based materials.

The qualitative research officer supplemented the searches above by reviewing the bibliographies of citations eligible for inclusion. See Appendix 2 for the literature search strategies, including all search terms.

ELIGIBILITY CRITERIA

Studies

Inclusion Criteria

- English-language full-text publications
- Primary qualitative studies or mixed-methods studies with a qualitative component, originating from any country
- Studies about the experiences and understandings of breast density and supplemental screening as an adjunct to mammography among people who have or may have dense breasts, their family members, and their health care providers
- Phenomena of interest: supplemental screening modalities for breast cancer (i.e., ultrasound, MRI, contrast-enhanced mammography, and digital breast tomosynthesis)

For this review, people who have dense breasts were defined as follows:

- Those who had breasts with greater than 50% dense tissue or met the criteria for Breast Imaging-Reporting and Data System (BI-RADS) categories C or D, or the equivalent[10]
- In the absence of reported clinical indicators, those who had been notified about or were classified as having dense breasts by a health care provider

People who may have dense breasts were defined as those eligible for screening for breast cancer whose breast density status was unassessed, unreported, or unknown.

Appendix 15, Table A25, describes the eligibility criteria created using the Sample, Phenomenon of Interest, Design, Evaluation, and Research Type (SPIDER) criteria to frame the research questions for the qualitative evidence synthesis.[179]

Exclusion Criteria

- Theses and dissertations, citations presented as abstracts, editorials, commentaries, case reports, and survey studies without a qualitative component
- Studies reporting the experiences of people considering or undergoing screening for male breast cancers
- Studies reporting the experiences of people who have been told they do not have dense breasts
- Studies reporting only the understandings and experiences of people with dense breasts and other high-risk factors for breast cancer (e.g., known high-risk genetic mutations, family history of high-risk genetic mutations or cancer, or a history of chest irradiation)
- Studies reporting experiences of diagnostic imaging (i.e., imaging used to investigate a detected or a suspected cancerous lesion)
- Studies reporting experiences of imaging as a primary screening modality (i.e., as a replacement for mammography)

Literature Screening

The qualitative research officer conducted an initial screening of the titles and abstracts of the citations captured by the electronic database search using DistillerSR.[180] They retrieved the full texts of all citations that appeared eligible for review according to the inclusion criteria. They then examined the full texts and selected citations eligible for inclusion.

CRITICAL APPRAISAL OF QUALITATIVE EVIDENCE

The qualitative research officer used the optimized version of the Critical Appraisal Skills Programme (CASP) tool to critically appraise the included studies.[181] This tool promotes an efficient and systematic appraisal that acknowledges, accepts, and considers the diverse philosophical underpinnings of qualitative inquiry.[181] The optimized CASP approach acknowledges that quality indicators for some research traditions (e.g., data saturation or member checking) might not be deemed appropriate by others who approach inquiry from different philosophical perspectives.[181]

The qualitative research officer used the 11 items from the optimized CASP tool as prompts for engaged and critical reflection about the trustworthiness and rigour of the included studies, rather than as a checklist. The qualitative research officer did not exclude articles based on quality; instead, they critically appraised the included studies to provide readers with insights into the studies' limitations and strengths.

DATA ANALYSIS AND SYNTHESIS

The qualitative research officer synthesized the qualitative data using Thomas and Harden's thematic synthesis.[177] The synthesis focused on exploring the experiences and understandings of breast density and supplemental screening for breast cancer among people who have or may have dense breasts, their family members, and their health care providers. They conducted the thematic synthesis in three analytical stages: line-by-line coding, developing descriptive themes, and generating analytical themes.[177]

To begin the analysis, the qualitative research officer first familiarized themselves with the studies by reading and rereading them in their entirety, making marginal notes and memos about their initial thoughts and insights in a Microsoft Word document. These initial notes included reflective notes to promote reflexivity (see Reflexivity, below); descriptions to promote familiarization with the content; and critiques relating to the questions in the optimized CASP tool to facilitate critical appraisal.

After making their initial notes and memos, the qualitative research officer used NVivo[182] to begin open, line-by-line coding of the text in the "findings" and "results" sections of the included reports, assigning codes according to meaning and content.[177] They did not code lines in these sections that reported methods or authors' conclusions, and they coded only qualitative findings in the included mixed-methods study.[183] When analyzing the literature on breast density notification, they coded only data relating to how people giving and receiving notifications understood breast density and considered supplemental screening; they did not code data detailing people's experiences of breast density notification itself.

During line-by-line coding, the qualitative research officer assigned the initial codes inductively,[177] but they remained attuned to areas of interest identified in the research questions. To ensure that the analysis was sensitive to the experiences of marginalized or racialized people, the qualitative research officer considered the PROGRESS-Plus[184,185] elements of race, ethnicity, culture, language, sex, gender,

socioeconomic status, education, age, and disability. These elements denote characteristics that stratify health opportunities and outcomes.[184,185] Instead of using PROGRESS-Plus as a coding framework, the qualitative research officer used the identified elements as concepts to prompt sensitivity to data that detailed the experiences of people who may have encountered marginalization or inequities in the health care system.

After line-by-line coding, the qualitative research officer employed a constant comparative method to compare codes with each other and across studies.[177,186] At this stage, they examined all text assigned a code to determine whether the codes had been consistently interpreted, or if additional levels of coding were needed.[177] Then, they created descriptive themes to capture the meanings of groups of initial codes.

After creating the descriptive themes, the qualitative research officer created analytical themes[177] by considering connections and relationships between the descriptive themes. They also considered areas of interest identified in the research questions, refining the descriptive themes into abstract themes relevant to the policy question.

REFLEXIVITY

In qualitative research, *reflexivity* refers to the examination of how a researcher's positions, prior experiences, assumptions, and preconceptions influence the research process.[186] To engage in reflexive practice, the qualitative research officer journalled about their preconceptions related to the topic of supplemental screening for people with dense breasts to reflect explicitly on how these preconceptions might have influenced the collection and interpretation of data. They made reflexive memos during their initial reading and rereading of the citations, and throughout data analysis and writing. They used these memos to challenge any initial assumptions or interpretations that might have been grounded in their preconceptions, rather than in the data.

Results

LITERATURE SEARCH

The original database search of the qualitative literature yielded 321 citations published from database inception to May 2, 2022. The research information specialist identified 40 additional citations from the grey literature search. After duplicates were removed, the qualitative research officer screened the titles and abstracts of 284 articles and excluded 263. They then assessed the full texts of 21 articles and excluded a further 11. Database alerts (monitored by the research information specialist and qualitative research officer until August 3, 2022) yielded no new eligible citations. In total, the qualitative research officer identified 10 citations that met the inclusion criteria for the thematic synthesis. Figure 7 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the qualitative literature search.

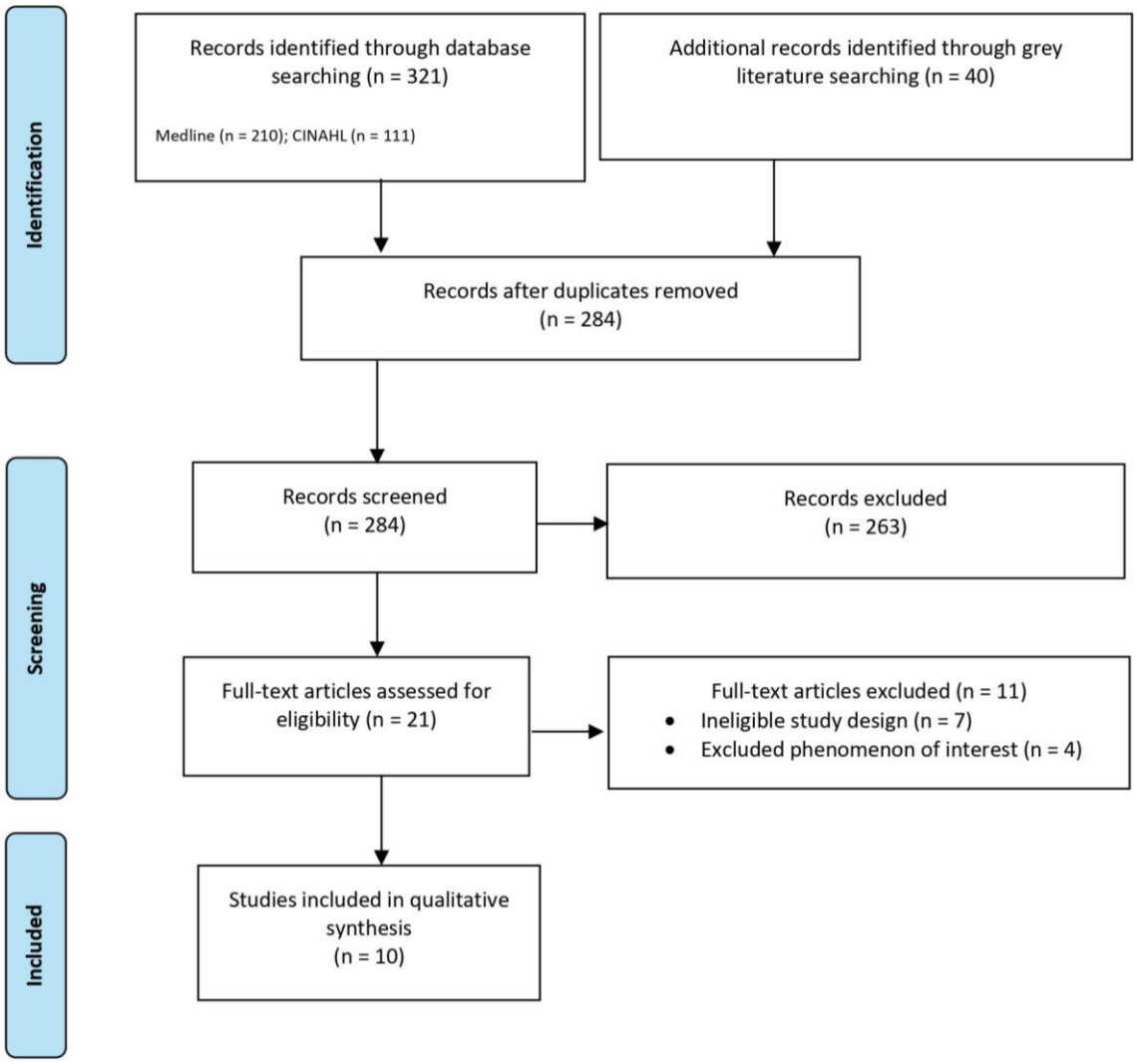


Figure 7: PRISMA Flow Diagram—Qualitative Evidence Search Strategy

PRISMA flow diagram showing the qualitative evidence strategy. The database search of the qualitative literature yielded 321 citations published from database inception to May 2, 2022. Forty additional eligible records were identified from other sources. After removing duplicates, the abstracts of 284 records were screened, and 263 were excluded. The full text of 21 articles were assessed and a further 11 were excluded. In the end, 10 articles were included in the qualitative evidence synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[90]

CHARACTERISTICS OF INCLUDED STUDIES

Characteristics of the included studies are summarized below; details are available in Appendix 16, Table A26.

Study Designs and Methods of Data Collection and Analysis

Of the 10 included studies, nine were qualitative[187-195] and one was a mixed-methods study.[183] Kressin et al[183] were the only authors to report a particular study design (i.e., a sequential mixed-methods design), but they did not report a design for the qualitative portion of their study. Similarly, the authors of the other included qualitative studies identified methods of data collection or analytical approaches but did not report a specific qualitative design. Six studies collected data using semistructured interviews,[183,187-191] three used focus groups,[192-194] and one used a combination of semistructured interviews and focus groups.[195] Six groups of authors specified the medium they used to collect their data: five used the telephone[183,188-191] and one used videoconferencing.[193] Six studies reported using a form of qualitative content analysis,[183,187-189,191,195] and one each reported using thematic analysis,[193] framework analysis,[190] and a general constant comparative method.[192] The authors of one study reported using a mixed deductive and inductive approach inspired by content analysis and grounded theory, respectively.[194]

Settings and Participant Characteristics

Except for one citation published in 2016,[195] all included studies were published within 5 years of the present rapid qualitative review. Seven of the included studies were conducted in the United States[183,188,189,191,192,194,195] in the context of a health care system that is funded using a mix of private and public insurance offered through federal and state government programs. Two studies were conducted in Australia[190,193] in a health care system that is primarily publicly funded, although patients may also access privately funded services. One of the studies was conducted in Sweden[187] in the context of a health care system that is primarily publicly funded. None of the studies were conducted in Canada.

The authors of all but one study[187] reported the number and characteristics of their study participants. The nine studies that reported this information obtained qualitative data from a combined total of 343 participants: 144 with a history of dense breasts, 155 whose breast density status was not known or specified, 37 general practitioners, and seven radiologists. Seven studies recruited people who had or may have had dense breasts,[183,188,189,191-194] two recruited health care providers,[187,190] and one recruited both people who had dense breasts and health care providers.[195] None of the studies included family members of people who had or may have had dense breasts. Reported sample sizes ranged from 19 to 78 participants.

Participants who had or may have had dense breasts were recruited from a variety of settings: specific hospitals, clinics, or centres offering breast cancer screening in urban areas in the United States[188,189,191,192]; US states with and without breast density notification laws[183,194]; and rural and urban areas across multiple regions in Australia.[193] Health care providers were recruited from urban breast cancer centres in Sweden[187] and the United States,[195] and from urban and rural regions in New South Wales and Queensland in Australia.[190]

With two exceptions,[191,195] none of the studies included participants with high-risk factors for breast cancer. Klinger et al[195] excluded participants with a known history of breast cancer or a high-risk genetic mutation, but three of the 16 participants described themselves as being at high risk for breast cancer. Pacsi-Sepulveda et al[191] reported that three of their 24 participants had a first-degree relative with a

history of breast cancer. Both of these studies were included in the synthesis because most of the participants did not have high-risk factors.

All studies that included people who had or may have had dense breasts described their participants as women. The ages of these participants ranged from 40 to 80 years. Eight studies included participants who identified as Black, Hispanic, Asian, Indigenous, or races and ethnicities other than White[183,188,189,191-195]; three studies included Spanish-speaking Americans[189,191,192]; and four studies included participants with low health literacy or less than a high school education.[183,191,192,194]

In studies that included health care providers and reported participant characteristics, the proportion of female-identifying participants varied from 76.7%[190] to 85.7%.[195] Health care providers' years of experience ranged from less than 10 to more than 30.[190,195]

FINDINGS OF THE CRITICAL APPRAISAL

Of the 10 included studies, nine were of moderate to high quality,[183,188-195] and one was of lower quality.[187] A summary of the strengths and limitations of each included study can be found in Appendix 17, Table A27.

Although only a subset of authors explicitly justified the use of a qualitative[187,188,192] or mixed-sequential[183] design, the reported aims and objectives of all 10 studies aligned with a qualitative approach. However, none specified the broader ontological or epistemological assumptions that underpinned their studies. Furthermore, no authors reported a specific qualitative design or methodology used, making it difficult to appraise the congruence between the broader assumptions underpinning the studies and the approaches taken.

All but one study[187] reported the number and characteristics of their participants. Reporting this information enhances the theoretical transferability of the studies' findings by providing information that would allow a reader to compare settings and participants to their own context. Most authors also provided rich descriptions of the methods used for data collection. However, one study required more information about who collected data and how.[187] Most studies also clearly reported rigorous methods of data analysis that were congruent with the analytical approaches cited. When such congruence was present, it indicated that the researchers likely had the knowledge and skills necessary to conduct qualitative inquiry, enhancing the credibility of their findings.[196] Four studies required more details about the analytical methods used.[191,192,194,195]

Eight studies explicitly discussed the methods used to enhance the credibility of their findings (e.g., pilot-testing interview guides, sampling until data saturation, calculating intercoder reliability, and validating preliminary findings with experiential experts).[183,188-191,193-195] All but one study discussed limitations of the research that could affect the transferability of the findings, allowing the reader to appraise the value of the research to their own context.[187]

ANALYTICAL FINDINGS

The findings of the present thematic synthesis focus on the understandings, meanings, and decisions made and ascribed to breast density and supplemental screening by people who had or may have had dense breasts and their health care providers. The extant literature contained little information about the experiences of offering or engaging with supplemental screening modalities, or about the experiences of family members.

The thematic synthesis yielded three analytical themes: *coming to know and understand breast density*, which included introductions to and making sense of breast density; *experiences of vulnerability*, which influenced and were influenced by understandings and misunderstandings of breast density and responses to breast density; and *choosing supplemental screening*, which was influenced by knowledge and perception of the risks and benefits of supplemental screening, as well as by the availability of resources.

Coming to Know and Understand Breast Density

Introductions to Breast Density

For many people who had or may have had dense breasts, breast density was a novel or unfamiliar concept; general practitioners also described having limited knowledge about the phenomenon.[188-190,192-194]

People with dense breasts often heard about the concept for the first time when they received information about their breast density status, most often through notification letters.[188,189,191,194] Health care providers noted that when public screening programs did not assess or provide notifications about breast density status, people learned about the concept and their breast density status only after they had accessed private screening.[190]

People with dense breasts and health care providers believed that a conversation with a health care provider would be an ideal means of introducing people to the concept of breast density and to personal breast density status.[188-193,195] They anticipated that such informative discussions would allow specific, personalized information to be shared and for questions to be asked and answered in real time.[188-191,195]

Still, many health care providers described reasons why they might be reluctant to share information about breast density with the people in their care.[187,190,195] For example, one Australian study[190] found that many general practitioners—especially those without a special interest in women's health—characterized their knowledge about breast density as inadequate or very limited and therefore felt unprepared to have discussions on this topic. Their primary source of information about breast density was mammography reports. Many noted that they had not received education about breast density during their medical training: "We know about the screening stuff, how to manage a breast lump or a clinical breast symptom. But I don't think there's been much education about breast density."[190]

General practitioners, radiographers, and radiologists were also hesitant to share breast density information with the people in their care because of a perceived difficulty in consistently identifying or grading breast density, a lack of time for patient education, and most commonly, a lack of clinical evidence or practice guidelines to inform appropriate courses of action in the context of a largely unmodifiable condition.[187,190,195] As one radiologist noted, "We don't really know what to do [about breast density], so now people are kind of burdened with this knowledge and not really knowing what to do with it. So I'm not sure that it's all that helpful."[195]

Other health care providers noted patient characteristics and contexts that contributed to their reluctance to share information about breast density. For example, many hesitated to provide information about breast density if they perceived that the people in their care would not have the financial means to access supplemental screening.[190] One female-identifying general practitioner noted:

> *I don't think it's fair to tell someone they're at … a higher risk of developing breast cancer than their neighbour … but we can't find that for you because we can't screen you more than every two years and we can't give you a free ultrasound.*[190]

General practitioners also noted that breast density is an abstract concept that cannot be seen or felt and is therefore difficult to explain well.[190] Some worried that providing poor explanations would increase anxiety and misinterpretations.[190] Perhaps for this reason, general practitioners described difficulty with or hesitation in providing information about breast density to people they perceived might find such explanations challenging, including those with lower health literacy levels or those who required a language interpreter.[190]

These findings indicate that opportunities for introductions to breast density as a concept and as an experience were available to some but not others. Specifically, those who could access breast cancer screening that notified them about high breast density, those able to afford supplemental screening, and those perceived to have the language and health literacy levels needed to understand abstract concepts were likely to receive this information, but others were not.

Making Sense of Breast Density

Confusion and Uncertainty

Overall, breast density as a concept was poorly understood among people who had or may have had dense breasts, regardless of their educational or health literacy levels.[188,189,191-194] A frequent cause of confusion and misunderstanding was the notification letter—the most common way for people with dense breasts to learn about the concept.[188,189,191,192,194] People who had or may have had dense breasts described the notification letters as difficult to understand, vague, unclear, seemingly contradictory, and laden with medical jargon.[188,189,191,192,194] One woman noted difficulty in ascribing meaning to breast density after reading a notification letter: "It [breast density] was never really explained. Is this a good thing? Is this a bad thing? Is this just a nothing?"[194]

Breast density notification letters delivered in a person's nonpreferred language exacerbated and prolonged confusion because people had to rely on an interpreter or the internet to begin to understand the concept.[189,190] Understanding proved especially challenging because the letters contained medical terminology. When attempting to make sense of her English notification letter, one Spanish-speaking woman with dense breasts said, "Here it says [patient tries to read medical terms in English] … it's in English and I can't even pronounce them in English. Fibroglandular densis-, heterogeneous densi- … I thought I had all four."[189]

Broadly experiencing the notification letters as inadequate sources of information, people with dense breasts proposed alternatives for coming to know and understand breast density. Those suggestions included the following: having health care providers deliver the notification; editing notification letters for clarity; and presenting notification letters along with informational pamphlets that contain simple explanations and images to help readers understand and visualize the concept of breast density.[189,191,192,195]

In the absence of such alternatives, people with dense breasts had to rely on other sense-making activities to understand breast density. Some—especially those who had received their notification in a nonpreferred language—consulted the internet, but information obtained in this way lacked personalized details.[188,189,194] As one Spanish-speaking woman described, "There are four type of dense

breasts. I didn't know which of the four I had because [the internet] only talked about dense breasts, and that was it."[189]

Others sought additional information from friends or family and intended to consult their health care providers as means of understanding the notification letters.[189,193] As detailed below, others used previous experiences of receiving breast cancer screening and their understanding of the word "dense" to give meaning to breast density.[189,191] These sense-making activities resulted in understandings that did and did not align with biomedical understandings of the concept.

Breast Density and Breast Cancer

Except for breast radiographers, radiologists, and some general practitioners with an interest in women's health,[187,190,195] most participants in the included studies had a limited understanding of the relationship between breast density and breast cancer. The few who had some knowledge knew only about the masking effect—that is, the tendency for high breast density to obstruct the visualization of cancerous lesions on mammograms.[183,190,192-194] Understanding breast density as an independent risk factor for breast cancer was uncommon.[183,189,190,194]

Many participants across the reviewed literature misunderstood the relationship between breast density and breast cancer in one of two ways. The first of these was the perception that breast density was abnormal or an early stage of cancer.[183,188,191,192] For some, this misunderstanding resulted directly from misinterpretation of the information provided in notification letters.[183,188,191] One woman noted, "It says here that you must pay attention when you have dense breasts. So, I think it's not normal. Other letters I have received never contained those explanations; they never came like that."[189] Others perceived that receiving a letter, being asked to discuss their findings with a health care provider, or being advised to get additional testing was out of the ordinary and therefore indicative of a malignant finding.[188,189,192] One woman noted, "Of course I thought the worst. Just the word dense … I had nothing ever wrong with my breasts before. And so I figured it was a form of cancer."[188]

The second, less common misunderstanding was that breast density did not increase cancer risk. Some people with dense breasts made this statement when recalling their notification letters, which presented indications of dense breast status alongside "normal" mammogram results.[188,189,194] As one woman recalled, "It said there was no risk of cancer, and that made you feel more at ease."[189] In a different study, another woman stated, "Not like if you have dense breasts you're going to get cancer … it's just that sometimes the abnormalities go unnoticed."[194] This misunderstanding could also stem from a lack of follow-up by health care providers, as one woman reported: "It must not be too serious, because they haven't called me."[189]

Breast Density as a Physical or Aesthetic Feature

People with dense breasts and general practitioners commonly understood breast density to be a physical phenomenon.[183,188-192] For example, many understood dense breasts to be thick, compact, hardened, inadequately plump or cushioned, or having too much or too little tissue.[183,188,190-192] Others believed density was related to aesthetic features of the breasts, such as perkiness[183] or size.[183,192,193]

These understandings often related to sense-making activities that involved previous understandings of the word "dense" or hypothesizing about physical features that would impact the effectiveness of mammograms in identifying cancers.[183,188,189,191,192] One woman speculated: "It's dense, there isn't a lot of tissue … the machinery works better when your breasts are plump, firm, have more cushioning."[188] Some people, learning of the masking effect, speculated that their breasts contained physical,

obstructive masses and voiced worry that such masses meant "there is no possibility to detect breast cancer."[189] A related understanding among people with dense breasts and general practitioners was that they could palpate breast density, assuming it would present as firmness, nodularity, or lumpiness.[183,190,192] Furthermore, one study[183] found that although some people with dense breasts correctly believed that breast density itself was not palpable, they also assumed that it eliminated the ability to palpate a mass "hiding behind all those tissues" during a physical breast exam.

Conceptions of Causes for Breast Density

Health care providers tended to propose causes for breast density that aligned with the biomedical understanding of the phenomenon. For example, general practitioners and radiographers associated breast density with younger people.[187,190] Breast radiographers further elaborated that dense breasts were more common among breastfeeding women and those on hormonal replacement therapy.[187]

In contrast, people with dense breasts offered explanatory models that varied in their alignment with biomedical conceptualizations of breast density. Some of these proposed etiologies were unmodifiable. For example, many people with dense breasts misunderstood breast density as being common among older rather than younger people.[183,188] Others proposed or questioned whether breast density was heritable[188,192,195] or related to the number or characteristics of breast cells.[183]

As well, unlike health care providers, people with dense breasts proposed modifiable etiologies for breast density more frequently. Some related their breast density to their decision not to breastfeed, often suggesting that their breasts remained dense because they had not been "deflated" of milk.[188] Another common misunderstanding was that breast density indicated fatty rather than non-fatty breast tissue and, relatedly, was caused by being overweight.[183,188] Others attributed breast density to a lack of exercise or touch focused on the chest; to smoking, alcohol intake, or caffeine consumption; or to exposure to environmental pollution.[188,192,195] However, it is possible that this focus on modifiable factors (i.e., factors within one's control) was in response to the vulnerability often inherent in the experience of learning about and living with dense breasts.

Experiences of Vulnerability

The experience of vulnerability (or lack of vulnerability) to breast cancer in the context of dense breasts was prevalent in the literature reviewed. Previously detailed understandings and misunderstandings about breast density, as well as responses to breast density, influenced and were influenced by the degree of vulnerability experienced.

Influence of Understandings and Misunderstandings

Some people with dense breasts felt particularly vulnerable to breast cancer after misunderstanding breast density as an early "warning sign" or stage of the disease.[183,188] For others, vulnerability resulted from the understanding that breast density rendered breast cancer screening useless. As one woman noted, "I feel very worried because when the breasts are dense, there is no possibility to detect breast cancer."[188] However, correctly understanding breast density—particularly its masking effect and associated increased risk for breast cancer—did not always alleviate such feelings of vulnerability. In referencing the masking effect, one woman noted, "It makes me a little nervous … it doesn't make me feel at ease that I'm absolutely free of it." Another explained, "When they say you're higher risk to get cancer, you get apprehensive."[191]

A minority of people who had or may have had dense breasts avoided the experience or perception of vulnerability because of previous understandings that breast density did not increase cancer risk[194] or

was not a cause for concern.[189] Of note, however, was the finding that even some radiographers believed most people with dense breasts did not need to worry about breast cancer, because they saw people with dense breasts as being primarily young and healthy without additional risk factors.[187]

Responses to Vulnerability

The experience of vulnerability to breast cancer influenced and was influenced by responses to learning about breast density. For example, many people with dense breasts responded to the idea of increased vulnerability to cancer with strong emotional reactions, including reported feelings of uneasiness, worry, fear, anxiety, and even panic.[183,188,189,191,192,195] As one woman noted, "I was very, very, very worried after I get [sic] the letter. Very worried. I can't sleep, you know, I was very depressed."[188] Others responded to such vulnerability with an attitude of acceptance.[191,193] Older people with previous experiences coping with cancer and other health complications sometimes adopted this attitude.[193] As one woman noted:

> *By the time we get to our age, in the 70s, you often have a variety of other things … if you've got good mental health and you get a diagnosis … in some way you're better off, you're better able to handle it than if you were a younger category.*[193]

People who accepted the potential for having breast cancer as a part of God's plan also sometimes expressed an attitude of acceptance: "If God sends it, then you have to take it. There is nothing to do. Take it calmly."[191]

For others, the experience of vulnerability led them to engage proactively in activities to promote their breast health, such as adopting a newfound dedication to participating in recommended routine screening, performing breast self-exams, or making lifestyle changes to reduce their overall breast cancer risk.[188,191,193] As one 69-year-old woman explained, "I think it was kind of a wake-up call that you should start taking more interest in your body and … not depend on your twice yearly visit to the doctor. That you have to be proactive."[188] Others who understood breast density as being caused mainly by modifiable factors voiced a desire to make lifestyle changes they believed would reduce breast density itself, such as limiting caffeine intake.[192]

Another response was placing trust in others (e.g., a higher power, family members, or health care providers) that could guide them toward mitigating or coping with vulnerability to breast cancer.[188,189,191,193-195] For example, some trusted that prayer might prevent breast cancer or that God would help them cope with a potential diagnosis.[188,191] Such trust in God sometimes complemented trust in health care providers. As one woman described, "I would think that I would have to go to the doctor, and God would give me the strength to resist anything that could happen … Anything I could have, I just have to trust God and the doctors."[191] People with dense breasts generally trusted that their health care providers had the expertise and willingness to guide them in detecting or preventing cancer.[188,191,193-195] As one woman said, "I think I would just ask somebody that I trust—a doctor that I trust … someone that I have a relationship with that I feel would make the best recommendation for me."[195]

The ways in which people with dense breasts responded or could respond to information about their breast density status also influenced their experience of vulnerability. For example, responding to breast density notification by consulting trusted family, friends, and health care providers helped reduce feelings of vulnerability when such people provided reassurance.[183,189] Responding to breast density notification by requesting or accessing supplemental screening could also reduce experienced vulnerability (see Choosing Supplemental Screening, below).[191,193,194] For this reason, some people with

dense breasts noted that being unable to access supplemental screening because of cost or a lack of a physician's order was emotionally distressing and frustrating.[191,194] As one woman stated, "I feel like I am at their [health care providers'] mercy, because I can't prescribe a test, only they can. So it's like you are at the person's mercy. If they don't detect anything, I can't do it."[191]

Choosing Supplemental Screening

Choosing to request, engage with, or offer supplemental screening was often a complex decision informed by an interplay between the perception of benefits and risks—often influenced by understandings, misunderstandings, and perceived vulnerability—and the availability of resources.

Perceptions of Benefits and Risks

When gaining an awareness of the masking effect—and sometimes following exposure to the opinions of family and friends—many people with dense breasts and their health care providers considered supplemental screening to be necessary for catching breast cancers in the context of dense breasts.[187-189,191,193,194] One general practitioner accepted the need to order sonograms as a fact: "I didn't know there was anything particular to understand, other than the fact people with dense breasts needed ultrasounds instead of mammograms, or as well as, to pick up their cancers."[190] Similarly, one person with dense breasts conceptualized supplemental screening as "the only way of knowing what's happening in the breasts."[191] Perceiving themselves as vulnerable to breast cancer, combined with an understanding of the masking effect, some people with dense breasts could not reconcile why supplemental screening would not be offered: "If I have something and they couldn't see it clearly, I think they should refer me for another exam where they can see things clearly."[189]

Relatedly, both people with dense breasts and health care providers considered supplemental screening modalities to be potentially beneficial in alleviating the emotional distress caused by the experience of vulnerability to cancer.[187,191,193,194] Supplemental screening offered "peace of mind."[193] As one woman noted:

> *This additional screening I suppose is good because I want the information. I want to take care of myself … in the event that I have something inside my dense breasts that could be cancerous, I'd like to catch it as early as possible … so that we could address it and I could live a longer life with my daughter.*[191]

Another woman questioned, *"*Why can't you just go to the next room, get the ultrasound and go on with your life?"[192]

Health care providers and people who had or may have had dense breasts valued the risks of supplemental screening differently when deciding whether to engage with or offer such screening. One study found that most people with dense breasts who wanted an ultrasound were unaware of any risks associated with this screening modality.[192] However, even in another study where people received education about the risks of supplemental screening—including false-positives, overdiagnosis, and overtreatment—the majority still placed greater value on the potential benefits of engaging with the intervention.[193] These desires were grounded in the experience of vulnerability to breast cancer. Illustrating this, one woman stated, "I'd much prefer to be alive and have known that I've done everything to be in that point, whether it was a false positive or not, than be dead."[193] Another similarly said, "I'd rather be overdiagnosed and cop the consequences."[193]

Although it was reported infrequently in the reviewed literature, some health care providers and a minority of people who had or may have had dense breasts placed greater value on the risks of false-positives and overdiagnosis.[190,192,193] For example, after learning about the risks of supplemental screening one woman reflected, "Overdiagnosis, I think that is … probably very worrying to, to go through all that and have all the treatment and if it's something that people don't want to have then probably why put them through it?"[193] Valuing these risks did not necessarily preclude people from considering supplemental screening to be worthy of engaging with or offering, but it did prompt deeper consideration for individual contexts and vulnerabilities in which they believed screening would be most appropriate.[190,193]

Availability of Resources

In contrast to the risks of false-positives, overdiagnosis, and overtreatment, perceived limitations in terms of financial, human, and health care system resources more frequently influenced decisions to engage with or offer supplemental screening.

Although many people with dense breasts wanted to have supplemental screening, the cost of accessing the intervention (when not publicly funded) made their choice to engage with it a financial decision, or a decision that was made for them.[193-195] As one woman recalled, "The doctor had actually ordered an MRI, but the insurance denied it … and that's an expense that's kind of hard to take out of your pocket."[194] On this note, although some perceived ultrasound to be less invasive than MRI, many people who had or may have had dense breasts said that they would choose to have an ultrasound instead of an MRI because of its affordability rather than its perceived effectiveness or comfort.[193] As discussed previously, some health care providers also voiced hesitation in sharing information about breast density with people in their care who they believed could not afford supplemental screening.[190] Health care providers were concerned that doing so would present people with potentially distressing knowledge that they could not act on.[190]

Some health care providers noted that the availability of human or health care resources at different levels of the health care system influenced their decisions and preferences for offering supplemental screening. For example, at the micro level, some radiographers in Sweden noted that they would alert a physician to order supplemental screening for a person with dense breasts if their workload made it possible for them to perform the additional test.[187] At the macro level, however, they were concerned that there would not be enough time, human resources, funding, or infrastructure to offer supplemental screening to all women with dense breasts.[187] One radiographer worried that broadly offering supplemental screening in their current context would decrease access to health care for others, because "all resources will go to those who are not really sick, but those who are only most worried and want extra examinations to feel safe."[187]

Discussion

Although breast radiographers and radiologists generally conveyed understandings about breast density that aligned with biomedical conceptualizations, breast density was a relatively unfamiliar and poorly understood phenomenon among most people who had or may have had dense breasts, and among general practitioners.[188-194] The means by which people with dense breasts and their general practitioners came to know about and understand breast density (i.e., notification letters and mammography reports, respectively) shaped their knowledge and understandings.[188-192,194] In turn, these understandings shaped people's experiences of and perceptions about breast density as a vulnerability

to breast cancer, informing their desire to engage with or offer supplemental screening. However, the availability of resources ultimately affected decisions to act on these intentions.

In the context of publicly funded supplemental screening, many people with dense breasts and their primary care providers may not have enough of an awareness or understanding of breast density to make informed decisions about whether to engage with or offer the intervention. The findings also indicate that limitations in knowing and understanding may disproportionally affect certain groups of people in Ontario: those at risk of being underscreened, such as immigrant women,[78] Black Canadian women,[79] people of lower economic status,[80] and Indigenous peoples[81]; those receiving notification or health care in a nonpreferred language[189,190]; and those perceived by health care providers to have low health literacy levels.[193]

Policies designed to fund interventions that would increase awareness and understanding of breast density and supplemental screening may promote equitable opportunities for making informed decisions. Interventions to equitably promote understandings of breast density and supplemental screening modalities may include the following: revising notification letters so they contain clear, simple, specific language; delivering notification letters alongside informational pamphlets with visual aids; and producing practice guidelines on breast density for health care providers.[187,189-192,195] That said, the ability to make informed decisions about supplemental screening depends on having access to routine breast cancer screening that assesses and reports breast density. It follows that interventions addressing knowledge-related, access-related, and culture-related barriers to accessing routine mammography[197] may also increase access to supplemental screening.

The findings of this review suggest that improving understandings of breast density may alleviate some of the experienced vulnerability, but not all of it. Many people with dense breasts continued to feel vulnerable to breast cancer when they understood the masking effect and the increased risk for breast cancer associated with dense breasts.[183,188,191] Most people with dense breasts and their health care providers understood supplemental screening as the only way to detect breast cancer and, in turn, alleviate some of this vulnerability.[187-189,191,193,194] For this reason, many people who had or may have had dense breasts wanted supplemental screening, ascribing little weight to its associated risks (i.e., false-positives, overdiagnosis, and overtreatment).[193] However, knowing about these risks allowed people to make informed decisions about supplemental screening in the context of individual risks and vulnerabilities.[190,193]

Although desires for broader access to supplemental screening are important to note, personal financial concerns and resource availability in the broader health care system can affect access to supplemental screening and, subsequently, experiences of vulnerability. Concerns raised by radiographers[187] identified potential inequities that may be accentuated by publicly funding the intervention for all people with dense breasts in the context of finite health care resources. As they noted,[187] providing publicly funded supplemental screening in a context of limited human and physical resources might divert care away from those with, or at risk for, other conditions that rely on medical imaging for detection and treatment. And yet, if supplemental screening were not publicly funded, affordability would influence individuals' ability to access it. Being unable to access screening because of an inability to pay out of pocket or the lack of a physician's order may exacerbate emotional distress related to vulnerability.[191]

Strengths and Limitations

This review had strengths and limitations that increased and decreased the trustworthiness of its findings, respectively. A strength was that most of the included citations were of high or moderate quality. As well, although only one group of authors explicitly compared the understandings and experiences of people with dense breasts from different demographic groups,[183] most of the studies included diverse populations with respect to race or ethnicity, economic status, and health literacy. The understandings and experiences detailed in the present review may also reflect those of the general population engaging in routine screening. Most participants did not have a history of breast cancer or high-risk factors for breast cancer, and no authors reported recruiting from special-interest groups that would have a higher-than-average awareness and knowledge of breast density and supplemental screening at baseline.

It is possible that this rapid qualitative review did not capture relevant citations or analytical findings, given that a single reviewer screened, selected, and analyzed the literature. Furthermore, none of the included studies took place in Canada, possibly limiting the transferability of this review's findings to the Ontario context. The reviewed articles also contained limited or no data related to the experiences of engaging with or offering supplemental screening; the understandings, experiences, and preferences related to specific supplemental screening modalities; and the understandings and experiences of family members.

Conclusions

The present review found that breast density was a relatively unfamiliar and poorly understood concept among people who had or may have had dense breasts. Similarly, general practitioners expressed having limited knowledge of this phenomenon. People with dense breasts were often introduced to the concept for the first time via notification letters, which generally led to uncertainty, confusion, and misunderstanding (particularly with respect to the relationship between breast density and breast cancer; breast density as a physical or aesthetic phenomenon; and the causes of breast density).

The findings of this review indicate that many people with dense breasts who access routine mammography (especially those who receive health care in their nonpreferred language or are perceived to have lower economic status or health literacy levels) and their health care providers may not have the awareness or knowledge to make informed decisions about supplemental screening. Policies that support initiatives to equitably enhance people's awareness and understanding of breast density and supplemental screening may be helpful complements to supplemental screening programs.

Misunderstandings about breast density influenced (and sometimes accentuated) the experience of vulnerability to breast cancer; however, people also experienced emotionally distressing vulnerability when they understood the concept. People with dense breasts and health care providers perceived supplemental screening to be the only way of detecting cancer in dense breasts. To protect themselves from breast cancer and obtain "peace of mind," many people who had or may have had dense breasts voiced a desire to engage in supplemental screening even when they had been educated about false-positives, overdiagnosis, and overtreatment. In the absence of publicly funded supplemental screening, the choice to engage with or offer such screening became a matter of a person's ability to pay and their access to a health care provider willing to order it. Some people experienced emotional distress from barriers to accessing supplemental screening.

Despite health care providers' broad desires to engage with or offer supplemental screening, some voiced concerns that it would be impossible to provide it equitably to all people with dense breasts, given that the health care resources available are finite. When people in the included studies were unable to access publicly funded supplemental screening, they preferred ultrasound over MRI because of its affordability.

Preferences and Values Evidence Conclusions

Ontario Health conducted direct engagement with people with dense breasts who may undergo screening for breast cancer in Ontario. CADTH completed a qualitative rapid review of the evidence for patient and health care provider preferences and values and included studies outside of the Ontario context.

Many of the findings from the qualitative evidence rapid review aligned with those of our direct engagement. The people we spoke with valued the idea of publicly funding supplemental screening as an adjunct to mammography for people with dense breasts because of its perceived clinical effectiveness compared to mammography alone and the potential impact of the screening results with respect to breast cancer prevention.

A key factor identified in both investigations was the continued need for patient education and equitable access to supplemental screening. The qualitative evidence rapid review found that some health care providers expressed concerns that finite healthcare resources would limit the ability to provide supplemental screening to all people with dense breasts in an equitable way. Furthermore, direct engagement revealed that people with dense breasts contend with gaps in patient education and self-advocacy for consistent access to supplemental screening. Publicly funding supplemental screening for people with dense breasts was favoured by patients and most health care providers, but equitable access to screening and patient education are important considerations.

Ethics Review

Research Questions

Two questions guided our exploration of the ethical considerations related to supplemental screening as an adjunct to mammography for breast cancer screening in people with dense breasts in Ontario:

- What are the major ethical issues raised by the implementation of supplemental screening as an adjunct to mammography for breast cancer screening in people with dense breasts?
- What are the normative implications of these issues for implementation and uptake in Ontario?

We considered these questions as matters of both systems-level (or population-level) and individual-level ethics. Systems-level ethics explores decisions that affect large numbers of people, and decisions for which outcomes and interests are considered in aggregate (i.e., organizational ethics, policy ethics, and public health ethics are all domains of systems-level ethics). In systems-level ethics, instead of asking whether supplemental screening as an adjunct to mammography for breast cancer screening creates benefits or leads to equity issues for individuals, we ask questions such as the following: "Does access to supplemental screening for people with dense breasts create benefit with minimized and proportional harms for the population of Ontario?" and "Does supplemental screening for people with dense breasts generate or worsen existing inequities in access to breast cancer screening in Ontario?"

We also considered such questions at the individual level, invoking individualist considerations that are typically concerns of clinical ethics. In a clinical ethics paradigm, the analysis considers matters of respect for people, autonomy, dignity, harms or benefits, and fairness from the perspective of the individual, including the patient, their loved ones, and their care providers. These considerations might inform recommendations for whether supplemental screening for people with dense breasts can be implemented and delivered in a way that aligns with these values and principles, as well as how that might take place. If the analysis determines that the technologies or programs cannot be implemented in a way that sufficiently lives up to the core individual values identified, those findings might also influence the acceptability of the technology at a systems level.

The results of the present ethics review are organized according to a principlist framework (one that operates by applying ethical principles to highlight ethical considerations), and it includes individual- and population-level considerations.

Methods

Inquiry

The present ethical analysis took a multistep approach to identifying the considerations related to supplemental screening as an adjunct to mammography for people with dense breasts and their implications for implementation and uptake in Ontario:

- A review of published literature
- Engagement with the clinical evidence review, qualitative evidence rapid review, and economic analyses in the present health technology assessment
- A de novo ethics analysis

This approach was truly iterative and resulted in frequent shifts between steps. For example, examination of the draft qualitative evidence rapid review and discussions with the qualitative research officer at the Canadian Agency for Drugs and Technologies in Health (CADTH) allowed for further refinement of the ethics literature search strategy. Early results from the ethics literature review led to conversations with the authors of the clinical evidence review to gauge the relevance of the ethics results to the clinical findings and the health technology assessment overall. Our approach allowed for further refinement in terms of scope, with the possibility of moving back and forth between the above steps if necessary.

We reviewed relevant literature to identify existing ethical analyses of supplemental screening as an adjunct to mammography for people with dense breasts. This included a search for formally published and grey literature that explicitly and specifically raised ethical issues related to supplemental screening, as well as for literature that did not focus explicitly on ethical issues, but whose content pointed to potential ethical issues even if the authors did not name them as such. The literature search also included publications about ethical issues related to analogous processes, including breast cancer screening and cancer screening more generally, to capture a broader set of ethical considerations in the context of screening.

The literature review proceeded with special attention to issues that we anticipated would be relevant to the ethics of supplemental screening for people with dense breasts, such as equity and access to screening; harm or safety relating to false-positives or -negatives; the potential for overdiagnosis or overtreatment; and implications for workforce utilization and resource allocation.

Ethics Literature Search

A research information specialist performed a literature search on May 18, 2022, to retrieve studies that identified ethical considerations. They used the Ovid interface in the following databases: MEDLINE and Philosopher's Index. The full search strategy is available on request.

The research information specialist developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The main search consisted of three components: first, a search of mammography and breast cancer combined with breast density. The research information specialist applied CADTH-developed search filters to limit retrieval to citations that explored empirical and normative ethical considerations. They then conducted a second search for literature on breast cancer screening or breast density more broadly, combined with focused terms for ethics and ethical issues. This search also included terms for equity (limited to Canada only), as well as other ethically relevant concepts such as informed consent and overdiagnosis. A third search combined focused terms for explicit ethical considerations with cancer screening or overdiagnosis more broadly. They limited retrieval to English-language publications. They did not limit the search by publication date. Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The final search strategy was peer-reviewed using the PRESS Checklist.[87]

The research information specialist updated the search with regular database alerts in MEDLINE and Philosopher's Index until August 3, 2022. They also performed a grey literature search of sources listed in relevant sections of *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* checklist,[178] which includes the websites of regulatory agencies, health technology assessment agencies,

clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. They used Google to search for additional internet-based materials.

Literature Screening and Selection

The selection of relevant literature proceeded in two stages. In the first stage, a single reviewer independently screened titles and abstracts from the original electronic database. A total of 1,830 citations were identified by the database search and subsequently screened (1,805 from the original search on May 18, 2022, and an additional 25 from a database alert in August 2022). The initial screening used the following inclusion criteria:

- The article provided a normative analysis of an ethical issue arising in the context of supplemental screening for people with dense breasts, breast cancer screening, or cancer screening in general
- The article presented empirical research that directly addressed an ethical issue arising in the context of supplemental screening for people with dense breasts, breast cancer screening, or cancer screening in general

The reviewer used the following additional criteria to focus and refine the search, and to identify the most relevant citations. Studies were excluded if:

- Their primary focus was on legislation requiring notification about dense breasts
- Their primary focus was on personalized risk stratification in breast cancer screening, including the relevance of genetic predisposition
- They were about overdiagnosis and were published earlier than 2016, except for papers explicitly about the ethics of overdiagnosis
- They were published earlier than 2012, except for conceptual ethics papers

Studies were included if:

- They discussed informed consent with respect to breast screening only
- They explored overdiagnosis in the context of breast screening only
- They were about equity issues relating to breast screening in a Canadian context

After these criteria had been applied, 1,502 publications were excluded from the original 1,830 citations, and 328 publications were included for review.

In the second stage, a single reviewer with ethics expertise read the full-text reports of the 328 publications. A further 220 articles were excluded. A total of 108 full-text articles were included in the ethics review.

Results and Analysis

Most of the relevant literature was related to the ethics of modalities that were analogous or related to supplemental screening for people with dense breasts (rather than offering a direct analysis of the ethics of supplemental screening). We completed an analysis of the ethics of these analogous technologies to determine which issues that were relevant to the analogous modalities were also relevant to supplemental screening for people with dense breasts.

The ethical considerations that emerged in the literature review can be organized according to four key ethical principles or duties: the duty to create benefits and minimize harms for individuals; the duty to create benefits and minimize harms for populations; the duty to respect individual autonomy and personhood; and the duty to promote equity and justice. These principles capture population-level concerns (harms and benefits to populations, equity, and justice) and individual-level concerns (harms and benefits to individuals, respect for autonomy); we have discussed their ethical relevance to supplemental screening for people with dense breasts below. For simplicity, when referring to the person who is considering or engaging in breast screening, we have used the term *individual* throughout (instead of *patient*). This is important because it points to an ethically relevant feature of screening that distinguishes it from other types of medical interventions: by definition, screening is intended for those who have no indication that they may have the disease being screened for; therefore, they are not patients.[198]

In addition to identifying the core ethical considerations related to supplemental screening for people with dense breasts, the present ethics review revealed two broad themes: apparent tensions between individual- and population-level interests in the context of screening programs, and uncertainty associated with supplemental screening. We have made reference to these themes in our discussion of the core ethical considerations and explore them more closely at the end of this section.

Many of the issues highlighted in this section are not unique to supplemental screening for people with dense breasts. Ethical issues relating to the balance of harms and benefits for individuals and populations, autonomy and informed consent, equity, and access to screening—as well as concerns relating to false-positives and overdiagnosis—have been matters of discussion for breast screening and other screening activities for as long as these types of activities have been taking place. However, supplemental screening for people with dense breasts also brings novel ethical concerns related to informed consent for interventions that have little robust evidence of their long-term benefit (see the clinical evidence review); equity in terms of risk differentials between people with dense breasts and those without; and equity and resource stewardship considerations with respect to the overall use of diagnostic technologies (including machinery, expert workforce, and time).

Benefits and Harms of Supplemental Screening for People With Dense Breasts

The principles of beneficence and nonmaleficence (i.e., the duties to create benefits and minimize harms) sit at the core of health ethics and are most familiarly part of the "four principles" approach to bioethics, alongside the principles of autonomy and justice.[199] They are typically considered in the context of a health care provider's duty to their patients, but they also apply at the population level. Accordingly, those involved in the funding and organization of health care (including health leaders and decision-makers) have obligations to minimize harms and maximize benefits for populations, while at the same time considering the effects their decisions may have on individuals. Indeed, this is one of the rationales behind health technology assessment: we have obligations to steward scarce public resources

and fund technologies that offer a balance of benefits over harms for the population,[200] and health technology assessment offers a means of following through on those obligations.

The intention behind breast screening activities (including supplemental screening for people with dense breasts) is to reduce breast cancer mortality by catching tumours early and preventing them from reaching large sizes or advanced stages at diagnosis.[201-203] The goal is not just to detect cancer, but to detect "cancer that matters"[204]: cancer that if caught would avoid a death, ultimately reducing the mortality associated with breast cancers.[205]

It is also important to be clear about the population intended for screening activities: that is, people who have no reason to believe that they have the disease being screened for.[198] Individuals who are at higher risk for the disease (e.g., because of genetic factors) or who have a concerning symptom (e.g., a lump in their breast tissue) have reason to believe they may have the disease; for those people, any follow-up imaging would be classified as surveillance or diagnostic imaging—not screening.

The distinction between screening and diagnosis aligns with another very relevant distinction: public health interventions versus clinical decisions in response to individual need. Historically, screening has been seen as a public health intervention.[206] However, because of increased emphasis on individual interests related to screening, it is likely understood more and more as an intervention that supports individual health interests as well as population-health goals.

There is a widespread assumption among members of the public that a cancer detected as a result of screening means a life saved that would have been lost otherwise,[206] but this is not always the case. Some cancers detected as a result of screening might have progressed slowly and had no impact in a person's lifetime.[207] Others, if not detected by screening, might have been detected clinically, treated, and cured.[206] Yet others detected by screening might have led to death even after treatment had been pursued. Ultimately, we cannot know for certain whether a life has been saved by detecting cancer through screening. This is not to say that breast screening (including mammography and supplemental modalities) does not offer benefit. Rather, it is meant to point to nuances that should be brought to bear when considering the effects of screening and its associated harms and benefits. Another common assumption[208] is that more screening is better. As will be discussed below, screening presents its own risks to both individuals and populations, and these risks are amplified with the increased technical proficiency of screening technologies and increased frequency of screening.[207]

The intended benefits (e.g., decreased morbidity and mortality) and potential harms (e.g., false-positives, overdiagnosis) of supplemental screening for people with dense breasts are likely to be similar to those for general breast screening. Therefore, it is reasonable to include findings from the literature on mammography when exploring the possible benefits and harms of supplemental screening for people with dense breasts and the extent to which funding it would deliver on the duties to fund services that offer a balance of benefits over harms.

INDIVIDUAL-LEVEL BENEFITS AND HARMS

Benefits

For individuals, the primary intended benefits of breast screening (including supplemental screening for people with dense breasts) are to save lives and reduce the burden of cancer treatments by detecting disease earlier.[209] Participation in screening can offer emotional and psychological benefits, including feelings of relief and reassurance as a result of clear screens or follow-up for abnormal screens (false-

positives),[209] and avoidance of future regret, which could occur if an individual chose not to be screened and discovered later that they had cancer.[210]

The clinical evidence review in the present health technology assessment found no evidence to confirm or quantify whether supplemental screening as an adjunct to mammography for people with dense breasts has led to reduced morbidity and mortality, or to an improved sense of well-being for those who have undergone screening.

When assessing the individual benefit of breast screening, it is important to distinguish between the perceived benefit and the actual benefit. In Western medicine over the past 40 years, a strong cultural perception has evolved of the unequivocal benefit of breast screening (for more detail, see Informed Consent or Dissent, below). Many people with breasts (and their clinicians) perceive breast screening to be obviously good, and such a perception can contribute to an understanding that participation in breast screening is beneficial, regardless of the outcome (e.g., reassurance when results are negative; belief that it was good to double-check after a recall and confirmation of a false-negative result; relief or gratitude at catching a cancer that may or may not have gone on to cause harm).[206,211] Individuals who have been screened (or who are contemplating screening) may be likely to describe screening as beneficial irrespective of whether their experiences resulted in improved physical health. It is important for decision-makers to be aware of this context, particularly when reviewing results from individual engagement initiatives (including those aimed at patients, providers, or members of the general public) or research that reports on individual beliefs and perspectives.

Some authors have proposed that interventions such as screening are worthwhile and should be provided even if their sole benefit is to relieve an individual's anxiety.[212] However, if such a rationale motivates the recommendations of an individual clinician, their patients would need to understand that such reassurance is temporary, because interval cancers (i.e., cancers that emerge between screenings) are possible (albeit reduced with supplemental screening for people with dense breasts), and are often more aggressive than those detected with screening.[203]

Harms

False-positives (i.e., the identification of an abnormality that is followed up and determined not to be cancer) are among the more substantial harms associated with cancer screening. A person who has a screening result that turns out to be a false-positive must return for further imaging and possibly biopsies, which come with potential emotional and physical risks. False-positives occur more frequently among people who are screened more often, are of a younger age, or who have higher breast density.[213,214]

Overdiagnosis and overtreatment (the identification and treatment of cancers that were never going to cause harm to the individual) is a second potential source of harm (see also Population-Level Benefits and Harms, below). From an individual perspective, identifying a benign or slow-growing cancer that was never going to cause harm may result in treatment that offers no benefit and introduces risks and harms. This could include surgery, radiotherapy, or systemic therapy, which could lead to physical, psychological, or economic harm for patients who are overdiagnosed.[215-218] Overtreatment can be mitigated by developing and using strong treatment guidelines.[218] Still, even if someone who is overdiagnosed avoids treatment and its associated harms, the knowledge of a diagnosis can cause psychological harm for them and their family.[217]

Summary

A review of the potential harms and benefits associated with screening (including supplemental screening for people with dense breasts) shows that participation in screening can be seen not only as a means of relieving anxiety, but also as a *source* of anxiety if the screening results are abnormal. There is some debate in the literature about the importance of screening-associated anxiety, especially when it is used as an argument against widespread screening. Some have noted that there is little evidence that abnormal screening results lead to acute or long-term distress.[219] Others have reported that such anxiety—especially anxiety associated with false-positives that required further investigation with biopsy or fine-needle aspiration—persisted for some people and was transient for others.[214]

As well, breast screening presents the potential benefit of avoiding burdensome treatment (if screening identifies a cancer that would have caused harm and the cancer is successfully treated early) but also the harm of unnecessary treatment. It may be possible to determine how to balance these conflicting harms and benefits by taking a closer look at the evidence for the frequency of these outcomes, but not all relevant outcomes can be quantified. Given current capacities for predicting the progression of cancers, it is difficult (if not impossible) to assess who benefits from breast screening (including supplemental screening for people with dense breasts) and who does not: that is, who has avoided a potentially lethal cancer and who has been treated unnecessarily.[220]

The clinical evidence review found that supplemental screening for people with dense breasts generally increased the sensitivity of screening (i.e., the ability to correctly identify patients with cancer), but it decreased the specificity (i.e., the ability to correctly identify patients without cancer), suggesting that people who undergo supplemental screening have increased potential for false-positives that require recall and follow-up. Supplemental screening modalities for people with dense breasts detected more cancers than mammography alone, suggesting that they might also increase overdiagnosis in this population.

Evidence from current breast screening practices (not including supplemental screening for people with dense breasts) has led many to conclude that screening may offer some emotional or psychological benefits, but that most of the people screened will not benefit physically from screening.[211,221,222] One study proposed that people who undergo screening are more likely to experience the harms associated with screening (e.g., recalls, false-positives, overdiagnosis) than the intended benefits.[203] At least one author has argued that in light of this distribution of harms and benefits, offering breast screening constitutes a violation of the duties of nonmaleficence.[223] Another, commenting specifically on supplemental screening for people with dense breasts, proposed that the potential benefit of detecting additional cancers may not outweigh the harms of false-positives, overdiagnosis, and overtreatment.[224]

Arriving at a consensus as to how such harms and benefits should be balanced continues to be a challenge, because it is difficult to compare the benefit preventing a single cancer death against harms that are less serious but more common, such as false-positives or overdiagnosis.[220]

POPULATION-LEVEL BENEFITS AND HARMS

Given the close connection between existing breast screening programs and supplemental screening for people with dense breasts, it is reasonable to look to the evidence of population-level benefits and harms of existing breast screening programs to anticipate the ethical considerations that would be likely to arise in relation to supplemental screening.

There is substantial debate in the literature about the effectiveness of breast screening programs. Some studies have suggested that breast screening does not reduce mortality associated with breast cancer.[201,216,225,226] Others have shown that although breast screening can save lives, programs must screen many individuals to save even a single life, and in the process, a substantial subset will experience false-positives, including those detected with biopsy.[227] This finding has led others to suggest that the harms of screening might offset any benefit at the population level.[228-230] Others have acknowledged that mammography is imperfect, but that it is the best tool available, and any risks or harms associated with its use are preferable to the potential for underdiagnosis of breast cancer.[231]

A full review of the literature on the outcomes of breast screening in general was beyond the scope and purview of the present health technology assessment. Nevertheless, it is important to note that although the evidence for supplemental screening in people with dense breasts is limited, the evidence for general breast screening is ample, and it raises many questions about the population-level benefits of this practice.

Benefits and Harms for the Population With Dense Breasts

Morbidity and Mortality

When considering the population-level benefits of a proposed intervention, morbidity and mortality tend to be of primary concern (other outcomes relating to equity, stewardship, and autonomy are also important, but they are generally not couched in terms of harms and benefits). As outlined above, the goals of supplemental screening for people with dense breasts (like other types of cancer screening) are to minimize the mortality associated with breast cancer and the morbidity and burdens of cancer diagnosed at later stages. In other words, the benefits of supplemental screening for people with dense breasts could include improved survival and decreased burdens of treatment.

The clinical evidence review found no evidence to indicate whether supplemental screening would reduce mortality or morbidity associated with cancer in people with dense breasts. However, as noted above, it did find that supplemental screening for people with dense breasts increased the sensitivity and decreased the specificity of breast screening. The cancer detection rate was higher after supplemental screening and the interval cancer rate was lower, but there were also more abnormal recalls, reflecting a higher number of false-positive results. It was not clear whether supplemental screening for people with dense breasts translated to decreased morbidity associated with late-stage cancer treatment or mortality.

Overdiagnosis

In light of the experiences and evidence related to other types of screening (including breast screening), one population-level harm is likely to be a factor for programs of supplemental screening for people with dense breasts: the overdiagnosis of breast cancer.

The term *overdiagnosis* refers to the identification of cancers through screening that would not have caused symptoms or death in a person's lifetime if the cancer had not been detected.[226,232,233] Overdiagnosis is not the same as a false-positive (where a lesion is identified and later determined not to be cancer) or a misdiagnosis.[234] Rather, it is a histologically confirmed cancer that, without screening, would not have gone on to cause morbidity or death (although it cannot be known at the time of diagnosis whether a particular cancer would have caused morbidity or death had it not been discovered).[218]

Overdiagnosis occurs as a result of screening because screening can detect smaller cancers. A subset of these smaller cancers grow slowly or not at all, so they are unlikely to become large enough to cause issues in a person's lifetime.[235] As new technologies are introduced that can detect smaller abnormalities, the rate of overdiagnosis increases.[225,230] The clinical evidence review found that supplemental screening found more cancers in people with dense breasts than mammography alone, suggesting that supplemental screening for people with dense breasts may lead to overdiagnosis. Overdiagnosis persists because there is a mismatch between our ability to detect cancers and our ability to predict cancer behaviour.[217,230]

Overdiagnosis cannot be observed directly; it can only be estimated using population-level data.[236-238] Such estimates can be calculated in a variety of ways, but there is no consensus among epidemiologists about how to do so.[232] Therefore, estimates of the rate of overdiagnosis as a result of breast screening range from 0% to 50% overall, and from 11% to 22% in randomized trials.[214] The Independent UK Panel on Breast Cancer Screening calculated that for each breast cancer death prevented, three people are overdiagnosed.[228] Another study estimated that overdiagnosis occurs in about one in six or seven individuals who are screened.[239]

As discussed above, overdiagnosis can cause individual-level harms in the form of unnecessary tests and treatments. At the population level, the harms of overdiagnosis come primarily in the form of costs to the system, including opportunity costs. Overdiagnosis results in the use of public funds and health care resources (including equipment, space, and expertise) that cannot then be devoted to other health services.[237]

One of the more difficult challenges of overdiagnosis is that it cannot be detected at the individual level; it is currently impossible to distinguish overdiagnosed cancers from other cancers using histology.[218] People who have been overdiagnosed are likely to believe that the detection and treatment of their cancer was necessary and life-saving.[230] Similarly, their oncologists are likely to believe that the screening and associated cancer treatment was beneficial. Based on their clinical experience, oncologists may reasonably conclude that screening is beneficial because they are treating patients whose cancers have been detected early (as a result of screening) and who are surviving longer than patients who present with cancers detected later (without screening). However, it is impossible to know whether patients with screening-detected cancers are living longer than they would have without cancer screening.[230]

The fact that overdiagnosis occurs does not mean that breast screening (including supplemental screening for people with dense breasts) is necessarily unethical, or that it should not happen. If the benefits of screening are sufficient, they can offset the harms of overdiagnosis, making screening more ethically justifiable (to the extent that a favourable balance of harms over benefits determines justifiability). Alternatively, if the harms associated with overdiagnosis can be minimized, screening can be justified even if the benefits are marginal. Some authors have expressed concern that overdiagnosis has been overemphasized, and that this may lead to fewer people choosing to be screened, which in turn could result in increased breast cancer–related morbidity and mortality.[236] In the context of supplemental screening for people with dense breasts, it is difficult to know whether an increase in overdiagnosis and its associated harms would be offset by the benefits of more lives saved and less treatment of more advanced cancer, because there has been insufficient time to generate this kind of evidence.

Overdiagnosis continues to be an issue for cancer screening programs. Although there has been an appropriate trend of ensuring that people understand the risks of overdiagnosis as part of their decision to participate in screening (see Informed Consent or Dissent, below), overdiagnosis cannot be dealt with by individuals alone (including individual screeners). Researchers and policy-makers must also remain aware of the problem and its associated harms, and take steps to minimize overdiagnosis in public screening programs.[240] In the case of breast screening, where overdiagnosis is a known harm, the balance can be improved by adopting risk-tailored screening strategies (i.e., targeting those most at risk) and factoring likely life expectancy and overall health into individual screening recommendations.[233] Further research is needed to improve the detection of biologically relevant cancers, and to distinguish them from cancers that will not negatively affect individuals.

Summary

Health leaders, acting on their obligations to fund programs that provide a balance of benefits over harms for the populations they serve, face a challenging decision when it comes to supplemental screening for people with dense breasts. The individuals who benefit from screening programs are not the same people who are harmed. Decision-makers face the difficult task of deciding how much benefit for a few is worth the harm for many others.[241] This challenge is enhanced because the harms and benefits at stake are somewhat incommensurate.[228] A balance is needed between variously tolerable harms (i.e., anxiety and discomfort associated with unnecessary treatment) and absolute harms (i.e., death or at least morbidity) and a consideration of how much survivable harm is acceptable for how many to prevent death for a few.[228]

Benefits and Harms for the Overall Population

Another important ethical consideration relates to opportunity costs. Health leaders and decision-makers usually have a duty to make decisions that maximize the benefits of allocated health resources across diverse populations with a range of health issues and needs. In the Canadian health care context (where budgets tend to be fixed), decisions to allocate funding or other resources to one population can result in reduced funding or resources for others, and this can lead to harms, including increased suffering and death.

If a substantial proportion of the population with dense breasts were invited to annual breast screening with some access to another modality (e.g., digital breast tomosynthesis or magnetic resonance imaging), it could lead to added pressure on existing resources (including access to imaging machines, technologists, and radiologists), potentially decreasing access to the same resources for others. If those other populations had more urgent medical needs or were more likely to derive more benefit from these services than people with dense breasts, then giving priority to people with dense breasts could result in a net decrease in benefit. It could also create equity issues.

Justice and Equity Considerations

The principles of promoting fairness, justice, and equity can be described in various ways, but in general, they outline duties to ensure that public goods are distributed equitably and according to need. In other words, justice and fairness require that benefits and burdens are distributed fairly across society, and that no one social group or community bears disproportionate burdens. As such, this principle is fundamentally about equity and the extent to which individuals have equal opportunities to benefit from health services, including imaging technologies. Equity considerations also require attention to those who may have reduced access to necessary health care resources as a result of the funding of a new technology, or the application of an existing technology for a novel purpose.

In the context of breast screening and breast cancer, equity considerations become relevant in several ways. They include access to breast screening services (regardless of breast density) in terms of timing or stage of diagnosis, access to treatment, and long-term survival. In the context of supplemental screening for people with dense breasts, there is inequity in terms of who may be at increased risk of having lesions or masses missed or overlooked during regular breast screening mammograms. There is also inequity with respect to risk distribution: who, in terms of age, genetics, physiology, and so forth, may be at increased risk of developing breast cancer.

Understanding where the inequities are most acute for breast screening and breast cancer treatment is important for decision-making related to resource allocation. We have duties to address inequities; to do so effectively, the possible sources of those inequities must be narrowed down. For example, one study found little difference across socioeconomic groups in terms of the stage and timing of a cancer diagnosis, but it did find differences in survival: people of higher socioeconomic status had higher survival rates.[242] This finding suggests that the inequities in survival were likely the result of other factors, such as existing comorbidities, access to therapy, and quality of care.[242] If this analysis is correct, then equity may be achieved not by investing in screening, but instead by improving people's access to treatment and the quality of that treatment, as well as other actions that lead to a more just distribution of wealth. Indeed, several studies in the Canadian context have shown substantial differences in the treatment provided to patients with cancer from different socioeconomic groups.[242]

EQUITY IN ACCESS TO SCREENING

An equity consideration for supplemental screening for people with dense breasts is whether there is equity in access to breast screening services in general. If inequities in access exist for regular breast screening, it is reasonable to suppose that the same types of inequities would exist for access to supplemental screening for dense breasts. Participation in the Ontario Breast Screening Program has remained relatively consistent from 2000 to 2018, at 61% to 66% of eligible people with breasts.[243] Breast screening is available at multiple locations across the province,[244] including at mobile sites.[245] However, in spite of considerable efforts to increase access to screening, multiple Canadian studies (including many from Ontario) have shown that people living in low-income areas,[80,246-252] immigrants and refugees,[80,246,250-258] members of Indigenous groups,[81,249] people with intellectual and developmental disabilities,[247,259] people living in rural areas,[260] people with severe mental illness,[261] people experiencing homelessness,[262] and people experiencing imprisonment[263] tend to have lower participation rates in cancer screening, including breast screening.

Barriers to participation in screening programs include lower health literacy levels,[247,262] lack of access to primary care,[80,251,252] reduced access to health information,[254,256,259,262] lack of transportation or the need to travel long distances to screening centres,[254,264] cultural and language barriers,[256] and costs associated with participation (including time off work, paying for transportation, and paying for childcare).[254]

Inequities also exist in relation to breast cancer treatment and survival. A higher prevalence of advanced disease, poorer 5-year survival rates, and higher rates of breast cancer mortality have been noted in members of lower socioeconomic groups[242] and racialized groups.[254,256,265] Differences in access to screening may explain these disparities,[256] but differences in people's access to cancer treatment and the quality of that treatment may also play a role.

Because of the relative novelty of supplemental screening for people with dense breasts and its limited implementation in Canada, the literature contains little evidence about specific inequities in access. One study from the United States found that racialized women with dense breasts were less likely to be

referred for supplemental screening.[265] Still, even without direct evidence, it is reasonable to suppose that existing inequities in access to general breast cancer screening would also apply to supplemental screening for people with dense breasts. By devoting more resources to supplemental screening for people with dense breasts, such inequities in access and outcomes could be amplified, especially if the barriers to screening faced by the marginalized groups described above remain unaddressed.

EQUITY IN THE EFFECTIVENESS OF SCREENING

Increased breast density is associated with decreased sensitivity and specificity in mammogram screening. Sensitivity is decreased because of the masking effect of the dense tissue,[266] and decreased effectiveness of mammography is associated with higher incidence of interval cancers (see the clinical evidence review). Furthermore, dense breasts also appear to be an independent risk factor for breast cancer. In short, people with dense breasts face a slightly higher risk of breast cancer than those without dense breasts (all other factors being equal), and current screening tools (without supplemental screening) are less effective at detecting cancer in this population. These findings can also be described in terms of equity: there is an unequal distribution of risk between those with dense breasts and those without.

As a result, the question arises of whether this inequity must be addressed (at least partially) by offering supplemental screening, so that screening effectiveness for people with dense breasts aligns more closely with that of people without. On the surface, achieving equity in screening effectiveness by offering supplemental screening for people with dense breasts seems unequivocally good; however, it is important to consider the anticipated outcomes of screening. As discussed above with respect to overdiagnosis, simply finding more cancers does not mean that more lives will be saved, or that more difficult courses of treatment will be avoided. Meaningful equity of screening effectiveness for people with or without dense breasts should entail equitable opportunities to avoid morbidity and mortality. Whether or not supplemental screening for people with dense breasts achieves this type of equity depends on whether it identifies more cancers in people with dense breasts, and on the consequences of those discoveries.

EQUITABLE RESOURCE ALLOCATION ACROSS THE POPULATION

When examining equity considerations for supplemental screening for people with dense breasts, it is also important to consider the population-level distribution of resources.[198] This includes the distribution of health care funding, as well as the allocation of existing imaging technology and expert workforce (including radiologists, oncologists, technologists, and other associated staff). The primary economic evaluation in the present health technology assessment concluded that supplemental screening for people with dense breasts may not be cost effective because of higher costs per quality-adjusted life-year (QALY) gained for each of the modalities examined (ultrasound, digital breast tomosynthesis, magnetic resonance imaging) compared to mammogram alone. Although the cost per QALY varied by screening modality and whether each modality was applied to people with extremely dense breasts only, or to people with heterogeneously dense and extremely dense breasts, in most cases the cost per QALY gained by supplemental screening for people with dense breasts compared to mammogram alone was higher than the commonly used willingness–to-pay values of $50,000 and $100,000 per QALY gained.

Funding treatments that cost more than the commonly used willingness-to-pay values displace additional health that could be achieved in the population at large,[267] posing equity concerns in at least two ways. First, if the commonly used willingness-to-pay values were not applied consistently and

supplemental screening were funded for people with dense breasts, this choice might not represent an equitable allocation of health care funding; supplemental screening might require a disproportionate investment of funds for the benefits it provides. The second equity concern arises over the displacement of health that could be achieved. With higher costs per QALY, funding supplemental screening for people with dense breasts would mean not funding other potentially QALY-generating activities (i.e., opportunity costs). If allocation of funding leads to disproportionate benefit to a particular group in society, it could produce or reinforce health inequities.

In addition to opportunity costs as a result of the allocation of health funding, supplemental screening for people with dense breasts may also create opportunity costs relating to access to equipment, workforce, and associated health services. Unless a supplemental screening program included the purchase of new imaging machines, funding supplemental screening for people with dense breasts would require a reallocation of time on existing machinery, away from people who need it for other purposes. As well, regardless of whether or not more equipment is purchased, a widespread supplemental screening program for people with dense breasts would require the reallocation of expertise to read and interpret screening images. We could also expect that implementing supplemental screening for people with dense breasts would create additional pressures on the resources necessary to follow up on higher numbers of abnormal findings. In short, supplemental screening for people with dense breasts could present opportunity costs for other programs and populations that currently rely on the resources supplemental screening would require. This could result in equity concerns if such a reallocation led to an unjust distribution of the benefits and burdens of health care resources.

SUMMARY

Although funding supplemental screening for people with dense breasts may address inequities in screening effectiveness, it is not clear whether it would lead to greater equity in positive outcomes for people with dense breasts. There is evidence of inequities in access to breast screening and treatment in general, as well as persisting inequities related to the outcomes of breast cancer and its treatment. Funding supplemental screening for people with dense breasts could have a neutral effect on these inequities, but it seems plausible that it would amplify them, especially if the barriers to screening faced by the marginalized groups listed above remain unaddressed. In this context, a funded program of supplemental screening for people with dense breasts would entail a further investment of resources in a subpopulation that already has access to breast screening services. It would also be important for decision-makers and health leaders to consider an equitable distribution of the benefits and burdens of health resources for everyone in the population they serve.

Respect for Autonomy

Duties to respect individual autonomy are central to Western bioethics; they derive from an individual's role and authority in determining what happens to their body and how their life unfolds.[199] In the context of a health technology assessment, how a particular technology or health intervention impacts individual autonomy is salient to questions of *whether* a particular technology or health intervention should be implemented, and *how* it should be implemented. When a health care intervention cannot be implemented in a way that reflects our obligations to respect individual autonomy, a decision may be made not to implement it at all. When it is possible to fund or implement an intervention and respect individual autonomy, attention to this principle still requires consideration of how to do it and what barriers exist.

INFORMED CONSENT OR DISSENT

In health care, the principle of respect for autonomy involves the following obligations: to enable individuals in making informed decisions about health interventions, and to enable health care providers or health systems in accepting and respecting those decisions.[199] Informed-consent processes are a means by which health care providers and health organizations can act on those duties. A central part of ethics analysis in health technology assessment is to examine whether or not a novel technology (or a new use of an existing technology) has implications for respect for autonomy and related informed-consent processes.[200]

There is general consensus in the bioethics literature that to make an informed decision about consenting to a medical intervention, an individual needs access to comprehensive and accurate information about the potential harms and benefits, and about the uncertainties associated with accepting or declining the intervention.[268] The information necessary for a person to make a decision about participating in screening includes the following: the purpose of the screening; the likelihood of positive or negative findings, as well as the potential for false-positives or -negatives; the uncertainties and risks associated with the process; the medical, social, or financial implications of screening for the condition; and what follow-up is available, including counselling and support.[268,269]

As well as being based on accurate information, truly informed consent also requires that the information be accessible to the person it is intended for. Information should be available in the most appropriate language, presented at an appropriate reading level or level of health literacy,[270] and provided in a medium that the person finds most clear.[206] Informed consent also requires that the person making the decision is presented with an actual choice—not an illusion of choice in which only one option is possible (even if the choice is whether to accept or decline this single option).[268] Furthermore, the options for choice must be practically available. Overall, without truly accurate and accessible information about an actual, available choice, informed consent is not possible.

Screening interventions in health care have been criticized for not being held to the same ethical requirements as other medical interventions.[269,271] This may be in part because in the early days of breast screening, it was seen more as a population-health initiative than as an individual medical intervention. Some observers have noted that early breast screening programs (and the care providers associated with them) did not seek out sufficiently informed consent from screening candidates.[206] Indeed, in some cases decision-makers discouraged seeking informed consent from screening participants and expressed concern that providing the comprehensive information necessary for informed consent would result in fewer people being screened and the program's failure to meet participation targets (which tended to be greater than 70% of the population).[209]

A 2018 article reported that to prevent one death from breast cancer for a person aged 40 to 49 years, 1,724 people would need to be screened; for a person aged 50 to 59 years, 1,333 people would need to be screened.[59] Failing to achieve those screening numbers means that fewer lives would be saved overall. Again, this approach views breast screening primarily as an intervention for the benefit of a population. Some have observed that the pressure to achieve certain participation targets has contributed to professional and organizational cultures that disproportionately emphasize the benefits of breast screening and underemphasize (or in some cases, fail to mention) the possible associated risks and harms.[208] It is likely that the population-focused aims of early screening programs—combined with established medical cultures that overemphasized the benefits of breast screening—impeded the ability of candidates to provide informed consent at the time. It is unclear whether such barriers to consent still exist in the current context.

More recent research has shown that people with breasts have shown enthusiasm for breast screening and are aware of the potential benefits of screening, but that they are less well informed about the potential risks and harms.[210,232] Health care providers may be similarly influenced by an overemphasis on the positives of cancer screening, contributing to the common view that it is obviously beneficial;[271] in some circumstances, clinicians have questioned patients who chose not to undergo screening.[206] Messaging in the media has also reinforced positive messages about the value of breast screening without giving equal (or indeed, any) airtime to the associated risks.[272]

Educational materials and other communication tools related to breast screening have also been positive about the benefits of breast screening without providing equivalent (or any) information about potential risks and harms.[210,273] They have also not typically quantified the potential benefits, stating them in general terms instead.[274] There has been considerable debate about how to present information in educational materials, and about the effect presentation may have on the decisions of those who receive such materials.

One debate that has arisen is about whether the risks associated with breast cancer and cancer screening should be communicated in terms of absolute or relative risk reduction. For example, consider a model in which two groups are followed over a 20-year period: 1,000 individuals are screened biannually and 1,000 are not screened. Over the 20 years, 14 deaths from breast cancer occur in the unscreened group and 9.1 deaths from breast cancer occur in the screened group (this example is outlined in Schwartz et al[274]). In this model, the absolute risk reduction for mortality as a result of screening would be 0.49% (14 per 1,000 minus 9.1 per 1,000) and the relative risk reduction would be 36% (4.9 per 1,000 divided by 14 per 1,000—the baseline for the unscreened group). A 36% reduction in relative risk is likely to be interpreted as more significant than an absolute risk reduction of 0.49%, and it could lead some to overestimate the benefits of screening if the data were presented in terms of relative risk. Indeed, studies have shown that people are more likely to accept screening if the benefit is quantified in terms of relative versus absolute risk reduction.[274]

Positive perceptions about the value of breast screening have been emerging at the same time as inaccurate beliefs about the risks of breast cancer. Many have overestimated their chances of getting breast cancer, as well as the likelihood that they would die from breast cancer. For example, one study found that women reported believing that 40% of all deaths in women were associated with breast cancer, whereas the correct figure is closer to 4%.[208,271]

Similarly, an overemphasis on the benefits of breast screening may also have contributed to people's misunderstanding of the potential or goals for screening. For example, one study found that people believed breast screening could prevent breast cancer, rather than detect it.[270] The study authors were concerned about this finding, because it suggested to them that some people who believed breast screening could prevent breast cancer would be less engaged in taking steps that could actually reduce their risk (such as increasing exercise or reducing alcohol consumption).

Other communication strategies, such as providing a prespecified appointment in invitations to screening (intended as means of increasing uptake[209]), have further disrupted the potential for recipients to make an informed choice, because the appointment could create the impression that attending screening was the default position and the correct choice.[272,273,275] Other less direct sources of influence may (at least unintentionally) lead individuals in their choice to be screened, or otherwise affect their ability to provide informed consent. For instance, if a person's primary care provider mentioned the possibility of screening or invited the person to be screened, the fact that this

information (or invitation) came from a trusted care provider could lead the individual to choose screening; they might reasonably assume that the provider would not mention it unless they expected that it would offer some benefit.[223] This perception of individual benefit has been observed even when the provider clearly outlines the risks of participation and makes it clear that the screening program is in place largely for population—rather than individual—benefit.[223] Even an organization's decision to fund a particular screening program can send the message that screening is a good thing on balance and should be engaged with.[208,276]

Overall, the culture and information-sharing practices related to breast screening are likely to have created a circumstance in which people making decisions about participation are doing so with an overestimate of the benefits and an underestimate of the risks and potential harms.[270] At the same time, people tend to be less aware of the potential risks associated with screening compared to the benefits.[277]

However, there is some indication that the landscape of breast screening has changed over recent years. Recommendations have changed in terms of who should be screened and when, and a shift has occurred toward informed choice about whether to engage in screening. There has also been a greater acknowledgement that breast screening brings with it a complex array of potential risks, harms, and benefits—for individuals and for populations. As well, the balance of harms and benefits does not indicate that screening is unequivocally beneficial. Some authors have suggested that breast screening should be understood as a "close call," and that it should fall to individual values, risk tolerances,[232] and preferences when determining whether to participate.[206,210] Hersch proposes that "a woman's choice to attend screening or not should be determined by how she values the small possibility of a large clinical benefit (e.g., extension of life) compared with the higher probability of undesirable events such as unnecessary investigations and overtreatment. After all, the woman who undergoes screening must live with the decision and its repercussions."[210]

With a move toward individual decision-making about screening comes further complications. People with breasts have generally indicated that they want to have a choice about whether to engage in screening, but there is variation the kind of information someone needs or wants to make such a decision, as well as the degree to which they want to make the decision independently, or decide with the guidance of a trusted health care provider.[208,232]

Recent literature on the role of informed consent in supplemental screening for people with dense breasts reflects concerns that are similar to those for breast screening in general. Some concerns make seeking informed consent for supplemental screening especially difficult. First, as outlined in the clinical evidence review, evidence for the effectiveness of supplemental screening for people with dense breasts is still emerging, so a solid clinical understanding of the benefits and harms of this intervention is unavailable. As well, supplemental screening for people with dense breasts is relatively new, and primary care providers may be unaware of it, leading some to be unprepared for conversations with their patients about engaging in such screening.[224]

Even when primary care providers are aware of supplemental screening for people with dense breasts, it can be difficult for them to help people understand what *dense breasts* means.[278] Educational materials have been criticized for being difficult for most readers to understand, and for failing to outline the risks and harms of screening for dense breasts, as well as the benefits.[190,224] The qualitative evidence rapid review in the present health technology assessment found that people with dense breasts were often confused about what having dense breasts meant. Some interpreted it to mean that

they had some kind of abnormality or cancer, an impression that can be reinforced when people with dense breasts are referred for further screening (suggesting that an abnormality that has triggered the further screening, and not the dense breasts alone).[278] Some of these issues foreshadow the difficulties of using a shared decision-making model for screening.

SHARED DECISION-MAKING

Shared decision-making is a model that involves a clinician and a patient, and that aims to be patient-centred, collaborative, and informed. In this model, both the patient and the clinician bring information to the decision-making process, both parties seek to reach consensus, and they reach an agreement about how to proceed.[279] Done well, shared decision-making not only involves deliberation about the clinical harms and benefits of an intervention, but also incorporates and responds to the patient's values and context.[268] This model is often purported to be the optimal approach for ensuring truly informed decision-making about screening.

Decision-making related to breast screening (including supplemental screening for people with dense breasts) is complex because of limited evidence and the fine balance of potential harms and benefits. As a result, a shared decision-making model could be an ideal means of helping people make autonomous decisions along with a supportive, informed, and caring professional.[211] At least one recent study found that participants valued the opportunity to discuss participation in screening mammography, and identified physicians as "key partners" in this process.[232]

However, although shared decision-making models sound promising,[203] relying on this approach for making decisions about engaging in supplemental screening for people with dense breasts could present challenges. First, as described above, many clinicians are unaware of the evidence base related to supplemental screening for people with dense breasts, and they may not be able to provide an informed clinical perspective on its potential risks and benefits,[278] exacerbated by the fact that the available evidence is minimal and potentially ambivalent.[203] Results from the qualitative evidence rapid review echo this concern, noting several studies in which clinicians said they did not feel comfortable discussing supplemental screening for their patients with dense breasts. As well, a backdrop of cultural pressures in Canadian society have emerged over the years and contributed to a general understanding (including among many physicians) that breast screening is unequivocally beneficial. Such an understanding may be related to documented instances in which physicians have mistakenly seen increased detection of cancer as evidence that cancer screening saves lives.[203]

Relying on a shared decision-making approach in the context of supplemental screening for people with dense breasts presents other potential challenges. For example, it is becoming increasingly difficult in Ontario for individuals to find a primary care physician, and it could be especially challenging to find one with the expertise, time, and knowledge to participate meaningfully in shared decision-making. Some patients have already noted this as a potential barrier to decisions about mammography in general (not only for screening in people with dense breasts).[232] Furthermore, some people may not wish to engage in this kind of decision-making with their primary care provider, choosing instead to make the decision on their own[232] or to deferring entirely to the recommendation of their physician.[203]

SUMMARY

As outlined above, the history of breast screening, the accompanying cultural beliefs surrounding the practice, and the various needs, preferences, and abilities of the individuals who provide informed consent have contributed to substantial barriers for informed consent when it comes to general breast

screening. These difficulties are likely exacerbated in the context of supplemental screening for people with dense breasts, because of the complexity of the information, the uncertain evidence base, and discomfort on the part of some clinicians when it comes to engaging in conversations about supplemental screening. Nevertheless, health care professionals and those who organize and implement health care delivery systems are obliged to respect the autonomy of the individuals who may engage with those professionals and seek care within these systems.

The challenges related to respecting autonomy in the context of supplemental screening for people with dense breasts do not mean that supplemental screening should not be funded. Rather, they are relevant to a discussion of *how* supplemental screening for people with dense breasts should be implemented (if funded) to uphold respect for autonomy. If systems to enable informed consent cannot be established now (e.g., because of unclear evidence or a lack of clinical comfort or expertise), then it might be worth postponing implementation of this type of screening or making it available on a smaller scale first.

Other Themes

This section discusses some additional themes that did not fall under the heading of particular ethical duties but still emerged when considering the ethical issues related to supplemental screening for people with dense breasts. They are offered here to provide further context or "food for thought" to support decision-makers in their deliberations.

TENSION BETWEEN POPULATION AND INDIVIDUAL HEALTH

Breast screening programs illustrate a tension between individual- and population-level interests and benefits. As discussed in Respect for Autonomy, above, early screening programs were adopted primarily as population-health initiatives; the emphasis was on encouraging substantial levels of participation at the population level to achieve reductions in mortality at the expense of individual autonomy and informed decision-making.[276] Health leaders involved in these early programs discouraged information-sharing because they thought that fully informing people about the risks and benefits of screening could decrease participation levels and reduce the overall effectiveness of the program.[209,269] Until relatively recently (and perhaps still), the message that that breast screening is good for individuals has been strong, but there has been less discussion of the risks that go with it.[203]

More recent discussions of the individual risks and harms of screening have disrupted the view that breast screening is unequivocally good, noting that screening programs cause harm to a proportion of screened individuals while simultaneously generating the population benefits of decreased morbidity and mortality.[223] In fact, individual harms and population benefits are not concurrent outcomes of screening; the individual harms are necessary to achieve the overall benefit, and the majority of a population must participate in screening programs to realize the benefit for a few.[280] Screening programs may bring meaningful benefit to a population as a whole, but at least one publication has noted that a screening program offers little benefit to most of the individuals who participate.[280]
This tension between individual risk and population benefit has been addressed (at least somewhat) by a greater emphasis on informed participation. Consensus has emerged that achieving greater participation in screening should not take precedence over individuals' ability to make informed decisions about participation.[281] Health systems may have an obligation to offer screening based on some assessment of population benefits, but individuals do not have a duty to take part in the screening. That said, if individual participation is not sufficiently high, the population benefits may never be realized.

Such an ethically appropriate shift toward enabling informed decision-making for those considering screening must be made with care to avoid circumstances in which individuals are burdened with or given too much authority with respect to population-health decisions. In the case of the former, some authors have noted that a more recent response to uncertainty about the utility of breast screening has been to download that uncertainty to the individual, leaving them to work out on their own whether to participate.[228] This approach is unfair to individuals, and to the care providers who may be supporting them in their decisions. Health leaders and public health experts have an obligation to make decisions about what options to provide (including screening programs). Once these decisions have been made, individuals and care providers can then choose from among these options.

A second point related to the role of individual choice in breast screening has to do with distinguishing between someone making an informed choice about a medical intervention that is available to them, and advocating for funding or access to an intervention that is not widely available. In the case of the former, there is an obligation to respect individuals' decisions; in the case of the latter, there is no obligation to provide a service simply because people say they want it. This is not to say that public and patient engagement is unimportant and should not influence decisions about service access and delivery; hearing from people who have experience with screening and who will be affected by systems-level decisions is certainly very important. However, including the perspectives of such individuals is not a response to the duty to respect individual autonomy.

This tension between individual- and population-level interests is not unique to supplemental screening for people with dense breasts. However, the current lack of evidence for population benefits (i.e., reduced morbidity and mortality associated with breast cancer) makes this tension more difficult to resolve, especially because collecting long-term outcome data on screening interventions is a challenge.

UNCERTAINTY

As this review has shown, supplemental screening for people with dense breasts comes with uncertainty of many types, including uncertainty about its benefits, the extent to which it will contribute to overdiagnosis, whether it will contribute to or exacerbate inequities, and more. When uncertainty interferes too much with decision-making (at the clinical or systems level), it can cause hesitancy, ambiguity, and inconsistency among decision-makers, all of which can be distressing and potentially harmful for the decision-makers and others. This makes uncertainty ethically relevant, because it can complicate a person's ability to live up to their ethical, social, and policy obligations.

Substantial evidentiary uncertainty exists with respect to supplemental screening for people with dense breasts. It is a newer approach to screening, and screening modalities generally require several years of data collection and monitoring to yield longer-term evidence for their effects. As a result (and as shown in the clinical evidence review), very little empirical evidence is available about the longer-term mortality or morbidity outcomes of supplemental screening for people with dense breasts. This evidentiary uncertainty sits atop existing uncertainty about the effectiveness of breast screening in general. Such uncertainty about breast screening is not because of a lack of data; multiple long-term studies have been conducted. However, these studies are hampered by both methodological disagreements and the challenges of measuring long-term practices (over decades) as screening technologies evolve and treatments improve. As shown in the qualitative evidence rapid review, such evidentiary uncertainty has generated clinical uncertainty among some health care providers, who are unsure about how to broach the topic of supplementary screening for dense breasts. This can lead to inconsistent approaches among such providers, some deciding not to discuss dense breasts because

they do not feel that they have a strong evidence base to work from and are unsure about what to recommend.

There is also substantial moral uncertainty about supplemental screening for people with dense breasts. Like general breast screening, supplemental screening brings with it risks of false-positives and overdiagnosis, both of which present harms to individuals. And yet this kind of harm is not only expected but also necessary to achieve the potential individual- and population-level benefits of reduced mortality and morbidity associated with breast cancer. Decisions about whether to fund and implement supplemental screening for people with dense breasts may be hampered by the moral uncertainty inherent in weighing up how much relatively frequent, mostly non–life-threatening harm (e.g., that associated with false-positives) is acceptable to avoid the absolute harms of death from cancer. These uncertainties also make their way into the clinical environment, where clinicians and people considering screening aim to arrive at an informed decision about whether it is worth accepting the more likely but manageable risks of false-positives (and other risks) to minimize (but not completely avoid) the more remote but also more serious risk of death.

Some of these sources of uncertainty are inherent in the current state of screening research and are difficult to change. Others—specifically those related to clinical communication and consent processes—have some potential for improvement with clearer guidelines and processes. However, even with improved clinical processes, evidentiary and moral uncertainty will continue to be impediments to decision-making of all types, although both could be improved with rigorous data on screening outcomes. If existing uncertainty goes unacknowledged, the informed-consent process may be compromised, and individuals may experience distress and other forms of harm as a result of unrealistic expectations about the benefits and risks of screening.

Discussion

Decisions about whether to fund supplemental screening for people with dense breasts should be informed primarily by the ethical obligations of health care leaders to allocate scarce resources in a way that maximizes the health benefit derived from these resources, while also being mindful of how the benefits are distributed.

There is currently no evidence that supplemental screening for people with dense breasts leads to reduced mortality or treatment burden associated with breast cancer. As well, supplemental screening for people with dense breasts and breast screening in general can lead individuals to feel that they have benefited from the process, regardless of the outcome. For this reason, access to screening often comes with a perception of benefit and an associated increase in well-being among those who have been screened. As a result, one might conclude that supplemental screening for people with dense breasts can generate a sense of overall well-being among the population, even if there is no evidence that it contributes to individual physical well-being. However, even if this were true, other factors must be considered when contemplating the funding of a large-scale screening program. Although it is likely to be ethically correct for an individual to consider the psychological and emotional benefits of screening when deciding whether to participate in screening, it is not as clear whether these types of benefits should be given weight when deciding whether to fund the service for a population, especially when doing so could divert resources from individuals or groups who may benefit from them in more important ways.

The existing evidence suggests that, like general breast screening, supplemental screening for people with dense breasts is likely to contribute to higher rates of false-positives and overdiagnosed cancers—generating harms associated with unnecessary diagnostic procedures and cancer treatments, and pulling resources away from other areas of health care. Individuals who have the experience of a false-positive finding will be aware of it; however, those whose cancers were overdiagnosed are unlikely to know that their treatment (and the associated risks and burdens) was unnecessary. This fact makes it a challenge to measure the harms associated with supplemental screening for people with dense breasts.

If we consider the question of offering supplemental screening for people with dense breasts from an equity perspective, it seems clear that mammography alone creates an inequity in the effectiveness of screening for people with and without dense breasts. This inequity could be addressed by implementing supplemental screening for people with dense breasts. However, it is not clear that supplemental screening would generate equity in other outcomes, such as decreased mortality and morbidity associated with breast cancer. There is ample evidence showing inequities in breast screening access and breast cancer outcomes for marginalized groups. Some worry that investing in supplemental screening for people with dense breasts without also investing in efforts to reduce overall barriers to screening and cancer treatment may amplify such inequities.

The long-standing cultural status of breast screening as a clearly beneficial health care intervention has made it difficult for individuals to provide meaningful informed consent for breast screening. Given the similarities between general breast screening and supplemental screening for people with dense breasts, it is likely that similar challenges would exist in enabling informed consent for supplemental screening. Problems of informed consent would likely be exacerbated by other features outlined in the qualitative evidence rapid review, including reluctance among primary care providers to engage in discussions about screening and dense breasts, and difficulties for individuals in accurately understanding the implications of having dense breasts. Although barriers exist to respecting autonomy through informed consent in the context of supplemental screening for people with dense breasts, such barriers are unlikely to be reasons not to fund programs of supplemental screening. However, they may contribute to a rationale for delaying funding (e.g., until more clear direction can be given to primary care providers), and they can certainly inform how supplemental screening for people with dense breasts is implemented (in terms of patient education initiatives and informed-consent procedures).

Conclusions

Given an overall lack of robust evidence about morbidity and mortality associated with breast cancer for people with dense breasts, it is not possible to determine whether funding supplemental screening as an adjunct to mammography for people with dense breasts delivers on the duties to maximize benefits and minimize harms for populations and individuals. Existing data confirm that supplemental screening for people with dense breasts identifies more cancers, but whether this leads to improved outcomes for people with dense breasts is unclear. The main harms of supplemental screening are false-positives and overdiagnosis, both of which lead to unnecessary and burdensome health care treatments. Funding supplemental screening for people with dense breasts may lead to improved equity in the effectiveness of identifying cancers in people with dense breasts (compared to mammography alone), but it is not clear whether this would lead to equity in improved survival and decreased morbidity.

It is likely that the existing inequities in access to breast screening and cancer treatment would persist, even if supplemental screening for people with dense breasts were funded. Continued efforts to address these inequities by removing barriers to screening might mitigate this concern. It might continue to be

difficult to deliver on duties to respect individual autonomy because of a lack of evidence and a resulting lack of knowledge on the part of clinicians and patients, as well as the influence of a persistent culture that perceives breast screening to be uniformly beneficial. It will be important to identify and minimize sources of uncertainty related to supplemental screening for people with dense breasts and breast screening in general to optimize the capacity for everyone involved to live up to their ethical obligations. Screening programs raise inherent tensions between individual- and population-level interests. Some of these may be resolved with further evidence related to the outcomes of supplemental screening for people with dense breasts.

Conclusions of the Health Technology Assessment

Supplemental ultrasound, digital breast tomosynthesis, and MRI as an adjunct to mammography detected more cancers, and fewer interval cancers occurred after supplemental screening. Supplemental screening led to many more recalls, including false-positive results, especially with ultrasound. The impact of supplemental screening on mortality is unclear.

Supplemental screening with ultrasound, digital breast tomosynthesis, or MRI led to better outcomes for people with dense breasts, but it increased costs. We estimate that publicly funding supplemental screening as an adjunct to mammography in Ontario over the next 5 years would cost an additional $15 million to $41 million for people with dense breasts, and $4 million to $10 million for people with extremely dense breasts.

Supplemental screening as an adjunct to mammography in people with dense breasts was viewed favourably by the people we interviewed. Participants perceived supplemental screening to be more effective than mammography alone, and they felt that publicly funding supplemental screening aligned with their values related to preventive and patient-centred care. Participants also shared their experiences with navigating current barriers to supplemental screening for breast cancer and highlighted how the patient–doctor partnership and access to information about breast tissue density were key drivers in their ability to self-advocate.

The qualitative evidence rapid review found that breast density was relatively unfamiliar and poorly understood among people who had or may have had dense breasts, as well as among many general practitioners. People with dense breasts (especially those who receive health care in their nonpreferred language and are perceived to have lower economic status or health literacy) and their general practitioners may lack the awareness or knowledge to make informed decisions about supplemental screening. Many people with dense breasts experienced emotionally distressing vulnerability to breast cancer, even when they understood the concept of breast density. Many who had or may have had dense breasts voiced a desire to engage in supplemental screening, even when educated about its potential harms. In the absence of publicly funded supplemental screening, the choice to engage with or offer such screening became a matter of a person's ability to pay and access to a health care provider willing to order it. Some health care providers were concerned that it would be impossible to equitably provide supplemental screening to all people with dense breasts in a context of finite health care resources.

A lack of robust evidence about morbidity and mortality associated with breast cancer for people with dense breasts makes it difficult to determine whether funding supplemental screening for people with dense breasts delivers on the duties to maximize benefits and minimize harms. Data confirm that supplemental screening identifies more cancers, but it is not clear that this leads to improved outcomes. Supplemental screening may lead to improved equity in the effectiveness of identifying cancers in people with dense breasts (compared to mammography alone), but it is not clear whether this would lead to equity in survival and morbidity. It is likely that existing inequities in access to breast screening and cancer treatment will persist, even if supplemental screening for dense breasts is funded. Continued efforts to address these inequities might mitigate this concern. Fulfilling duties to respect

individual autonomy may continue to be difficult because of a lack of evidence and a resulting lack of knowledge on the part of clinicians and patients, as well as the influence of a persistent culture that perceives breast screening to be uniformly beneficial. It will be important to identify and minimize sources of uncertainty related to supplemental screening for dense breasts and breast screening to optimize the capacity of everyone involved to live up to their ethical obligations.

Abbreviations

ABUS: automated breast ultrasound

ACR: American College of Radiology

BI-RADS: Breast Imaging Reporting and Data System

BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm

BRCA1/BRCA2: breast cancer susceptibility gene 1/2

CADTH: Canadian Agency for Drugs and Technologies in Health

CASP: Critical Appraisal Skills Programme

CI: confidence interval

CINAHL: Cumulative Index to Nursing and Allied Health Literature

DBT: digital breast tomosynthesis

DCIS: ductal carcinoma in situ

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

IBIS: International Breast Cancer Intervention Study breast cancer risk prediction tool

ICER: incremental cost-effectiveness ratio

MRI: magnetic resonance imaging

OBSP: Ontario Breast Screening Program

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

RoBANS: risk of bias assessment tool for nonrandomized studies

SD: standard deviation

SPIDER: Sample, Phenomenon of Interest, Design, Evaluation, Research Type

Glossary

Adverse event: An unexpected medical problem that happens during treatment for a health condition. Adverse events may be mild, moderate, or severe and may be caused by something other than the treatment.

Base case: In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Dense breasts: High proportion of fibroglandular tissue in the breast composition. Generally refers to heterogeneously or extremely dense breast categories (Breast Imaging Reporting and Data System [BI-RADS] C or D, or ACR 3 or 4).

Deterministic sensitivity analysis: Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to

reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

Ductal carcinoma in situ: A condition in which abnormal cells are found in the lining of a breast duct and have not spread outside the duct to other tissues in the breast. In some cases, DCIS may become invasive breast cancer and spread to other tissues. At this time, there is no way to know which abnormal cells could become invasive.[282]

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Estrogen–progesterone receptor status: Describes whether the cancer cells have proteins that bind to the hormone estrogen or progesterone, respectively. Rated as positive (protein present) or negative (proteins absent) and may affect how the cancer is treated.

Extravasation of contrast agent: The leakage of liquid contrast agent from the blood vessels into the tissue around it.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Human epidermal growth factor receptor 2: A protein involved in cell growth that may be high and cause faster growth and spread of some breast cancers. A test can determine the level of HER2 and aid in planning treatment.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Microsimulation model: In economic evaluations, a microsimulation model (e.g., an individual-level or patient-level model) is used to simulate the health outcomes for a heterogeneous group of patients (e.g., patients of different ages or with different sets of risk factors) after receiving a particular health care intervention. The health outcomes and health events of each patient are modelled, and the outcomes of several patients are combined to estimate the average costs and benefits accrued by a group of patients. In contrast, a cohort model follows a homogeneous cohort of patients (e.g., patients of the same age or with the same set of risk factors) through the model and estimates the proportion of the cohort who will experience specific health events.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Natural history of a disease: The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.

Node-negative or -positive: Describes if the cancer has spread to the lymph nodes (node-positive) or not (node-negative).

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Overdiagnosis and overtreatment: Finding cases of cancer with a screening test (such as a mammogram) that will never cause any symptoms. These cancers may just stop growing or go away on their own. Some of the harms caused by overdiagnosis are anxiety and having treatments that are not needed.[282]

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Risk difference: Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity: When referring to a medical test, sensitivity describes how well a test can detect a specific disease or condition in people who actually have the disease or condition.[283]

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Specificity: When referring to a medical test, specificity refers to the percentage of people who test negative for a specific disease among a group of people who do not have the disease.[283]

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Tornado diagram: In economic evaluations, a tornado diagram is used to determine which model parameters have the greatest influence on results. Tornado diagrams present the results of multiple one-way sensitivity analyses in a single graph.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care

intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Selected International Practices for Supplemental Screening as an Adjunct to Mammography for People With Dense Breasts

Globally, it appears that Austria and Switzerland may offer supplemental ultrasound,[284] but most organized breast screening programs do not recommend routine supplemental screening for people with dense breasts. Table A1, below, summarizes some international practices around breast screening for people with dense breasts that were noted in the literature or online publications (including supplemental screening) identified from around the world.

Several countries offer supplemental screening ultrasound with opportunistic screening (e.g., Turkey, Bulgaria, Croatia, Cyprus, Greece, Hungary, Italy, Portugal, Sweden, and the United Kingdom). France performs supplemental ultrasound routinely for all women with dense breasts (Breast Imaging Reporting and Data System [BI-RADS] C and D) in their population-based screening program. Ireland, Serbia, Spain also offer this in their national screening programs (densebreast-info.org/205pprop/map-screening-guidelines/)

Table A1: Summary of Identified Practices for Dense Breast Screening

Country	Recommendations or practice	Source
Japan	Mammography alone is recommended for population-based breast cancer screening in Japan. Supplemental ultrasonography is available as determined by shared decision-making for women with dense breasts	Ohnuki et al[285]
Brazil	Only opportunistic breast screening is available. Ultrasound can be considered in women with dense breast tissue, as an adjunct to mammography	Philadelpho et al[36]
France	Supplemental ultrasound is available for people with dense breasts	Vourtsis et al[286]
Switzerland	Women with high breast density (BI-RADS D) may be recommended to have an additional ultrasound, outside of the screening program Ultrasound is also used as a supplement for opportunistic screening for women with high breast density. In some cases, newer mammography devices also offer tomosynthesis, which facilitates very good assessment of heterogeneously dense breasts (BI-RADS C). Therefore, ultrasound may not be used	Healthcare In Europe[287]
Austria	With the introduction of organized breast screening in 2016, people with dense breasts (BI-RADS C and D) are screened with both mammography and ultrasound as part of the Austrian National Breast Cancer Early Detection Programme	Wengert et al, Cruwys et al[26,284]

Abbreviation: BI-RADS, Breast Imaging Reporting and Data System.

Appendix 2: Literature Search Strategies

Ontario Health

CLINICAL EVIDENCE SEARCH

Search date: October 29, 2021

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, NHS Economic Evaluation Database

Database: EBM Reviews—Cochrane Central Register of Controlled Trials <September 2021>, EBM Reviews—Cochrane Database of Systematic Reviews <2005 to October 27, 2021>, EBM Reviews—Health Technology Assessment <4th Quarter 2016>, EBM Reviews—NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2021 Week 42>, Ovid MEDLINE(R) ALL <1946 to October 28, 2021>

Search strategy:

1 exp Breast Neoplasms/ (895609)
2 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).ti,ab,kf. (913450)
3 "Carcinoma, Intraductal, Noninfiltrating"/ (17666)
4 ((carcinoma* adj2 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS).ti,ab,kf. (51854)
5 Mammography/ (82957)
6 mammogra*.ti,ab,kf. (81476)
7 or/1-6 (1144046)
8 ((fibroglandular* or glandular* or fibrous* or tissue* or assess*) adj3 (dense* or densit*)).ti,ab,kf. (37200)
9 7 and 8 (4101)
10 Breast Density/ (4192)
11 ((breast* or mammogra*) adj3 (dense* or densit*)).ti,ab,kf. (12307)
12 ((BI-RADS or BIRADS or Breast* Imag* Report*) adj5 (heterogeneous* or extrem* or dense* or densit*)).ti,ab,kf. (914)
13 or/9-12 (14187)
14 Mass Screening/ and (adjunct* or supplement* or additive* or addition* or complement* or accompan* or augment*).ti,ab,kf. (17563)
15 ((adjunct* or supplement* or additive* or addition* or complement* or accompan* or augment*) adj5 (imaging* or screen*)).ti,ab,kf. (79660)
16 "Early Detection of Cancer"/ (39854)
17 (((early or earlier or earliest) adj3 (detect* or diagnos* or identif* or recogni*)) or cancer detect*).ti,ab,kf. (733474)
18 (((3D* or 3-D* or three dimension* or optical*) adj3 mammograph*) or tomosynth* or tomo-synthe* or DBT).ti,ab,kf. (10805)
19 Ultrasonography, Mammary/ (15209)
20 (ultrasound* or ultrasonograph* or ultrasonic* or sonograph* or echomammograph* or breast* US or ABUS or HHUS).ti,ab,kf. (1127199)
21 exp Magnetic Resonance Imaging/ (1565920)
22 (((magnet* or nuclear*) adj2 resonance*) or MRI or MRIs or mr tomograph* or mr mammograph* or mr imaging*).ti,ab,kf. (1408664)
23 Contrast Media/ (153660)

24 ((contrast* adj3 (enhance* or media* or medium* or material* or agent*)) or CEM or CEDM or CESM).ti,ab,kf. (293497)
25 (Somo-v* or Invenia* or SenoClaire* or Selenia* Dimension* or Mammomat* or SenoBright* or Sofia* Automated* or SonoCin*).ti,ab,kf. (288)
26 or/14-25 (3889962)
27 13 and 26 (6112)
28 exp Animals/ not Humans/ (16591032)
29 27 not 28 (4715)
30 Case Reports/ (2220797)
31 29 not 30 (4637)
32 limit 31 to english language [Limit not valid in CDSR; records were retained] (4301)
33 limit 32 to yr="2015 -Current" (2597)
34 33 use medall,cctr,coch,cleed,clhta (1377)
35 exp breast tumor/ (894646)
36 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).tw,kw,kf. (917659)
37 ((carcinoma* adj2 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS).tw,kw,kf. (52030)
38 mammography/ (82957)
39 mammogra*.tw,kw,kf. (81854)
40 or/35-39 (1146414)
41 ((fibroglandular* or glandular* or fibrous* or tissue* or assess*) adj3 (dense* or densit*)).tw,kw,kf. (37394)
42 40 and 41 (4118)
43 breast density/ (4192)
44 ((breast* or mammogra*) adj3 (dense* or densit*)).tw,kw,kf. (12549)
45 "breast imaging reporting and data system"/ and (heterogeneous* or extrem* or dense* or densit*).tw,kw,kf. (252)
46 ((BI-RADS or BIRADS or Breast* Imag* Report*) adj5 (heterogeneous* or extrem* or dense* or densit*)).tw,kw,kf. (923)
47 or/42-46 (14478)
48 mass screening/ and (adjunct* or supplement* or additive* or addition* or complement* or accompan* or augment*).tw,kw,kf,dv. (18228)
49 ((adjunct* or supplement* or additive* or addition* or complement* or accompan* or augment*) adj5 (imaging* or screen*)).tw,kw,kf,dv. (80494)
50 early cancer diagnosis/ (9376)
51 (((early or earlier or earliest) adj3 (detect* or diagnos* or identif* or recogni*)) or cancer detect*).tw,kw,kf,dv. (735330)
52 breast tomosynthesis system/ (188)
53 (((3D* or 3-D* or three dimension* or optical*) adj3 mammograph*) or tomosynth* or tomo-synthe* or DBT).tw,kw,kf,dv. (10877)
54 echomammography/ (9367)
55 (ultrasound* or ultrasonograph* or ultrasonic* or sonograph* or echomammograph* or breast* US or ABUS or HHUS).tw,kw,kf,dv. (1131458)
56 exp nuclear magnetic resonance imaging/ (1064342)
57 (((magnet* or nuclear*) adj2 resonance*) or MRI or MRIs or mr tomograph* or mr mammograph* or mr imaging*).tw,kw,kf,dv. (1413926)
58 contrast medium/ (69119)

59 ((contrast* adj3 (enhance* or media* or medium* or material* or agent*)) or CEM or CEDM or CESM).tw,kw,kf,dv. (294422)
60 (Somo-v* or Invenia* or SenoClaire* or Selenia* Dimension* or Mammomat* or SenoBright* or Sofia* Automated* or SonoCin*).tw,kw,kf,dv. (741)
61 or/48-60 (3691158)
62 47 and 61 (5958)
63 (exp animal/ or nonhuman/) not exp human/ (11199829)
64 62 not 63 (5923)
65 Case Report/ (4791768)
66 64 not 65 (5665)
67 limit 66 to english language [Limit not valid in CDSR; records were retained] (5304)
68 limit 67 to yr="2015 -Current" (3083)
69 68 use emez (1875)
70 34 or 69 (3252)
71 70 use medall (1270)
72 70 use emez (1875)
73 70 use cctr (107)
74 70 use coch (0)
75 70 use clhta (0)
76 70 use cleed (0)
77 remove duplicates from 70 (2155)

ECONOMIC EVIDENCE SEARCH
Search date: November 01, 2021
Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews—Cochrane Central Register of Controlled Trials <September 2021>, EBM Reviews—Cochrane Database of Systematic Reviews <2005 to October–27, 2021>, EBM Reviews—Health Technology Assessment <4th Quarter 2016>, EBM Reviews—NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 202®eek 43>, Ovid MEDLINEI ALL <1946 to October 29, 2021>

Search strategy:
1 exp Breast Neoplasms/ (896451)
2 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).ti,ab,kf. (914091)
3 "Carcinoma, Intraductal, Noninfiltrating"/ (17663)
4 ((carcinoma* adj2 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS).ti,ab,kf. (51880)
5 Mammography/ (83045)
6 mammogra*.ti,ab,kf. (81538)
7 or/1-6 (1144974)
8 ((fibroglandular* or glandular* or fibrous* or tissue* or assess*) adj3 (dense* or densit*)).ti,ab,kf. (37235)
9 7 and 8 (4104)
10 Breast Density/ (4201)
11 ((breast* or mammogra*) adj3 (dense* or densit*)).ti,ab,kf. (12320)

12 ((BI-RADS or BIRADS or Breast* Imag* Report*) adj5 (heterogeneous* or extrem* or dense* or densit*)).ti,ab,kf. (915)
13 or/9-12 (14201)
14 Mass Screening/ and (adjunct* or supplement* or additive* or addition* or complement* or accompan* or augment*).ti,ab,kf. (17559)
15 ((adjunct* or supplement* or additive* or addition* or complement* or accompan* or augment*) adj5 (imaging* or screen*)).ti,ab,kf. (79660)
16 "Early Detection of Cancer"/ (39964)
17 (((early or earlier or earliest) adj3 (detect* or diagnos* or identif* or recogni*)) or cancer detect*).ti,ab,kf. (734527)
18 (((3D* or 3-D* or three dimension* or optical*) adj3 mammograph*) or tomosynth* or tomo-synthe* or DBT).ti,ab,kf. (10815)
19 Ultrasonography, Mammary/ (15233)
20 (ultrasound* or ultrasonograph* or ultrasonic* or sonograph* or echomammograph* or breast* US or ABUS or HHUS).ti,ab,kf. (1128415)
21 exp Magnetic Resonance Imaging/ (1568740)
22 (((magnet* or nuclear*) adj2 resonance*) or MRI or MRIs or mr tomograph* or mr mammograph* or mr imaging*).ti,ab,kf. (1410344)
23 Contrast Media/ (153809)
24 ((contrast* adj3 (enhance* or media* or medium* or material* or agent*)) or CEM or CEDM or CESM).ti,ab,kf. (293771)
25 (Somo-v* or Invenia* or SenoClaire* or Selenia* Dimension* or Mammomat* or SenoBright* or Sofia* Automated* or SonoCin*).ti,ab,kf. (290)
26 or/14-25 (3889962)
27 13 and 26 (6112)
28 exp Animals/ not Humans/ (16639624)
29 27 not 28 (4712)
30 Case Reports/ (2221553)
31 29 not 30 (4633)
32 limit 31 to english language [Limit not valid in CDSR; records were retained] (4297)
33 limit 32 to yr="2015 -Current" (2593)
34 33 use cleed,clhta,coch (0)
35 economics/ (262994)
36 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (956564)
37 economics.fs. (451952)
38 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1100684)
39 exp "costs and cost analysis"/ (639630)
40 (cost or costs or costing or costly).ti. (303715)
41 cost effective*.ti,ab,kf. (397829)
42 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (263641)
43 models, economic/ (14921)
44 markov chains/ or monte carlo method/ (96616)
45 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (55276)
46 (markov or markow or monte carlo).ti,ab,kf. (158483)
47 quality-adjusted life years/ (48674)

48 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (95407)
49 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (159370)
50 or/35-49 (3011836)
51 33 and 50 (235)
52 51 use medall,cctr (110)
53 exp breast tumor/ (895488)
54 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).tw,kw,kf. (918302)
55 ((carcinoma* adj2 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS).tw,kw,kf. (52056)
56 mammography/ (83045)
57 mammogra*.tw,kw,kf. (81916)
58 or/53-57 (1147344)
59 ((fibroglandular* or glandular* or fibrous* or tissue* or assess*) adj3 (dense* or densit*)).tw,kw,kf. (37429)
60 58 and 59 (4121)
61 breast density/ (4201)
62 ((breast* or mammogra*) adj3 (dense* or densit*)).tw,kw,kf. (12563)
63 "breast imaging reporting and data system"/ and (heterogeneous* or extrem* or dense* or densit*).tw,kw,kf. (259)
64 ((BI-RADS or BIRADS or Breast* Imag* Report*) adj5 (heterogeneous* or extrem* or dense* or densit*)).tw,kw,kf. (924)
65 or/60-64 (14496)
66 mass screening/ and (adjunct* or supplement* or additive* or addition* or complement* or accompan* or augment*).tw,kw,kf,dv. (18228)
67 ((adjunct* or supplement* or additive* or addition* or complement* or accompan* or augment*) adj5 (imaging* or screen*)).tw,kw,kf,dv. (80494)
68 early cancer diagnosis/ (9449)
69 (((early or earlier or earliest) adj3 (detect* or diagnos* or identif* or recogni*)) or cancer detect*).tw,kw,kf,dv. (736383)
70 breast tomosynthesis system/ (194)
71 (((3D* or 3-D* or three dimension* or optical*) adj3 mammograph*) or tomosynth* or tomo-synthe* or DBT).tw,kw,kf,dv. (10887)
72 echomammography/ (9386)
73 (ultrasound* or ultrasonograph* or ultrasonic* or sonograph* or echomammograph* or breast* US or ABUS or HHUS).tw,kw,kf,dv. (1132678)
74 exp nuclear magnetic resonance imaging/ (1066669)
75 (((magnet* or nuclear*) adj2 resonance*) or MRI or MRIs or mr tomograph* or mr mammograph* or mr imaging*).tw,kw,kf,dv. (1415607)
76 contrast medium/ (69217)
77 ((contrast* adj3 (enhance* or media* or medium* or material* or agent*)) or CEM or CEDM or CESM).tw,kw,kf,dv. (294698)
78 (Somo-v* or Invenia* or SenoClaire* or Selenia* Dimension* or Mammomat* or SenoBright* or Sofia* Automated* or SonoCin*).tw,kw,kf,dv. (746)
79 or/66-78 (3691158)
80 65 and 79 (5958)
81 (exp animal/ or nonhuman/) not exp human/ (11207079)
82 80 not 81 (5923)

83 Case Report/ (4795649)
84 82 not 83 (5665)
85 limit 84 to english language [Limit not valid in CDSR; records were retained] (5304)
86 limit 85 to yr="2015 -Current" (3083)
87 Economics/ (262994)
88 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (139786)
89 Economic Aspect/ or exp Economic Evaluation/ (502995)
90 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1121427)
91 exp "Cost"/ (639630)
92 (cost or costs or costing or costly).ti. (303715)
93 cost effective*.tw,kw,kf. (407641)
94 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw,kf. (273764)
95 Monte Carlo Method/ (75495)
96 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (58677)
97 (markov or markow or monte carlo).tw,kw,kf. (161941)
98 Quality-Adjusted Life Years/ (48674)
99 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (98894)
100 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (180068)
101 or/87-100 (2576576)
102 86 and 101 (259)
103 102 use emez (164)
104 34 or 52 or 103 (274)
105 104 use medall (97)
106 104 use emez (164)
107 104 use cctr (13)
108 104 use coch (0)
109 104 use cleed (0)
110 104 use clhta (0)
111 remove duplicates from 104 (197)

GREY LITERATURE SEARCH

Performed on: November 10–16, 2021

Websites searched: Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Health Technology Assessment Database, Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S), Italian National Agency for Regional Health Services (AGENAS), Belgian Health Care

Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used: breast density, breast densities, dense breast*, mammographic density; mammogram density; breast cancer screening; breast AND ultrasound*; HHUS; ABUS; tomosynth*; breast AND magnetic; breast AND MRI; breast AND contrast*; breast AND adjunct*; breast AND supplement*

Clinical results (included in PRISMA): 21
Economic results (included in PRISMA): 24
Ongoing HTAs (PROSPERO/EUnetHTA/): 10
Ongoing RCTs (clinicaltrials.gov): 34

Table A2: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Keyword heading word
.pt	Publication type
.jw	Journal title word (MEDLINE)

QUALITATIVE EVIDENCE OF PREFERENCES AND VALUES SEARCH

Search date: May 2, 2022

Databases searched: Ovid MEDLINE All (1946–present)

Alerts: Monthly search updates until August 3, 2022

Search filters applied: Qualitative studies

Publication date limit: No date limit

Language limit: English-language publications

Search strategy:

1 exp Breast Neoplasms/
2 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).ti,ab,kf.
3 Carcinoma, Intraductal, Noninfiltrating/
4 ((carcinoma* adj2 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS).ti,ab,kf.
5 Mammography/
6 mammogra*.ti,ab,kf.
7 or/1-6
8 ((fibroglandular* or glandular* or fibrous* or tissue* or assess*) adj3 (dense* or densit*)).ti,ab,kf.
9 7 and 8
10 Breast Density/
11 ((breast* or mammogra*) adj3 (dense* or densit*)).ti,ab,kf.
12 ((BI-RADS or BIRADS or Breast* Imag* Report*) adj5 (heterogeneous* or extrem* or dense* or densit*)).ti,ab,kf.

13 or/9-12
14 exp Empirical Research/ or Interviews as Topic/ or Personal Narratives as Topic/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/
15 (Interview or Personal Narrative).pt.
16 interview*.ti,ab,kf.
17 qualitative.ti,ab,kf,jw.
18 (theme* or thematic).ti,ab,kf.
19 ethnological research.ti,ab,kf.
20 ethnograph*.ti,ab,kf.
21 ethnomedicine.ti,ab,kf.
22 ethnonursing.ti,ab,kf.
23 phenomenol*.ti,ab,kf.
24 (grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
25 life stor*.ti,ab,kf.
26 (emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
27 (data adj1 saturat*).ti,ab,kf.
28 participant observ*.ti,ab,kf.
29 (social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern*).ti,ab,kf.
30 (action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
31 (humanistic or existential or experiential or paradigm*).ti,ab,kf.
32 (field adj (study or studies or research or work)).ti,ab,kf.
33 (human science or social science).ti,ab,kf.
34 biographical method.ti,ab,kf.
35 theoretical sampl*.ti,ab,kf.
36 ((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
37 (open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
38 (life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
39 ((lived or life) adj experience*).ti,ab,kf.
40 cluster sampl*.ti,ab,kf.
41 observational method*.ti,ab,kf.
42 content analysis.ti,ab,kf.
43 (constant adj (comparative or comparison)).ti,ab,kf.
44 ((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
45 (heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
46 (van adj manen*).ti,ab,kf.
47 (van adj kaam*).ti,ab,kf.
48 (corbin* adj2 strauss*).ti,ab,kf.
49 or/14-48
50 13 and 49
51 limit 50 to english language

Other Databases

CINAHL

Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for EBSCO platform, including the addition of CINAHL headings. The search strategy is available on request.

ETHICS REVIEW SEARCH

Search date: May 18, 2022
Databases searched: Ovid MEDLINE All (1946–present), Philosopher's Index
Alerts: Monthly search updates until August 3, 2022
Search filters applied: Empirical and normative ethical considerations studies
Publication date limit: No date limit
Language limit: English-language publications

Multi-Database Strategy

MEDLINE–Breast Density

1 exp Breast Neoplasms/
2 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).ti,ab,kf.
3 "Carcinoma, Intraductal, Noninfiltrating"/
4 ((carcinoma* adj2 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS).ti,ab,kf.
5 Mammography/
6 mammogra*.ti,ab,kf.
7 1 or 2 or 3 or 4 or 5 or 6
8 ((fibroglandular* or glandular* or fibrous* or tissue* or assess*) adj3 (dense* or densit*)).ti,ab,kf.
9 7 and 8
10 Breast Density/
11 ((breast* or mammogra*) adj3 (dense* or densit*)).ti,ab,kf.
12 ((BI-RADS or BIRADS or Breast* Imag* Report*) adj5 (heterogeneous* or extrem* or dense* or densit*)).ti,ab,kf.
13 9 or 10 or 11 or 12

MEDLINE–Ethics

14 exp Ethics/
15 exp Privacy/ or exp Confidentiality/ or Duty to Recontact/ or exp Informed Consent/ or exp Malpractice/ or Presumed Consent/
16 exp Morals/ or Paternalism/
17 exp Prejudice/ or Social Values/ or Stereotyping/ or Social Stigma/
18 exp Geography, Medical/ or Medically Underserved Area/ or exp Health Services Accessibility/ or Healthcare Disparities/
19 Medical Overuse/
20 Overdiagnosis/
21 exp Disclosure/
22 exp Human Rights/
23 Coercion/
24 exp Mandatory Programs/
25 exp Social Problems/
26 ethics.fs.

27 ((healthcare or health care or nonclinical or non clinical or community based or public health or preventive care) adj (access or deliver* or distribution* or system*)).ti,kf.
28 (ethic or ethics or ethical or unethical or moral or morals or immoral or bioethic*).ti,ab,hw,kf,jw.
29 (justice or complicit*).ti,ab,hw,kf,jw.
30 (human right* or civil right*).ti,ab,kf.
31 (prejudice* or stigma or stigmas or stigmatization or stigmatize or stigmatise or stigmatisation or stereotyp*).ti,ab,kf.
32 (inequalit* or equalit* or inequit* or equit* or disparit* or fair or fairness or unfair or unfairness).ti,ab,kf.
33 (distributive justice or precautionary principle or solidarity or paternalis*).ti,ab,kf.
34 ((care or treatment) adj2 (duty or obligat*)).ti,ab,kf.
35 (social* adj (responsib* or obligat* or justice)).ti,ab,kf.
36 (socioeconomic or socio-economic).ti,kf.
37 ((social or socioeconomic or socio-economic) adj2 (impact* or burden*)).ti,ab,kf.
38 (communitarian* or beneficence or nonmaleficence or maleficence or accountability).ti,ab,kf.
39 (harm or harms or harming or harmful).ti,ab,kf.
40 (privacy or confidential*).ti,ab,kf.
41 ((informed or presumed or shared or parent* or guardian* or family or families or child* or pediatric or paediatric or adolescent* or youth) adj2 (consent or choice* or decision making or assent or dissent)).ti,ab,kf.
42 (coercion or persuasion or information provision).ti,ab,kf.
43 ((conflict or financial or industry) adj3 interest*).ti,ab,kf.
44 (industry adj3 (funding or involvement or sponsor*)).ti,ab,kf.
45 autonomy.ti,ab,hw,kf.
46 transparency.ti,ab,kf.
47 (overdiagnos* or over-diagnos* or overscreen* or over-screen* or underscreen* or under-screen* or overtreat* or over-treat* or undertreat* or under-treat*).ti,ab,kf.
48 underserved.ti,ab,kf.
49 or/14-48

MEDLINE–A. Breast Density combined with Ethics
50 13 and 49

MEDLINE–Breast Cancer Screening
51 exp Breast Neoplasms/
52 ((breast* or mammar*) adj2 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).ti,ab,kf.
53 "Carcinoma, Intraductal, Noninfiltrating"/
54 ((carcinoma* adj2 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS).ti,ab,kf.
55 or/51-54
56 Mass Screening/ or Diagnosis/ or exp Early Diagnosis/ or Diagnostic Screening Programs/ or Diagnostic Services/ or Diagnostic Imaging/ or Delayed Diagnosis/ or Diagnostic Errors/ or exp Diagnosis, Computer-Assisted/ or Diagnostic Tests, Routine/
57 (screen* or test* or detect* or diagnos* or overdiagnos* or surveill* or exam*1 or examinat* or imaging).ti,kf.
58 screening.ab. /freq=2
59 (di or dg).fs.
60 or/56-59

61 55 and 60
62 Mammography/
63 mammogra*.ti,ab,kf.
64 ((breast* or mammar* or fibroglandular* or glandular* or fibrous*) adj3 (dense* or densit*)).ti,ab,kf.
65 (BI-RADS or BIRADS or Breast* Imag* Report*).ti,ab,kf.
66 (breast cancer adj3 screen*).ti,ab,kf.
67 *Early Detection of Cancer/
68 (cancer* and screen*).ti. and breast*.ti,ab,kf.
69 or/61-68

MEDLINE–Focused Ethics Terms
70 exp *Ethics/
71 exp *Privacy/
72 *Confidentiality/ or *Duty to Warn/ or *Personally Identifiable Information/ or *Duty to Recontact/ or exp *Informed Consent/ or *Presumed Consent/
73 exp *Morals/
74 *Paternalism/
75 *Social Values/
76 *Disclosure/es or *Truth Disclosure/es or *Mandatory Reporting/ or *Parental Notification/ or *Whistleblowing/
77 exp *Human Rights/
78 *Coercion/
79 exp *Mandatory Programs/
80 *Medical Overuse/
81 *Overdiagnosis/
82 (ethic or ethics or ethical* or unethical* or moral or morals or immoral or bioethic*).ti,kf,jw.
83 (ethic or ethics or ethical* or unethical* or moral or morals or immoral or bioethic*).ab. /freq=2 not (ethic* adj2 (approval* or dissemination or committee*)).ab.
84 (justice or unjust or complicit*).ti.
85 (human right* or civil right*).ti.
86 (distributive justice or precautionary principle or solidarity or paternalis*).ti.
87 ((care or treatment) adj2 (duty or obligat*)).ti.
88 (social* adj (responsib* or obligat* or justice)).ti.
89 (communitarian* or accountability).ti.
90 (beneficence or nonmaleficence or maleficence).ti,ab,kf.
91 (privacy or confidential*).ti.
92 ((informed or presumed) adj2 (choice* or decision making or assent or dissent)).ti.
93 consent*.ti.
94 (informed adj3 patient*).ti.
95 (coercion or persuasion or information provision).ti.
96 ((conflict or financial or industry) adj3 interest*).ti.
97 (industry adj3 (funding or involvement or sponsor*)).ti.
98 (autonomy or transparency or freedom*).ti.

99 (overdiagnos* or over-diagnos* or overscreen* or over-screen* or underscreen* or under-screen* or overtreat* or over-treat* or undertreat* or under-treat*).ti.
100 or/70-99

MEDLINE–B. Breast Cancer Screening combined with Focused Ethics Terms
101 69 and 100

MEDLINE–Equity
102 *Stereotyping/ or *Social Stigma/ or exp *Prejudice/
103 exp *Geography, Medical/ or *Medically Underserved Area/ or exp *Health Services Accessibility/ or *Healthcare Disparities/
104 *Social Problems/ or exp *Human Rights Abuses/ or exp *Poverty/ or exp *Social Segregation/ or *Socioeconomic Factors/
105 (prejudice* or stigma or stigmas or stigmatization or stigmatize or stigmatise or stigmatisation or stereotyp*).ti,kf.
106 (inequalit* or equalit* or inequit* or equit* or disparit* or fair or fairness or unfair or unfairness).ti,kf.
107 ((social or socioeconomic or socio-economic) adj2 (impact* or burden*)).ti,kf.
108 underserved.ti,kf.
109 or/102-108
110 69 and 109

MEDLINE–Canada
111 exp Canada/
112 (canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or (ottawa* not newcastle ottawa) or calgary* or edmonton* or winnipeg* or first nation*1 or metis).ti,ab,hw,kf.
113 (canadian* or canada* or british columbia* or alberta* or saskatchewan* or manitoba* or ontario* or quebec* or new brunswick* or prince edward island* or nova scotia* or labrador* or newfoundland* or nunavut* or northwest territor* or yukon* or toronto* or montreal* or vancouver* or ottawa* or calgary* or edmonton* or winnipeg* or first nation* or metis).jw.
114 111 or 112 or 113

MEDLINE–C. Breast Cancer Screening combined with Equity and Canada Terms
115 110 and 114

MEDLINE–D. Additional Focused Terms for Ethics of Screening
116 Mammography/ and es.fs.
117 Overdiagnosis/ and es.fs.
118 Overdiagnosis/ and exp *ethics/
119 Overdiagnosis/ and (ethic or ethics or ethical* or unethical* or moral or morals or immoral or bioethic*).ti.
120 *Early Detection of Cancer/es
121 (cancer* and screen* and (ethic or ethics or ethical* or unethical* or moral or morals or immoral or bioethic*)).ti.
122 *Mass Screening/es and exp neoplasms/
123 *Mass Screening/es and cancer*.ti,ab,kf.

124 exp breast neoplasms/ and es.fs. and screening.ti,ab,kf.
125 or/116-124

MEDLINE–Final Results (A. or B. or C. or D.)
126 50 or 101 or 115 or 125
127 126 use medall

Philosopher's Index–Breast Cancer Screening, Breast Density, or Focused Terms for Cancer Screening or Overdiagnosis
128 ((breast* or mammar*) and (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).af.
129 ((carcinoma* and (intraductal* or ductal*)) or ductal hyperplasia* or DCIS).af.
130 128 or 129
131 (test* or screen* or surveill* or detect* or diagnos* or exam*1 or examinat* or imaging).af.
132 130 and 131
133 mammogra*.af.
134 ((breast* or fibroglandular* or glandular* or fibrous* or tissue*) and (dense* or densit*)).af.
135 (BI-RADS or BIRADS or Breast* Imag* Report*).af.
136 ((cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*) and (test* or screen* or surveill* or detect* or diagnos* or exam*1 or examinat* or imaging)).ti.
137 ((cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*) adj3 (test* or screen* or surveill* or detect* or diagnos* or exam*1 or examinat* or imaging)).af.
138 ((breast* or mammar*) and (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*)).ti.
139 (overdiagnos* or over-diagnos* or overscreen* or over-screen* or underscreen* or under-screen* or overtreat* or over-treat* or undertreat* or under-treat*).ti.
140 ((cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma*) and (overdiagnos* or over-diagnos* or overscreen* or over-screen* or underscreen* or under-screen* or overtreat* or over-treat* or undertreat* or under-treat*)).af.
141 or/132-140

Philosopher's Index–Final Results
142 141 use phil

MEDLINE or Philosopher's Index–All Results
143 127 or 142
144 limit 143 to english
145 remove duplicates from 144

GREY LITERATURE SEARCH
Performed on: April 27 to May 6, 2022

Websites searched: Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature*[178] were searched:

- Health technology assessment agencies
- Databases (free)
- Internet search
- Open access journals

Keywords used: breast density, dense breast, dense breasts, breast cancer, mammography
Publication date limit: No date limits
Language limits: English or French

Appendix 3: Diagnostic Accuracy Definitions and Calculations

Table A3: Summary of Calculations Used to Assess Diagnostic Performance

Measure	Formula
Sensitivity (true-positive rate)	TP/TP + FN
Specificity	TN/FP + TN
False-positive rate	1 − Specificity

Abbreviations: FN, false-negative; FP, false-positive; TN, true negative; TP, true positive.

Appendix 4: Critical Appraisal of Clinical Evidence

Supplemental Ultrasound

Table A4: Risk of Bias[a] Among Randomized Controlled Trials for the Comparison of Mammography Plus Supplemental Ultrasound Versus Mammography Alone (Cochrane Risk-of-Bias Tool Version 2)

Trial name	Imaging modality	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result
J-START trial[93]	Handheld ultrasound	Low	Some concerns[b]	Low	Low	Low

Abbreviations: J-START, Japan Strategic Anti-cancer Randomized Trial; MRI, magnetic resonance imaging.

[a] Possible risk of bias judgments: low, high, or some concerns.

[b] Participants and clinicians were aware of group assignment; however, the outcome assessment panel was unaware. No information was available about deviations from group assignment; however, intention-to-treat analysis was used.

Table A5: Risk of Bias[a] Among Nonrandomized Studies for the Comparison of Mammography Plus Supplemental Ultrasound Versus Mammography Alone

Author, year	Selection of participants	Confounding variables	Measurement of exposure (intervention)	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Gatta et al, 2021[109]	Low	Low	Low	Low	Low	Low
Wilczek et al, 2016[110]	Low	Low	Low	Unclear[b]	Low	Low

Abbreviations: ABUS, automated breast ultrasound; RoBANS, Risk of Bias Assessment Tool for Nonrandomized Studies.

[a] Risk of bias assessed using RoBANS.[95] Possible risk of bias levels: low, moderate, serious, critical, and no information.

[b] Two separate readers read mammography + ABUS or ABUS and were blinded to the others' assessment. ABUS was not double-read unless a concern was raised by either reader.

Table A6: GRADE Evidence Profile for the Comparison of Mammography Plus Supplemental Ultrasound Versus Mammography Alone

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Sensitivity (positive test: BI-RADS 3, 4, 5)							
1 RCT[93]	No serious limitations	No serious limitations	Very serious limitations (−2)[a]	No serious limitations[b]	Undetected	None	⨁⨁ Low
1 nonrandomized study[110]	No serious limitations	No serious limitations[c]	Serious limitations (−1)[d]	Serious limitations (−1)[e]	Undetected	None	⨁ Very low
Sensitivity(positive test: BI-RADS 4, 5)							
1 nonrandomized study[109]	No serious limitations	None[f]	Serious limitations (−1)[d]	Serious limitations (−1)[e]	Undetected	None	⨁ Very low
Specificity (positive test: BI-RADS 3, 4, 5)							
1 RCT[93]	No serious limitations	No serious limitations	Very serious limitations (−2)[a]	No serious limitations[b]	Undetected	None	⨁⨁ Low
1 nonrandomized study[110]	No serious limitations	No serious limitations[c]	Serious limitations (−1)[d]	Serious limitations (−1)[g]	Undetected	None	⨁ Very low
Specificity (positive test: BI-RADS 4, 5)							
1 nonrandomized study[109]	No serious limitations	None[f]	Serious limitations (−1)[d]	Serious limitations (−1)[e]	Undetected	None	⨁ Very low
Cancer detection rate							
1 RCT[93]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	No serious limitations[b]	Undetected	None	⨁⨁⨁ Moderate
2 nonrandomized studies[109,110]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Serious limitations (−1)[e]	Undetected	None	⨁ Very low
Interval cancers							
1 RCT[93]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Serious limitations (−1)[h]	Undetected	None	⨁⨁ Low
2 nonrandomized studies[109,110]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Serious limitations (−1)[e]	Undetected	None	⨁ Very low

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Recall rate							
1 RCT[93]	No serious limitations	No serious limitations	Serious limitations (−1)[a]	No serious limitations[b]	Undetected	None	⨁⨁⨁ Moderate
2 nonrandomized studies[109,110]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Serious limitations (−1)[e]	Undetected	None	⨁ Very low

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

[a] The screening protocol included clinical breast examination in most cases and independent double-reading of all imaging, which differs from local clinical practice. The screening population was Japanese and did not reflect the ethnic diversity of the target population. Screening occurred annually, which was reflective of Ontario's screening interval for those with extremely dense breasts (≥ 75% dense tissue). No information was provided on confounders. The positive test definition included BI-RADS 3, which is considered negative in Ontario.

[b] Confidence intervals were a bit wide. The trial met the sample size calculation for 80% power to detect cancers (α = .05), sensitivity and specificity (i.e., > 42,500 per group). The secondary analysis assessing outcomes in the intervention versus control groups among those with dense breasts had fewer participants (i.e., approx. 5,600 per group), but it was still a large sample, so given observed test performance and assumed 2% breast cancer prevalence, the optimal information size criterion was likely met.

[c] No pooled estimate because of heterogeneity in imaging protocols and patient characteristics. Notable overlap of confidence intervals around point estimates across studies. Baseline accuracy of mammography alone varied across studies but was reasonably similar.

[d] Screening occurred biennially, which was reflective of the screening interval in Ontario for those with heterogeneously dense breasts but not extremely dense breasts. Screening protocols involved independent double-reading. In the study that did not restrict eligibility on these factors, all or the vast majority of participants had no personal history of breast cancer or family history of breast cancer. The definition of a positive test included BI-RADS 3, which is considered negative in Ontario and changes the case definition.

[e] Wide confidence intervals around the point estimate. Assuming a breast cancer prevalence of 2% and observed test performance, the optimal information size criterion may not have been met.

[f] Not evaluable because of a single study.

[g] Confidence intervals were tight around the point estimate. Assuming a breast cancer prevalence of 2% and observed test performance, the optimal information size criterion may not have been met.

[h] Very few interval cancers (low event rate), so given the sample size, the optimal information size criterion was unlikely to be met.

Supplemental Handheld Ultrasound Versus Supplemental Automated Breast Ultrasound

Table A7: Risk of Bias[a] Among Nonrandomized Studies for the Comparison of Supplemental Handheld Ultrasound Versus Supplemental Automated Breast Ultrasound

Author, year	Selection of participants	Confounding variables	Measurement of exposure (intervention)	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Philadelpho et al, 2021[36]	Low	Unclear[b]	Low	Unclear[c]	Unclear[d]	Low

Abbreviations: ABUS, automated breast ultrasound; RoBANS, Risk of Bias Assessment Tool for Nonrandomized Studies.

[a] Risk of bias assessed using RoBANS.[95] Possible risk of bias levels: low, moderate, serious, critical, and no information.

[b] People with breast treatment (surgery or radiotherapy) within the previous 12 months were excluded, and no statistical adjustment was made for this risk.

[c] Mammogram was available to radiologists when they were reading the ultrasound images to confirm density assessment. Readers were blinded to ABUS when reading handheld ultrasound, and vice versa.

[d] Authors reported that 4 of 444 people were excluded from the analysis because of major artifacts during ABUS but were included in denominator anyway. No characteristics of the missing people were provided.

Table A8: GRADE Evidence Profile for the Comparison of Supplemental Handheld Ultrasound Versus Supplemental Automated Breast Ultrasound

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Cancer Detection Rate							
1 nonrandomized study[36]	No serious limitations	None[a]	No serious limitations[b]	Serious limitations (−1)[c]	Undetected	None	⨁ Very low

Abbreviations: ABUS, automated breast ultrasound; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a] Not evaluable because of a single study.

[b] Study population included people with heterogeneously or extremely dense breasts but no information was provided about other participant risk factors (e.g., family history of breast cancer) or ethnic composition to judge applicability. It was unclear whether images from handheld ultrasound and ABUS were single- or double-read. Test positivity threshold reflected current Ontario practice.

[c] Given the cancer detection rates observed and the small sample size, it was unlikely that the optimal information size criterion was met.

Supplemental Handheld Ultrasound Versus Supplemental Digital Breast Tomosynthesis

Table A9: Risk of Bias[a] Among Nonrandomized Studies for the Comparison of Supplemental Handheld Ultrasound Versus Supplemental Digital Breast Tomosynthesis

Author, year	Selection of participants	Confounding variables	Measurement of exposure (intervention)	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
ASTOUND trial[91]	Low	Unclear[b]	Low	Low	Low	Low
ASTOUND-2 trial[92]	Unclear[c]	Unclear[b]	Low	Low	Unclear[d]	Low[e]

Abbreviations: RoBANS, Risk of Bias Assessment Tool for Nonrandomized Studies.

[a] Risk of bias assessed using RoBANS.[95] Possible risk of bias levels: low, moderate, serious, critical, and no information.

[b] No family history was noted for eligibility, and no participants characteristics were reported.

[c] Participants were all mammography-negative at enrolment, with dense breasts from the same sites and time period; all underwent both adjunct digital breast tomosynthesis and handheld ultrasound. However, 21% had synthetic 2-dimensional mammography rather than acquired mammography, which may or may not have the same accuracy. The authors stated that a sensitivity analysis found similar cancer detection and recall rates when excluding the 1,104 people with synthetic mammography, but data were not provided.

[d] 1-year follow-up data were not available for all patients. The missing data were the same cases for both modalities, and authors stated that they would not affect the comparative detection.

[e] Protocol registered was for the ASTOUND trial, not ASTOUND-2, which included some of the same sites and participants, but also new ones who did not participate in ASTOUND. All outcomes in the protocol and methods were reported in the publication.

Table A10: GRADE Evidence Profile for the Comparison of Supplemental Handheld Ultrasound Versus Supplemental Digital Breast Tomosynthesis

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Sensitivity (positive test: BI-RADS 4, 5)							
2 nonrandomized studies[91,92]	No serious limitations	No serious limitations	No serious limitations[a]	Serious limitations (–1)[b]	Undetected	None	⨁ Very low
Specificity (positive test: BI-RADS 4, 5)							
2 nonrandomized studies[91,92]	No serious limitations	No serious limitations	No serious limitations[a]	No serious limitations[c]	Undetected	None	⨁⨁ Low
Cancer detection rate							
2 nonrandomized studies[91,92]	No serious limitations	No serious limitations	No serious limitations[a]	Serious limitations (–1)[d]	Undetected	None[e]	⨁ Very low
Recall rate							
2 nonrandomized studies[91,92]	No serious limitations	Serious limitations (–1)[f]	No serious limitations[a]	No serious limitations	Undetected	None	⨁ Very low

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a] Handheld ultrasound and digital breast tomosynthesis images were each read independently by single reader, similar to Ontario practice. Women with high-risk factors were excluded. The screening interval was unclear.

[b] Wide confidence intervals around the point estimate. Assuming a breast cancer prevalence of 2% and observed test performance, the optimal information size criterion may not have been met.

[c] Confidence intervals were tight around the point estimate. Assuming a breast cancer prevalence of 2% and observed test performance, the optimal information size criterion may have been met.

[d] Variability in cancer detection rate for both interventions across studies. The optimal information size criterion was likely not met, given wide confidence intervals around the point estimates and low event rates.

[e] Almost twice as many cancers were detected and statistically significant differences were found; however, these did not warrant upgrading the quality for this outcome.

[f] Almost double the proportion of recalls occurred in ASTOUND[91] versus ASTOUND-2[92]. Confidence intervals were reasonably narrow. No significant differences in recall rate were found in ASTOUND but statistically significantly more recalls occurred with handheld ultrasound versus digital breast tomosynthesis in ASTOUND-2.

Supplemental MRI

Table A11: Risk of Bias[a] Among Randomized Controlled Trials for Supplemental MRI (Cochrane Risk-of-Bias Tool Version 2)

Trial name	Imaging modality	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result
DENSE trial[106-108]	MRI	Low	Some concerns[b]	Low	Low	Low

Abbreviations: DENSE, Dense Tissue and Early Breast Neoplasm Screening; MRI, magnetic resonance imaging.

[a] Possible risk of bias judgments: low, high, or some concerns.

[b] Participants or providers aware of group allocation. No information available about deviations from intended intervention because of experimental context; however, appropriate analysis comparing mammography versus mammography plus MRI was used for the primary outcome of interval cancers, but not for cancer detection rate or recalls.

Table A12: Risk of Bias[a] Among Nonrandomized Studies for Supplemental MRI

Author, year	Selection of participants	Confounding variables	Measurement of exposure (intervention)	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Chen et al, 2017[41]	Unclear[b]	Unclear[c]	Unclear[d]	Unclear[e]	Low	Low

Abbreviations: MRI, magnetic resonance imaging; RoBANS, Risk of Bias Assessment Tool for Nonrandomized Studies.

[a] Risk of bias assessed using RoBANS.[95] Possible risk of bias levels: low, moderate, serious, critical, and no information.

[b] The definition of "dense" was unclear, because the authors reported the inclusion of people with dense breasts classified by the American College of Radiology rubric, of which the two highest categories (heterogeneously dense and extremely dense) are typically considered "dense."

[c] Women with a family history of breast cancer were excluded from eligibility; however, the presence or absence of other confounders as characteristics of the study participants were not reported.

[d] Data were obtained from trustworthy sources, and MRI images were interpreted independently by two radiologists; however no information was provided on the test positivity.

[e] Readers of MRI images were not blinded to results from the full diagnostic protocol or abbreviated protocol; however, reading of the two sets of images was spaced out by at least 1 month and cases were read in random order.

Table A13: GRADE Evidence Profile for Supplemental MRI

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Sensitivity (positive test: BI-RADS 4,5)							
1 RCT[106,107]	No serious limitations	No serious limitations	No serious limitations[a]	Serious limitations (−1)[b]	Undetected	None	⨁⨁⨁ Moderate
Sensitivity (positive test threshold unclear)							
1 nonrandomized study[41]	No serious limitations	No serious limitations	Serious limitations (–1)[c]	Serious limitations (−1)[d]	Undetected	None	⨁ Very low
Specificity (positive test: BI-RADS 4,5)							
1 RCT[106,107]	No serious limitations	No serious limitations	No serious limitations[a]	Serious limitations (−1)[e]	Undetected	None	⨁⨁⨁ Moderate
Specificity (positive test threshold unclear							
1 nonrandomized study[41]	No serious limitations	No serious limitations	Serious limitations (–1)[c]	Serious limitations (−1)[f]	Undetected	None	⨁ Very low
Cancer detection rate							
1 RCT[106,107]	Serious limitations (−1)[g]	None[h]	No serious limitations[a]	No serious limitations[i]	Undetected	None	⨁⨁⨁ Moderate
Interval cancers							
1 RCT[106,107]	No serious limitations	None[h]	No serious limitations[a]	No serious limitations[j]	Undetected	None	⨁⨁⨁⨁ High
Recall rate							
1 RCT[106,107]	Serious limitations (−1)[g]	None[h]	No serious limitations[a]	No serious limitations	Undetected	None	⨁⨁⨁ Moderate
Adverse events/reactions to contrast media							
1 RCT[106,107]	No serious limitations	None[h]	No serious limitations[a]	Serious limitations (−1)[k]	Undetected	None	⨁⨁⨁ Moderate

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MRI, magnetic resonance imaging; RCT, randomized controlled trial.

Notes continued on the following page.

Continued from the previous page.

[a] Participants were only those with extremely dense breasts (American College of Radiology 4/BI-RADS D), which represented a subset of the target population. No information was provided on the ethnic composition of the sample. Screening frequency was biennial, and the test positivity threshold was similar to Ontario practice, but the MRI images were all independently double-read, which is not Ontario practice.

[b] Confidence intervals were reasonably narrow, and the optimal information size criterion was likely met, given the large sample size. Sensitivity was not reported or calculable from the second (incidence) screening round.

[c] Study included only a Chinese population, which may not reflect our target population. The definition of dense breasts for inclusion was unclear, and no information was provided about other breast cancer risk factors. The imaging protocols included a standard breast MRI protocol (full diagnostic protocol) that was similar to current Ontario practice, save for independent double-reading of imaging. The imaging also included an experimental abbreviated protocol that is not used in routine screening practice broadly.

[d] Confidence intervals around the point estimate were wide. Assuming a breast cancer prevalence of 2% and observed test performance, the optimal information size criterion may not have been met. Interval cancers were not measured in this study, so accuracy measures may have been inflated.

[e] Confidence intervals were not provided and could not be calculated from available data. The optimal information size criterion was likely met given the large sample size.

[f] Confidence intervals around the point estimate were tight. Assuming a breast cancer prevalence of 2% and observed test performance, the optimal information size criterion may not have been met.

[g] No analysis comparing outcome to mammography alone. See risk of bias assessment.

[h] Not evaluable because of a single study.

[i] Confidence intervals were fairly wide around all point estimates, but the optimal information size criterion was likely met.

[j] The study was designed and powered statistically to assess the primary outcome.

[k] Because of a very low event rate and the small sample size of MRI participants relative to the entire sample size, the optimal information size criterion was likely not met.

Appendix 5: Selected Excluded Studies—Clinical Evidence

Excluded Systematic Reviews

The primary studies included in these systematic reviews had one or more ineligible feature such as imaging in a mixed diagnostic or preoperative setting; inclusion of exclusively or largely participants who were at high risk for breast cancer; publication date prior to 2015; or did not examine the imaging modalities as adjunctive to mammography (i.e., imaging used as a replacement for mammography).

Author, Year	Scope	Literature search	Summary of main conclusions
Cozzi A, Magni V, Zanardo M, Schiaffino S, Sardanelli F. Contrast-enhanced mammography: a systematic review and meta-analysis of diagnostic performance. Radiology. 2022;302(3):568-81	**P:** Any breast imaging **I:** Contrast-enhanced mammography **C**: Not explicitly stated	Databases searched: MEDLINE (PubMed), Embase, Web of Science, Cochrane Library Search dates: up to Dec 3, 2018; updated March 1, 2018	Contrast-enhanced mammography had high diagnostic performance for cancer detection rate. Heterogeneity was high, and sensitivity and specificity were highest when interpreting both low-energy and recombined images. A common interpretation framework is needed for contrast-enhanced mammography[98]
Zeng A, Brennan ME, Young S, Mathieu E, Houssami N. The effect of supplemental imaging on interval cancer rates in mammography screening: systematic review. Clin Breast Cancer. 2022;22(3):212-22	**P:** Breast mammography screening or surveillance population (asymptomatic or < 10% symptomatic if mixed) **I:** Handheld ultrasound, MRI **C:** Mammography alone	Databases searched: MEDLINE Search dates: inception to August 2020	The addition of ultrasound or MRI to screening mammography increased the cancer detection rate in some subgroups of people undergoing screening mammography. Supplemental imaging also increased recall and biopsy rates and led to a potential modest reduction in interval cancer rate. Further research is required in this area[97]
Hadadi I, Rae W, Clarke J, McEntee M, Ekpo E. Diagnostic performance of adjunctive imaging modalities compared to mammography alone in women with non-dense and dense breasts: a systematic review and meta-analysis. Clin Breast Cancer. 2021;21(4):278-91	**P:** Dense breasts or non-dense breasts (no age limit, included those at high risk) **I:** Handheld ultrasound, ABUS, DBT, CESM, MRI **C:** Mammography alone	Databases searched: MEDLINE, Embase, PubMed, CINAHL, Scopus, Web of Science Search dates: up to October 2019	Adjunctive imaging increased the cancer detection rate in dense and non-dense breasts. Handheld ultrasound, ABUS, and MRI increased recall rates in people with dense and non-dense breasts. DBT performed better in reducing false-positives[21]
Yang L, Wang S, Zhang L, Sheng C, Song F, Wang P, et al. Performance of ultrasonography screening for breast cancer: a systematic review and meta-analysis. BMC Cancer. 2020;20(1)	**P:** Asymptomatic screening population with negative mammography, including all risk and density levels **I:** Handheld ultrasound, ABUS **C:** None	Databases searched: PubMed, Scopus, Web of Science, Embase Other sources: reference lists reviewed Search dates: January 2003 to May 2018	Supplemental ultrasound could detect additional cancers not seen on mammography. Further long-term studies are needed to confirm[102]

Author, Year	Scope	Literature search	Summary of main conclusions
Yuan WH, Hsu HC, Chen YY, Wu CH. Supplemental breast cancer-screening ultrasonography in women with dense breasts: a systematic review and meta-analysis. Br J Cancer. 2020;123(4):673-88	**P:** Females with heterogeneously or extremely dense breasts **I:** Supplemental handheld ultrasound, ABUS as an adjunct to mammography or after negative mammography **C:** Mammography alone or none	Databases searched: MEDLINE, Cochrane, Embase, Google Scholar Search dates: January 1980 to April 10, 2019	Supplemental ultrasound screening increased sensitivity and slightly decreased specificity compared to mammography alone. Cost-effectiveness should also be considered. Further studies are needed to confirm[103]
UK National Screening Committee. Additional screening with ultrasound after negative mammography screening in women with dense breasts [Internet]. London (UK): The Committee; 2019 [cited 2022 Dec 19]. Available from: view-health-screening-recommendations.service.gov.uk/document/465/download	**P:** Women aged 47 to 73 y with dense breasts participating in screening from general population **I:** Handheld ultrasound, ABUS **C:** Reference standard: biopsy test for cancer; follow-up for interval cancers	Databases searched: MEDLINE, Embase, Cochrane Library, Web of Science Search dates: 2000 to July 2017	The evidence is strong and consistent that dense breasts increase risk of breast cancer and reduce the sensitivity of mammography. Supplemental ultrasound can detect additional cancers, but with additional false-positives, leading to anxiety. The numbers of additional false-positives and biopsies are unlikely to be justifiable, and there is no clear cost-effectiveness to balance benefits, harm, and costs[68]
Phi XA, Tagliafico A, Houssami N, Greuter MJW, de Bock GH. Digital breast tomosynthesis for breast cancer screening and diagnosis in women with dense breasts—a systematic review and meta-analysis. BMC Cancer. 2018;18(1)	**P:** Asymptomatic people with dense breasts for screening or recalled **I:** Screening or diagnostic DBT **C:** With or without mammography	Databases searched: PubMed, Web of Science Other sources: Reference lists reviewed Search dates: January 2007 to May 2017	DBT plus digital mammography increased cancer detection rates in both the screening and diagnosis of dense breasts. In diagnosis, sensitivity but not specificity was increased. The recall rate after DBT and digital mammography varied between studies[105]
Rebolj M, Assi V, Brentnall A, Parmar D, Duffy SW. Addition of ultrasound to mammography in the case of dense breast tissue: systematic review and meta-analysis. Br J Cancer. 2018;118(12):1559-70.	**P:** Any age, with or without additional breast cancer risk factors asymptomatic women with dense breasts **I:** Handheld ultrasound, ABUS **C:** Mammography alone or none (i.e., mammography-negative population)	Databases searched: PubMed Search dates: January 2000 to June 29, 2016 (updated July 26, 2017)	Studies have consistently shown increased breast cancer detection with supplemental ultrasound in women with dense breasts. Cancers were predominantly small but invasive. The feasibility of adding supplemental ultrasound to routine screening needs to consider the availability of ultrasound and diagnostic assessment capacities, and could start by targeting the highest-risk women among those with dense breasts[100]

Author, Year	Scope	Literature search	Summary of main conclusions
Bowles D, Quinton A. The use of ultrasound in breast cancer screening of asymptomatic women with dense breast tissue: a narrative review. J Med Imaging Radiation Sci. 2016;47(3 Suppl):S21-8	**P:** Asymptomatic, dense breasts, any risk level **I:** Screening handheld ultrasound **C:** Negative film or digital mammography	Databases searched: DiscoverIT, PubMed/MEDLINE, CINAHL, Cochrane Library Other sources: Reference lists reviewed Search dates: not reported; no limits applied	The available evidence shows that adding supplemental ultrasound to a screening program in an asymptomatic population with dense breast tissue detects additional cancers compared with mammography alone. Whether there is or not a survival or cost benefit associated with increased cancer detection, and the psychological impact of supplemental ultrasound, are unknown. Further research is needed to make recommendations to screening programs[99]
Houssami N, Turner RM. Rapid review: estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts. Breast. 2016;30:141-5	**P:** Women with dense breasts (extremely or heterogeneously dense) **I:** DBT for population screening **C:** Digital mammography	Databases searched: MEDLINE Other sources: Content experts Search dates: up to July 2016	The currently available evidence in different study designs and screening contexts showed that supplemental DBT in mammography screening of women with dense breasts improves breast cancer detection and can reduce recalls. The screening benefit in terms of the mortality reduction with supplemental screening has not been investigated. Further research is needed to assess DBT for primary screening[104]
Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(4):268-78.	**P:** Dense breasts or mixed density with a dense breast subgroup separate, aged 40 y or older **I:** Handheld ultrasound, ABUS, MRI, DBT after negative screening mammography **C:** Mammography alone in the same participants or reference cohort; reference standard for test accuracy studies biopsy results and 12+ months' clinical follow-up	Databases searched: MEDLINE, PubMed, Embase, Cochrane Library Other sources: clinicaltrials.gov and suggestions from experts, bibliographic review of full texts Search dates: January 2000 to July 2015	Limited evidence suggests that more breast cancers will be detected by supplemental screening in women with dense breasts (most cancers will be invasive) and false-positives will be increased. DBT may reduce recall rates, but very limited evidence is available to support this. The impacts of supplemental screening on clinical outcomes remain unclear and require well-designed long-term studies to clarify[69]

Author, Year	Scope	Literature search	Summary of main conclusions
Scheel JR, Lee JM, Sprague BL, Lee CI, Lehman CD. Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts. Am J Obstet Gynecol. 2015;212(1):9-17	**P:** Dense breasts **I:** Screening handheld ultrasound, ABUS **C:** None—after negative screening mammography	Databases searched: PubMed Other sources: Reference lists reviewed Search dates: January 2000 to April 2013	There is consistent evidence that supplemental ultrasound detects more invasive cancers compared to mammography alone, but there is no evidence of long-term mortality benefit, and also a nearly 5-fold increase in the associated number of unnecessary breast biopsies resulting from supplemental ultrasound beyond that of screening mammography alone[101]

Abbreviations: ABUS, automated breast ultrasound; CESM, contrast-enhanced spectral mammography; DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging.

Selected Excluded Primary Studies

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Bernardi D, Macaskill P, Pellegrini M, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. Lancet Oncol. 2016;17(8):1105-13.	Insufficient information for subset of participants with dense breasts
Carbonaro LA, Di Leo G, Clauser P, et al. Impact on the recall rate of digital breast tomosynthesis as an adjunct to digital mammography in the screening setting. A double reading experience and review of the literature. Eur J Radiol. 2016;85(4):808-14.	Insufficient information for subset of participants with dense breasts
Cheung YC, Lin YC, Wan YL, Yeow KM, Huang PC, Lo YF, et al. Diagnostic performance of dual-energy contrast-enhanced subtracted mammography in dense breasts compared to mammography alone: interobserver blind-reading analysis. Eur Radiol. 2014;24:2394-2403.	Published prior to 2015
Comstock CE, Gatsonis C, Newstead GM, et al. Comparison of abbreviated breast MRI vs digital breast tomosynthesis for breast cancer detection among women with dense breasts undergoing screening. JAMA. 2020;323(8):746-56. [correction in JAMA. 2020;323(12):1194]	Wrong population (included ineligible risk factors)
Fallenberg EM, Dromain C, Diekmann F, Engelken F, Krohn M, Singh JM, et al. Contrast-enhanced spectral mammography versus MRI: initial results in the detection of breast cancer and assessment of tumour size. Eur Radiol. 2014;24:256-64.	Published prior to 2015
Health Quality Ontario. Magnetic resonance imaging as an adjunct to mammography for breast cancer screening in women at less than high risk for breast cancer: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2016 November;16(20):1-30. Available from: www.hqontario.ca/Evidence-to-Improve-Care/Journal-Ontario-Health-Technology-Assessment-Series	No data on the dense breast population (empty review)
Health Quality Ontario. Ultrasound as an adjunct to mammography for breast cancer screening: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2016 July;16(5):1-71. Available from: www.hqontario.ca/Evidence-to-Improve-Care/Journal-Ontario-Health-Technology-Assessment-Series	No data on the dense breast population and no high-risk factors
l'Institut national d'excellence en santé et en services sociaux. Densité mammographique et dépistage du cancer du sein [Internet]. Quebec (QC): The Institute; 2021. Available from: www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/INESSS_Densite_mammographique_EC.pdf	No English full text
Li T, Houssami N, Noguchi N, Zeng A, Marinovich ML. Differential detection by breast density for digital breast tomosynthesis versus digital mammography population screening: a systematic review and meta-analysis. Br J Cancer. 2022;127(1):116-25.	Wrong comparison (not adjunct DBT)
Østerås BH, Martinsen ACT, Gullien R, Skaane P. Digital mammography versus breast tomosynthesis: impact of breast density on diagnostic performance in population-based screening. Radiology. 2019;293(1):60-8.	Insufficient information for subset of participants with dense breasts
Pattacini P, Nitrosi A, Giorgi Rossi P, et al. A randomized trial comparing breast cancer incidence and interval cancers after tomosynthesis plus mammography versus mammography alone. Radiology. 2022;303(2):256-66.	Insufficient information for subset of participants with dense breasts
Singla D, Chaturvedi AK, Aggarwal A, Rao SA, Hazarika D, Mahawar V. Comparing the diagnostic efficacy of full field digital mammography with digital breast tomosynthesis using BIRADS score in a tertiary cancer care hospital. Indian J Radiol Imaging. 2018;28(1):115-22.	Insufficient information for subset of participants with dense breasts
Skaane P, Bandos AI, Niklason LT, et al. Digital mammography versus digital mammography plus tomosynthesis in breast cancer screening: the Oslo tomosynthesis screening trial. Radiology. 2019;291(1):23-30.	Insufficient information for subset of participants with dense breasts

Citation	Primary reason for exclusion
Sorin V, Yagil Y, Yosepovich A, Shalmon A, Gotlieb M, Neiman OH, et al. Contrast-enhanced spectral mammography in women with intermediate breast cancer risk and dense breasts. Am J Roentgenol. 2018;211:W267-74.	Insufficient information for subset of participants with dense breasts
Sung JS, Lebron L, Keating D, et al. Performance of dual-energy contrast-enhanced digital mammography for screening women at increased risk of breast cancer. Radiology. 2019;293(1):81-8.	Insufficient information for subset of participants with dense breasts
Upadhyay N, Soneji N, Stewart V, Ralleigh G. The effect of the addition of tomosynthesis to digital mammography on reader recall rate and reader confidence in the UK prevalent screening round. Clin Radiol. 2018;73(8):744-9.	Insufficient information for subset of participants with dense breasts

Appendix 6: Selected Excluded Studies—Economic Evidence

For transparency, we provide a list of some studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Khan SA, Hernandez-Villafuerte KV, Muchadeyi MT, Schlander M. Cost-effectiveness of risk-based breast cancer screening: a systematic review. Int J Cancer. 2021;149(4):790-810	Non-primary study[a]
Arribas EM, Whitman GJ, De Bruhl N. Screening breast ultrasound: where are we today? Curr Breast Cancer Rep. 2016;8(4);221-9	Non-primary study[a]
Baltzer PAT. Supplemental screening using breast MRI in women with mammographically dense breasts. Eur J Radiol. 2021;136(109513)	Non-primary study[a]
Berg WA, Gur D. Supplemental ultrasonography screening for women with dense breasts. Ann Intern Med. 2015;162(11):801	Non-primary study[a]
Tilanus-Linthorst M, Geuzinge A, Obdeijn IM, Rutgers E, Mann R, et al. FaMRIsc trial shows: MRI breast screening for women with ≥20% lifetime risk is also cost-effective in Europe. Eur J Surg Oncol.2021;47(2):e19-2021	Abstract/poster only
Sprague BL, Lehman CD, Tosteson ANA. supplemental ultrasonography screening for women with dense breasts. Ann Intern Med. 2015;162(11):802-3	Non-primary study[a]
Tilanus-Linthorst MMA, Geuzinge HA, Obdeijin IMM, Rutgers EJT, et al. Costs and effects in the first randomized trial comparing MRI breast cancer screening with mammography in women with a familial risk: FaMRIsc. Cancer Res Conf. 2019;80(4 Suppl 1)	Abstract/poster only
Miller JD, Bonafede MM, Phlman SK, Troeger KA. Comparative costs of dense breast cancer screening and recall: tomosynthesis vs. ultrasound. Value Health. 2018;21(Suppl 1):S166	Abstract/poster only
Shen Y, Doug W, Xu Y, Shih YCT. Pcn311 optimal breast cancer screening policy stratifying by breast density. Value Health. 2019;22(Suppl 3):S496	Abstract/poster only
Abbey CK, Wu Y, Burnside ES, Wunderlich A, Samuelson FW, Boone JM. A utility/cost analysis of breast cancer risk prediction algorithms. Proc SPIE. 2016; 9787(27):27	Not an economic evaluation
Tilanus-Linthorst MMA, Geuzinge HA, Obdeijin IMM, Rutgers EJT, et al. Cost-effective strategies according to the first randomized trial comparing MRI breast cancer screening with mammography in women with a familial risk: FaMRIsc. Eur J Surg Oncol. 2020;138(Suppl 1):S2	Incorrect intervention
Bromly L, Xu J, Loh SW, Yeo B. OP2 Role of breast ultrasound in breast cancer surveillance: incremental cancers found at what cost? Breast. 2020;50(153)	Incorrect study population
Phi XA, Greuter MJ, Obdeijn IM, Oosterwijnk JC, Feenstra TL, Houssami N, et al. Should women with a BRCA1/2 mutation aged 60 and older be offered intensified breast cancer screening? A cost-effectiveness analysis. Breast. 2019;45:82-8	Incorrect study population
Semprini J, Vaughan-Sarrazin M. Breast density notification with adjunctive digital breast tomosynthesis (DBT): a cost-effectiveness analysis. J Clin Oncol. 2020:38(15)	Abstract/poster only

[a] Nonprimary studies included reviews, letters/editorials, commentaries, case reports, and study protocols.

Appendix 7: Results of Applicability and Limitation Checklists for Studies Included in the Economic Evidence

Table A14: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Supplemental Screening as an Adjunct to Mammography for Breast Cancer Screening in People With Dense Breasts

Author, year, country	Is the study population similar to the question?[a]	Are the interventions similar to the question?[b]	Is the health care system studied sufficiently similar to Ontario?[c]	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?[d]	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?[e]	Overall judgment[f]
Tollens et al, 2022,[118] Germany	Unclear: density classification was not defined	Partially	No: different breast screening frequency practices	Yes: United States health care payer	Partially: QALYs were the only health effects estimated	Yes: 3%	Yes	Partially: excluded combined costs with mammography	Not applicable
Geuzinge et al, 2021,[115] Netherlands	Partially: included only extremely dense breasts	Partially	No: different breast screening frequency practices	Yes: Netherlands health care payer	Yes	Yes: 3%	Yes	Yes: direct medical costs	Partially applicable
Kaiser et al, 2021,[116] Germany	Partially: included only extremely dense breasts	Partially	No: different breast screening frequency practices	Yes: United States health care payer (Medicare and Medicaid)	Partially: QALYs were the only health effects estimated	Yes: 3%	Yes	Partially: excluded combined costs with mammography and positive finding cost values were not reported	Partially applicable
Tollens et al, 2021,[117] Germany	Partially: included only extremely dense breasts	Partially	No: different breast screening frequency practices	Yes: United States health care payer	Partially: QALYs were the only health effects estimated	Yes: 3%	Yes	Partially: excluded combined costs with mammography	Partially applicable

Author, year, country	Is the study population similar to the question?[a]	Are the interventions similar to the question?[b]	Is the health care system studied sufficiently similar to Ontario?[c]	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?[d]	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?[e]	Overall judgment[f]
Gray et al, 2017,[119] United Kingdom	Partially: included women aged 40–49 y, and people with heterogeneously and extremely dense breasts in one population	Partially: United Kingdom NBSP is every 3 y	No: United Kingdom NBSP has minor differences in screening interval and eligible age	Yes: United Kingdom national health care payer	Partially: QALYs were the only health effects estimated	Yes: 3.5%	Yes	Yes	Partially applicable
Movik et al, 2017,[120] Norway	Unclear: density classification was not defined (whether it was extremely dense breasts only or heterogeneously and extremely dense breasts)	Yes	No: Norwegian NBSP has minor differences in screening interval	Yes: Norwegian health care payer	Partially: QALYs were the only health effects estimated	Partially: health outcomes and screening costs were discounted by 3%. Breast cancer treatment costs were not discounted because the sources of these costs were already discounted by 4%	Yes	Partially: costs related to positive findings were not reported	Partially applicable
Lee et al, 2015,[121] United States	Yes	Yes	No: different breast screening frequency practices	Yes: United States health care payer (Medicare and Medicaid)	Yes	Yes: 3%	Yes	Yes	Partially applicable
Sprague et al, 2015,[39] United States	Yes	Yes	No: difference in Medicare reimbursement rate and breast screening frequency practices	Yes: United States health care payer (Medicare and Medicaid)	Yes	Yes: 3%	Yes	Partially: costs related to positive findings, diagnostic assessment, and breast cancer treatment were not reported	Partially applicable

Author, year, country	Is the study population similar to the question?[a]	Are the interventions similar to the question?[b]	Is the health care system studied sufficiently similar to Ontario?[c]	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?[d]	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?[e]	Overall judgment[f]
Ollendorf et al, 2014,[122] United States	Partially: included heterogeneously and extremely dense in one population[g] and included women aged 40–49 y	Partially: only the first year of a screening interval was evaluated because of the 1 y time horizon	No: Washington state difference in Medicare reimbursement rate, screening practices, and eligible age	Yes: state of Washington health care perspective (United States Medicare and Medicaid)	Yes	NA: time horizon was 1 y	No: health effects were expressed as natural units (e.g., biopsies performed, cancers detected, false-positive results, interval cancers)	Yes	Not applicable

Abbreviations: ABUS, automated breast ultrasound; BI-RADS, Breast Imaging Reporting and Data System; DCIS, ductal carcinoma in situ; NA, not applicable; NBSP, National Breast Screening Program; QALY, quality-adjusted life-year.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA."

[a] Study population: "yes" if the study included people who were asymptomatic, were aged > 40 years old, had negative or benign breast screening mammography (i.e., BI-RADS category 1 or 2 assessment), had no high-risk factors, and had dense breasts (i.e., 51%–75%, BI-RADS C [heterogeneously dense breasts] and/or or ≥ 75%, BI-RADS D [extremely dense breasts]); "partially" if the study excluded one or more of the eligibility criteria.

[b] Intervention: "yes" if the study included supplemental screening (after mammography screening) with ultrasound (handheld ultrasound or ABUS), MRI, contrast-enhanced mammography, or digital breast tomosynthesis; "partial" if the study did not include mammography prior to the supplemental modality (i.e., focused only on the supplemental modality), or if the screening interval was not similar to the Ontario setting (i.e., annual mammography screening for people with extremely dense breasts and biennial for people with heterogeneously dense breasts).

[c] Health care system: "yes" if the study was conducted in Canada and was sufficiently recent to reflect a recent Canadian system; "partially" if the study was conducted in a public health care system similar to Canada or if differences existed in the age eligibility of the target population, the frequency of screening, or the cost-effectiveness threshold (e.g., $100,000 USD/QALY, £20,000 GBP/QALY).

[d] Direct health effects: "yes" if the measure of health outcomes included life-years, breast cancer mortality, cancer detection, abnormal recall, interval cancer, prognostic feature of cancer detected (e.g., invasive ductal carcinoma or invasive lobular carcinoma, DCIS) or cancer stage; "partially" if only some of these outcomes were included.

[e] Cost and health outcomes: "yes" if direct medical costs related to screening, diagnostic assessment, and breast cancer–related treatment were included; "partial" if some costs were not included or were discussed and referenced but cost values were not reported.

[f] Overall judgment may be "directly applicable," "partially applicable," or "not applicable." Not applicable: the study failed to meet one or more applicability criteria, and this was likely to change the conclusions about cost-effectiveness; such studies would be excluded from further consideration. Partially applicable: the study failed to meet one or more applicability criteria and may change the conclusions about cost-effectiveness (e.g., studies conducted in non-Canadian settings, but that used the same cut-off values as recommended by the Canadian guidelines, similar breast screening and clinical practice and guidelines [e.g., eligible age population, screening frequency], or similar reimbursement costs from the health care payer perspective). Directly applicable: the study met all applicability criteria, or failed to meet one or more applicability criteria, but this was unlikely to change the conclusions about cost-effectiveness (e.g., studies conducted in a Canadian setting).

[g] Population of interest (moderate risk) was mixed with a population of women aged 40–49 y, BI-RADS density 3 or 4, and a family history of breast cancer *or* high risk included women aged 50–75 y, BI-RADS density 3 or 4, with a family history of breast cancer.

Table A15: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Supplemental Screening as an Adjunct to Mammography for Breast Cancer Screening in People With Dense Breasts

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?[a]	Are the clinical inputs[b] obtained from the best available sources?	Do the clinical inputs[b] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[c]
Tollens et al, 2022,[118] Germany	Yes	Yes: lifetime ~30 y	Partially[a]	Partially: several assump-tions in natural history and utilities	Yes	Partially: excluded combined costs with mammo-graphy	Yes	Yes	Yes	Partially: assumptions in natural history and utilities were not assessed, no PSA was conducted	No	Potentially serious limitations
Geuzinge et al, 2021,[115] Netherlands	Yes	Yes, lifetime ~25 y	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Kaiser et al, 2021,[116] Germany	Yes	Yes: lifetime ~30 y	Partially[a]	Partially: several assump-tions in natural history and utilities	Yes	Partially: excluded combined costs with mammo-graphy, and positive finding cost values not reported	Yes	Yes	Yes	Yes	No	Potentially serious limitations

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?[a]	Are the clinical inputs[b] obtained from the best available sources?	Do the clinical inputs[b] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[c]
Tollens et al, 2021,[117] Germany	Yes	Yes: lifetime ~20 y	Partially[a]	Partially: several assump-tions in natural history and utilities	Yes	Partially: excluded combined costs with mammo-graphy	Yes	Yes	Yes	Partially: assumptions in natural history and utilities were not assessed; unclear whether this was assessed in the PSA	No	Potentially serious limitations
Gray et al, 2017,[119] United Kingdom	Yes	Yes: lifetime	Partially[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations
Movik et al, 2017,[120] Norway	Partially: model structure and health states were unclear	Yes: 20 y	Partially[a]	Partially: sources for some parameters were unclear	Partially: sources for some parameters were unclear	Yes	Yes	Yes	Yes	Partially: diagnostic accuracy of the modalities was not evaluated	No	Very serious limitations
Lee et al, 2015,[121] United States	Yes	Yes: lifetime	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Minor limitations

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?[a]	Are the clinical inputs[b] obtained from the best available sources?	Do the clinical inputs[b] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[c]
Sprague et al, 2015,[39] United States	Yes	Yes: lifetime	Yes	Yes	Yes	Partially: costs related to positive findings, diagnostic assess-ment, and breast cancer treatment were not reported	Yes	Yes	Yes	Yes	Partially[d]	Potentially serious limitations
Ollendorf et al, 2014,[122] United States	Partially: unclear model type	No: 1 y time horizon	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Potentially serious limitations

Abbreviations: NA, not applicable; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA.”

[a] Important and relevant health outcomes: "yes" if included health outcomes other than QALYs (e.g., cancer detection, abnormal recall, biopsies conducted, breast cancer mortality, life-years); "partially" if included only QALYs.

[b] Clinical inputs included relative treatment effects, natural history, and utilities.

[c] Overall judgment may be “minor limitations,” “potentially serious limitations,” or “very serious limitations.”

[c] Potential conflict of interest: one author worked as a consultant at GE Healthcare and Renaissance Rx, and one author as an advisory member at General Electric and Bayer Healthcare.

Appendix 8: Cost-Effectiveness of Supplemental Screening as an Adjunct to Mammography for Breast Cancer Screening in People With Dense Breasts—Summary

Table A16: Studies Evaluating the Cost-Effectiveness of Supplemental Screening as an Adjunct to Mammography for Breast Cancer Screening in People With Dense Breasts—Summary

Author, year, country	Population	Cost-effectiveness
MRI		
Tollens et al, 2022,[118] Germany (United States health care perspective)	Dense breasts	CUA: cost-effective MRI vs. mammography alone in abbreviated or full protocol (abbreviated protocol: $4,163 USD/QALY to $28,458 USD/QALY; full protocol: $15,018 USD/QALY)
Geuzinge et al, 2021,[115] Netherlands	Extremely dense breasts	CUA: not cost-effective Supplemental screening with MRI as an adjunct to mammography was dominated by mammography alone and interventions with MRI alone Commonly accepted cost-effectiveness value: €22,000 (£20,000 GBP) per QALY based on the lower bound of the NICE threshold range
Tollens et al, 2021,[117] Germany (United States health care perspective)	Extremely dense breasts	CUA: cost-effective ICER $13,493 USD/QALY for biennial supplemental screening with MRI as an adjunct to mammography compared to mammography alone Commonly accepted cost-effectiveness value: $100,000 USD/QALY
Kaiser et al, 2021,[116] Germany (United States health care perspective)	Extremely dense breasts	CUA: cost-effective ICER $8,797 USD/QALY for biennial supplemental screening with MRI as an adjunct to mammography compared to mammography alone Commonly accepted cost-effectiveness value: $100,000 USD/QALY
Ollendorf et al, 2014,[122] United States	Heterogeneously and extremely dense breasts	CEA (1 y time horizon): unable to determine if cost-effective (natural units used to measure effectiveness) ICER $93,077 USD per cancer detected for biennial mammography supplemented with MRI compared to mammography alone[d]
Ultrasound		
Gray et al, 2017,[119] United Kingdom	Heterogeneously and extremely dense breasts	CUA: not cost-effective (dominated by mammography alone) ICER £212,947 GBP/QALY for mammography supplemented with ultrasound compared to mammography alone (every 3 y) Commonly accepted cost-effectiveness value: £20,000 GBP/QALY
Sprague et al, 2015,[39] United States	Extremely dense breasts, and heterogeneously and extremely dense breasts	CUA and CEA: not cost-effective compared to mammography alone ICER $246,000 USD/QALY for biennial mammography supplemented with ultrasound for extremely dense breasts; $325,000 USD/QALY for biennial mammography supplemented with ultrasound for heterogeneously and extremely dense breasts Commonly accepted cost-effectiveness value: $100,000 USD/QALY
Ollendorf et al, 2014,[122] United States	Heterogeneously and extremely dense breasts	CEA (1 y time horizon): unable to determine if cost-effective ICER $37,955 USD and $57,046 USD per cancer detected for biennial mammography supplemented with handheld ultrasound or ABUS, respectively, compared to mammography alone

Author, year, country	Population	Cost-effectiveness
DBT		
Tollens et al, 2022,[118] Germany	Dense breasts	CUA: cost-effective $19,785 USD/QALY for biennial supplemental screening with DBT vs. mammography alone
Movik et al, 2017,[120] Norway	Dense breasts[e]	CUA and CEA: cost-effective ICER 143,966 NOK/QALY for biennial mammography supplemented with DBT Commonly accepted cost-effectiveness value was not indicated. However, previous studies have cited that the Norwegian Ministry of Health and Care Services compare estimated ICERs to a value of 275,000 NOK ($33,805 USD) to 500,000 NOK ($61,464 USD)[123-125]
Lee et al, 2015,[121] United States	Heterogeneously and extremely dense breasts	CUA and CEA: cost-effective ICER $53,893 USD/QALY for biennial mammography supplemented by DBT compared to mammography alone Commonly accepted cost-effectiveness value: $100,000 USD/QALY

Abbreviations: ABUS, automated breast ultrasound; CEA, cost-effectiveness analysis; CUA, cost–utility analysis; DBT, digital breast tomosynthesis; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; NICE, National for Health and Care Excellence; QALY, quality-adjusted life-year; NOK, Norwegian kroner.

Appendix 9: Model Input Parameters Prepopulated in the OncoSim-Breast Model

Table A17: Inputs for Demographic Characteristics, Natural History of Breast Cancer, Detection, and Disease Progression Used in the OncoSim-Breast Model

Model parameter		Value	Source
Demographic characteristics	Age distribution of women in Ontario	Prepopulated in the OncoSim model	Statistics Canada population and demography statistics[136]
	All-cause mortality	Prepopulated in the OncoSim model	Canadian life tables[288]
	Screening participation and retention rate	64.81% (screened through the OBSP)	CSQI 2020 Ontario Cancer System Performance report[139]
Natural history of breast cancer[a]	Occult tumour onset (oncogenesis)	Oncogenesis rate[b] = baseline (age, year) × RR predisposition × RR HRT × $RR_{density}$ + AR previous	Yong et al, 2022[136] Supplemental Appendix 2: Natural History
	Incidence of tumour type by age group[c]	*DCIS* 0–54 y: 19% 55–64 y: 10% 65–69 y: 16% 70–79 y: 11% 80+ y: 2% *Invasive cancer* 0–54 y: 81% 55–64 y: 90% 65–69 y: 84% 70–79 y: 89% 80+ y: 98%	Yong et al, 2022[136] Supplemental Appendix 2: Natural History Table 2
	Tumour growth	Gompertz distribution described by[d] $d(t) = d_0([d_{max}/d_0]^{(1-\exp[-\alpha t])})$	Yong et al, 2022[136] Supplemental Appendix 2: Natural History Figure 2 and Table 5 (equation coefficients)
	Tumour spread	*Spread to lymph nodes* Number of positive nodes affected is estimated by the size and growth rate of the tumour, years since tumour onset described by[e]: $\lambda(t) = \mu_N(b_1 + b_2V[t] + b_3V'[t])$	Yong et al, 2022[136] Supplemental Appendix 2: Natural History; equation developed from the CISNET-Wisconsin model[161,289]
		Metastasis Spread beyond the breast depends on the tumour size and number of positive nodes (N*) described by[f]: hazard of metastasis = µM* k(tumour size, N*)	Yong et al, 2022 [136] Supplemental Appendix 2: Natural History
Cancer detection, staging, and tumour biology[a]	Probability of clinical detection of tumour	Determined by tumour size	Yong et al, 2022[136] Supplemental Appendix 3: Cancer detection, staging and tumour biology Table 7

Model parameter		Value	Source
	Stage at detection[g]	Assigned based on tumour size (T), nodal status (N) and metastasis (M)	American Joint Committee on Cancer (AJCC) version 7 classification[290]
	Tumour biology: hormone receptor status, HER2 status and grade	Estimated by tumour size, nodal involvement, metastatic status, and age of woman at tumour detection	Canadian Cancer Registry[140]
Disease progression	Time to disease progression	Estimated using Weibull regression models, adjusted to years since diagnosis, age, grade, hormone status, HER2 status, screening status, method of detection, and variable interactions	Yong et al, 2022[136] Supplemental Appendix 5: Disease Progression Figure 6

Abbreviations: AR, adjusted risk; CISNET, Cancer Intervention and Surveillance Modeling Network; CSQI, Cancer System Quality Index; DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2; HRT, hormone replacement therapy; OBSP, Ontario Breast Screening Program; RR, relative risk; Wisconsin model, University of Wisconsin Breast Cancer Epidemiology Simulation Model.

[a] The natural history of breast cancer component of the OncoSim model and corresponding inputs (including tumour onset, growth, spread and metastasis, and clinical detection) were adapted from the Wisconsin model[289] and calibrated to the incidence of cancer by age group and year in the National Cancer Incidence Reporting System (1969–1991), the Canadian Cancer Registry (1992–2013) and the Canadian Breast Cancer Screening Database (2007–2008).

[b] Oncogenesis rate or tumour onset is calculated by the *baseline* term, which is the assumed hazard of developing an occult tumour based on age and year for all simulated women, multiplied by the increased risk of breast cancer due to high breast density ($RR_{density}$, women with dense breasts vs. without dense breasts).

[c] Once a tumour is simulated (oncogenesis), the model determines the tumour type (DCIS or invasive) using incidence of tumour type by age group.

[d] Tumours are assumed to grow according to a Gompertz distribution that estimates the tumour diameter (d, in cm) as a function of years since tumour onset (t), scaled to the maximum diameter allowed for a particular tumour type (d_{max}), where d_0 is the diameter of the tumour at occult onset (0.2 cm) and α represents the tumour growth rate (model fitting).

[e] Invasive tumour can spread into the lymph nodes in which the spread (number of positive nodes, λ) is estimated by the size and growth rate of the tumour and years since tumour onset (t), where μ_N is the random term drawn at time of tumour onset that allows for heterogeneity of tumours to generate positive nodes (Yong et al,[136] Supplemental Appendix 2, Natural History Table 6); b_1, b_2, and b_3 are coefficients estimated through calibration of natural history; $V(t)$ is the volume of the spherical tumour; and $V'(t)$ represents the growth rate of the volume, and is the derivative of $V(t)$. The equation was developed from the CISNET-Wisconsin model and calibrated to positive node data in the Canadian Cancer Registry (1992–2013) and the Canadian Breast Cancer Screening Database (2007–2008).

[f] μ_M is a random term drawn at the time of tumour onset that allows for heterogeneity (Yong et al,[136] Supplemental Appendix 2: Natural History Table 6); and k is an annual hazard rate estimated through model calibration. It is a function of tumour size and number of positive nodes.

[g] The model assigns tumour size (T) at the time of detection − random draw to determine whether it is a T4 tumour, where the probability of a T4 tumour is a function of age, tumour size (T^*), number of nodes (N^*), and metastatic status. T is estimated based on T^* for non-T4 tumours. The model assigns a nodal status (N) at the time of detection from a distribution estimated by age, N*, and T, fitted using the Canadian Cancer Registry data.

Breast Cancer Cost Parameters

We used breast cancer–related costs prepopulated in the OncoSim model, including breast cancer surgery, radiation treatment, chemotherapy, imaging and oncology physician fees, acute hospitalizations, emergency department visits, home care, long-term care, and continuing care.[136] The model estimates breast cancer costs based on three phases of care: the first 18 months after diagnosis, continuing care, and terminal care. The OncoSim model includes projected lifetime costs for breast cancer by stage, based on Ontario costing data (Table A18).

- First 18 months: The model estimates the cost in the first 18 months after cancer diagnosis or recurrence (acute treatment costs), which are specific to breast cancer treatments, obtained from health administrative databases at ICES including the cancer registry (Ontario Health [Cancer Care Ontario]), hospitalizations (inpatient, day, surgery), physician billings (Ontario Health Insurance Plan), the Ontario Drug Benefit program, the New Drug Funding Program and Activity Level Reporting data. Breast cancer treatment costs incurred in the first 18 months after diagnosis include surgery, radiation treatment, chemotherapy, hormonal treatment, molecular subtypes, and grade. Patients incur additional treatment costs for recurrent cancer diagnosis. Costs varied by stage and age at diagnosis, molecular subtype, and grade
- Continuing care (after 18 months): Patients incur continuing care costs based on age group, stage, molecular subtype, grade, and time after diagnosis, including follow-up care with oncology and primary care physicians, laboratory tests. and imaging for surveillance. Continuing care costs were obtained from the Ontario Health Insurance Plan schedule of benefits and clinical expert opinion. The model assumed that 5 years after a diagnosis of stages 0 to III cancer, continuing care costs would decrease to minimal physician-based visits and imaging. This was assumed in the model to avoid overestimation of treatment costs, because most patients diagnosed with 0 to III breast cancer have good survival. In addition, costing studies often have short-term follow-up periods to accurately estimate long-term continuing care costs
- Terminal care: People who die from breast cancer incur terminal care costs in the last 3 months before death. Terminal care costs were estimated using a health administrative database, leveraging a previously published end-of-life care costing study.[291] For acute treatment costs, the cost of terminal care would include acute hospitalizations, emergency department visits, home care, long-term care, complex continuing care, and other costs (e.g., mental health, rehabilitation, dialysis, medical devices)

Table A18: Projected Lifetime Costs Associated With Breast Cancer by Stage at Diagnosis Used in the OncoSim-Breast Model

Stage at diagnosis	Cost, average per case in 2019 Canadian dollars (2022 Canadian dollars)[a]
DCIS	16,900 (20,079.21)
Stage IA	26,500 (31,485.15)
Stage IB	38,200 (45,386.14)
Stage IIA	34,800 (41,346.53)
Stage IIB	42,800 (50,851.49)
Stage III	54,100 (64,277.23)
Stage IV	82, 100 (97,544.55)

Abbreviation: DCIS, ductal carcinoma in situ.

[a] Costs in 2019 Canadian dollars were converted to 2022 Canadian dollars using the Consumer Price Index.[157]

Sensitivity and Specificity Parameters

We applied a calibrated multiplicative odd factor for the sensitivity and specificity of breast screening using sensitivity and specificity estimates from the studies (Figures A1 and A2). The 100% laboratory sensitivity refers to the scenario where we set the sensitivity of screening input parameter at 100% for a tumour size greater than 9 mm.

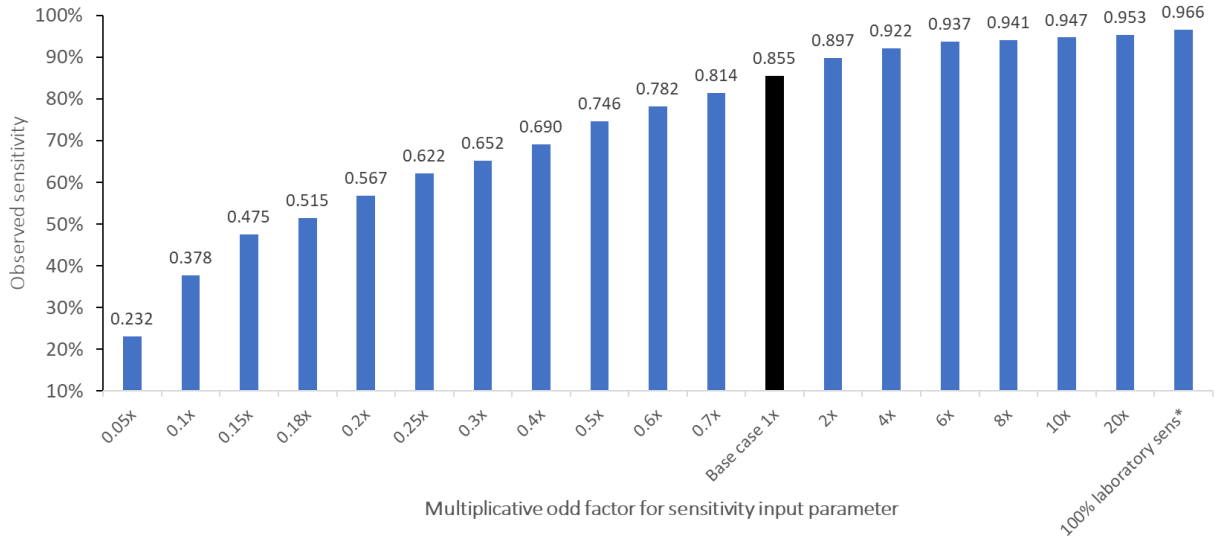


Figure A1: Calibrated Multiplicative Odd Factors for Sensitivity From Observed Clinical Data

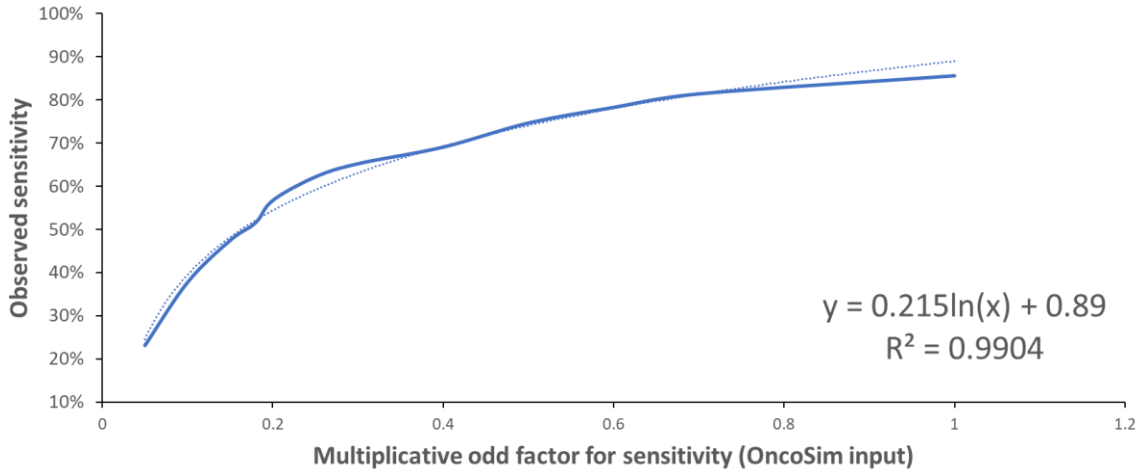


Figure A2: Calibration Curve, Multiplicative Odd Factors for Sensitivity From Observed Clinical Data

Appendix 10: Breast Cancer Cases and Treatment Costs by Breast Cancer Stage

Table A19: Breast Cancer Cases and Total Treatment Costs by Breast Cancer Stage for Mammography Alone and Supplemental Screening With Ultrasound in People With Dense Breasts and Extremely Dense Breasts

	Breast cancer cases			Total treatment costs, $[a]		
Breast cancer stage	Mammography alone	Supplemental screening with handheld ultrasound as an adjunct to mammography	Difference (supplemental handheld ultrasound and mammography vs. mammography alone)	Mammography alone	Supplemental screening with handheld ultrasound as an adjunct to mammography	Difference (supplemental handheld ultrasound and mammography vs. mammography alone)
People with dense breasts (BI-RADS C and D)						
Stage I	7,921	9,321	1,400	146,877,741	173,217,300	26,339,559
Stage II	35,010	37,509	2,499	1,030,034,487	1,094,070,069	64,035,582
Stage III	30,363	30,105	−258	1,250,149,244	1,238,867,526	−11,281,718
Stage IV	9,557	9,313	−244	558,993,884	545,054,012	−13,939,872
People with extremely dense breasts (BI-RADS D)						
Stage I	7,921	8,287	366	146,877,741	153,646,195	6,768,454
Stage II	35,010	35,540	530	1,030,034,487	1,043,090,094	13,055,607
Stage III	30,363	30,276	−87	1,250,149,244	1,246,463,498	−3,685,746
Stage IV	9,557	9,482	−75	558,993,884	554,884,697	−4,109,187

Abbreviation: BI-RADS, Breast Imaging Reporting and Data System.

[a] In 2022 Canadian dollars.

Table A20: Breast Cancer Cases and Total Treatment Costs by Breast Cancer Stage for Mammography Alone and Supplemental Screening With MRI in People With Dense Breasts and Extremely Dense Breasts

Breast cancer stage	Breast cancer cases			Total treatment costs, $[a]		
	Mammography alone	Supplemental screening with MRI as an adjunct to mammography	Difference (supplemental MRI and mammography vs. mammography alone)	Mammography alone	Supplemental screening with MRI as an adjunct to mammography	Difference (supplemental MRI and mammography vs. mammography alone)
People with dense breasts (BI-RADS C and D)						
Stage I	7,880	11,477	3,597	146,134,244	213,806,249	67,672,005
Stage II	34,873	40,069	5,196	1,026,226,145	1,153,528,808	127,302,663
Stage III	30,372	29,574	−798	1,250,250,126	1,216,719,445	−33,530,681
Stage IV	9,560	9,148	−412	559,036,117	535,376,272	−23,659,845
People with extremely dense breasts (BI-RADS D)						
Stage I	7,880	8,607	727	146,134,244	159,508,462	13,374,218
Stage II	34,873	35,847	974	1,026,226,145	1,048,622,292	22,396,147
Stage III	30,372	30,167	−205	1,250,250,126	1,241,960,077	−8,290,049
Stage IV	9,560	9,446	−114	559,036,117	553,108,585	−5,927,532

Abbreviation: BI-RADS, Breast Imaging Reporting and Data System; MRI, magnetic resonance imaging.

[a] In 2022 Canadian dollars.

Table A21: Breast Cancer Cases and Total Treatment Costs by Breast Cancer Stage for Mammography Alone and Supplemental Screening With DBT in People With Dense Breasts and Extremely Dense Breasts

Breast cancer stage	Breast cancer cases			Total treatment costs, $[a]		
	Mammography alone	Supplemental screening with DBT as an adjunct to mammography	Difference (supplemental DBT and mammography vs. mammography alone)	Mammography alone	Supplemental screening with DBT as an adjunct to mammography	Difference (supplemental DBT and mammography vs. mammography alone)
People with dense breasts (BI-RADS C and D)						
Stage I	7,880	8,227	347	146,134,244	152,509,556	6,375,312
Stage II	34,873	35,887	1,014	1,026,226,145	1,052,929,343	26,703,198
Stage III	30,372	30,298	−74	1,250,250,126	1,244,417,741	−5,832,385
Stage IV	9,560	9,469	−91	559,036,117	552,739,390	−6,296,727
People with extremely dense breasts (BI-RADS D)						
Stage I	7,880	7,996	116	146,134,244	148,321,318	2,187,074
Stage II	34,873	35,182	309	1,026,226,145	1,033,334,309	7,108,164
Stage III	30,372	30,342	−30	1,250,250,126	1,249,205,410	−1,044,717
Stage IV	9,560	9,531	−30	559,036,117	557,595,047	−1,441,070

Abbreviation: BI-RADS, Breast Imaging Reporting and Data System; DBT, digital breast tomosynthesis.

[a] In 2022 Canadian dollars.

Appendix 11: Budget Impact Analysis—Cost Component Results, Reference Case

Table A22: Budget Impact Analysis Results—Supplemental Screening With Handheld Ultrasound for People With Dense Breasts and Extremely Dense Breasts

	Budget impact, $[a,b,c]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario—mammography screening alone						
Total cost	763,779,796	786,594,360	795,938,114	809,826,759	815,871,138	3,972,010,166
Screening	79,115,921	85,251,907	85,156,645	87,907,140	87,841,291	425,272,903
Diagnostic for true-positive screen	1,292,394	1,542,423	1,650,195	1,654,505	1,763,138	7,902,655
Diagnostic for false-positive screen	18,663,409	20,431,721	20,198,935	20,808,490	20,584,325	100,686,880
Clinical detection diagnostic	2,685,450	2,696,589	2,711,469	2,763,219	2,727,092	13,583,819
Cancer management	662,022,622	676,671,720	686,220,871	696,693,405	702,955,290	3,424,563,909
New scenario—supplemental screening with ultrasound for people with dense breasts						
Total cost	764,434,392	789,069,010	799,558,846	813,613,888	820,237,675	3,986,913,811
Screening	79,647,307	86,550,360	87,020,126	90,437,993	90,972,944	434,628,732
Diagnostic for true-positive screen	1,294,679	1,566,104	1,678,733	1,682,726	1,798,417	8,020,659
Diagnostic for false-positive screen	18,670,802	20,450,408	20,223,923	20,842,592	20,627,057	100,814,782
Clinical detection diagnostic	2,685,256	2,693,375	2,703,737	2,749,635	2,711,189	13,543,192
Cancer management	662,136,348	677,808,763	687,932,326	697,900,942	704,128,068	3,429,906,446
Budget impact	654,596	2,474,651	3,620,731	3,787,129	4,366,537	14,903,644
Budget impact, cost of screening	531,387	1,298,453	1,863,481	2,530,854	3,131,653	9,355,828
New scenario—supplemental screening with ultrasound for people with extremely dense breasts						
Total cost	763,904,317	787,326,672	796,950,687	810,872,466	816,959,060	3,976,013,202
Screening	79,216,456	85,638,492	85,707,165	88,627,137	88,748,941	427,938,191
Diagnostic for true-positive screen	1,292,846	1,550,312	1,657,372	1,660,368	1,770,790	7,931,689
Diagnostic for false-positive screen	18,664,831	20,436,764	20,205,725	20,817,025	20,596,288	100,720,634
Clinical detection diagnostic	2,685,450	2,695,252	2,709,270	2,760,633	2,723,212	13,573,818
Cancer management	662,044,732	677,005,851	686,671,155	697,007,303	703,119,829	3,425,848,870
Budget impact	124,521	732,312	1,012,573	1,045,706	1,087,923	4,003,035
Budget impact, cost of screening	100,536	386,585	550,520	719,997	907,650	2,665,288

[a] In 2022 Canadian dollars.

[b] In the new scenario, the cost estimated corresponds to slow uptake of supplemental ultrasound from 2.5% to 12.5% for Year 1 to Year 5.

[c] Results may appear inexact due to rounding.

Table A23: Budget Impact Analysis Results—Supplemental Screening With MRI for People With Dense Breasts and Extremely Dense Breasts

Scenario	Budget impact, $[a,b,c]					
	Year 1	Year 2	Year 1	Year 4	Year 1	Total
Current scenario—mammography screening alone						
Total cost	763,429,716	784,878,348	794,249,919	809,498,356	815,003,627	3,967,059,966
Screening	79,115,921	85,251,907	85,158,402	87,911,529	87,839,755	425,277,513
Diagnostic for true-positive screen	1,290,669	1,513,972	1,626,916	1,639,849	1,742,447	7,813,853
Diagnostic for false-positive screen	18,419,415	20,105,820	19,908,383	20,555,012	20,305,844	99,294,473
Clinical detection diagnostic	2,685,450	2,698,313	2,722,676	2,776,152	2,739,162	13,621,754
Cancer management	661,918,262	675,308,336	684,833,542	696,615,814	702,376,419	3,421,052,373
New scenario—supplemental screening with MRI for people with dense breasts						
Total cost	765,263,392	791,346,973	804,131,000	820,093,759	826,689,599	4,007,524,723
Screening	80,696,900	89,109,235	90,686,827	95,397,246	97,087,249	452,977,457
Diagnostic for true-positive screen	1,296,273	1,568,849	1,700,373	1,695,804	1,802,368	8,063,667
Diagnostic for false-positive screen	18,424,954	20,121,037	19,929,981	20,579,583	20,339,253	99,394,808
Clinical detection diagnostic	2,685,148	2,693,571	2,710,972	2,754,598	2,712,974	13,557,264
Cancer management	662,160,116	677,854,280	689,102,847	699,666,528	704,747,756	3,433,531,527
Budget impact	1,836,696	6,475,224	9,891,107	10,608,618	11,702,366	40,464,757
Budget impact, cost of screening	1,581,494	3,858,500	5,530,146	7,488,066	9,250,414	27,699,944
New scenario—supplemental screening with MRI for people with extremely dense breasts						
Total cost	763,853,717	786,760,640	796,534,659	811,946,837	817,849,408	3,976,945,261
Screening	79,415,034	86,398,685	86,787,362	90,042,506	90,526,580	433,170,168
Diagnostic for true-positive screen	1,293,471	1,529,189	1,637,779	1,647,695	1,753,224	7,861,359
Diagnostic for false-positive screen	18,420,859	20,111,338	19,916,595	20,563,461	20,316,298	99,328,550
Clinical detection diagnostic	2,685,299	2,695,942	2,718,926	2,771,669	2,732,265	13,604,101
Cancer management	662,039,054	676,025,486	685,473,996	696,921,507	702,521,041	3,422,981,083
Budget impact	424,001	1,882,292	2,284,740	2,448,481	2,845,781	9,885,295
Budget impact, cost of screening	299,114	1,146,778	1,628,961	2,130,977	2,686,826	7,892,655

Abbreviation: MRI, magnetic resonance imaging.

[a] In 2022 Canadian dollars.

[b] In the new scenario, the cost estimated corresponds to slow uptake of supplemental MRI from 2.5% to 12.5% for Year 1 to Year 5.

[b] Results may appear inexact due to rounding.

Table A24: Budget Impact Analysis Results—Supplemental Screening With DBT for People With Dense Breasts and Extremely Dense Breasts

Scenario	Budget impact, $[a,b,c] Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario—mammography screening alone						
Total cost	763,429,716	784,878,348	794,249,919	809,498,356	815,003,627	3,967,059,966
Screening	79,115,921	85,251,907	85,158,402	87,911,529	87,839,755	425,277,513
Diagnostic for true-positive screen	1,290,669	1,513,972	1,626,916	1,639,849	1,742,447	7,813,853
Diagnostic for false-positive screen	18,419,415	20,105,820	19,908,383	20,555,012	20,305,844	99,294,473
Clinical detection diagnostic	2,685,450	2,698,313	2,722,676	2,776,152	2,739,162	13,621,754
Cancer management	661,918,262	675,308,336	684,833,542	696,615,814	702,376,419	3,421,052,373
New scenario—supplemental screening with DBT for people with dense breasts						
Total cost	765,876,802	790,480,351	801,783,400	817,395,843	824,328,777	3,999,865,172
Screening	81,453,101	89,532,944	90,630,020	94,899,228	96,133,856	452,649,150
Diagnostic for true-positive screen	1,293,514	1,538,803	1,658,127	1,668,085	1,779,951	7,938,480
Diagnostic for false-positive screen	18,419,932	20,107,631	19,911,487	20,558,245	20,309,465	99,306,759
Clinical detection diagnostic	2,685,105	2,694,045	2,712,503	2,758,693	2,718,212	13,568,559
Cancer management	662,025,149	676,606,928	686,871,264	697,511,592	703,387,292	3,426,402,225
Budget impact	2,458,460	5,619,807	7,557,500	7,927,841	9,361,792	32,805,205
Budget impact, cost of screening	2,338,660	4,283,501	5,474,867	6,991,881	8,299,103	27,371,637
New scenario—supplemental screening with DBT for people with extremely dense breasts						
Total cost	763,910,042	786,633,079	796,621,490	811,620,564	817,674,411	3,976,459,587
Screening	79,558,104	86,527,539	86,781,049	89,905,706	90,252,800	433,025,198
Diagnostic for true-positive screen	1,291,531	1,524,577	1,636,917	1,649,117	1,755,897	7,858,040
Diagnostic for false-positive screen	18,420,190	20,108,018	19,912,004	20,558,245	20,309,724	99,308,182
Clinical detection diagnostic	2,685,450	2,696,503	2,718,193	2,769,686	2,731,144	13,600,976
Cancer management	661,954,766	675,776,442	685,573,327	696,737,810	702,624,846	3,422,667,192
Budget impact	480,326	1,754,731	2,371,572	2,122,208	2,670,784	9,399,621
Budget impact, cost of screening	442,183	1,275,632	1,622,647	1,994,177	2,413,046	7,747,685

Abbreviation: DBT, digital breast tomosynthesis.

[a] In 2022 Canadian dollars.

[b] In the new scenario, the cost estimated corresponds to slow uptake of supplemental DBT from 2.5% to 12.5% for Year 1 to Year 5.

[c] Results may appear inexact due to rounding.

Appendix 12: Letter of Information

LETTER OF INFORMATION

Ontario Health

Ontario Health is conducting a review of **supplemental screening as an adjunct to mammography for breast cancer** in those with dense breasts. The purpose is to understand whether this technology should be publicly funded in Ontario.

An important part of this review involves learning more about the experiences of patients, families, and caregivers to better understand the context and impact of breast tissue density on screening for breast cancer.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 20-40 minutes of your time for a phone
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 20-40 minutes. It will be held over the telephone and with your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives on screening options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however, no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project's completion, the records will be destroyed.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experiences.

IF YOU ARE INTERESTED, PLEASE CONTACT US BEFORE JULY 15, 2022

Appendix 13: Interview Guide

Introduction
Thank you—again, if at any point you would like for me to pause or to completely stop the recording, please do not hesitate to let me know. Now before we begin, I would like to see if you have any questions regarding the project or our work at Ontario Health in general.

Description of Ontario Health: Ontario Health is a government agency, which can be viewed as an extension of the Ministry of Health and Long-Term Care. The role of the Health Technology Assessment program is to use scientific methods to analyze evidence and assess new and existing healthcare services and medical devices. Our reviews cover three (3) domains of evidence: clinical, economic impact, and preferences and values. In addition, each health technology assessment includes recommendations for the Ministry on whether these health services and/or medical devices should be publicly funded.

The aim of the Patient and Public Partnering team is to ensure that equal consideration is given to the lived experience and preferences of patients, families, and caregivers through evidence generation.

Description of Technology Under Review: For this health technology assessment, we are reviewing supplemental screening technology (examples include ultrasound or MRI) to be used in addition to mammograms for those with dense breasts. It is important to note that, currently, supplemental breast cancer screening for those with dense breasts is not publicly funded in Ontario.

Aim of Direct Engagement: the goal of today's interview is to learn from your experience as someone with dense breasts and to get a better understanding of your values, decision-making, and preferences in relation to breast cancer screening.

Journey to Findings

- I'd like to start by asking you to please describe the events that led up to you finding out you had dense breasts.

  Probes/prompts: Routine screening appointment? Family history? Following a diagnostic appointment for a suspicious finding (e.g., palpable breast tumour)?
  Probes/prompts: Barriers to access? Rural setting?
  Probes/prompts: Experience with different imaging?
  Probes/prompts: Self-advocacy? Support team? Who was coordinating your care?

Access to Information about Breast Tissue Density

- What information about breast tissue density and supplemental was available prior to learning you had dense breasts? After?

  Probes/prompts: What were your thoughts and feelings about this information (or lack of information) at the time?
  Probes/prompts: Primary source of information? Was it accessible?
  Probes/prompts: Access to informal sources of information (e.g., social media Groups, independent research, family members … etc.)?
  Probes/prompts: Understanding of breast tissue density in relation to personal risk and breast cancer screening?

Impact of Findings

- After confirming the finding, how did it impact your care plan?

  Probes/prompts: Access to supplemental screening or diagnostic testing?
  Probes/prompts: Support from the care team?
  Probes/prompts: Access to care? Barriers?

- How did the findings impact your decision-making as a patient?

  Probes/prompts: Participation in screening program?
  Probes/prompts: Advocacy? Community engagement?
  Probes/prompts: Surgical preferences? (where applicable)

Supplemental Screening for People with Dense Breasts

- Do you have any experience with supplementary imaging techniques as screening tools for breast cancer?
- Does broad access to supplemental breast cancer screening align with your preferences and values as someone with dense breasts? Why or why not?

  Probes/Prompts: Perceived impact of supplemental screening (i.e., emotional, physical, or work-life)?
  Probes/Prompts: Access? Care coordination?
  Probes/Prompts: Online access to test results? Patient education?

- Do you have any concerns with publicly funding supplemental screening for those with dense breasts in Ontario? Why or why not?

  Probes/Prompts: Perceived barriers (i.e., access, equity, or false-positives)?

Conclusion

- Thank you—those are all the questions that I have today but is there anything else you would like to add?
- Lastly, do you have any questions for me?

Appendix 14: Online Survey

Introduction
Thank you for participating in Ontario Health's Health Technology Assessment (HTA) on "Supplemental Screening as an Adjunct to Mammography for Breast Cancer Screening in People with Dense Breasts"

What is a Health Technology Assessment?
An HTA is a review of scientific evidence about health care services and interventions. This includes speaking with patients and family members to find out about the perceived benefits and disadvantages of health interventions and technologies.

Our review will conclude a recommendation about public funding of the intervention in Ontario.

What is this survey about?
We would like to know your views on a potential supplemental screening program for breast cancer in people with dense breasts.

Supplemental screening refers to additional breast imaging that happens with a screening mammogram.

In Ontario, there is currently no standardized funding or access to supplementary screening for people with dense breasts.

The last day to participate in this assessment is June 30th, 2022.

Important note
Your participation in this HTA is completely voluntary. You are under no obligation to participate, and you can withdraw from the HTA at any time and/or refuse to answer any questions without any negative consequences.

If you choose to participate, please note that all information collected from participants will be kept confidential and your privacy will be protected, except as required by law. The overall findings from this survey will be published, however, we will not use your name or any personally identifiable information (e.g., names of clinics or doctors) in any presentations or publications related to this HTA.

If you have any questions about the survey or would like to submit your feedback in another format, please contact:

Thank you for your time and input! Your experience is valued and appreciated.

Survey Questions

Care Journey
So far, we've heard many different stories about how individuals found out that they have dense breasts. Each story is unique. Some people were told by a technologist after a routine mammogram, or by their family doctor. Others did not find out until after breast cancer was discovered.

Can you share a little bit about how you found out you had dense breasts in the text box below?

Access to information about breast density
We would like to know more about how accessible information surrounding dense breasts is and if it can be improved. For example:

- When did you become aware that dense breasts were a risk factor for breast cancer?
- When finding out more information about dense breasts, where did you seek it out (from family doctor? from family? did you do your own research?) and why?
- How did this information (or lack of information) impact you?

Please share your experiences and thoughts in the text box below.

Preferences and experiences with supplemental screening
One of the aspects of a supplemental screening program that is being considered is the different types of imaging possible. Supplemental screening could be done through an ultrasound, MRI, contrast-enhanced mammography and/or tomosynthesis. We would like to know the following:

- Do you have any experience with these imaging techniques as screening tools?
- Given the potential types of supplemental imaging possible—everything from ultrasound to MRI—how would a particular type of imaging impact the likelihood of your participation in supplemental screening?

Please share your experiences and thoughts in the text box below.

Additional Comments
Please share any additional thoughts you may have about supplemental screening for breast cancer in people with dense breasts by using the text box below.

Appendix 15: Eligibility Criteria for the Qualitative Rapid Review

Table A25: SPIDER Criteria for the Qualitative Rapid Review

Sample	Phenomenon of interest	Design	Evaluation	Research type
People who have or may have dense breasts, their family members, and their health care providers This review focused on people being screened for female breast cancers	Supplemental screening modalities (i.e., ultrasound, MRI, contrast-enhanced spectral mammography, and digital breast tomosynthesis)	Any qualitative design	Experiences, understandings, views, perspectives, perceptions of, and meanings regarding breast density and supplemental screening for dense breasts	Primary qualitative studies Mixed-methods studies with a qualitative component (excluding surveys)

Abbreviation: MRI, magnetic resonance imaging; SPIDER, Sample, Phenomenon of Interest, Design, Evaluation, and Research Type.
Source: Cooke et al.[179]

Appendix 16: Characteristics of Studies Included in the Qualitative Rapid Review

Table A26: Characteristics of the Included Studies—Qualitative Rapid Review

Author, year	Aims/objectives	Methodology/design Data collection method Data analysis method	Setting	Inclusion criteria and sample size	Participant characteristics[a]
Cicvara et al, 2020[187]	To describe radiographers' thoughts and reflections on breast density in connection with mammography examination	NR Semistructured interviews (mode of delivery NR) Manifest content analysis	Stockholm, Sweden Participants were recruited from 3 breast cancer centres and 2 breast cancer organizations	Radiographers with at least 1 y of experience in mammography (N = NR)	NR
Gunn et al, 2018[188]	To understand how breast density notifications affect women's perceptions about breast density and their participation in follow-up care	NR Semistructured telephone interviews Manifest content analysis	Massachusetts, United States Participants had received a routine mammogram at an urban safety-net hospital	English-speaking women (N = 30 interviewed; N = 29 included in the analytical sample) aged 40–75 y who recalled receiving a breast density notification after obtaining a routine mammogram with a normal result	Mean age (± SD): 55.3 ± 7.0 y Race/ethnicity: African American, 53.3% (n = 16); Other/refused, 20% (n = 6); White, non-Hispanic, 13.3% (n = 4); White, Hispanic, 13.3% (n = 4) Health literacy/education: NR Other relevant characteristics: commercial/private health insurance, 50% (n = 15); public health insurance, 46.7% (n = 14); unknown insurance coverage, 3.3% (n = 1)
Gunn et al, 2019[189]	To understand Spanish-speaking women's experiences receiving breast density notification in a Massachusetts safety-net hospital	NR Semistructured telephone interviews Content analysis	Massachusetts, United States Participants had received a routine mammogram at an urban safety-net hospital	Spanish-speaking women (N = 19) aged 40–74 y who recalled receiving a breast density notification after obtaining a routine mammogram with a normal result	Mean age (± SD): 48.3 ± 7.7 y Race/ethnicity: Hispanic, 100% Health literacy/education: NR Other relevant characteristics: public health insurance, 94.7% (n = 18)

Author, year	Aims/objectives	Methodology/design Data collection method Data analysis method	Setting	Inclusion criteria and sample size	Participant characteristics[a]
Klinger et al, 2016[195]	To understand varied perspectives on breast density notification and inform best practices around its implementation	NR Focus groups with patients (mode of delivery NR); semistructured interviews with primary care physicians and breast radiologists (mode of delivery NR) Content analysis (referenced in the abstract, but not the full text)	Massachusetts, United States Participants were patients at Brigham and Women's Hospital or physicians recruited from practices affiliated with the hospital	*Patients* Women (n = 16) who had undergone breast imaging in the previous 6 mo, did not have a history of breast cancer, and did not have a known breast cancer susceptibility gene mutation *Physicians* Primary care physicians (n = 7) and breast radiologists (n = 7)	*Patients* Age: mean 57 y (range 47–70 y) Race/ethnicity: Black or mixed race, 31.3% (n = 5) Health literacy/education: completed some graduate education, 62.5% (n = 10) Other relevant characteristics: 3 participants self-reported being at "high risk" for breast cancer (risk factors not specified) *Physicians* 86% female Age: NR Race/ethnicity: NR Average years of practice: primary care physicians, 23 y; radiologists, 19 y
Kressin et al, 2022[183]	To assess women's knowledge about and perceptions around the meaning of breast density after receiving a breast density notification	Sequential mixed-methods design Semistructured telephone interviews Content analysis	Various states, United States Recruitment prioritized women living in states without breast density notification laws (proportion of participants from each state NR)	Women (N = 61) aged 40–76 y who had had a mammogram within the previous 2 y, had no personal history of breast cancer, and had heard of the term "dense breasts" or "breast density"	Age: NR for qualitative sample Race/ethnicity (self-reported) and health literacy/education: at least six participants each from eight demographic groups defined by health literacy (high or low) and race/ethnicity (i.e., non-Hispanic Black, Hispanic, Asian/Other, non-Hispanic White)

Author, year	Aims/objectives	Methodology/design Data collection method Data analysis method	Setting	Inclusion criteria and sample size	Participant characteristics[a]
Marcus et al, 2022[192]	To explore women's beliefs about breast density and their preferences for how information about breast density is conveyed	NR Five semistructured focus groups: four conducted in English, one in Spanish (mode of delivery NR) Constant comparative method	Miami, United States Participants had received a mammogram from an academic breast imaging centre serving a largely Latin American and Caribbean population	Women (N = 25) aged 40–69 y who had undergone mammography screening and were identified as having dense breasts	Age: mean 51 y (range 42–65 y) Race/ethnicity: Hispanic/Latina, 36% (n = 9); Black, 32% (n = 8); White 16% (n = 4); Asian, 12% (n = 3); Other 4% (n = 1) Health literacy/education: college degree or greater, 60% (n = 15); high school diploma, 36% (n = 9); less than a high school diploma, 4% (n = 1); 96% (n = 24) felt extremely/quite a bit comfortable filling out medical forms without help (a measure of health literacy); 4% (n = 1) felt not at all comfortable filling out medical forms without help Other relevant characteristics: 100% of participants reported having health insurance (type NR) and a regular primary care physician; 56% (n = 14) reported a household income of > $50,000 USD; 92% (n = 23) received their mammogram for "a checkup"; 8% (n = 2) for "other," unspecified reasons; none for a problem (i.e., a lump, pain, or discharge)

Author, year	Aims/objectives	Methodology/design Data collection method Data analysis method	Setting	Inclusion criteria and sample size	Participant characteristics[a]
Nickel et al, 2021[190]	To understand general practitioners' awareness and knowledge of mammographic breast density and their perspectives around information and potential breast density notification for women	NR Semistructured telephone interviews Framework analysis	Australia Participants working in a variety of states and practice contexts, including urban (n = 24) and rural (n = 6) settings	General practitioners (N = 30) currently practising in public and private settings throughout Australia	76.7% female Age: NR Race/ethnicity: NR Years of practice: less than 10 y, 56.7% (n = 17); 10–19 y, 16.7% (n = 5); 20–29 y, 10% (n = 3); 30 y or more, 16.7% (n = 5) Other relevant characteristics: special interest in women's health or breast health, 36.7% (n = 11)
Nickel et al, 2022[193]	To explore Australian women's current knowledge, perspectives, and attitudes about breast density and information needs to inform effective evidence-based communication strategies	NR 14 online focus groups Thematic analysis	New South Wales and Queensland, Australia Participants were recruited using digit dialling and social media advertising; they lived in urban (n = 47), regional (n = 30), and remote (n = 1) areas	Women (N = 78) aged 40–74 y without a personal diagnosis of breast cancer	Age: 40–49 y, 29.5% (n = 23); 50–59 y, 29.5% (n = 23); 60–69 y, 27% (n = 21); 70–75 y, 14% (n = 11) Race/ethnicity: Aboriginal or Torres Strait Islander, 2.6% (n = 2) Health literacy/education: university degree, 47.4% (n = 37); diploma or certificate, 34.6% (n = 27); high school or leaving certificate (or equivalent), 10.3% (n = 8); school or intermediate certificate (or equivalent), 7.7% (n = 6)

Author, year	Aims/objectives	Methodology/design Data collection method Data analysis method	Setting	Inclusion criteria and sample size	Participant characteristics[a]
Pacsi-Sepulveda et al, 2019[191]	To gain greater insight into Hispanic women's understanding of and reactions to breast density notification information, and any proposed or taken actions in response	NR Semistructured telephone interviews conducted in participants' preferred language Inductive content analysis	New York City, United States Participants were enrolled in an ongoing observational study at a large screening mammography clinic	Women (N = 24) self-identifying as Hispanic with history of dense breasts on mammography	Mean age (± SD): 49.4 ± 5.5 y Race/ethnicity (self-reported): Hispanic, 100% Health literacy/education: adequate health literacy,[b] 50% (n = 12); low health literacy, 29.2% (n = 7); marginal health literacy, 20.8% (n= 5); Bachelor's degree or higher, 29.2% (n = 7); some college, 33.3% (n= 8); high school diploma, 12.5% (n = 3); less than a high school diploma, 25% (n = 6) Other relevant characteristics: history of breast cancer in first-degree relatives, 12.5% (n = 3); personal history of breast biopsy, 33.3% (n = 8)
Schifferdecker et al,2020[194]	To explore women's knowledge and perceptions of breast density and experiences of breast cancer screening across three states with and without breast density notification laws	NR Focus groups (mode of delivery NR) Mixed deductive (directed content analysis) and inductive (grounded theory) analytical approach	Washington, California, and North Carolina, United States Participants were recruited based on their results in the Breast Cancer Surveillance Consortium registries in the above states	Women (N =47) aged 40–80 y with no personal history of breast cancer and who had a normal mammogram with heterogeneously or extremely dense breasts in the previous 12 mo	Demographic information NR for 4 participants Age: mean 58 y (range 40–80 y) Race/ethnicity (self-reported): White, 69.8% (n = 30); Black or African American, 18.6% (n = 8); Asian, 7.0% (n = 3); Hispanic or Latino, 4.7% (n = 2) Health literacy/education: more than a 4 y college degree, 32.6% (n = 14); 4 y college degree, 16.3% (n = 7); some college or a 2 y degree, 46.5% (n = 20); high school diploma or GED, 2.3% (n = 1); some high school, but did not graduate, 2.3% (n = 1)

Abbreviations: GED, General Educational Development; NR, not reported; SD, standard deviation.

[a] The language used to report race or ethnicity in this table reflects that used by the original study authors.

[b] As assessed using three questions developed by Chew et al.[292]

Appendix 17: Critical Appraisal of Qualitative Evidence

Table A27: Appraisal of Included Citations Guided by the Optimized CASP Tool[a]

Author, year	Strengths	Limitations
Cicvara et al,2020[187]	• The authors clearly stated the study's aim and supported its relevance via the background section • They appropriately justified the use of a qualitative methodology • They described the methods used for data analysis, which were appropriate for the analytical approach cited (i.e., manifest content analysis) • They clearly reported the recruitment strategy, which was appropriate for obtaining access to experiential experts • They supported their findings through direct quotations and discussed them in relation to the research aim	• The authors did not report the ontological or epistemological assumptions underpinning their study • Although the authors listed relevant ethical considerations, important information was missing (e.g., how they upheld confidentiality and whether involving "heads of operations" in the recruitment strategy affected free and informed consent) • They did not report who conducted the interviews and how • They did not report the number and demographic characteristics of their participants • They reported analyzing interviews with "representatives of breast cancer organizations" separately; however, it is unclear if they included findings from these interviews in their results • They did not describe reflexive practices or report the relationship between the researchers and participants • It is unclear if statements in the results section were grounded in participants' reflections or the authors' reporting of general information about breast density and mammography in Sweden • They did not report strategies to improve the credibility or rigour of their research • They did not discuss their study's limitations or areas for future research

Author, year	Strengths	Limitations
Gunn et al, 2018[188]	• The authors clearly stated the study's aim and supported its relevance via the introduction section • They appropriately justified the use of a qualitative methodology • They clearly reported the recruitment strategy, which was appropriate for obtaining access to experiential experts • They provided a statement of ethical approval and clearly described procedures for obtaining informed consent • They clearly described the methods used for data collection, which were guided by an appropriate theoretical framework (i.e., Health Belief Model) • They described the methods used for data analysis, which were appropriate for the analytical approach cited (i.e., manifest content analysis) • They reported strategies to improve the credibility or rigour of their research, and these strategies aligned with the cited analytical method • They clearly reported their setting and the number and demographic characteristics of their participants (enhancing the transferability of their findings) • They explicitly reported their findings, which were supported with participant quotations, and they discussed their findings in relation to the research aim • They discussed their study's limitations and areas for future research	• The authors did not report the ontological or epistemological assumptions underpinning their study • They did not describe reflexive practices or report the relationship between the researchers and participants

Author, year	Strengths	Limitations
Gunn et al, 2019[189]	• The authors clearly stated the study's aim and supported its relevance via the introduction section • A qualitative methodology was appropriate, given the study's aims • The authors clearly reported the recruitment strategy, which was appropriate for obtaining access to experiential experts (they recruited until they obtained theoretical saturation) • They provided a statement of ethical approval and clearly described procedures for obtaining informed consent • They clearly described the methods used for data collection, which were guided by an appropriate theoretical framework (i.e., Health Belief Model) • They described the methods used for data analysis, which were appropriate for the analytical approach cited (i.e., content analysis) • They reported strategies to improve the credibility or rigour of their research, and these strategies aligned with the cited analytical method • They clearly reported their setting and the number and demographic characteristics of their participants (enhancing the transferability of their findings) • They explicitly reported their findings, which were supported with participant quotations, and they discussed their findings in relation to the research aim • They discussed their study's limitations and areas for future research	• The authors did not report the ontological or epistemological assumptions underpinning their study • They did not describe reflexive practices or report the relationship between the researchers and participants

Author, year	Strengths	Limitations
Klinger et al, 2016[195]	• The authors clearly stated the study's aim (in the abstract, not the full text) and supported its relevance via the introduction section • A qualitative methodology was appropriate, given the study's aim • The reported recruitment strategy was appropriate for obtaining access to experiential experts • The authors provided a statement of ethical approval • They clearly described the methods used for data collection (although additional justification for the chosen methods is required) • They reported strategies to improve the credibility or rigour of their research, and these strategies aligned with the cited analytical method • They clearly reported the number and demographic characteristics of their participants (enhancing the transferability of their findings) • They explicitly reported their findings, which were supported via participant quotations, and discussed their findings in relation to the research aim • They discussed their study's limitations and areas for future research	• The authors did not report the ontological or epistemological assumptions underpinning their study • More information was required on the convenience sampling procedure used for recruitment • The authors did not justify why they used focus groups for women and interviews for primary care providers and radiologists • More information about the process for data analysis was required. The authors reported using content analysis in their abstract, but not in the full text. They broadly described using "both inductive and deductive coding schemes," but did not cite a particular method used • The authors did not describe reflexive practices or report the relationship between the researchers and participants
Kressin et al, 2022[183]	• The authors clearly stated the study's aim and supported its relevance via the introduction section • They appropriately justified the use of a sequential mixed-methods study design • The authors clearly reported the recruitment strategy, which was appropriate for obtaining access to experiential experts • The authors reported how they upheld ethical standards (e.g., confidentiality, free and informed consent) • They clearly described the methods used for the collection of qualitative data • They described the methods used for data analysis, which were appropriate for the analytical approach cited (i.e., content analysis) • They reported strategies to improve the credibility or rigour of their research	• The authors did not report the ontological or epistemological assumptions underpinning their study • They did not describe reflexive practices or report the relationship between the researchers and participants

Author, year	Strengths	Limitations
Marcus et al, 2022[192]	• The authors clearly stated the study's aim and supported its relevance via the introduction section • They appropriately justified the use of a qualitative methodology • The authors clearly reported the recruitment strategy, which was appropriate for obtaining access to experiential experts • They provided a statement of ethical approval and clearly described procedures for obtaining informed consent • They clearly described and justified the structure of the focus groups and methods used for data collection • They clearly reported the number and demographic characteristics of their participants (enhancing the transferability of their findings) • They explicitly reported their findings, which were supported via participant quotations, and discussed their findings in relation to the research aim • They discussed their study's limitations and areas for future research	• The authors did not report the ontological or epistemological assumptions underpinning their study • More information was needed about the methods of data analysis used to appraise whether the methods were congruent with the general constant comparative method cited • More information was needed about strategies employed to improve the credibility or rigour of the research • They authors did not describe reflexive practices or report the relationship between the researchers and participants

Author, year	Strengths	Limitations
Nickel et al, 2021[190]	• The authors clearly stated the study's aim and supported its relevance via the introduction section • A qualitative methodology was appropriate, given the study's aim • The authors clearly reported the recruitment strategy, which was appropriate for obtaining access to experiential experts (they recruited until obtaining theoretical saturation) • They provided a statement of ethical approval and clearly described procedures for obtaining informed consent • They clearly described and justified the methods used for data collection • They described the methods used for data analysis, which were appropriate for the analytical approach cited (i.e., framework analysis) • They reported strategies to improve the credibility or rigour of their research, and these strategies aligned with the cited analytical method • They clearly reported the number and demographic characteristics of their participants (enhancing the transferability of their findings) • They explicitly reported their findings, which were supported via participant quotations, and discussed their findings in relation to the research aim • They discussed their study's limitations and areas for future research	• The authors did not report the ontological or epistemological assumptions underpinning their study • They did not describe reflexive practices or report the relationship between the researchers and participants

Author, year	Strengths	Limitations
Nickel et al, 2022[193]	• The authors clearly stated the study's aim and supported its relevance via the introduction section • A qualitative methodology was appropriate, given the study's aim • The authors clearly reported the recruitment strategy, which was appropriate for obtaining access to experiential experts (they recruited until obtaining theoretical saturation) • They provided a statement of ethical approval and clearly described procedures for obtaining informed consent • They clearly described and justified the structure of the focus groups and methods used for data collection • They described the methods used for data analysis, which were appropriate for the analytical approach cited (i.e., thematic analysis) • They reported strategies to improve the credibility or rigour of their research, and these strategies aligned with the cited analytical method • They clearly reported the number and demographic characteristics of their participants (enhancing the transferability of their findings) • They explicitly reported their findings, which were supported via participant quotations, and discussed their findings in relation to the research aim • They discussed their study's limitations and areas for future research	• The authors did not report the ontological or epistemological assumptions underpinning their study • They did not describe reflexive practices or report the relationship between the researchers and participants

Author, year	Strengths	Limitations
Pacsi-Sepulveda et al, 2019[191]	• The authors clearly stated the study's aim and supported its relevance via the introduction section • A qualitative methodology was appropriate, given the study's aim • The authors clearly reported the recruitment strategy, which was appropriate for obtaining access to experiential experts (they recruited until obtaining theoretical saturation) • They provided a statement of ethical approval and clearly described procedures for obtaining informed consent • They clearly described and justified the methods used for data collection • They reported strategies to improve the credibility or rigour of their research • They clearly reported the number and demographic characteristics of their participants (enhancing the transferability of their findings) • They explicitly reported their findings, which were supported through participant quotations and discussed them in relation to the research aim • They discussed their study's limitations and areas for future research	• The authors did not report the ontological or epistemological assumptions underpinning their study • Additional information is required on the methods used for data analysis to appraise whether they aligned with the "inductive [conventional] content analysis" approach cited by the authors • The authors did not describe reflexive practices or report the relationship between the researchers and participants
Schifferdecker et al, 2020[194]	• The authors clearly stated the study's aim and supported its relevance via the introduction section • A qualitative methodology was appropriate, given the study's aim • The authors provided a statement of ethical approval and clearly described procedures for obtaining informed consent • They clearly described and justified the structure of the focus groups and methods used for data collection • They reported strategies to improve the credibility or rigour of their research • They clearly reported the number and demographic characteristics of their participants (enhancing the transferability of their findings) • They explicitly reported their findings, which were supported via participant quotations, and discussed their findings in relation to the research aim • They discussed their study's limitations and areas for future research	• The authors did not report the ontological or epistemological assumptions underpinning their study • More information was required about the sampling approach (e.g., Did they send a recruitment letter to all eligible women? How did they purposefully select participants from those who responded?) • More information was required about the methods used for data analysis to appraise whether they aligned with the analytical approaches cited (i.e., directed content analysis and grounded theory) • The authors did not describe reflexive practices or report the relationship between the researchers and participants

Abbreviation: CASP, Critical Appraisal Skills Programme.

[a] As presented by Long et al.[181]

References

(1) Breast cancer statistics [Internet]. Toronto (ON): Canadian Cancer Society; c2021 [cited 2021 Jul 12]. Available from: www.cancer.ca/en/cancer-information/cancer-type/breast/statistics/?region=on

(2) Canadian Partnership Against Cancer. Breast cancer control in Canada: a system performance special focus report. Toronto (ON): Canadian Partnership Against Cancer; 2012.

(3) SEER cancer statistics review, 1975–2017 [Internet]. Bethesda (MD): National Cancer Institute; 2020 [cited 2022 Dec 19]. Available from: https://seer.cancer.gov/csr/1975_2017

(4) Types of cancer: breast cancer [Internet]. Toronto (ON): Cancer Care Ontario; [cited 2021 May 22]. Available from: www.cancercareontario.ca/en/types-of-cancer/breast-cancer

(5) PDQ Screening and Prevention Editorial Board. PDQ breast cancer screening [Internet]. Bethesda (MD): National Cancer Institute; 2021 [cited 2021 May 26]. Available from: www.cancer.gov/types/breast/hp/breast-screening-pdq

(6) PDQ Screening and Prevention Editorial Board. PDQ breast cancer prevention [Internet]. Bethesda (MD): National Cancer Institute; 2021 [cited 2021 May 25]. Available from: www.cancer.gov/types/breast/hp/breast-prevention-pdq

(7) Antoni S, Sasco AJ, dos Santos Silva I, McCormack V. Is mammographic density differentially associated with breast cancer according to receptor status? A meta-analysis. Breast Cancer Res Treat. 2013;137(2):337-47.

(8) McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(6):1159-69.

(9) Boyd N, Berman H, Zhu J, Martin LJ, Yaffe MJ, Chavez S, et al. The origins of breast cancer associated with mammographic density: a testable biological hypothesis. Breast Cancer Res. 2018;20(1):17.

(10) ACR BI-RADS Atlas: Mammography. Reston (VA): American College of Radiology; 2013.

(11) Rao AA, Feneis J, Lalonde C, Ojeda-Fournier H. A pictorial review of changes in the BI-RADS fifth edition. Radiographics. 2016;36(3):623-39.

(12) Seely JM, Peddle SE, Yang H, Chiarelli AM, McCallum M, Narasimhan G, et al. Breast density and risk of interval cancers: the effect of annual versus biennial screening mammography policies in Canada. Can Assoc Radiol J. 2021:8465371211027958.

(13) Kerlikowske K, Zhu W, Tosteson AN, Sprague BL, Tice JA, Lehman CD, et al. Identifying women with dense breasts at high risk for interval cancer: a cohort study. Ann Intern Med. 2015;162(10):673-81.

(14) Sindi R, Sa Dos Reis C, Bennett C, Stevenson G, Sun Z. Quantitative measurements of breast density using magnetic resonance imaging: a systematic review and meta-analysis. J Clin Med. 2019;8(5):745.

(15) van der Waal D, Ripping TM, Verbeek AL, Broeders MJ. Breast cancer screening effect across breast density strata: a case-control study. Int J Cancer. 2017;140(1):41-9.

(16) Moody-Ayers SY, Wells CK, Feinstein AR. "Benign" tumors and "early detection" in mammography-screened patients of a natural cohort with breast cancer. Arch Intern Med. 2000;160(8):1109-15.

(17) Brenner DR, Weir HK, Demers AA, Ellison LF, Louzado C, Shaw A, et al. Projected estimates of cancer in Canada in 2020. CMAJ. 2020;192(9):E199-E205.

(18) Duffy SW, Tabar L, Yen AM, Dean PB, Smith RA, Jonsson H, et al. Beneficial effect of consecutive screening mammography examinations on mortality from breast cancer: a prospective study. Radiology. 2021;299(3):541-7.

(19) Tabar L, Chen TH, Yen AM, Dean PB, Smith RA, Jonsson H, et al. Early detection of breast cancer rectifies inequality of breast cancer outcomes. J Med Screen. 2021;28(1):34-8.
(20) Medical Advisory Secretariat. Scintimammography as an adjunctive breast imaging technology: an evidence-based analysis. Ont Health Technol Assess Ser. 2007;7(2):1-47.
(21) Hadadi I, Rae W, Clarke J, McEntee M, Ekpo E. Diagnostic performance of adjunctive imaging modalities compared to mammography alone in women with non-dense and dense breasts: a systematic review and meta-analysis. Clin Breast Cancer. 2021;21(4):278-91.
(22) Sorin V, Yagil Y, Yosepovich A, Shalmon A, Gotlieb M, Neiman OH, et al. Contrast-enhanced spectral mammography in women with intermediate breast cancer risk and dense breasts. Am J Roentgenol. 2018;211(5):W267-74.
(23) Wanders JO, Holland K, Veldhuis WB, Mann RM, Pijnappel RM, Peeters PH, et al. Volumetric breast density affects performance of digital screening mammography. Breast Cancer Res Treat. 2017;162(1):95-103.
(24) Health Quality Ontario. Magnetic resonance imaging as an adjunct to mammography for breast cancer screening in women at less than high risk for breast cancer: a health technology assessment. Ont Health Technol Assess Ser. 2016;16(20):1-30.
(25) Health Quality Ontario. Ultrasound as an adjunct to mammography for breast cancer screening: a health technology assessment. Ont Health Technol Assess Ser. 2016;16(15):1-71.
(26) Wengert GJ, Helbich TH, Kapetas P, Baltzer PA, Pinker K. Density and tailored breast cancer screening: practice and prediction—an overview. Acta Radiol Open. 2018;7(9):2058460118791212.
(27) Patterson SK, Helvie MA, Aziz K, Nees AV. Outcome of men presenting with clinical breast problems: the role of mammography and ultrasound. Breast J. 2006;12(5):418-23.
(28) Coldman AJ, Phillips N. Breast cancer survival and prognosis by screening history. Br J Cancer. 2014;110(3):556-9.
(29) Canadian Partnership Against Cancer. Breast screening in Canada: 2019/2020 environmental scan. Toronto (ON): Canadian Partnership Against Cancer; 2020.
(30) Popli MB, Popli V, Bahl P, Solanki Y. Pictorial essay: mammography of the male breast. Indian J Radiol Imaging. 2009;19(4):278-81.
(31) Overarching policy for the screening of trans people in the Ontario Breast Screening Program and the Ontario Cervical Screening Program. Toronto (ON): Cancer Care Ontario; 2022.
(32) Braun H, Nash R, Tangpricha V, Brockman J, Ward K, Goodman M. Cancer in transgender people: evidence and methodological considerations. Epidemiol Rev. 2017;39(1):93-107.
(33) Meggetto O, Peirson L, Yakubu M, Farid-Kapadia M, Costa-Fagbemi M, Baidoobonso S, et al. Breast cancer risk and breast screening for trans people: an integration of 3 systematic reviews. CMAJ Open. 2019;7(3):E598-E609.
(34) Public Health England. NHS population screening: information for trans and non-binary people [Internet]. London, UK: NHS; 2019 [updated 20 May 2019; cited 2021 Jul 18]. Available from: www.gov.uk/government/publications/nhs-population-screening-information-for-transgender-people/nhs-population-screening-information-for-trans-people
(35) Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. JAMA. 2005;293(10):1245-56.
(36) Philadelpho F, Calas MJG, Carneiro GAC, Silveira IC, Vaz ABR, Nogueira AMC, et al. Comparison of automated breast ultrasound and hand-held breast ultrasound in the screening of dense breasts. Rev Bras Ginecol Obstet. 2021;43(3):190-9.
(37) Zanotel M, Bednarova I, Londero V, Linda A, Lorenzon M, Girometti R, et al. Automated breast ultrasound: basic principles and emerging clinical applications. Radiol Med. 2018;123(1):1-12.

(38) Lee SH, Yi A, Jang MJ, Chang JM, Cho N, Moon WK. Supplemental screening breast US in women with negative mammographic findings: effect of routine axillary scanning. Radiology. 2018;286(3):830-7.
(39) Sprague BL, Stout NK, Schechter C, van Ravesteyn NT, Cevik M, Alagoz O, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. Ann Intern Med. 2015;162(3):157-66.
(40) Mann RM, Kuhl CK, Moy L. Contrast-enhanced MRI for breast cancer screening. J Magn Reson Imaging. 2019;50(2):377-90.
(41) Chen SQ, Huang M, Shen YY, Liu CL, Xu CX. Application of abbreviated protocol of magnetic resonance imaging for breast cancer screening in dense breast tissue. Acad Radiol. 2017;24(3):316-20.
(42) Kuhl CK. Abbreviated breast MRI for screening women with dense breasts: the EA1141 trial. Br J Radiol. 2018;91(1090):20170441.
(43) Canadian Association of Radiologists. Gadolinium-based contrast agents in kidney disease: a comprehensive review and clinical practice guideline issues by the Canadian Association of Radiology and supported by the Canadian Society of Nephrology. Ottawa (ON): The Association; 2017.
(44) Weinreb JC, Rodby RA, Yee J, Wang CL, Fine D, McDonald RJ, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. Radiology. 2021;298(1):28-35.
(45) Cozzi A, Schiaffino S, Sardanelli F. The emerging role of contrast-enhanced mammography. Quant Imaging Med Surg. 2019;9(12):2012-8.
(46) Ghaderi KF, Phillips J, Perry H, Lotfi P, Mehta TS. Contrast-enhanced mammography: current applications and future directions. Radiographics. 2019;39(7):1907-20.
(47) Lalji UC, Houben IP, Prevos R, Gommers S, van Goethem M, Vanwetswinkel S, et al. Contrast-enhanced spectral mammography in recalls from the Dutch breast cancer screening program: validation of results in a large multireader, multicase study. Eur Radiol. 2016;26(12):4371-9.
(48) Roh S, Laroia A. Practicing safe use of nonionic, low-osmolarity iodinated contrast. Appl Radiol. 2015;44(7):16-9.
(49) Tomosynthèse et cancer du sein: évaluation diagnostique et autres utilisations [English summary] [Internet]. Quebec (QC): Institut national d'excellence en santé et en services sociaux; 2020 [cited 2022 Dec 19]. Available from: www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/Tomosynthese_cancer_du_sein_SUMMARY.pdf
(50) Medical Devices Active Licence Listing database [Internet]. Ottawa (ON): Health Canada. 2022 Jan 6 [cited 2023 Feb 10]. Available from: www.health-products.canada.ca/mdall-limh
(51) Guidelines and advice: breast density information for healthcare providers [Internet]. Toronto (ON): Cancer Care Ontario; [cited 2021 Aug 11]. Available from: www.cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/breast-density-provider-information
(52) Breast density information for Ontario Breast Screening Program participants [Internet]. Toronto (ON): Cancer Care Ontario; 2021 [cited 2021 Aug 11]. Available from: www.cancercareontario.ca/en/types-of-cancer/breast-cancer/screening/breast-density
(53) Breast cancer screening and diagnosis pathway map (version 2021.03). Toronto (ON): Cancer Care Ontario; 2021.
(54) Ministry of Health and Long-Term Care. Schedule of benefits: physician services under the Health Insurance Act. Toronto (ON): Queen's Printer for Ontario; 2021.

(55) Breast cancer screening in Canada: environmental scan [Internet]. Toronto (ON): Canadian Partnership Against Cancer; 2018 [cited 2022 Dec 19]. Available from: www.partnershipagainstcancer.ca/wp-content/uploads/2019/04/Breast-Cancer-Screening-Environmental-Scan_EN_2018_final.pdf
(56) Supplemental screening with MRI reduces interval cancers in women with extremely dense breasts [Internet]. Ottawa (ON): Canadian Association of Radiologists; 2020 [cited 2022 Dec 19]. Available from: https://car.ca/news/supplemental-screening-with-mri-reduces-interval-cancers-in-women-with-extremely-dense-breasts/
(57) Breast density and screening mammograms: information about BC's recent announcement to report breast density results [Internet]. Vancouver (BC): BC Cancer Breast Screening; 2019 [cited 2022 Dec 19]. Available from: www.bccancer.bc.ca/screening/Documents/Breast_20191104_BDProviderGuidance_V07_OPT.pdf
(58) Nyante SJ, Marsh MW, Benefield T, Earnhardt K, Lee SS, Henderson LM. Supplemental breast imaging utilization after breast density legislation in North Carolina. J Am Coll Radiol. 2020;17(1 Pt A):6-14.
(59) Klarenbach S, Sims-Jones N, Lewin G, Singh H, Theriault G, Tonelli M, et al. Recommendations on screening for breast cancer in women aged 40-74 years who are not at increased risk for breast cancer. CMAJ. 2018;190(49):E1441-51.
(60) Canadian Association of Radiologists, Canadian Society of Breast Imaging. CAR/CSBI position statement on mammographic breast density and supplemental screening. [Internet]. Vancouver (BC): The Society; 2019 [cited 2022 Dec 19]. Available from: https://csbi.ca/wp-content/uploads/2019/07/CAR-CSBI-Breast-Density-Position-Statement-En.pdf
(61) Ren W, Chen M, Qiao Y, Zhao F. Global guidelines for breast cancer screening: a systematic review. Breast. 2022;64:85-99.
(62) Expert Panel on Breast Imaging, Weinstein SP, Slanetz PJ, Lewin AA, Battaglia T, Chagpar AB, et al. ACR appropriateness criteria: supplemental breast cancer screening based on breast density. J Am Coll Radiol. 2021;18(11S):S456-73.
(63) Mann RM, Athanasiou A, Baltzer PAT, Camps-Herrero J, Clauser P, Fallenberg EM, et al. Breast cancer screening in women with extremely dense breasts: recommendations of the European Society of Breast Imaging (EUSOBI). Eur Radiol. 2022;32(6):4036-45.
(64) Recommended screening for women with dense breasts [Internet]. Camberwell, Australia: Breast Cancer Network Australia; c2021 [cited 2021 Jul 17]. Available from: www.bcna.org.au/breast-health-awareness/mammographic-density-and-screening/recommended-screening-for-women-with-dense-breasts/
(65) Urban L, Chala LF, Bauab SDP, Schaefer MB, Dos Santos RP, Maranhao NMA, et al. Breast cancer screening: updated recommendations of the Brazilian College of Radiology and Diagnostic Imaging, Brazilian Breast Disease Society, and Brazilian Federation of Gynecological and Obstetrical Associations. Radiol Bras. 2017;50(4):244-9.
(66) European breast cancer guidelines: tests for women with high breast density [Internet]. Brussels, Belgium: European Commission Initiative on Breast Cancer; c2021 [updated 2021 Jun 30; cited 2021 Sep 2]. Available from: https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/dense-breast
(67) Adult screening programme: breast cancer [Internet]. London, UK: UK National Screening Committee; 2019 [updated 2019 Dec; cited 2021 Aug 31]. Available from: https://view-health-screening-recommendations.service.gov.uk/breast-cancer/
(68) UK National Screening Committee. Additional screening with ultrasound after negative mammography screening in women with dense breasts [Internet]. London, UK: The Committee;

2019 [cited 2022 Dec 19]. Available from: https://view-health-screening-recommendations.service.gov.uk/document/465/download
(69) Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(4):268-78.
(70) Siu AL, U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164(4):279-96.
(71) Welch VA, Petkovic J, Jull J, Hartling L, Klassen T, Kristjansson E, et al. Equity and specific populations. 2022. In: Cochrane handbook for systematic reviews of interventions (version 63) [Internet]. London, UK: Cochrane Collaboration. Available from: www.training.cochrane.org/handbook
(72) Ursin G, Ma H, Wu AH, Bernstein L, Salane M, Parisky YR, et al. Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev. 2003;12(4):332-8.
(73) Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, et al. Is breast cancer the same disease in Asian and Western countries? World J Surg. 2010;34(10):2308-24.
(74) Maskarinec G, Meng L, Ursin G. Ethnic differences in mammographic densities. Int J Epidemiol. 2001;30(5):959-65.
(75) Rajaram N, Mariapun S, Eriksson M, Tapia J, Kwan PY, Ho WK, et al. Differences in mammographic density between Asian and Caucasian populations: a comparative analysis. Breast Cancer Res Treat. 2017;161(2):353-62.
(76) Wang J, Zheng S, Ding L, Liang X, Wang Y, Greuter MJW, et al. Is ultrasound an accurate alternative for mammography in breast cancer screening in an Asian population? A meta-analysis. Diagnostics (Basel). 2020;10(11):985.
(77) Osei-Twum JA, Gedleh S, Lofters A, Nnorom O. Differences in breast cancer presentation at time of diagnosis for Black and White women in high resource settings. J Immigr Minor Health. 2021;23(6):1305-42.
(78) Lofters AK, McBride ML, Li D, Whitehead M, Moineddin R, Jiang L, et al. Disparities in breast cancer diagnosis for immigrant women in Ontario and BC: results from the CanIMPACT study. BMC Cancer. 2019;19(1):42.
(79) Nnorom O, Findlay N, Lee-Foon NK, Jain AA, Ziegler CP, Scott FE, et al. Dying to learn: a scoping review of breast and cervical cancer studies focusing on Black Canadian women. J Health Care Poor Underserved. 2019;30(4):1331-59.
(80) Vahabi M, Lofters A, Kumar M, Glazier RH. Breast cancer screening disparities among urban immigrants: a population-based study in Ontario, Canada. BMC Public Health. 2015;15:679.
(81) Tobias JK, Tinmouth J, Senese LC, Jumah N, Llovet D, Kewayosh A, et al. Health policy as a barrier to First Nations peoples' access to cancer screening. Healthc Policy. 2020;15(3):28-46.
(82) Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2013(6):CD001877.
(83) Health Quality Ontario. Women's experiences of inaccurate breast cancer screening results: a systematic review and qualitative meta-synthesis. Ont Health Technol Assess Ser. 2016;16(16):1-22.
(84) Overdiagnosis from mammographic screening [Internet]. Strawberry Hills, Australia: Cancer Australia; 2008 [updated 2014; cited 2021 Jul 22]. Available from: www.canceraustralia.gov.au/resources/position-statements/overdiagnosis-mammographic-screening
(85) Odle TG. Radiation dose in breast imaging. Radiol Technol. 2018;89(4):371-90.
(86) Radiation risk with digital mammography in breast screening [Internet]. London, UK: Public Health England; 2017 [updated 2017 Oct 23; cited 2022 Dec 19]. Available from:

www.gov.uk/government/publications/breast-screening-radiation-risk-with-digital-mammography/radiation-risk-with-digital-mammography-in-breast-screening
(87) McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40-6.
(88) Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.
(89) Garritty C, Gartlehner G, Nussbaumer-Streit B, King VJ, Hamel C, Kamel C, et al. Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. J Clin Epidemiol. 2021;130:13-22.
(90) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178-89.
(91) Tagliafico AS, Calabrese M, Mariscotti G, Durando M, Tosto S, Monetti F, et al. Adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts: interim report of a prospective comparative trial. J Clin Oncol. 2016;34(16):1882-8.
(92) Tagliafico AS, Mariscotti G, Valdora F, Durando M, Nori J, La Forgia D, et al. A prospective comparative trial of adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts (ASTOUND-2). Eur J Cancer. 2018;104:39-46.
(93) Harada-Shoji N, Suzuki A, Ishida T, Zheng YF, Narikawa-Shiono Y, Sato-Tadano A, et al. Evaluation of adjunctive ultrasonography for breast cancer detection among women aged 40-49 years with varying breast density undergoing screening mammography: a secondary analysis of a randomized clinical trial. JAMA Network Open. 2021;4(8):e2121505.
(94) Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J. 2011;343:d5928.
(95) Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol. 2013;66(4):408-14.
(96) Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook [Internet]. Hamilton (ON): Grade Working Group; 2013 [cited 2017 Dec]. Available from http://gdt.guidelinedevelopment.org/app/handbook/handbook.html.
(97) Zeng A, Brennan ME, Young S, Mathieu E, Houssami N. The effect of supplemental imaging on interval cancer rates in mammography screening: systematic review. Clin Breast Cancer. 2022;22(3):212-22.
(98) Cozzi A, Magni V, Zanardo M, Schiaffino S, Sardanelli F. Contrast-enhanced mammography: a systematic review and meta-analysis of diagnostic performance. Radiology. 2022;302(3):568-81.
(99) Bowles D, Quinton A. The use of ultrasound in breast cancer screening of asymptomatic women with dense breast tissue: a narrative review. J Med Imaging Radiat Sci. 2016;47(3 Suppl):S21-8.
(100) Rebolj M, Assi V, Brentnall A, Parmar D, Duffy SW. Addition of ultrasound to mammography in the case of dense breast tissue: systematic review and meta-analysis. Br J Cancer. 2018;118(12):1559-70.
(101) Scheel JR, Lee JM, Sprague BL, Lee CI, Lehman CD. Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts. Am J Obstet Gynecol. 2015;212(1):9-17.
(102) Yang L, Wang S, Zhang L, Sheng C, Song F, Wang P, et al. Performance of ultrasonography screening for breast cancer: a systematic review and meta-analysis. BMC Cancer. 2020;20(1):499.

(103) Yuan WH, Hsu HC, Chen YY, Wu CH. Supplemental breast cancer-screening ultrasonography in women with dense breasts: a systematic review and meta-analysis. Br J Cancer. 2020;123(4):673-88.
(104) Houssami N, Turner RM. Rapid review: estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts. Breast. 2016;30:141-5.
(105) Phi XA, Tagliafico A, Houssami N, Greuter MJW, de Bock GH. Digital breast tomosynthesis for breast cancer screening and diagnosis in women with dense breasts—a systematic review and meta-analysis. BMC Cancer. 2018;18(1):380.
(106) Bakker MF, De Lange SV, Pijnappel RM, Mann RM, Peeters PHM, Monninkhof EM, et al. Supplemental MRI screening for women with extremely dense breast tissue. N Engl J Med. 2019;381(22):2091-102.
(107) Veenhuizen SGA, de Lange SV, Bakker MF, Pijnappel RM, Mann RM, Monninkhof EM, et al. Supplemental breast MRI for women with extremely dense breasts: results of the second screening round of the DENSE trial. Radiology. 2021;299(2):278-86.
(108) Emaus MJ, Bakker MF, Peeters PHM, Loo CE, Mann RM, De Jong MDF, et al. MR imaging as an additional screening modality for the detection of breast cancer in women aged 50-75 years with extremely dense breasts: the DENSE trial study design. Radiology. 2015;277(2):527-37.
(109) Gatta G, Cappabianca S, La Forgia D, Massafra R, Fanizzi A, Cuccurullo V, et al. Second-generation 3D automated breast ultrasonography (Prone ABUS) for dense breast cancer screening integrated to mammography: effectiveness, performance and detection rates. J Pers Med. 2021;11(9):875.
(110) Wilczek B, Wilczek HE, Rasouliyan L, Leifland K. Adding 3D automated breast ultrasound to mammography screening in women with heterogeneously and extremely dense breasts: report from a hospital-based, high-volume, single-center breast cancer screening program. Eur J Radiol. 2016;85(9):1554-63.
(111) Barham L. Public and patient involvement at the UK National Institute for Health and Clinical Excellence. Patient. 2011;4(1):1-10.
(112) Gordon PB. The impact of dense breasts on the stage of breast cancer at diagnosis: a review and options for supplemental screening. Curr Oncol. 2022;29(5):3595-636.
(113) Sung JS, Lebron L, Keating D, D'Alessio D, Comstock CE, Lee CH, et al. Performance of dual-energy contrast-enhanced digital mammography for screening women at increased risk of breast cancer. Radiology. 2019;293(1):81-8.
(114) National Institute for Health and Care Excellence. Process and methods guides. Appendix I: quality appraisal checklist–economic evaluations [Internet]. London: The Institute; 2012 [cited 2016 Jan]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-i-quality-appraisal-checklist-economic-evaluations
(115) Geuzinge HA, Bakker MF, Heijnsdijk EAM, van Ravesteyn NT, Veldhuis WB, Pijnappel RM, et al. Cost-effectiveness of magnetic resonance imaging screening for women with extremely dense breast tissue. J Natl Cancer Inst. 2021;113(11):1476-83.
(116) Kaiser CG, Dietzel M, Vag T, Froelich MF. Cost-effectiveness of MR-mammography vs. conventional mammography in screening patients at intermediate risk of breast cancer: a model-based economic evaluation. Eur J Radiol. 2021;136:109355.
(117) Tollens F, Baltzer PAT, Dietzel M, Schnitzer ML, Kunz WG, Rink J, et al. Cost-effectiveness of MR-mammography in breast cancer screening of women with extremely dense breasts after two rounds of screening. Front Oncol. 2021;11:724543.

(118) Tollens F, Baltzer PAT, Dietzel M, Schnitzer ML, Schwarze V, Kunz WG, et al. Economic potential of abbreviated breast MRI for screening women with dense breast tissue for breast cancer. Eur Radiol. 2022;32(11):7409-19.
(119) Gray E, Donten A, Karssemeijer N, van Gils C, Evans DG, Astley S, et al. Evaluation of a stratified national breast screening program in the United Kingdom: an early model-based cost-effectiveness analysis. Value Health. 2017;20(8):1100-9.
(120) Movik E, Dalsbo T, Fagelund B, Friberg E, Haheim L, Skar A. Digital breast tomosynthesis with hologic 3D mammograhy Selenia Dimensions System for use in breast cancer screening. Oslo, Norway: Norwegian Institute of Public Health; 2017.
(121) Lee CI, Cevik M, Alagoz O, Sprague BL, Tosteson ANA, Miglioretti DL, et al. Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. Radiology. 2015;274(3):772-80.
(122) Ollendorf D, Loos A, Tice J, Lee J, Pearson S. Appropriate imaging for breast cancer screening in special populations. No. 20150116B. Olympia (WA): Institute for Clinical and Economic Review; 2014.
(123) Norwegian Ministry of Health Care Services. Principles for priority setting in health care—summary of a white paper on priority setting in the Norwegian health care sector. Oslo, Norway: The Ministry; 2015.
(124) Ottersen T, Førde R, Kakad M, Kjellevold A, Melberg HO, Moen A, et al. A new proposal for priority setting in Norway: open and fair. Health Policy. 2016;120(3):246-51.
(125) Zhang K, Garau M. International cost-effectiveness thresholds and modifiers for HTA decision making: OHE consulting report [Internet]. London, UK: Office of Health Economics; 2020 [cited 2022 Dec 19]. Available from: www.ohe.org/publications/international-cost-effectiveness-thresholds-and-modifiers-hta-decision-making
(126) Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology. 2013;267(1):47-56.
(127) Evans DG, Astley S, Stavrinos P, Harkness E, Donnelly LS, Dawe S, et al. Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study. Southampton, UK: NIHR Journals Library; 2016.
(128) Brentnall AR, Harkness EF, Astley SM, Donnelly LS, Stavrinos P, Sampson S, et al. Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. Breast Cancer Res. 2015;17(1):147.
(129) Breast Density and Mammography Reporting Act of 2014, H.R. 5145 (2014).
(130) Comstock CE, Gatsonis C, Newstead GM, Snyder BS, Gareen IF, Bergin JT, et al. Comparison of abbreviated breast MRI vs digital breast tomosynthesis for breast cancer detection among women with dense breasts undergoing screening. JAMA. 2020;323(8):746-56.
(131) Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.
(132) Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. 4th ed [Internet]. Ottawa (ON): The Agency; 2017 [cited 2018 Jan]. Available from: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf

(133) Glossary [Internet]. London, UK: National Institute for Health and Care Excellence; c2019-01 [cited 2022 Jan 12]. Available from: www.nice.org.uk/Glossary
(134) Ontario Breast Screening Program (OBSP) guidelines summary [Internet]. Toronto (ON): Cancer Care Ontario; 2015 [cited 2022 Dec 19]. Available from: www.cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/breast-screening-guidelines-summary
(135) Gauvreau CL, Fitzgerald NR, Memon S, Flanagan WM, Nadeau C, Asakawa K, et al. The OncoSim model: development and use for better decision-making in Canadian cancer control. Curr Oncol. 2017;24(6):401-6.
(136) Yong JHE, Nadeau C, Flanagan WM, Coldman AJ, Asakawa K, Garner R, et al. The OncoSim-Breast cancer microsimulation model. Curr Oncol. 2022;29(3):1619-33.
(137) OncoSim-Breast: fact sheet [Internet]. Toronto (ON): Canadian Partnership Against Cancer; 2019 [cited 2022 Dec 19]. Available from: https://s22457.pcdn.co/wp-content/uploads/2019/10/OncoSim-Breast-EN.pdf
(138) The Ontario cancer screening performance report 2020. Toronto (ON): Ontario Health (Cancer Care Ontario); 2021.
(139) Chaudhry M, Kandasamy S, Habbous S, Chan C, Barisic A, Faisal A, et al. Cancer system quality index 2021 [Internet]. Toronto (ON): Cancer Quality Council of Ontario, Ontario Health 2021 [cited 2022 Dec 19]. Available from: www.csqi.on.ca/sites/csqipub/files/assets/CSQI2021Report.pdf
(140) Canadian Cancer Registry (CCR) [Internet]. Ottawa (ON): Statistics Canada; c2018-01 [updated 2021 May; cited 2022 Jan 1]. Available from: www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3207
(141) Population projections for Canada (2018 to 2068), provinces and territories (2018 to 2043). Cat. no. 91-520-x [Internet]. Ottawa (ON): Statistics Canada; 2019 Sept [cited 2022 Dec 19]. Available from: www.150.statcan.gc.ca/n1/pub/91-520-x/91-520-x2019001-eng.htm
(142) Coldman A. Report on breast density [Internet]. Vancouver (BC): BC Cancer; 2018 [cited 2022 Dec 19]. Available from: www.bccancer.bc.ca/screening/Documents/Breast_Coldman%20-%20Report%20on%20Breast%20Density.pdf
(143) Sprague BL, Gangnon RE, Burt V, Trentham-Dietz A, Hampton JM, Wellman RD, et al. Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst. 2014;106(10):dju255.
(144) Alagoz O, Ergun MA, Cevik M, Sprague BL, Fryback DG, Gangnon RE, et al. The University of Wisconsin Breast Cancer Epidemiology Simulation model: an update. Med Decis Making. 2018;38(1 Suppl):99-111.
(145) Kerlikowske K, Cook AJ, Buist DS, Cummings SR, Vachon C, Vacek P, et al. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. J Clin Oncol. 2010;28(24):3830-7.
(146) Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med. 2012;156(9):635-48.
(147) Chiarelli AM, Blackmore KM, Mirea L, Done SJ, Majpruz V, Weerasinghe A, et al. Annual vs biennial screening: diagnostic accuracy among concurrent cohorts within the Ontario Breast Screening Program. J Natl Cancer Inst. 2020;112(4):400-9.
(148) Guertin JR, Feeny D, Tarride J. Health Utilities Index Mark 3 scores for major chronic conditions: population norms for Canada based on the 2013 and 2014 Canadian Community Health Survey. Cat. no. 82-003-X [Internet]. Ottawa (ON): Statistics Canada; 2018 [cited 2022 Dec 19]. Available

from: www.150.statcan.gc.ca/n1/en/pub/82-003-x/2018011/article/00001-eng.pdf?st=6TCrrwwO
(149) McIntosh CN, Connor Gorber S, Bernier J, Berthelot JM. Eliciting Canadian population preferences for health states using the Classification and Measurement System of Functional Health (CLAMES). Chronic Dis Can. 2007;28(1-2):29-41.
(150) Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. Med Care. 2002;40(2):113-28.
(151) Ware JE, Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000;25(24):3130-9.
(152) Krabbe PF, Stouthard ME, Essink-Bot ML, Bonsel GJ. The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system. J Clin Epidemiol. 1999;52(4):293-301.
(153) Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337-43.
(154) Flanagan W, McIntosh CN, Le Petit C, Berthelot J-M. Deriving utility scores for co-morbid conditions: a test of the multiplicative model for combining individual condition scores. Popul Health Metr. 2006;4:13.
(155) Boswell-Purdy J, Flanagan WM, Roberge H, Le Petit C, White KJ, Berthelot JM. Population health impact of cancer in Canada, 2001. Chronic Dis Can. 2007;28(1-2):42-55.
(156) Mittmann N, Seung SF, Diong C, Gatley JM, Wolfson M, Simard J, et al. Using real-world data to determine preliminary health system costs of Canadian women screened for breast cancer. Poster session presented at: Annual Canadian Association for Population Therapeutics; 2021 Oct 25-26; Virtual conference.
(157) Canadian Consumer Price Index [Internet]. Ottawa (ON): Statistics Canada; 2022 Jan [updated 2022 Jan; cited 2022 Jan 31]. Available from: www.150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000413
(158) Alberta Health Care Insurance Plan: Schedule of medical benefits as of 01 October 2021 [Internet]. Edmonton (AB): Alberta Health Services; 2021 Oct [cited 2022 Dec 19]. Available from: https://open.alberta.ca/publications/somb-2021-10-01#summary
(159) Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. Lancet. 2006;368(9552):2053-60.
(160) Moss SM, Wale C, Smith R, Evans A, Cuckle H, Duffy SW. Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age trial at 17 years' follow-up: a randomised controlled trial. Lancet Oncol. 2015;16(9):1123-32.
(161) van den Broek JJ, van Ravesteyn NT, Mandelblatt JS, Huang H, Ergun MA, Burnside ES, et al. Comparing CISNET breast cancer incidence and mortality predictions to observed clinical trial results of mammography screening from ages 40 to 49. Med Decis Making. 2018;38(1 Suppl):140-50.
(162) Automated breast ultrasound (ABUS) at the Toronto Centre for Medical Imaging [Internet]. Toronto (ON): Toronto Centre For Medical Imaging; c2022-08 [cited 2022 Aug 24]. Available from: https://tcfmi.com/our-procedures/automated-breast-ultrasound-toronto/
(163) Yaffe MJ, Mainprize JG. The value of all-cause mortality as a metric for assessing breast cancer screening. J Natl Cancer Inst. 2020;112(10):989-93.
(164) Pader J, Ruan Y, Poirier AE, Asakawa K, Lu C, Memon S, et al. Estimates of future cancer mortality attributable to modifiable risk factors in Canada. Can J Public Health. 2021;112(6):1069-82.

(165) Brezden-Masley C, Fathers KE, Coombes ME, Pourmirza B, Xue C, Jerzak KJ. A population-based comparison of treatment patterns, resource utilization, and costs by cancer stage for Ontario patients with hormone receptor-positive/HER2-negative breast cancer. Breast Cancer Res Treat. 2021;185(2):507-15.
(166) CADTH pan-Canadian Oncology Drug Review Expert Review Committee. Final recommendation for ribociclib plus fulvestrant for advanced or metastatic breast cancer [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2022 Apr [cited 2022 Dec 19]. Available from: www.cadth.ca/sites/default/files/pcodr/Reviews2020/10195RibociclibFulvestrantMBC_fnRec_pERC%20Chair%20Approved_22April2020_final.pdf
(167) Messina J, Grainger DL. A pilot study to identify areas for further improvements in patient and public involvement in health technology assessments for medicines. Patient. 2012;5(3):199-211.
(168) Ontario Health Technology Advisory Committee Public Engagement Subcommittee. Public engagement for health technology assessment at Health Quality Ontario—final report from the Ontario Health Technology Advisory Committee Public Engagement Subcommittee [Internet]. Toronto (ON): Queen's Printer for Ontario; 2015 Apr [cited 2018 Apr 30]. Available from: www.hqontario.ca/Portals/0/documents/evidence/special-reports/report-subcommittee-20150407-en.pdf
(169) Kvale S. Interviews: an introduction to qualitative research interviewing. Thousand Oaks (CA): Sage; 1996.
(170) Kuzel AJ. Sampling in qualitative inquiry. In: Miller WL, Crabtree BF, editors. Doing qualitative research. Thousand Oaks (CA): Sage; 1999. p. 33-45.
(171) Morse J. Emerging from the data: cognitive processes of analysis in qualitative research. In: Morse J, editor. Critical issues in qualitative research methods. Thousand Oaks (CA): Sage; 1994. p. 23-41.
(172) Patton MQ. Qualitative research and evaluation methods. 3rd ed. Thousand Oaks (CA): Sage; 2002.
(173) Strauss AL, Corbin JM. Basics of qualitative research: techniques and procedures of developing a grounded theory. 2nd ed. Thousand Oaks (CA): Sage; 1998.
(174) Health Technology Assessment International. Introduction to health technology assessment [Internet]. Edmonton (AB): Health Technology Assessment International; 2015 [cited 2018 Apr 30]. Available from: http://www.htai.org/fileadmin/HTAi_Files/ISG/PatientInvolvement/v2_files/Resource/PCISG-Resource-Intro_to_HTA__KFacey__Jun13.pdf
(175) Strauss AL, Corbin JM. Grounded theory research: procedures, canons, and evaluative criteria. Qual Sociol. 1990;13(1):3-21.
(176) Strauss AL, Corbin JM. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. Thousand Oaks (CA): Sage; 1994. p. 273-85.
(177) Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8:45.
(178) Grey matters: a practical tool for searching health-related grey literature [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 [cited 2022 Apr 28]. Available from: www.cadth.ca/grey-matters
(179) Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. Qual Health Res. 2012;22(10):1435-43.
(180) DistillerSR [computer program]. Ottawa (ON): Evidence Partners; 2011.

(181) Long HA, French DP, Brooks JM. Optimising the value of the critical appraisal skills programme (CASP) tool for quality appraisal in qualitative evidence synthesis. Research Methods in Medicine and Health Sciences. 2020;1(1):31-42.
(182) NVivo qualitative data analysis [software]. Doncaster, Australia: QSR International Pty Ltd; 2015.
(183) Kressin NR, Wormwood JB, Battaglia TA, Maschke AD, Slanetz PJ, Pankowska M, et al. Women's understandings and misunderstandings of breast density and related concepts: a mixed methods study. J Womens Health (Larchmt). 2022;31(7):983-90.
(184) PROGRESS-Plus [Internet]. London, UK: The Cochrane Collaboration; 2022 [cited 2022 Mar 14]. Available from: https://methods.cochrane.org/equity/projects/evidence-equity/progress-plus
(185) O'Neill J, Tabish H, Welch V, Petticrew M, Pottie K, Clarke M, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. J Clin Epidemiol. 2014;67(1):56-64.
(186) Charmaz K. Constructing grounded theory. 2nd ed. London, UK: Sage Publications Ltd; 2014.
(187) Cicvara M, Mohamed A, Ekberg J, Fridell K. Radiographers' reflections on women with high breast density tissue—an interview study. J Radiol Nurs. 2020;39(2):125-31.
(188) Gunn CM, Battaglia TA, Paasche-Orlow MK, West AK, Kressin NR. Women's perceptions of dense breast notifications in a Massachusetts safety net hospital: "So what is that supposed to mean?". Patient Educ Couns. 2018;101(6):1123-9.
(189) Gunn CM, Fitzpatrick A, Waugh S, Carrera M, Kressin NR, Paasche-Orlow MK, et al. A qualitative study of Spanish-speakers' experience with dense breast notifications in a Massachusetts safety-net hospital. J Gen Intern Med. 2019;34(2):198-205.
(190) Nickel B, Dolan H, Carter S, Houssami N, Brennan M, Hersch J, et al. General practitioners' (GPs) understanding and views on breast density in Australia: a qualitative interview study. BMJ Open. 2021;11(8):e047513.
(191) Pacsi-Sepulveda AL, Shelton RC, Rodriguez CB, Coq AT, Tehranifar P. "You probably can't feel as safe as normal women": Hispanic women's reactions to breast density notification. Cancer. 2019;125(12):2049-56.
(192) Marcus EN, Yepes M, Dietz N. Perception of breast density information among women in Miami, FL: a qualitative study. J Cancer Educ. 2022;37(1):188-95.
(193) Nickel B, Dolan H, Carter S, Houssami N, Brennan M, Hersch J, et al. "It's about our bodies… we have the right to know this stuff": a qualitative focus group study on Australian women's perspectives on breast density. Patient Educ Couns. 2022;105(3):632-40.
(194) Schifferdecker KE, Tosteson ANA, Kaplan C, Kerlikowske K, Buist DSM, Henderson LM, et al. Knowledge and perception of breast density, screening mammography, and supplemental screening: in search of "informed". J Gen Intern Med. 2020;35(6):1654-60.
(195) Klinger EV, Kaplan CP, St Hubert S, Birdwell RL, Haas JS. Patient and provider perspectives on mammographic breast density notification legislation. MDM Policy Pract. 2016;1(1):2381468316680620.
(196) Lincoln YS, Guba EG. But is it rigorous? Trustworthiness and authenticity in naturalistic evaluation. New Dir Eval. 1986;1986(30):73-84.
(197) Baird J, Yogeswaran G, Oni G, Wilson EE. What can be done to encourage women from Black, Asian and minority ethnic backgrounds to attend breast screening? A qualitative synthesis of barriers and facilitators. Public Health. 2021;190:152-9.
(198) Miller AB. The public health basis of cancer screening: principles and ethical aspects. Cancer Treat Res. 1996;86:1-7.
(199) Beauchamp TL, Childress JF. Principles of biomedical ethics. 8th ed. New York: Oxford University Press; 2019.

(200) EUnetHTA Joint Action 2 Work Package 8. HTA Core Model version 3.0 [Internet]. Diemen, Netherlands: European Network for Health Technology Assessment (EUnetHTA); 2016 [cited 2022 Apr 15]. Available from: https://www.eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf
(201) Harding C, Pompei F, Burmistrov D, Wilson R. Long-term relationships between screening rates, breast cancer characteristics, and overdiagnosis in US counties, 1975-2009. Int J Cancer. 2019;144(3):476-88.
(202) Tornberg SA. Screening for early detection of cancer—ethical aspects. Acta Oncol. 1999;38(1):77-81.
(203) Bradley SH, Thompson MJ, Nicholson BD. Ensuring informed decision-making for cancer screening. J Am Board Fam Med. 2021;34(2):435-8.
(204) Brawley OW, Paller CJ. Overdiagnosis in the age of digital cancer screening. J Natl Cancer Inst. 2021;113(1):1-2.
(205) Puliti D, Duffy SW, Miccinesi G, de Koning H, Lynge E, Zappa M, et al. Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. J Med Screen. 2012;19 Suppl 1:42-56.
(206) Baum M. Informed choice and breast cancer screening. Womens Health. 2006;2(6):835-8.
(207) Plutynski A. Ethical issues in cancer screening and prevention. J Med Philos. 2012;37(3):310-23.
(208) Forbes LJ, Ramirez AJ, Expert Group on Information about Breast Screening. Offering informed choice about breast screening. J Med Screen. 2014;21(4):194-200.
(209) Boenink M. Debating the desirability of new biomedical technologies: lessons from the introduction of breast cancer screening in the Netherlands. Health Care Anal. 2012;20(1):84-102.
(210) Hersch J, Jansen J, Irwig L, Barratt A, Thornton H, Howard K, et al. How do we achieve informed choice for women considering breast screening? Prev Med. 2011;53(3):144-6.
(211) Dickinson JA, Pimlott N, Grad R, Singh H, Szafran O, Wilson BJ, et al. Screening: when things go wrong. Can Fam Physician. 2018;64(7):502-8.
(212) Appavoo S. Imaging, paternalism and the worried patient: rethinking our approach. Can Assoc Radiol J. 2022;73(1):121-4.
(213) McGuinness JE, Ueng W, Trivedi MS, Yi HS, David R, Vanegas A, et al. Factors associated with false positive results on screening mammography in a population of predominantly Hispanic women. Cancer Epidemiol Biomarkers Prev. 2018;27(4):446-53.
(214) Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of breast cancer screening: systematic review to update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med. 2016;164(4):256-67.
(215) Chaltiel D, Hill C. Estimations of overdiagnosis in breast cancer screening vary between 0% and over 50%: why? BMJ Open. 2021;11(6):e046353.
(216) Autier P, Boniol M. Mammography screening: a major issue in medicine. Eur J Cancer. 2018;90:34-62.
(217) Evans A, Vinnicombe S. Overdiagnosis in breast imaging. Breast. 2017;31:270-3.
(218) Milch V, Aranda S, Canfell K, Varlow M, Roder DM, Currow D, et al. Overdiagnosis of screen-detected breast cancer. Med J Aust. 2021;214(10):455-6.e1.
(219) Dale J, Di Tomaso M, Gay V. Marrying story with science: the impact of outdated and inconsistent breast cancer screening practices in Canada. Curr Oncol. 2022;29(5):3540-51.
(220) Kim MS, Nishikawa G, Prasad V. Cancer screening: a modest proposal for prevention. Cleve Clin J Med. 2019;86(3):157-60.
(221) Plevritis SK, Ikeda DM. Ethical issues in contrast-enhanced magnetic resonance imaging screening for breast cancer. Top Magn Reson Imaging. 2002;13(2):79-84.

(222) Malm HM. Medical screening and the value of early detection. When unwarranted faith leads to unethical recommendations. Hastings Cent Rep. 1999;29(1):26-37.
(223) Elton L. Non-maleficence and the ethics of consent to cancer screening. J Med Ethics. 2020;21:21.
(224) Nickel B, Farber R, Brennan M, Hersch J, McCaffery K, Houssami N. Breast density notification: evidence on whether benefit outweighs harm is required to inform future screening practice. BMJ Evid Based Med. 2021;26(6):309-11.
(225) Autier P, Boniol M, Koechlin A, Pizot C. Effectiveness of and overdiagnosis from mammography screening in the Netherlands: population based study. BMJ. 2017;359:j5224.
(226) Concin H, Nagel G. Preventing overdiagnosis in mammography screening—a public health perspective. Horm Mol Biol Clin Investig. 2017;32(1):16.
(227) Tonelli M, Connor Gorber S, Joffres M, Dickinson J, Singh H, Lewin G, et al. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. CMAJ. 2011;183(17):1991-2001.
(228) Attena F. Too much medicine? Scientific and ethical issues from a comparison between two conflicting paradigms. BMC Public Health. 2019;19(1):97.
(229) Houssami N, Lee CI. The impact of legislation mandating breast density notification—review of the evidence. Breast. 2018;42:102-12.
(230) Reid L. Is an indistinct picture "exactly what we need"? Objectivity, accuracy, and harm in imaging for cancer. J Eval Clin Pract. 2018;24(5):1055-64.
(231) Neal CH, Helvie MA. Overdiagnosis and risks of breast cancer screening. Radiol Clin North Am. 2021;59(1):19-27.
(232) Abelson J, Tripp L, Sussman J. "I just want to be able to make a choice": Results from citizen deliberations about mammography screening in Ontario, Canada. Health Policy. 2018;122(12):1364-71.
(233) Houssami N. Overdiagnosis of breast cancer in population screening: does it make breast screening worthless? Cancer Biol. 2017;14(1):1-8.
(234) Davies L, Petitti DB, Martin L, Woo M, Lin JS. Defining, estimating, and communicating overdiagnosis in cancer screening. Ann Intern Med. 2018;169(1):36-43.
(235) Researchers find that many small breast cancers may be overdiagnosed. Cancer. 2017;123(19):3653.
(236) Monticciolo DL, Helvie MA, Hendrick RE. Current issues in the overdiagnosis and overtreatment of breast cancer. AJR Am J Roentgenol. 2018;210(2):285-91.
(237) Carter SM, Degeling C, Doust J, et al. A definition and ethical evaluation of overdiagnosis. J Med Ethics. 2016;42(11):705-14.
(238) Rogers WA, Entwistle VA, Carter SM. Risk, overdiagnosis and ethical justifications. Health Care Anal. 2019;27(4):231-48.
(239) Tanne JH. Breast cancer is overdiagnosed in one in six or seven cases, finds large US study. BMJ. 2022;376:o581.
(240) Carter SM. Overdiagnosis, ethics, and trolley problems: why factors other than outcomes matter. BMJ. 2017;358:j3872.
(241) Robra BP. Harms and benefits of cancer screening. Recent Results Cancer Res. 2021;218:85-104.
(242) Booth CM, Li G, Zhang-Salomons J, Mackillop WJ. The impact of socioeconomic status on stage of cancer at diagnosis and survival: a population-based study in Ontario, Canada. Cancer. 2010;116(17):4160-7.
(243) Ontario Cancer Screening Performance Report 2020 [Internet]. Toronto (ON): Ontario Health (Cancer Care Ontario); 2021 [cited 2022 Nov 8]. Available from:

https://www.cancercareontario.ca/en/cancer-care-ontario/programs/screening-programs/screening-performance-report-2020
(244) Ontario Breast Screening Program locations [Internet]. Toronto (ON): Ontario Health (Cancer Care Ontario); 2022 [cited 2022 Nov 8]. Available from: https://www.cancercareontario.ca/en/find-cancer-services/breast-screening-locations
(245) Mobile screening [Internet]. Toronto (ON): Ontario Health (Cancer Care Ontario); 2022 [cited 2022 Nov 8]. Available from: https://www.cancercareontario.ca/en/find-cancer-services/mobile-screening
(246) Borkhoff CM, Saskin R, Rabeneck L, Baxter NN, Liu Y, Tinmouth J, et al. Disparities in receipt of screening tests for cancer, diabetes and high cholesterol in Ontario, Canada: a population-based study using area-based methods. Can J Public Health. 2013;104(4):e284-90.
(247) Cobigo V, Ouellette-Kuntz H, Balogh R, Leung F, Lin E, Lunsky Y. Are cervical and breast cancer screening programmes equitable? The case of women with intellectual and developmental disabilities. J Intellect Disabil Res. 2013;57(5):478-88.
(248) Glazier RH, Creatore MI, Gozdyra P, Matheson FI, Steele LS, Boyle E, et al. Geographic methods for understanding and responding to disparities in mammography use in Toronto, Canada. J Gen Intern Med. 2004;19(9):952-61.
(249) Kerner J, Liu J, Wang K, Fung S, Landry C, Lockwood G, et al. Canadian cancer screening disparities: a recent historical perspective. Curr Oncol. 2015;22(2):156-63.
(250) Zha N, Alabousi M, Patel BK, Patlas MN. Beyond universal health care: barriers to breast cancer screening participation in Canada. J Am Coll Radiol. 2019;16(4 Pt B):570-9.
(251) Vahabi M, Lofters A, Kumar M, Glazier RH. Breast cancer screening disparities among immigrant women by world region of origin: a population-based study in Ontario, Canada. Cancer Med. 2016;5(7):1670-86.
(252) Vahabi M, Lofters AK, Kopp A, Glazier RH. Correlates of non-adherence to breast, cervical, and colorectal cancer screening among screen-eligible women: a population-based cohort study in Ontario, Canada. Cancer Causes Control. 2021;32(2):147-55.
(253) Lofters AK, Schuler A, Slater M, Baxter NN, Persaud N, Pinto AD, et al. Using self-reported data on the social determinants of health in primary care to identify cancer screening disparities: opportunities and challenges. BMC Fam Pract. 2017;18(1):31.
(254) Ferdous M, Goopy S, Yang H, Rumana N, Abedin T, Turin TC. Barriers to breast cancer screening among immigrant populations in Canada. J Immigr Minor Health. 2020;22(2):410-20.
(255) Woods RR, McGrail KM, Kliewer EV, Kazanjian A, Mar C, Kan L, et al. Breast screening participation and retention among immigrants and nonimmigrants in British Columbia: a population-based study. Cancer Med. 2018;7(8):4044-67.
(256) Raynault MF, Fethiere C, Cote D. Social inequalities in breast cancer screening: evaluating written communications with immigrant Haitian women in Montreal. Int J Equity Health. 2020;19(1):209.
(257) Lofters AK, Kopp A, Vahabi M, Glazier RH. Understanding those overdue for cancer screening by five years or more: a retrospective cohort study in Ontario, Canada. Prev Med. 2019;129:105816.
(258) Lévesque E, Hagan J, Knoppers BM, Simard J. Organizational challenges to equity in the delivery of services within a new personalized risk-based approach to breast cancer screening. New Genetics & Society. 2019;38(1):38-59.
(259) Ouellette-Kuntz H, Cobigo V, Balogh R, Wilton A, Lunsky Y. The uptake of secondary prevention by adults with intellectual and developmental disabilities. J Appl Res Intellect Disabil. 2015;28(1):43-54.

(260) Olson RA, Nichol A, Caron NR, Olivotto IA, Speers C, Chia S, et al. Effect of community population size on breast cancer screening, stage distribution, treatment use and outcomes. Can J Public Health. 2012;103(1):46-52.
(261) Howard LM, Barley EA, Davies E, Rigg A, Lempp H, Rose D, et al. Cancer diagnosis in people with severe mental illness: practical and ethical issues. Lancet Oncol. 2010;11(8):797-804.
(262) Lawrie K, Charow R, Giuliani M, Papadakos J. Homelessness, cancer and health literacy: a scoping review. J Health Care Poor Underserved. 2020;31(1):81-104.
(263) McConnon A, Fung K, Lofters A, Hwang SW, Kouyoumdjian FG. Colorectal and breast cancer screening status for people in Ontario provincial correctional facilities. Am J Prev Med. 2019;56(4):487-93.
(264) St-Jacques S, Philibert MD, Langlois A, Daigle JM, Pelletier E, Major D, et al. Geographic access to mammography screening centre and participation of women in the Quebec Breast Cancer Screening Programme. J Epidemiol Community Health. 2013;67(10):861-7.
(265) Ezratty C, Vang S, Brown J, Margolies LR, Jandorf L, Lin JJ. Racial/ethnic differences in supplemental imaging for breast cancer screening in women with dense breasts. Breast Cancer Res Treat. 2020;182(1):181-5.
(266) Dayaratna S, Jackson R. The conundrum of breast density; guidance for healthcare providers. Best Pract Res Clin Obstet Gynaecol. 2022;83:24-35.
(267) Siverskog J, Henriksson M. On the role of cost-effectiveness thresholds in healthcare priority setting. Int J Technol Assess Health Care. 2021;37:e23.
(268) Jepson RG, Hewison J, Thompson AG, Weller D. How should we measure informed choice? The case of cancer screening. J Med Ethics. 2005;31(4):192-6.
(269) Millett C, Parker M. Informed decision making for cancer screening—not all of the ethical issues have been considered. Cytopathology. 2003;14(1):3-4.
(270) Seaman K, Dzidic P, Breen L, Saunders C. Exploring breast health practices of post-menopausal women: implications to informed consent. J Health Psychol. 2018;23(14):1820-31.
(271) Baines CJ. Mammography screening: are women really giving informed consent? J Natl Cancer Inst. 2003;95(20):1508-11.
(272) Johansson M, Brodersen J. Informed choice in screening needs more than information. Lancet. 2015;385(9978):1597-9.
(273) Jorgensen KJ, Brodersen J, Hartling OJ, Nielsen M, Gotzsche PC. Informed choice requires information about both benefits and harms. J Med Ethics. 2009;35(4):268-9.
(274) Schwartz PH, Meslin EM. The ethics of information: absolute risk reduction and patient understanding of screening. J Gen Intern Med. 2008;23(6):867-70.
(275) Osterlie W, Solbjor M, Skolbekken JA, Hofvind S, Saetnan AR, Forsmo S. Challenges of informed choice in organised screening. J Med Ethics. 2008;34(9):e5.
(276) Cribb A, Haran D. The benefits and ethics of screening for breast cancer. Public Health. 1991;105(1):63-7.
(277) Hersch J, Jansen J, Barratt A, Irwig L, Houssami N, Howard K, et al. Women's views on overdiagnosis in breast cancer screening: a qualitative study. BMJ. 2013;346:f158.
(278) Marcus EN, Yepes M. The conundrum of explaining breast density to patients. Cleve Clin J Med. 2013;80(12):761-5.
(279) Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med. 1997;44(5):681-92.
(280) O'Hagan J. The ethics of informed consent in relation to prevention screening programmes. N Z Med J. 1991;104(908):121-3.

(281) Ritchie D, Van Hal G, Van den Broucke S. How is informed decision-making about breast cancer screening addressed in Europe? An international survey of 28 countries. Health Policy. 2020;124(9):1017-31.
(282) NCI Dictionary of Cancer Terms [Internet]. Bethesda (MD): National Institutes of Health; c2022 [cited 2016 Feb 8]. Available from: www.cancer.gov/publications/dictionaries/cancer-terms/
(283) National Cancer Institute [Internet]. Rockville (MD): The Institute; c2022 [updated 2023 Jan 24; cited 2023 Feb 10]. Available from: www.cancer.gov
(284) Cruwys C, Pushkin J. Breast density and impacts on health. Ecancermedicalscience. 2017;11:ed70.
(285) Ohnuki K, Tohno E, Tsunoda H, Uematsu T, Nakajima Y. Overall assessment system of combined mammography and ultrasound for breast cancer screening in Japan. Breast Cancer. 2021;28(2):254-62.
(286) Vourtsis A, Berg WA. Breast density implications and supplemental screening. Eur Radiol. 2019;29(4):1762-77.
(287) Ultrasound: controversies and practices in breast cancer screening: comparisons in Germany, Austria, Switzerland [Internet]. Germany: Healthcare-in-Europe.com; 2017 [updated 2017 Oct 25; cited 2021 Aug 31]. Available from: https://healthcare-in-europe.com/en/news/controversies-practices-in-breast-cancer-screening.html
(288) Life tables, Canada, provinces and territories 1980/1982 to 2018/2020 (three-year estimates), and 1980 to 2020 (single-year estimates). Cat. no. 84-537-X [Internet]. Ottawa (ON): Statistics Canada; c1971 [cited 2022 Dec 19]. Available from: www.150.statcan.gc.ca/n1/pub/84-537-x/84-537-x2021001-eng.htm
(289) Fryback DG, Stout NK, Rosenberg MA, Trentham-Dietz A, Kuruchittham V, Remington PL. The Wisconsin Breast Cancer Epidemiology Simulation model. J Natl Cancer Inst Monogr. 2006(36):37-47.
(290) Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.
(291) Cheung MC, Earle CC, Rangrej J, Ho TH, Liu N, Barbera L, et al. Impact of aggressive management and palliative care on cancer costs in the final month of life. Cancer. 2015;121(18):3307-15.
(292) Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. Fam Med. 2004;36(8):588-94.

About Us

We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being. We work to enhance patient experience, improve population health, enhance provider experiences, improve value and advance health equity.

For more information about Ontario Health, visit OntarioHealth.ca.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

ontariohealth.ca/equity-inclusion-diversity-and-anti-racism

About the Ontario Health Technology Advisory Committee

How to Obtain Reports From the Ontario Health Technology Assessment Series

Disclaimer

Ontario Health
500 – 525 University Avenue
Toronto, Ontario
M5G 2L3
Toll Free: 1-877-280-8538
TTY: 1-800-855-0511
Email: OH-HQO_HTA@OntarioHealth.ca
hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4868-7154-4 (PDF)