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Screening Mammography for Women Aged 40 to 49 Years at Average Risk for Breast Cancer

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series.*

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and information from practicing medical experts and industry, adds important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to maximize patient outcomes.

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http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html

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Abbreviations

CBE	Clinical breast examination
CI	Confidence interval
DCIS	Ductal carcinoma in situ
FM	Film mammography
RCT	Randomized controlled trial
RR	Relative risk
RCT	Randomized controlled trial
SD	Standard deviation
USPSTF	United States Preventive Services Task Force

Executive Summary

Objective

The aim of this review was to determine the effectiveness of screening mammography in women aged 40 to 49 years at average risk for breast cancer.

Clinical Need

The effectiveness of screening mammography in women aged over 50 years has been established, yet the issue of screening in women aged 40 to 49 years is still unsettled. The Canadian Task Force of Preventive Services, which sets guidelines for screening mammography for all provinces, supports neither the inclusion nor the exclusion of this screening procedure for 40- to 49-year-old women from the periodic health examination. In addition to this, 2 separate reviews, one conducted in Quebec in 2005 and the other in Alberta in 2000, each concluded that there is an absence of convincing evidence on the effectiveness of screening mammography for women in this age group who are at average risk for breast cancer.

In the United States, there is disagreement among organizations on whether population-based mammography should begin at the age of 40 or 50 years. The National Institutes of Health, the American Association for Cancer Research, and the American Academy of Family Physicians recommend against screening women in their 40s, whereas the United States Preventive Services Task Force, the National Cancer Institute, the American Cancer Society, the American College of Radiology, and the American College of Obstetricians and Gynecologists recommend screening mammograms for women aged 40 to 49 years. Furthermore, in comparing screening guidelines between Canada and the United States, it is also important to recognize that "standard care" within a socialized medical system such as Canada's differs from that of the United States. The National Breast Screening Study (NBSS-1), a randomized screening trial conducted in multiple centres across Canada, has shown there is no benefit in mortality from breast cancer from annual mammograms in women randomized between the ages of 40 and 49, relative to standard care (i.e. physical exam and teaching of breast-self examination on entry to the study, with usual community care thereafter).

At present, organized screening programs in Canada systematically screen women starting at 50 years of age, although with a physician's referral, a screening mammogram is an insured service in Ontario for women under 50 years of age.

International estimates of the epidemiology of breast cancer show that the incidence of breast cancer is increasing for all ages combined, whereas mortality is decreasing, though at a slower rate. These decreasing mortality rates may be attributed to screening and advances in breast cancer therapy over time. Decreases in mortality attributable to screening may be a result of the earlier detection and treatment of invasive cancers, in addition to the increased detection of ductal carcinoma in situ (DCIS), of which certain subpathologies are less lethal. Evidence from the SEER cancer registry in the United States indicates that the age-adjusted incidence of DCIS has increased almost 10-fold over a 20-year period (from 2.7 to 25 per 100,000).

The incidence of breast cancer is lower in women aged 40 to 49 years than in women aged 50 to 69 years (about 140 per 100,000 versus 500 per 100,000 women, respectively), as is the sensitivity (about 75% versus 85% for women aged under and over 50, respectively) and specificity of mammography (about 80% versus 90% for women aged under and over 50, respectively). The increased density of breast tissue

in younger women is mainly responsible for the lower accuracy of this procedure in this age group. In addition, as the proportion of breast cancers that occur before the age of 50 are more likely to be associated with genetic predisposition as compared with those diagnosed in women after the age of 50, mammography may not be an optimal screening method for younger women.

Treatment options vary with the stage of disease (based on tumor size, involvement of surrounding tissue, and number of affected axillary lymph nodes) and its pathology, and may include a combination of surgery, chemotherapy, and/or radiotherapy.

Surgery is the first-line intervention for biopsy confirmed tumours. The subsequent use of radiation, chemotherapy, or hormonal treatments is dependent on the histopathologic characteristics of the tumor and the type of surgery. There is controversy regarding the optimal treatment of DCIS, which is noninvasive.

With such controversy as to the effectiveness of mammography and the potential risk associated with women being overtreated or actual cancers being missed, and the increased risk of breast cancer associated with exposure to annual mammograms over a 10-year period, the Ontario Health Technology Advisory Committee requested this review of screening mammography in women aged 40 to 49 years at average risk for breast cancer. This review is the first of 2 parts and concentrates on the effectiveness of screening mammography (i.e., film mammography, FM) for women at average risk aged 40 to 49 years. The second part will be an evaluation of screening by either magnetic resonance imaging or digital mammography, with the objective of determining the optimal screening modality in these younger women.

Review Strategy

The following questions were asked:

- Does screening mammography for women aged 40 to 49 years who are at average risk for breast cancer reduce breast cancer mortality?
- What is the sensitivity and specificity of mammography for this age group?
- What are the risks associated with annual screening from ages 40 to 49?
- What are the risks associated with false positive and false negative mammography results?
- What are the economic considerations if evidence for effectiveness is established?

The Medical Advisory Secretariat followed its standard procedures and searched these electronic databases: Ovid MEDLINE, EMBASE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the International Network of Agencies for Health Technology Assessment.

Keywords used in the search were breast cancer, breast neoplasms, mass screening, and mammography.

In total, the search yielded 6,359 articles specific to breast cancer screening and mammography. This did not include reports on diagnostic mammograms. The search was further restricted to English-language randomized controlled trials (RCTs), systematic reviews, and meta-analyses published between 1995 and 2005. Excluded were case reports, comments, editorials, and letters, which narrowed the results to 516 articles and previous health technology policy assessments.

These were examined against the criteria outlined below. This resulted in the inclusion of 5 health technology assessments, the Canadian Preventive Services Task Force report, the United States Preventive Services Task Force report, 1 Cochrane review, and 8 RCTs.

Inclusion Criteria

- English-language articles, and English and French-language health technology policy assessments, conducted by other organizations, from 1995 to 2005
- Articles specific to RCTs of screening mammography of women at average risk for breast cancer that included results for women randomized to studies between the ages of 40 and 49 years
- Studies in which women were randomized to screening with or without mammography, although women may have had clinical breast examinations and/or may have been conducting breast self-examination.
- UK Age Trial results published in December 2006.

Exclusion Criteria

- Observational studies, including those nested within RCTs
- RCTs that do not include results on women between the ages of 40 and 49 at randomization
- Studies in which mammography was compared with other radiologic screening modalities, for example, digital mammography, magnetic resonance imaging or ultrasound.
- Studies in which women randomized had a personal history of breast cancer.

Intervention

- Film mammography

Comparators

- Within RCTs, the comparison group would have been women randomized to not undergo screening mammography, although they may have had clinical breast examinations and/or have been conducting breast self-examination.

Outcomes of Interest

- Breast cancer mortality

Summary of Findings

There is Level 1 Canadian evidence that screening women between the ages of 40 and 49 years who are at average risk for breast cancer is not effective, and that the absence of a benefit is sustained over a maximum follow-up period of 16 years.

All remaining studies that reported on women aged under 50 years were based on subset analyses. They provide additional evidence that, when all these RCTs are taken into account, there is no significant reduction in breast cancer mortality associated with screening mammography in women aged 40 to 49 years.

Conclusions

There is Level 1 evidence that screening mammography in women aged 40 to 49 years at average risk for breast cancer is not effective in reducing mortality.

Moreover, risks associated with exposure to mammographic radiation, the increased risk of missed cancers due to lower mammographic sensitivity, and the psychological impact of false positives, are not inconsequential.

The UK Age Trial results published in December 2006 did not change these conclusions.

Objective

The aim of this review was to determine the effectiveness of screening mammography in women aged 40 to 49 years at average risk for breast cancer.

Background

Clinical Need: Target Population and Condition

The Ontario Breast Screening Program, under the auspices of Cancer Care Ontario, conducts screening mammography of women aged 50 to 69 years, and up to 74 years. To date, Ontario has not provided a screening program for women under the age of 50 years who are at average risk for breast cancer. However, a screening mammogram, with a physician's referral, is an insured service in the province for women under the age of 50.

The effectiveness of screening mammography in women aged over 50 years has been established, yet the issue of screening in women aged 40 to 49 years is remains unsettled. The Canadian Task Force of Preventive Services, which sets guidelines for screening mammography for all provinces, supports neither the inclusion nor the exclusion of this screening procedure for 40- to 49-year-old women within the periodic health examination. In addition to this, 2 separate reviews, one conducted in Quebec in 2005 and the other in Alberta in 2000, each concluded that there is an absence of convincing evidence on the effectiveness of screening mammography for women in this age group who are at average risk for breast cancer.

In the United States, there is disagreement among organizations on whether population-based mammography should begin at the age of 40 or 50 years. The National Institutes of Health, the American Association for Cancer Research, and the American Academy of Family Physicians recommend against screening women in their 40s, whereas the United States Preventive Services Task Force, the National Cancer Institute, the American Cancer Society, the American College of Radiology, and the American College of Obstetricians and Gynecologists recommend screening mammograms for women aged 40 to 49 years. Furthermore, in comparing screening guidelines between Canada and the United States, it is also important to recognize that "standard care" within a socialized medical system such as Canada's differs from that of the United States. The National Breast Screening Study (NBSS-1), a randomized screening trial conducted in multiple centres across Canada, has shown there is no benefit in mortality from breast cancer from annual mammograms in women randomized between the ages of 40 and 49, relative to standard care (i.e. physical exam and teaching of breast-self examination on entry to the study, with usual community care thereafter).

At present, organized screening programs in Canada systematically screen women starting at 50 years of age, although with a physician's referral, a screening mammogram is an insured service in Ontario for women under 50 years of age.

International estimates of the epidemiology of breast cancer show that the incidence of breast cancer is increasing for all ages combined, whereas mortality is decreasing, though at a slower rate. These decreasing mortality rates can be considered to be attributable to screening and advances in breast cancer

therapy over time. Decreases in mortality attributable to screening may be a result of the earlier detection and treatment of invasive cancers, in addition to the increased detection of ductal carcinoma in situ (DCIS), of which certain subpathologies are less lethal. Evidence from the SEER cancer registry in the United States indicates that the age-adjusted incidence of DCIS has increased almost 10-fold over a 20-year period (from 2.7 to 25 per 100,000).

The incidence of breast cancer is lower in women aged 40 to 49 years than in women aged 50 to 69 years (about 140 per 100,000 versus 500 per 100,000 women, respectively), as is the sensitivity (about 75% versus 85% for women aged under and over 50, respectively) and specificity of mammography (about 80% versus 90% for women aged under and over 50, respectively). The increased density of breast tissue in younger women is mainly responsible for the lower accuracy of this procedure in this age group. In addition, as the proportion of breast cancers that occur before the age of 50 are more likely to be associated with genetic predisposition as compared with those diagnosed in women after the age of 50, mammography may not be an optimal screening method for younger women.

The mean age-standardized incidence rates of breast cancer in Canada has increased at a rate of 0.2% per year (from 1992 to 2001), whereas the mean age-standardized mortality rate has decreased at a rate of 2.8% per year (from 1993–2002). (1) This translates to an estimated 21,600 new cases of breast cancer annually in Canada. Of these, 8,200 are expected in Ontario, and of these, approximately 1,368 will occur in women aged 40 to 49 years at diagnosis. The death rate for all stages of breast cancer combined is about 25% (an estimated 2,000 deaths are expected in Ontario in 2005) of which about 400 will occur in women aged 40 to 49 years. (2)

Treatment options vary with the stage of disease (based on tumor size, involvement of surrounding tissue, and number of affected axillary lymph nodes) and its pathology, and may include a combination of surgery, chemotherapy, and/or radiotherapy.

Surgery is the first-line intervention for biopsy confirmed tumours. The subsequent use of radiation, chemotherapy, or hormonal treatments is dependent on the histopathologic characteristics of the tumor and the type of surgery. There is controversy regarding the optimal treatment of DCIS, which is noninvasive.

With such controversy as to the effectiveness of mammography and the potential risk associated with women being overtreated or actual cancers being missed, and the increased risk of breast cancer associated with exposure to annual mammograms over a 10-year period, the Ontario Health Technology Advisory Committee requested a review of screening mammography in women aged 40 to 49 years at average risk for breast cancer. This review is the first of 2 parts and concentrates on the effectiveness of screening mammography (i.e., film mammography, FM) for women at average risk aged 40 to 49 years. The second part will be an evaluation of screening by either magnetic resonance imaging or digital mammography.

Existing Screening Technologies Other Than Mammography

Breast cancer screening technologies other than (film) mammography include digital mammography, magnetic resonance imaging, and ultrasound. The effectiveness of both digital mammography and magnetic resonance imaging as a first line screening tool will be examined in a subsequent assessment by the Medical Advisory Secretariat, as the present assessment focuses on (film) mammography.

New Technology Being Reviewed

Screening Mammography

The effectiveness of screening mammography in younger women is a contentious issue. The screening modality to date has been (film) mammography (FM), but evidence suggests that this procedure may not significantly reduce the mortality rate in women aged 40 to 49 years. The Canadian Task Force on Preventive Health Care (2) recommends screening mammography and clinical breast exams for women aged 50 to 69 years, yet it does not support screening for women in their 40s. However, the United States Preventive Services Task Force (3) recommends screening mammography, with or without clinical breast examination, every 1 or 2 years for women aged 40 and over.

The sensitivity and specificity of mammography varies with breast density and other factors. Breast density decreases the radiologist's ability to correctly rule in and rule out the presence of a lesion. Therefore, as the proportion of women with more dense breast tissue is highest in the premenopausal years, the sensitivity and specificity of mammography is lower for women in their forties than for women aged 50 years or over.

Accuracy of Mammography

While the technical quality of mammograms has improved over time, changes in measures of sensitivity, specificity, and rates of interval cancers are likely indicators of clinical impact. Although the interval cancer rate will vary with the amount of time elapsed since the last screen, an interval cancer is generally defined as a primary breast cancer diagnosis in a woman who had a negative result on a previous mammogram. The time period seen most often in estimations of interval cancer rates is 1 year since the last screen.

To determine whether the quality of technology used in the RCTs is comparable to present-day technology, data from the British Columbia Cancer Agency, which collects information on screening mammography for women aged 40 years and older, was used. Whereas data from British Columbia specific to 40- to 49–year-old women were not readily available, the sensitivity (approximately 85%), specificity (approximately 93%), and interval cancer rates (approximately 0.7 per 1,000 screens) for women aged 40 to 74 years combined had not changed over a 7-year period from 1996 to 2003. (British Columbia Cancer Agency data, Personal Communication, January 2006)

The issue of sensitivity and specificity has been thoroughly reviewed in the IARC publication on breast cancer screening (2002). (4) Overall, sensitivity was reported to range from 52% to 82% for women aged over 50 years. Estimates were lower for women in their 40s (44% and 64%), depending on the method of calculation. This lower sensitivity in younger women is as expected on the basis of increased breast density: compared with postmenopausal women, premenopausal women have more dense breasts, which reduces the ability of the technology to detect lesions if they exist. The sensitivity and specificity in the Canadian NBSS-1 RCT for the 40- to 49- year-old women was 81% and 82% (first round), respectively, showing that these parameters do not appear to have changed markedly over a 20-year period.

Literature Review on Effectiveness

Objectives

To determine the effectiveness of screening mammography for women aged 40 to 49 years at average risk for breast cancer.

Questions Asked

- Does screening mammography for women aged 40 to 49 years who are at average risk for breast cancer reduce breast cancer mortality?
- What is the sensitivity and specificity of mammography for this age group?
- What are the risks associated with annual screening from ages 40 to 49?
- What are the risks associated with false positive and false negative mammography results?
- What are the economic considerations if evidence for effectiveness is established?

Methods

The Medical Advisory Secretariat followed its standard procedures and searched these electronic databases: Ovid MEDLINE, EMBASE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and The International Network of Agencies for Health Technology Assessment.

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Exclusion Criteria

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- RCTs that do not include results on women between 40 and 49 years of age at randomization.
- Studies in which mammography was compared with other radiologic screening modalities, for example, digital mammography, magnetic resonance imaging or ultrasound.
- Studies in which women randomized had a personal history of breast cancer.

Intervention

- Film mammography.

Comparators

- Within RCTs, the comparison group would have been women randomized to not undergo screening mammography, although they may have had clinical breast examinations and/or have been conducting breast self-examination.

Outcomes of Interest

- Breast cancer mortality.

Results of Literature Review

Included in this review are 5 health technology assessments, the Canadian Preventive Services Task Force report, the United States Preventive Services Task Force, 1 Cochrane Review, and 8 RCTs that address the issue of screening mammography between the ages of 40 and 49 years.

The earliest of these trials, the Health Insurance Plan (HIP) trial (5) was conducted in New York in the 1960s. Subsequent trials were conducted in Canada (NBSS-1 and NBSS-2) (6-8), and in Sweden [Malmo (9), Kopparberg and Ostergotland – also referred to as the Two-County trial (10), the Stockholm (11) and Gothenburg trials (12;13)], and in the United Kingdom [UK Age Trial (14-17), and Edinburgh (18;19) trials]. As these trials began at different times, the maximum follow-up for which data has been reported is 20 years, although all trials have published results for a mean follow-up of 7 and 10 years, with the exception of the UK Age Trial with only 10-year results published (in December 2006).

Until March 2006, the Canadian National Breast Screening Study (NBSS-1) (6) was the only trial conducted to specifically address the issue of effectiveness of mammography in women 40 to 49 years of age. All of the other RCTs presented results as analyses stratified by age at randomization. The earliest of these was the HIP trial (5) which was the first to observe a differential effect of mammography on breast cancer mortality by menopausal status (i.e., above and below the age of 50 years). The most recent is the UK Age Trial (17) which was designed to capture the effect of screening mammography in women in their 40s, although only women 40 and 41 years of age were randomized.

Summary of Existing Health Technology Assessments

The authors and foci of the health technology assessments for screening by mammography in 40- to 49-year-old women are shown in Table 1.

Table 1: Summary and Focus of Previous Health Technology Assessments and Other Reviews of Screening Mammography

Year	Author	Focus of Assessment*
2005	Agence d'evaluation des technologies et des modes d'intervention en sante (AETMIS) (20)	- What is the strength of the scientific evidence on which screening mammography programs are based? - What evidence is there in support of screening for women aged 40 to 49 years? - What are the implications of research studies for maximizing the effectiveness of modern programs such as the 'Program québécois de depistage du cancer du sein' ?
2004	French National Agency for Accreditation and Evaluation in Healthcare (ANAES) (21)	- To determine whether the breast cancer screening program in France should be extended to women aged 40 to 49 years with no history of breast cancer or hereditary risk - To update the ANAES 1999 guidelines
2002	AHRQ, United States, for the United States Preventive Services Task Force (22)	- To summarize the current USPSTF recommendations on screening for breast cancer and the supporting scientific evidence - To update the 1996 recommendations for women 40 years and older
2001	Canadian Task Force on Preventive Health Care (2)	- To summarize the evidence on the effect of screening mammography in women aged 40 to 49 years at average risk for breast cancer - To update a 1994 recommendation of fair evidence to exclude screening mammography of these younger women from the periodic health exam
2001	Cochrane Review (23)	- To study the effect of screening for breast cancer with mammography on mortality and morbidity
2000	Alberta Heritage Foundation for Medical Research (24)	- To address the evidence on appropriate screening intervals for asymptomatic women aged 50 to 69 years and 40 to 49 years - To assess the efficacy of screening mammography in asymptomatic women aged 40 to 49 years
1999	New Zealand Health Technology Assessment (25)	- To identify and appraise the literature examining the early diagnosis of breast cancer by primary care health professionals - To update a previous review from 1996
1997	NHMRC National Breast Cancer Centre – Australia (26)	- To review the evidence on impact of screening on breast cancer mortality among women aged 40 to 49 years and to review the methodological issues likely to affect the analysis of effect - To assess the incremental benefit of commencing screening at age 40 years rather than 50 years - Estimate the likely relative risk reduction, absolute risk reduction, and number needed to screen if screening commenced at age 40 rather than at age 50

*USPSTF indicates United States Preventive Services Task Force.

Canadian Evidence

The Canadian evidence to date, from most to least recent, is based on the AETMIS review from Quebec (published August 2005), (20) the Canadian Task Force on Preventive Services (published 2001) (2) and a review conducted by the Alberta Heritage Foundation for Medical Research (published 2000). (24) All 3 reviews concluded that the evidence is not sufficient to warrant mass screening of women aged 40 to 49

years, and that the harmful effects may outweigh any potential benefits. Each of these documents is reviewed below.

Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS), Quebec, Canada, 2005

Screening Mammography: A Reassessment

Objectives: There were 3 objectives as listed in Table 1, 2 of which pertain to women aged 50 to 69 years, and 1 that was specific to women aged 40 to 49 years and thus of interest to this review by the Medical Advisory Secretariat: What evidence is there in support of screening women aged 40 to 49 years?

Search: All published RCTs on screening mammography.

Studies Included	Comments	Conclusions
All RCTs*	➢ Much less data to answer question in women aged 40 to 49 years as most trials were in women aged over 50. ➢ Best available data show no significant reduction in breast cancer mortality in women aged under 50 years. ➢ In the absence of convincing data on efficacy, harmful effects may outweigh any positive effects.	➢ Trial data to date do not provide scientific justification to recommend screening for women younger than 50. ➢ This conclusion does not exclude possibility that screening of individual women, based on a personalized risk assessment, could be of benefit. ➢ These conclusions should be reviewed when results from the UK Age Trial become available.

*RCT indicates randomized controlled trial.

The most recently published health technology policy assessment was conducted by AETMIS (20) in Quebec in August 2005. The review consists of the scoring of the validity of each of the RCTs (with results published by 2005) on the following criteria:

i. the strength of contrast, that is, the technical contrast between the screening and control interventions, the era in which these techniques were applied, the quality of the intervention, the rates of participation and contamination measured among screening and control cohorts, and the timing of the measurement of the effects of screening on mortality, and
ii. the trial's biases of unknown direction, in particular randomization, the equivalence of the risk of breast cancer mortality between the screening and control cohorts, the equivalence of criteria for exclusion from the 2 cohorts, and the equivalence of the follow-up of the 2 groups.

Of all the RCTs included in the assessment, the 2 trials with the highest scores were the Canadian NBSS-1 and the Swedish Malmo trials. The American HIP trial, the Scottish Edinburgh trial, and the Swedish Two-County trials were considered to be flawed for the purpose of their analysis. For women of all ages combined, the authors concluded that the more valid studies combined tend to show less of a reduction in mortality than do the less valid studies. Moreover, confidence intervals sometimes include the null value (1.00). Inclusion of the null value in the confidence interval indicates that the effect is not statistically significant. For example, when all studies were considered for all age groups, irrespective of validity, the reduction in mortality was 29%. However, it was only 9% when studies of moderate quality (the highest quality ranking) were included. In women aged under 50 years, a similar inverse relation between the quality of the study and the reduction in breast cancer mortality was observed. In moderate-quality RCTs (the highest quality raking), the cumulative risk reduction was 2% (RR, 0.98; 95% CI, 0.77–1.25), whereas inclusion of weaker studies increased the mortality reduction to 8% (RR, 0.92; 95% CI, 0.74–1.13). Overall, the reduction in mortality was much smaller for women in their 40s, and confidence intervals included the null value for all combinations of studies.

The authors indicated that the trial data to date, which are based on the RCTs included in this Medical Advisory Secretariat review (excluding the UK Age Trial, whose results have only recently been published), do not provide scientific justification to recommend screening for women from the age of 40 years. They concluded that the best available data do not show a significant reduction in breast cancer mortality in these younger women and that in the absence of convincing data on efficacy, the harmful effects may outweigh any positive effects. Nevertheless, they report that these findings do not preclude the possibility that screening of individual women, based on a personalized risk assessment, could be of benefit. The authors also noted that these conclusions should be reviewed when results from the UK Age Trial became available.

Canadian Task Force on Preventive Health Care, Canada, 2001

Preventive Health Care, 2001 update: screening mammography among women aged 40–49 years at average risk of breast cancer.

Objective: To update a previous review from 1994 that indicated fair evidence to exclude screening mammography of women aged 40 to 49 years from the periodic health examination.

Search Date: 1966 to January 2000

Studies Included	Comments	Conclusions
All RCTs*	➢ Benefits include a potential reduction in mortality, and less aggressive therapy and improved cosmetics with early diagnosis. ➢ Risks include increased biopsy rates and psychological effects of false reassurance or false-positive results.	➢ Current evidence does not suggest the inclusion of, or the exclusion from, the periodic health examination of women aged 40 to 49 years. ➢ Canadian women should be informed of potential benefits and risks of screening and assisted in deciding at what age they wish to initiate the procedure.

*RCT indicates randomized controlled trial.

To determine whether screening mammography in Canada should begin at the age of 40, the Canadian Task Force on Preventive Health Care (2) reviewed RCTs of women in their 40s and meta-analyses of these RCTs. Inclusion criteria for this review included RCTs with a minimum follow-up of 10 years, within which one arm of randomization was mammography, used either alone or in combination with clinical breast examination. The outcome of interest was breast cancer mortality.

The authors identified potential benefits of screening not related to mortality: the detection of tumors at earlier stages (possibly predictive of less toxic treatment), improved cosmesis, reassurance (72% of cases), and reduced anxiety about cancer at the time of screening. However, there were negative effects of screening mammography: radiation-induced carcinoma, unnecessary biopsies (0.6%–0.9% of cases in Sweden; 5%–9% of cases in the United States), psychological stress of call-back (40% of cases), additional x-ray films (3%–13% of cases in Sweden; 56% of cases in the United States), and possibly false reassurance.

The Canadian Task Force report emphasizes that the Canadian NBSS-1 was the only RCT designed to assess screening mammography in 40- to 49-year-old women. All other RCT results were based on subgroup analyses. In conclusion, the Task Force reported a smaller benefit in terms of mortality for women aged 40 to 49 years than for women 50 years of age or older.

The Canadian Task Force reported a relative risk reduction of 18% to 45% for breast cancer mortality at

10 years as shown in 2 RCTs and 1 meta-analysis, whereas no benefit was shown in 6 other trials. More importantly, the report addresses a methodological concern that may be affecting study results. This methodological concern is based on the follow-up period of the trial, suggesting that as the period increases, the likelihood of including mortality benefits from screening in later years (i.e., 50 years of age and over) also increases. Therefore, within the RCTs that show a reduction in breast cancer mortality for women in their 40s, it is unclear at to how much of the reported reduction is attributable to screening in the women's 50s. This methodological issue was addressed in the UK Age Trial, whose study design was intended to determine the effects of screening and anticipated benefits/risks within one's 40's: over 160,000 women 40 or 41 years of age at randomization were screened annually and followed for 10 years, or up to 50 years of age, to clarify the effect of screening (and any anticipated benefits) attributable to screening in one's 40s.

Based on the evidence of all RCTs with published results by early 2000, the Canadian Task Force recommendations were to neither include nor exclude screening mammography of women aged 40 to 49 years at average risk of breast cancer from the periodic health examination.

Alberta Heritage Foundation for Medical Research, Alberta, Canada, 2000

Mammography screening: mortality rate reduction and screening interval

Objective: To determine the efficacy of screening mammography in asymptomatic women aged 40 to 49 years, and to determine the appropriate screening interval for asymptomatic women aged 50 to 69 years and 40 to 49 years.

Search Date: Trials launched between 1963 and 1983 and meta-analyses published from 1997 to 2000.

Studies Included	Comments	Conclusions
All RCTs*	➢ Canadian NBSS-1 was the only RCT that specifically addressed issue in 40- to 49-year-old women. ➢ Mortality reduction smaller in younger than older women. ➢ Interval between initiation of screening and showing of benefit longer in younger women.	➢ Effectiveness of screening asymptomatic 40- to 49-year-old women remains unresolved. ➢ UK Age Trial to assess efficacy of annual screening of women aged 40 and 41 years.

*RCT indicates randomized controlled trial

This health technology assessment from Alberta suggested that although the Canadian NBSS-1 was the only trial to specifically address the issue of screening of 40 to 49-year-old women, all studies had insufficient power to determine the efficacy of screening mammography in these younger women. (24) Nevertheless, several meta-analyses indicated that the evidence is inconclusive for asymptomatic women, although there was general agreement that the reduction in mortality is smaller for younger women than it is for those aged 50 to 69 years.

This report also discussed the marked increased detection of ductal carcinoma in situ (DCIS) since the early 1980s, a result owing to screening mammography. Ductal carcinoma in situ is usually found by mammography in its clinically undetectable state, and studies have shown that 15% to 20% of cancers detected by mammography are DCIS. However, the proportion of DCIS cases is expected to be higher in younger women. As the natural history of DCIS is not known, it is also not known whether its detection is harmful or beneficial, as DCIS progresses in some women, and certain histopathologies of DCIS are considered to be more aggressive than others. The negative effect of detecting DCIS is that it could lead to overtreatment. The authors of this report cited evidence from the United States, revealing that of

women diagnosed with DCIS in 1992, 44% were treated with mastectomy, 23% with lumpectomy and radiation, and 30% by lumpectomy alone.

Similar to other reviews, this report concluded that the estimated reduction in mortality was smaller in women aged 40 to 49 years than in women aged 50 years and older. Nevertheless, the overall conclusion was that the effectiveness of screening mammography in women aged 40 to 49 years remains unresolved and should be addressed once the UK Age Trial results became available.

Evidence from the United States

In a review conducted by AHRQ (22) in the United States (published in 2002) investigating screening with mammography, clinical breast exam, and breast self-examination for women aged 40 years and older, recommendations differed from those in Canada. The AHRQ review was conducted for the United States Preventive Services Task Force and formed the basis of their recommendations to promote screening mammography from the age of 40. However, these recommendations are in complete contrast to those of the National Institutes of Health, the American Association for Cancer Research, and the American Academy of Family Physicians, who recommend against screening in the 40s.

AHRQ for the United States Preventive Services Task Force (USPSTF), United States, 2002

Screening for breast cancer: recommendations and rationale

Objective: To summarize the current USPSTF recommendations on screening for breast cancer and the supporting scientific evidence, and to update the 1996 recommendations.

Search Date: 1994 to September 2001

Studies Included	Comments	Conclusions
All RCTs* reporting results from 11–20 years of follow-up	➢ Mortality reductions ranged from no significant effect to 32% reduction in breast cancer mortality. ➢ Meta-analysis performed by AHRQ found a significant reduction in mortality from breast cancer.	➢ USPSTF recommends screening mammography, with or without clinical breast examination, every 1–2 years for women aged 40 years and older.

*RCT indicates randomized controlled trial.

The AHRQ (22) conducted a meta-analysis of 6 RCTs they deemed to be of "fair" quality and found the summary relative risk of breast cancer mortality to be 0.85 (95% CI, 0.73–0.99) among women screened in their 40s after 13 years of follow-up. However, the authors specify that, as studies were based on subgroup analyses (and not an a priori hypothesis), and were not designed to test the benefits of beginning screening at a specific age, there remain unresolved issues about the benefits of screening before the age of 50 years. The authors also acknowledged that some of the mortality benefit observed in these younger women may be attributable to screening after the age of 50, and thus, definitive conclusions of the benefits of starting screening at age 40 cannot be made.

On the basis of the AHRQ review, the USPSTF recommended screening mammography, with or without clinical breast examination, every 1 to 2 years for women aged 40 years and older. The rationale for this outcome was based on "fair" evidence that mammography every 12 to 33 months significantly reduces mortality from breast cancer. However, the evidence was stronger for 50- to 69-year-old women and weaker for those aged 40 to 49 years, and the absolute benefit of mammography was smaller for the younger women compared with the older women. The delay in observed benefit in the younger women (8 years compared with 4 to 6 years in the older women) also made it difficult to determine the

incremental benefit of beginning screening at age 40 rather than at age 50 years.

European Evidence

National Agency for Accreditation and Evaluation in Healthcare (ANAES), France, 2004

Should the French breast cancer screening programme be extended to women aged 40-49? Update

Objective: To assess whether the breast cancer screening program should be extended to women aged 40 to 49 years with no history of breast cancer or hereditary risk; and to update the ANAES 1999 guidelines.

Search Date: 1998 to December 2003

Studies Included	Comments	Conclusions
3 RCTs* in women aged 40 to 70 years, 1 RCT specific to 40- to 49-year old women, 1 non-RCT; 2 historical cohort studies.	➢ Report submitted to working group of 16 experts for evaluation of mass screening mammography, peer-reviewed by 25 experts. ➢ No evidence that screening of younger women had any benefit with respect to breast cancer mortality.	➢ No extension of the French program to women aged 40– 49 years should be envisaged until efficacy and cost-effectiveness in older women (50–74 years) have been proven.

*RCT indicates randomized controlled trial.

The overall objective of this review by ANAES (21) was to evaluate the benefit of mass screening by conventional mammography in France. Included were 3 RCTS, only 1 of which was specific to 40- to 49-year-old women, 1 non-randomized comparative study, and 2 historical cohort studies. On the basis of no evidence that screening of younger women had any benefit with respect to breast cancer mortality, the conclusion was to not extend the French program to women aged 40 to 49 years until efficacy and cost-effectiveness has been proven in older women (50–74 years). The report was submitted to a working group of 16 experts and then to a multidisciplinary peer-review group of 25 experts.

Evidence from New Zealand and Australia

New Zealand Health Technology Assessment, New Zealand, 1999

The early detection and diagnosis of breast cancer: a literature review – an update

Objective: To update a previous report undertaken in 1996.

Search Date: January 1996 to October 1998.

Specific to screening mammography, this review (25) concluded that among women aged 50 to 65 years (and probably 65–75 years) evidence exists that population-based screening mammography improves survival, and that there may be a benefit for women younger than 50 years, but it appears to be smaller and less certain.

NHMRC National Breast Cancer Centre – Australia, 1997

Review of the evidence about the value of mammographic screening in 40-49 year old women

Objective: To review the evidence on impact of screening on breast cancer mortality among women aged 40 to 49 years and to review the methodological issues likely to impact the analysis of effect; to assess the incremental benefit of commencing screening at 40 years rather than at 50 years; and to estimate the likely relative risk reduction, absolute risk reduction and number needed to screen if screening commences at age 40 rather than at age 50.

Search Date: Prior to 1997

Studies Included	Comments	Conclusions
8 RCTs*, 7 meta-analyses	➢ Modest (nonsignificant) benefit observed after 8 years in meta-analyses.	Benefit of second yearly screening from 40 years is modest, and the harms and costs are not inconsequential.

*RCT indicates randomized controlled trial.

This report (26) was based on a review of 7 meta-analyses and all RCT data published by 1997. The overall conclusion was that from meta-analyses, there was a nonsignificant benefit observed after 8 years to start screening at 40 years rather than at 50 years. However, the authors stated that the potential benefits should be weighed against the increased rate of false positive and false negative tests, with about 5% of women reported as "abnormal" at each screen and requiring further investigation. About 95% of these women will not have breast cancer but will experience anxiety, inconvenience, cost and discomfort to varying degrees. Furthermore, about 25% of women aged 40 to 49 years (compared with 7%–8% of women aged 50 to 69 years) with invasive breast cancer will be incorrectly diagnosed as normal.

Cochrane Collaboration, 2001

Screening for breast cancer with mammography (Review)

Objective: To study the effect of screening for breast cancer with mammography on mortality and morbidity.

Search Date: All published RCTs and meta-analyses as of 2000.

Studies Included	Comments	Conclusions
All RCTs*	➢ Two best trials are the Canadian NBSS-1 and the Swedish Malmo studies; they provided medium quality evidence.	Currently available reliable evidence does not show a survival benefit of mass screening.

*RCT indicates randomized controlled trial.

The Cochrane review (23) was based on a critical appraisal of all available studies. The results showed that the effectiveness of screening mammography in 50- to 69-year-old women was clear at 7 years and at 13 years of follow-up (for breast cancer mortality), but less so for women aged 40 to 49 years. An additional observation from these data, as observed in other reports, is that it is unclear how much of the potential benefit in studies of women randomized in their 40s is attributable to screening in one's 50s. That is, as women tend to be screened as of the age of 50 years, the benefits of screening observed in women who start screening in their 40s may be partly attributable to screening in their 50s.

Having included the Canadian NBSS-1 and the Swedish Malmo trials as the best evidence in this Cochrane review, the relative risk estimate for screening mammography for women aged under 50 years was 1.33 (95% CI, 0.92–1.92) at 10 years of follow-up. This suggestion of an increased risk of dying of breast cancer, though not significant, was also observed when all RCT results were combined (NBSS-1, Malmo, Two-County, Gothenburg and Stockholm trials): RR=1.10; 95% CI, 0.84–1.45. At 13 years of

follow-up, however, the results from the two best trials combined (the NBSS-1 and Malmo trials) was a RR of 1.03 (95% CI, 0.77–1.38), though the RR for all RCTs combined was 0.89 (95% CI, 0.72–1.10). In comparing the point estimates at 7 (RR, 1.10) and 13 (RR, 0.89) years of follow-up from all RCTs combined, the RR of less than 1.00 at 13 years suggests there is a beneficial effect of screening mammography with longer follow-up. However the likely explanation for this effect at 13 years may be a result of the benefits of screening in one's 50s.

To demonstrate the lack of benefit of screening women in their 40s, the Cochrane review also included analyses based on beginning screening at the age of 50 years. Results from all RCTs combined for this age group of women show a significant benefit with respect to breast cancer mortality at 7 years and at 13 years of follow-up (RR, 0.75; 95% CI, 0.62–0.89; and RR, 0.76; 95% CI, 0.66–0.86, respectively). However, results from the 2 better quality studies (NBSS-1 and Malmo trials) showed the absence of a statistically significant benefit at 7 years (RR, 0.88; 95% CI, 0.64–1.20) and at 13 years (RR, 0.94; 95% CI, 0.77–1.15) of follow-up for women randomized at 50 years of age or older.

Summary of Findings on Effectiveness

In summary, all health technology assessments and the Cochrane review do not recommend screening mammography for women in their 40s, except for that conducted by the AHRQ in the United States, which is based on their own meta-analysis. In reviewing the evidence below, it is also important to balance the recommendation of the AHRQ against evidence from other organizations in the United States that recommend against screening women in their 40's.

The findings and conclusions on the effectiveness of screening mammography in women aged 40 to 49 years are summarized below. Presented first are the Canadian reviews, followed by those from the United States, Europe, Australia and New Zealand. The Cochrane review is presented at the end of this section.

Summary of Medical Advisory Secretariat Review

Table 2 outlines the quality of the evidence, as defined by the Medical Advisory Secretariat, for screening mammography.

Table 2: Quality of Evidence of Studies for Screening Mammography*

Study Design	Level of Evidence	Number of Eligible Studies
Systematic reviews of RCTs	1a	0
Large RCT	1b	2 + 6
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

*RCT refers to randomized controlled trial; g, grey literature.

Randomized Clinical Trials

Seven RCTs on screening mammography met the inclusion and exclusion criteria for this assessment. These were conducted in Canada, Sweden, the United States, and the UK, have been included in worldwide scientific reviews of the evidence. Several reviews (prior to December 2006) refer to either 7 or 8 trials, to describe all RCTs ever conducted on the issue at hand, but this discrepancy is due to differences in reporting of RCTs. That is, some authors refer to the Swedish Malmo trial as the Malmo I and II, and the Two-County trial is sometimes referred to as 2 separate studies, the Kopparberg and Ostergotland trials. In this health technology policy assessment, results of the Malmo trial are based on the combination of Malmo I and II, and the Two-County study results are based on the Kopparberg and Ostergotland trials together.

Table 3 outlines the overall structure of the RCTs (results published prior to December 2006) with a description of the ages at which women were randomized in the studies, the years during which screening was conducted, and the type, frequency, and duration of screening. The screening period for all RCTs combined was from 1963 (year of the first screen in the HIP trial) to 1992 (year of the last screening round in the Gothenburg trial). The studies have been listed in the chronological order in which screening began.

Table 3: Methods of Randomized Controlled Trials on Screening Mammography*

Randomized Controlled Trial	Age at Randomization, Years	Screening Period	Intervention x Duration
HIP (NY) (5)	40–64	1963–1970	M + CBE (12 mos) x 4 in 4 yrs
Malmo (9)	43–70	1976–1990	M (18–24 mos) x 4 in 8 yrs
Two-County (10)	40–74 40–74	1976–1978	M (24 mos) x 3 in 6 yrs M (24 mos) x 4 in 8 yrs
Edinburgh (19)	45–64	1979–1988	M + CBE (24 mos) x 4 in 8 yrs
NBSS-1 (6)	40–49 40–64	1980–1988	M+CBE (12 mo) x 5 in 5 yrs.
Stockholm (11;27)	39–59	1981–1985	M (28 mo) x 2 in 4 yrs.
Gothenburg (12;13;28)		1982–1992	M (18 mo) x 3 in 5 yrs.

*M indicates mammography, CBE, clinical breast examination; mos, months; yrs, years.

Listed in Table 3 are RCTs published prior to December 2006 that included women randomized in their 40s. Of these, only the Canadian NBSS-1 was specifically designed to test the effectiveness of mammography in women aged 40 to 49 years, whereas all other RCTs addressed the issue among younger women on the basis of subset analyses. This distinction between the Canadian NBSS-1 and other trials has been emphasized in several health technology assessment organizations (e.g., AETMIS in Quebec, Cochrane Collaboration) and as it has been reported as one of the best trials conducted on breast cancer screening, and the only one to specifically assess the effectiveness of screening women in their 40s, it will be reviewed first.

Canadian National Breast Screening Study: Two trials have been conducted by Miller et al. in Canada to determine the effectiveness of screening mammography; the NBSS-1 was specific to women randomized between the ages of 40 and 49 years, whereas the NBSS-2 involved the randomization of women 50 to 59 years of age. The issue of effectiveness was examined in these 2 separate trials to enable the testing of

hypotheses specific to each age group. The trial of interest for this MAS review is the NBSS-1 with its focus on women 40 to 49 years of age at randomization. Sample size estimations for this trial were based on a 90% power to detect a reduction of breast cancer mortality of 40%. On the basis of the actual number of breast cancer cases observed, the study was found to have a power of 80% to detect a 30% reduction in mortality (2-sided). (2)

The arms of randomization in this trial were annual mammography and physical examination or usual care after an initial physical examination. Results were published at mean follow-up periods of 8.5 years, 8.8 to 13 years, and 11 to 16 years, with relative risk (RR) estimates for breast cancer mortality (for mammography relative to usual care) of 1.36 (95% CI, 0.84–2.21), 1.14 (95% CI, 0.83–1.56) and 1.06 (95% CI, 0.80–1.40), respectively. All analyses gave rise to a nonsignificant increased risk for breast cancer mortality, although the risk was higher for the shortest period of follow-up and decreased with longer periods of follow-up, which may partly be explained by the different hormonal profiles of premenopausal compared with postmenopausal women.

The HIP Trial: This trial, conducted in New York State in the 1960s, included 29,133 women aged 40 to 64 years at randomization. Mammography plus clinical breast exam was conducted annually for 4 years. After a mean follow-up of 18 years, the relative risk for breast cancer mortality was 0.78 (95% CI, 0.61–1.00). The HIP trial was the first to identify a potential differential effect of mammography in women above and below 50 years of age. Although this study was not designed to examine this issue, subsequent trials set out to show results for younger women based on stratified analyses.

Swedish Trials: Of the 4 trials conducted in Sweden (Malmo, Two-County, Stockholm and Gothenburg), all assessed the effectiveness of mammography alone. Two of the trials combined are referred to as the Malmo trials: Malmo I included randomization of women aged 45 to 70 years, and Malmo II included 43- to 49-year old women from Malmo I. In both trials, women were screened every 18 to 24 months for 8 years. Both trials showed a nonsignificant decrease in breast cancer mortality (Table 4). The benefit associated with mammography was a RR of 0.65 (95% CI, 0.39–1.08) for a mean follow-up of 9.1 years and a RR of 0.81 (95% CI, 0.66–1.00) for a mean follow-up of 19.2 years (4), although both results were not statistically significant. In such cases of unclear benefits, however, it is important to weigh the potential harms against the potential benefits (9).

Two-County Trials: These trials, conducted in Kopparberg and Ostergotland, included the randomization of 35,448 women aged 40 to 74 years screened between 1976 and 1990. Both trials screened with mammography alone, every 2 years for 6 rounds in Kopparberg and 8 rounds in Ostergotland. After a mean follow-up of 17.4 years, a nonsignificant effect (RR, 0.89; 95% CI, 0.72–1.09) was observed; after 20 years, however, there was a significant 41% reduction in breast cancer mortality (RR, 0.59; 95% CI, 0.47–0.75). Results of the reanalysis of all of the Swedish trials (29) gave rise to a nonsignificant increase in breast cancer mortality for 40- to 49-year-old women (RR, 1.05; 95% CI, 0.64–1.71).

Gothenburg Trial: This trial randomized women aged 39 to 59 years, with screening mammography conducted every 18 months for 3 screening rounds in 5 years. Results for 39- to 49-year-old women at randomization reveal a nonsignificant reduction of 22% (RR, 0.78; 95% CI, 0.57–1.07). However, results of the reanalysis of all the Swedish trials (29) gave rise to a significant decrease in breast cancer mortality for women aged 40 to 49 years at randomization (RR, 0.58; 95% CI, 0.35–0.96).

Edinburgh Trial: This trial involved screening mammography every 2 years and a physical exam annually, compared with normal medical care in Scotland. The authors specified there was no a priori hypothesis about age groups. At 12.6 years of follow-up, the effect was significant with a RR of 0.78 (95% CI, 0.62–0.97). However, this trial has been designated as poor quality evidence in the AHRQ (22) technology assessment; thus, it has been excluded from the United States Preventive Services Task Force

assessment.

Table 4: Results of Randomized Controlled Trials on Screening Mammography*

Trial	Mammo. Group/ Control No. women	Follow-up, Years	Relative Risk (95% Confidence Interval)
HIP (5)	14,432 / 14,701	18.0	0.78 (0.61–1.00)
Malmo (9)	13,528 / 12,242	19.2	0.81 (0.66–1.00)
		9.1	0.65 (0.39–1.08)
Two-County (10)	19,844 / 15,604	20.0	0.59 (0.47–0.75)
		17.4	0.89 (0.72–1.09)
Edinburgh (19)	11,505 / 10,269	12.6	0.78 (0.62–0.97)
NBSS-1 (6)	25,214 / 24,216	8.8–13.0	1.14 (0.83–1.56)
		11.0–16.0	1.06 (0.80–1.40)
Stockholm (11;27)	14,842 / 7,108	14.9	0.90 (0.63–1.28)
Gothenburg (12;13;28)	11,724 / 14,217	13.3	0.78 (0.57–1.07)

The UK Age Trial:

UK Age Trial (17;30), the most recently conducted study, included the randomization of 160,921 women aged 40 and 41 years. This trial was designed to randomize 195,000 women aged 40 to 41 years at entry (for an 80% power) to detect a 20% reduction in breast cancer mortality at 10 years, although accrual was stopped at 160,921 (for a power of 73%).

The mortality reduction at an average follow-up of 10.7 years was not statistically significant: RR=0.83, 95%CI: 0.66-1.04. This finding was based on the actual observed deaths from breast cancer in the study, however, the authors attributed this lack of significance to the decreased power of the study. To address this issue, they conducted a meta-analysis and reported a significant 16% reduction in breast cancer mortality, RR=0.84, 95%CI: 0.74-0.95. This analysis, however, combined data from other RCTs, regardless of the length of follow-up and ages of the women when breast cancer was detected. They also included results of the Edinburgh trial which has been excluded from several other reviews. The most important weakness of the meta-analysis they performed, however, was the fact that the meta-analysis combined the UK Age results with those of other RCTs that were thought to include mortality benefits attributable to screening in their 50s. As well, the UK Age trial was based on the randomization of women 40 or 41 years of age only and is not necessarily comparable to trials in which women were other than these ages. A more valid analysis would have been the combination of results from RCTs of women in their early 40s. Such a comparison was also reported with the UK Age trial results combined with that of the 14.7 year follow-up of women 40 to 44 years of age at randomization from the Swedish trials. The reported 16% reduction in mortality in this case was not significant (RR: 0.84, 95%CI: 0.69-1.01). Furthermore, as the methodology of the UK Age trial was designed to eliminate the possibility of attributing the potential benefit of screening in one's 50s to women in their 40s, particularly as the duration of follow-up is extended into the 50s, it would have been appropriate to combine the 10 year UK results with the Swedish trial data for a similar follow-up period, rather than for a mean follow-up of 14.7 years.

If the Canadian NBSS-1 results for 40 to 44 year old women (at randomization) had been included in this latter meta-analysis, the reduction in mortality (16%) would have been reduced and likely would have remained nonsignificant.

Sensitivity and Specificity

The accuracy of mammography can be measured by examining sensitivity and specificity. Sensitivity is defined as the proportion of truly diseased persons in the screened population who are identified as diseased by the screening test. (4) With respect to screening mammography, sensitivity refers to the ratio of true positives (breast cancers correctly identified at the screening examination) / true positives + false negatives (breast cancers not identified at the screening examination, detected as interval cases).

Specificity, on the other hand, is the proportion of truly nondiseased persons in the screened population who are identified as nondiseased by the screening test. In the context of screening mammography, it is the ratio of true negatives / (true negatives + false positives). (4)

Table 5: Sensitivity and Specificity Data for Screening Mammography*

Source (Age Range if Other Than 40–49)	Sensitivity 40–49 Years	Sensitivity 50–59 Years	Specificity 40–49 Years	Specificity 50–59 Years
British Columbia Cancer Agency	76%	85%	90% (ages 40 - 70+ years)	
UK Age Trial				
1st round	74%		—	
subsequent rounds	47%–64%		—	
Canadian NBSS-1				
1st round	(from all rounds)		82%	83%
subsequent rounds	81%	88%	93%	96%
All RCTs (all ages) (1/2 view, 12-24 mos.)	53%–92%		—	

* RCT indicates randomized controlled trial.

As shown in Table 5, the sensitivity of the Canadian NBSS-1 for 40 to 49 year old women is similar to that of the UK Age trial and that of the British Columbia Cancer Agency. This analysis was included to demonstrate the validity of the Canadian NBSS-1 study results (trial conducted in the 1980s), relative to more modern technology that is assumed in centers in the UK (trial conducted in the 1990s) and in British Columbia.

Summary of Findings of Literature Review

There is Level 1 Canadian evidence that screening women between the ages of 40 and 49 years who are at average risk for breast cancer is not effective, and that the absence of a benefit is sustained over a maximum follow-up period of 16 years.

All remaining studies that reported on women aged under 50 years were based on subset analyses. They provide additional evidence that, when all these RCTs are taken into account, there is no significant reduction in breast cancer mortality associated with screening mammography in women aged 40 to 49 years.

The UK Age Trial results published in December 2006 did not change these findings.

Economic Analysis

Because screening of women aged 40 to 49 years women was not found to be effective, an economic analysis was not performed.

Policy Development

Diffusion – Provincial

Provinces and territories in Canada were contacted regarding screening mammography. All, except Nunavut where the incidence of breast cancer is low, reported having screening mammography services for women aged over 50 years. Across Canada, with the exception of the Yukon Territories, women younger than 50 years can have a screening mammogram with a physician's referral.

Risks Associated with Screening of Younger Women

The risks most often cited with respect to screening mammography of younger women are radiation-induced breast cancer, the increased risk of missed cancers (or false negatives) owing to lower mammographic sensitivity in younger than older women, the psychological impact of false positive mammograms, and the potential overtreatment of cases of DCIS.

Several studies have been conducted to determine the risk of breast cancer associated with exposure to radiation from mammograms. However, the risk associated with cumulative exposure of radiation remains unclear. Although a mammogram conducted annually from the age of 40 to 49 years of age would result in 10 mammograms in a 10-year period (more if women are recalled). In addition to radiation exposure from screening at 50 years of age and over, there remain uncertainties about the true clinical effect of such exposures.

A commentary published at the time of the UK Age Trial results (31) emphasizes the importance of balancing the risks against the potential benefits of screening of women in their 40s. The authors conclude that in cases of unclear effectiveness and potential for harm, there is no certainty of a net benefit.

Overtreatment of breast cancer cases, mainly with DCIS, is also considered a potential harm of screening younger women. In a recent American study of women aged 40 to 69 years who were screened for breast cancer, about 10% had an abnormal mammogram and required further diagnostic testing. (32) Of these, 15% were sent for biopsy. Among those who had a biopsy, about 20% were diagnosed with cancer (including DCIS). It is important to note that these data are specific to practices in the United States and are based on women younger and older than 50 years.

Ontario-specific data from the Ontario Breast Screening Program (33) shows that of 205,215 screens in women aged over 50 years, 8.9% had an abnormal mammogram. Of these, 81.7% required further work-up, and 16.8% required a biopsy. These data are similar to those from the United States, with the exception of the proportion of women diagnosed with cancer. In the Ontario Breast Screening Program, the proportion of women diagnosed with breast cancer was 36%. This information from Ontario, in conjunction with the American data, suggests that the inclusion of women in their 40s may result in more women being sent for further (unnecessary) diagnostic imaging and invasive biopsy procedures in their 40s. The psychological impact of such interventions should not be underestimated.

Conclusions

There is Level 1 evidence that screening mammography in women aged 40 to 49 years at average risk for breast cancer is not effective in reducing mortality.

Moreover, risks associated with exposure to mammographic radiation, the increased risk of missed cancers due to lower mammographic sensitivity, and the psychological impact of false positives, are not inconsequential.

The UK Age Trial results published in December 2006 did not change these conclusions.

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