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Health Quality Ontario

Prostate-Specific Antigen (PSA)–Based Population Screening for Prostate Cancer: An Economic Analysis

A TAWFIK

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ABSTRACT

Background

The prostate-specific antigen (PSA) blood test has become widely used in Canada to test for prostate cancer (PC), the most common cancer among Canadian men. Data suggest that population-based PSA screening may not improve overall survival.

Objectives

This analysis aimed to review existing economic evaluations of population-based PSA screening, determine current spending on opportunistic PSA screening in Ontario, and estimate the cost of introducing a population-based PSA screening program in the province.

Methods

A systematic literature search was performed to identify economic evaluations of population-based PSA screening strategies published from 1998 to 2013. Studies were assessed for their methodological quality and applicability to the Ontario setting. An original cost analysis was also performed, using data from Ontario administrative sources and from the published literature. One-year costs were estimated for 4 strategies: no screening, current (opportunistic) screening of men aged 40 years and older, current (opportunistic) screening of men aged 50 to 74 years, and population-based screening of men aged 50 to 74 years. The analysis was conducted from the payer perspective.

Results

The literature review demonstrated that, overall, population-based PSA screening is costly and cost-ineffective but may be cost-effective in specific populations. Only 1 Canadian study, published 15 years ago, was identified. Approximately $119.2 million is being spent annually on PSA screening of men aged 40 years and older in Ontario, including close to $22 million to screen men younger than 50 and older than 74 years of age (i.e., outside the target age range for a population-based program). A population-based screening program in Ontario would cost approximately $149.4 million in the first year.

Limitations

Estimates were based on the synthesis of data from a variety of sources, requiring several assumptions and causing uncertainty in the results. For example, where Ontario-specific data were unavailable, data from the United States were used.

Conclusions

PSA screening is associated with significant costs to the health care system when the cost of the PSA test itself is considered in addition to the costs of diagnosis, staging, and treatment of screen-detected PCs.

PLAIN LANGUAGE SUMMARY

The prostate-specific antigen (PSA) blood test is a test for prostate cancer, the most common cancer among men in Canada. The test is widely used for early detection of the disease. In cases where the cancer progresses, it can decrease a man's quality of life or cause death. However, most prostate cancers grow slowly and have a good prognosis, even without treatment.

Health Quality Ontario was asked to investigate the appropriate use of PSA screening and its economic impact on the health care system. The evidence-based analysis (reported separately) looked at the usefulness of the PSA test as a tool to screen men in the general population for prostate cancer and showed that screening does not provide an overall survival benefit. Ontario currently pays for the PSA test for men who are considered to be at high risk for prostate cancer or who have had the disease and are being followed after treatment. Other men can opt to pay for the test themselves. If a man receives follow-up tests or treatment based on his PSA test result, the health care system generally carries those costs.

According to existing health economics research, population-wide PSA screening is costly and ineffective but may be cost-effective in selected populations. No recent studies had looked at the economic impact of PSA screening in Canadian men for the early detection of prostate cancer. Our economic analysis, the first of its kind in Canada in almost 15 years, showed that PSA screening is associated with significant costs to Ontario's health care system. We estimated that PSA screening currently costs Ontario approximately $119.2 million a year, including the cost of the test itself and also the costs of follow-up tests and treatment for cancers detected through screening. To introduce a program that would encourage all men 50 to 74 years old to get screened, Ontario would spend approximately $149.4 million in the first year. These estimates are for 1 year only and do not include the likely changes in costs and savings over the longer term.

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LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AS	Active surveillance
CEA	Cost-effectiveness analysis
CIHI	Canadian Institute for Health Information
CT	Computed tomography
CUA	Cost-utility analysis
DRE	Digital rectal exam
ERSPC	European Randomized Study of Screening for Prostate Cancer
ICER	Incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
LY	Life-year
NACRS	National Ambulatory Care Reporting System
OCCI	Ontario Case Costing Initiative
OCR	Ontario Cancer Registry
ODB	Ontario Drug Benefit program database
OHIP	Ontario Health Insurance Plan
PC	Prostate cancer
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PSA	Prostate-specific antigen
QALY	Quality-adjusted life-year
RPDB	Registered Persons Database
RP	Radical prostatectomy
RT	Radiation therapy
SDS	Same-Day Surgery database

BACKGROUND

The Toronto Health Economic and Technology Assessment (THETA) Collaborative was commissioned by Health Quality Ontario to evaluate the appropriate use of prostate-specific antigen screening for prostate cancer in asymptomatic males in the general population. This report summarizes the methods and results of the systematic economic literature review and original economic evaluation developed for this analysis.

Health Quality Ontario conducts full evidence-based analyses, including economic analyses, of health technologies being considered for use in Ontario. These analyses are then presented to the Ontario Health Technology Advisory Committee, whose mandate it is to examine proposed health technologies in the context of available evidence and existing clinical practice, and to provide advice and recommendations to Ontario health care practitioners, the broader health care system, and the Ontario Ministry of Health and Long-Term Care.

DISCLAIMER: Health Quality Ontario uses a standardized costing method for its economic analyses. The main cost categories and associated methods of retrieval from the province's perspective are described below.

Hospital costs: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency department visit, and day procedure costs for the designated International Classification of Diseases diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in the estimated costs of the diagnoses and procedures under consideration. Due to difficulties in estimating indirect costs in hospitals associated with a particular diagnosis or procedure, Health Quality Ontario normally defaults to a consideration of direct treatment costs only.

Non-hospital costs: These include physician services costs obtained from the Ontario Schedule of Physician Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible, or from the device manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied (to both costs and effects/QALYs), as recommended by economic guidelines.

Downstream costs: All reported downstream costs are based on assumptions of population trends (i.e., incidence, prevalence, and mortality rates), time horizon, resource utilization, patient compliance, health care patterns, market trends (i.e., rates of intervention uptake or trends in current programs in place in the province), and estimates of funding and prices. These may or may not be realized by the Ontario health care system or individual institutions and are often based on evidence from the medical literature, standard listing references, and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach.

The economic analysis represents ***an estimate only***, based on the assumptions and costing methods explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

NOTE: Numbers may be rounded to the nearest decimal point, as they may be reported from an Excel spreadsheet

Prostate Cancer

Prostate cancer (PC) is the most common cancer in Canadian men, affecting more than 175,000 Canadians. An estimated 23,600 new cases will be diagnosed in Canada in 2013, including 9,600 in Ontario. (1) Most PCs are slow-growing and have a good prognosis, even without treatment. (2) The estimated 5-year survival of men with the disease in Ontario is 97%. However, for men in whom the cancer progresses, PC is associated with significant morbidity and mortality. It remains the third leading cause of cancer death in Canadian men, with 1 in 28 Canadian men dying from PC in their lifetimes. (1)

PSA Screening

Prostate-specific antigen (PSA) is a protein produced by normal and malignant prostatic cells. In men with a normal prostate, only small amounts of PSA leak into circulation, but an abnormal

prostate leaks much larger amounts of the antigen. (3) In the early 1990s, the PSA blood test was developed as a test for PC and has become widely used in Canada. Close to 50% of Canadian men aged 40 years and older report receiving a PSA test in their lifetimes. (4) As part of a man's regular check-up, physicians will usually perform a digital rectal exam (DRE), whereby the physician inserts a gloved finger into the rectum to check for growths in or enlargement of the prostate gland. Following a suspicious DRE, a physician may order a PSA test or may prefer that the two tests be conducted simultaneously.

Canadian guidelines on the appropriate use of PSA screening are conflicting. For example, the Canadian Urological Association recommends that men at average risk for PC, and with a life expectancy of at least 10 years, be screened from ages 50 to 70 years, and that men at high risk be screened from ages 40 to 70 years (no screening interval specified). (5) In contrast, Prostate Cancer Canada recommends that all men at aged 40 years receive a baseline PSA test and that the test be repeated every 5 years until they reach 50 years of age, at which point they should be screened annually or semi-annually (no age specified to stop testing). (6) The Canadian Task Force on Preventive Health Care is currently developing a guideline on screening for PC. (2)

The question of whether the PSA test should be used to screen for PC at the population-level has been the subject of great controversy. A recent Cochrane review of randomized controlled trials of PSA screening for PC, either with or without DRE, concluded that screening did not significantly decrease PC-specific or overall mortality. (7) The review also found that the test can result in a high number of false-positives, leading to overdiagnosis, overtreatment, and a potential decrease in quality of life. (7) Screening itself can cause anxiety, and prostate biopsy resulting from an elevated PSA level can cause bleeding, pain, and infection. In addition, initial treatment options following an abnormal biopsy result typically involve radical prostatectomy (RP), radiation therapy (RT), pharmacological androgen deprivation therapy (ADT), or surgical ADT in the form of orchiectomy, all of which can cause incontinence and erectile dysfunction. (7) Patients can also be put on active surveillance (AS), whereby they receive no treatment and are monitored carefully by their physician.

Of the 5 studies included in the Cochrane review, most were assessed as posing a high risk of bias. Only the 2 most recent trials—the European Randomized Study of Screening for Prostate Cancer (ERSPC) (8) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial conducted in the United States (9)—demonstrated a low risk of bias. The ERSPC trial was the only trial to report a significant reduction in any type of mortality (21% reduction in PC-specific mortality in a prespecified subgroup of men 55 to 69 years of age). (7)

Ontario Context

The Ontario Ministry of Health and Long-Term Care does not currently fund a population-based PSA screening program. The province pays for the test for men who are receiving treatment for PC, being followed after treatment, or at high risk for PC because of family history, African ancestry, or the results of their physical exam (including DRE). The PSA test is available to asymptomatic men who, with the help of their physician, make an informed decision to be tested, but they must pay for it themselves. (10) In contrast to organized screening programs of asymptomatic men, this type of screening, whereby asymptomatic men receive the test based on individual choice, is called opportunistic screening.

No province or territory in Canada currently has a population-based screening program. With results from the long-awaited PLCO and ERSPC trials now available, an evaluation of the

appropriate use of PSA screening in Ontario was requested. Health Quality Ontario conducted a clinical review of PSA screening in Ontario, which demonstrated that population-wide PSA screening may not be effective at reducing overall mortality. (11) This report describes our evaluation of the potential economic impact of population-based PSA screening in Ontario.

Objectives

This analysis had 3 objectives: to conduct a literature review of existing economic evaluations of population-based PSA screening, to determine how much is currently being spent on opportunistic screening in Ontario, and to estimate how much it would cost to introduce a population-based PSA screening program in the province.

ECONOMIC ANALYSIS

Research Questions

- What is known from published economic evaluations of population-based PSA screening programs for prostate cancer?
- How much is currently being spent on opportunistic PSA screening of men in Ontario?
- How much would it cost to introduce a population-based PSA screening program for men aged 50 to 74 years in Ontario?

Economic Literature Review

Methods

Literature Search

A search of the economic literature was performed on October 22, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid EMBASE, and the Cochrane Library, for economic analyses looking at opportunistic PSA screening or population-based PSA screening programs for the early detection of PC. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Appendix 1 describes the literature search strategy.

Inclusion Criteria

- Cost-utility analyses (CUAs), cost-effectiveness analyses (CEAs), cost-benefit analyses, budget impact analyses, and cost analyses
- Studies that included both costs associated with the screening process and the treatment of screen-detected prostate cancer (including radiation therapy, radical prostatectomy, surgical and pharmacological hormonal therapy, and active surveillance)

Exclusion Criteria

- Studies published before January 1, 1998
- Abstracts, posters, reviews, letters/editorials, foreign language publications, and unpublished studies
- Studies that only considered the costs associated with screening and not treatment costs

Results of Economic Literature Review

From a total of 258 abstracts, 18 full-text articles were retrieved based on the inclusion criteria, and 7 were identified as relevant and included in the analysis. All included studies were conducted from the payer perspective and consisted of a CUA, (12) 4 CEAs, (13-16) and 2 cost analyses. (17;18) Four studies were excluded because their comparators were not relevant: one study compared derivatives of the PSA test with each other; (19) another study compared the addition of the PSA test to transrectal ultrasound-guided prostate biopsy (TRUS-Bx) with TRUS-Bx alone for diagnosing prostate cancer; (20) a third study evaluated whether the introduction of a physician education program would improve decision-making around PSA screening; (21) and the fourth study evaluated a new risk index for the detection of prostate cancer. (22) Three studies were excluded because they did not include the relevant treatment costs associated

with screen-detected prostate cancer patients. (23-25) Finally, 4 studies were excluded because their research questions were not relevant to our objectives: one study evaluated the economic impact of false-positive cancer screens; (26) the second study evaluated the cost-effectiveness of basing rescreening intervals on baseline PSA values; (27) the third study evaluated the economic impact of PSA screening in a single hospital in the United Kingdom; (28) and the fourth study aimed to predict the minimal improvement in mortality required to make PSA screening cost-effective in the United States. (29). Appendix 2 provides a summary of the included studies, which are further described below.

The only CUA identified through the systematic review was the Australian study by Martin et al, (12) which compared no PSA screening with screening of men aged 50 years and older every 4 years. Patients were stratified by their risk for PC, and the model was run once for each risk group (average, high, and very high risk). The incidence of screen-detected and non-screen-detected cancers used in the model were based on the ERSPC trial, age-adjusted based on Australian incidence data. Screening of men every 4 years would cost $291,817 per quality-adjusted life-year (QALY) gained, $110,726 per QALY gained, and $30,572 per QALY gained, for men at average, high, and very high risk, respectively. The results showed that screening at 4-year intervals was only cost-effective in men at very high risk for PC. The authors refer to patients with a family history of PC as high risk and patients carrying genetic markers for PC as very high risk, and it is in this latter group that screening might afford the greatest benefit. The authors concluded that further research is required to determine the size of the clinical benefit of screening in this subgroup.

Holmberg et al (15) conducted a CEA based on the results of a screening trial in a Swedish community, whereby 1,492 men, aged 50 to 69 years, were randomized to 4 rounds of screening over a 12-year period, and 7,679 men acted as controls. Men were screened by DRE for the first 2 rounds and by DRE and PSA for the last 2. Over the first 10 years, screening cost 158,000 Swedish krona (Sk) per extra cancer case detected, 167,000 Sk per extra localized cancer case detected, and 249,000 Sk per extra cancer case treated curatively. In 2004, Sennfalt et al (16) updated this analysis using an improved costing methodology and additional data on long-term costs and effects, for a total of 15 years of follow-up. Over the 15 years, the authors found that the cost of screening was 168,000 Sk per extra localized cancer case detected and 356,000 Sk per extra cancer case treated curatively. Both studies yielded similar results, but it is difficult to compare these studies with the results of other CEAs because the denominators of the incremental cost-effectiveness ratios (ICERs) are not the standard life-years (LYs) gained (or QALYs gained, as in CUAs).

Hamashima and Yoshida (14) conducted a CEA comparing no screening with 3 annual screening strategies (screen all with DRE, screen all with PSA, and screen all with a combination of DRE and PSA) in asymptomatic Japanese men aged 40 to 69 years. The model had a lifetime horizon and was run 3 times, once for each age group (40–49, 50–59, and 60–69 years old). The older the patient, the less cost-effective each screening strategy was found to be (results were presented as a range, from the 40-to-49-year age group to the 60-to-69-year age group). Compared with no screening, screening with DRE had an ICER of $3,700 per LY to $74,200 per LY, screening with PSA had an ICER of $3,000 per LY to $32,900 per LY, and screening with both had an ICER of $3,200 per LY to $75,500 per LY. Overall, screening with PSA was more cost-effective than screening with DRE alone, followed by screening with both. The only strategies that were not cost-effective were screening with DRE and screening with both in men aged 60 to 69 years old.

The fourth CEA, conducted by Benoit et al, (13) compared 4 screening strategies in American men with a life expectancy of at least 10 years. The 4 strategies were: screen men aged 50 to 59, 60 to 69, and 50 to 69 years with both PSA and DRE, and screen men aged 50 to 70 years with PSA alone. All strategies were found to be cost-effective except for screening men aged 50 to 59 years with both PSA and DRE, which had an ICER between $66,210 per LY and $89,041 per LY.

The only Canadian study identified was a descriptive costing analysis by Krahn et al, (18) which looked at the 1-year cost of opportunistic and population-wide PSA screening in asymptomatic Canadian males. They compared the following strategies: current practice in 1995 (opportunistic screening of men aged 40 to 74 years), screening of all men aged 50 to 74 years in 1995, and screening of all men aged 50 to 74 years in 2005. The 3 strategies cost $45 million, $317 million, and $219 million, respectively. The authors explained that the lower cost in the year 2005 was a result of decreased uptake of population-based screening strategies over time.

The second cost analysis, conducted by Heijnsdijk et al, (17) used the Microsimulation Screening Analysis model to predict the costs associated with population-based PSA screening in the Netherlands, based on data from the ERSPC trial. The analysis was run over 25 years for all males in the general population, with screening starting and ending at varying ages. Five strategies were compared: no screening; screen every 4 years, from aged 50 to 70 years; screen every year, aged 55 to 70 years; screen every second year, aged 55 to 70 years; screen every 4 years, aged 55 to 75 years. No screening was the cheapest strategy (€30.3 million), followed by screening from age 50 to 70 years every 4 years (€60.7 million). Screening from age 55 to 75 years every 4 years was the most expensive strategy (€83.4 million).

The results of the literature review demonstrate that PSA screening is expensive and cost-ineffective overall but may be cost-effective in select populations, depending on age, genetic predisposition to PC, and whether or not patients are also screened by DRE. Except for the cost analysis by Krahn et al, (18) none of the studies included in this review are directly relevant to the Ontario context, as they were conducted outside of Canada. However, that study has 2 limitations: first, it was conducted 15 years ago and patterns of care for patients with screen- and non-screen-detected PC have changed dramatically since that time; second, most of the data used in the study came from a single hospital in Quebec and the costs are not representative of the Ontario (or even the Canadian) context.

Primary Economic Evaluation

Several economic evaluations identified in the literature review addressed population-based PSA screening, but only 1 study was potentially relevant to Ontario and it was published 15 years ago. Due to these limitations, a primary costing study was conducted.

Methods

Type of Analysis

A descriptive cost analysis was performed to estimate the 1-year costs associated with the following 4 PSA screening strategies in Ontario:

- Opportunistic screening of men aged 40 years and older (i.e., current practice)
- Opportunistic screening of men aged 50 to 74 years
- Population-based screening of men aged 50 to 74 years
- No screening

Perspective

The analysis was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care.

Target Population

The target population for this economic analysis was asymptomatic men in the general Ontario population, at varying ages.

Model Parameters

Incidence of PC and Initial Treatment Distribution

To understand trends in PC incidence over time in Ontario, we used linked administrative data housed at the Institute for Clinical and Evaluative Sciences (ICES) in Toronto. We estimated the incidence of newly diagnosed cases of nonmetastatic PC in the province in each year from January 1, 2003, to December 31, 2010, for 10-year age groups, ages 40 years and older (Table 1). We also used these linked data sources to determine the initial treatment distribution for these patients during their first year after diagnosis (Table 2). Specifically, we identified all newly diagnosed PC cases in the Ontario Cancer Registry (OCR) for each of the study years and used the date of entry in the registry as the index date. We then excluded patients based on the following criteria (in order): sex coded as female or missing, not Ontario resident, invalid or missing Ontario Health Insurance Plan (OHIP) number, diagnosis of another malignancy in the OCR (any time prior to or within 1 year following PC diagnosis date), age less than 40 years at diagnosis, orchiectomy prior to index date, and probable metastatic disease (i.e., diagnosis of metastases, receiving palliative care, or receiving chemotherapy).[1]

We followed the remaining patients forward for 1 year after the index date to identify the initial treatment they received (including radical prostatectomy [RP], radiation therapy [RT], androgen deprivation therapy [ADT], active surveillance [AS], or ADT as adjuvant or neo-adjuvant therapy

[1]Information about a patient's age, sex, and residence was obtained from Ontario's Registered Persons Database (RPDB). Metastatic disease was considered present if a patient had any of the following within 6 months after prostate cancer diagnosis: admission to a palliative care unit recorded in the Discharge Abstract Database (DAD), > 2 physician billings for palliative care recorded in the OHIP database, diagnosis of metastases or secondary malignancy in DAD, or 1 record in DAD or National Ambulatory Care Reporting System (NACRS) Oncology or > 2 physician billings for chemotherapy in OHIP.

to RP or RT). Patients who were not treated were assumed to be on AS. Of the men on ADT, 97% received pharmacological ADT and the rest received surgical ADT. None of the men receiving either RT or RP, along with ADT as adjuvant (or neo-adjuvant) therapy, received the ADT surgically. Since information on pharmacological ADT in men aged 40 to 64 years was not available in Ontario, we assumed that men aged 40 to 59 years did not receive this treatment and that men aged 60 to 64 years received it at the same rate as men aged 65 to 69 years. (*Personal communication, clinical expert, November 13, 2013*)

We used 2010 as the stop date for identifying the index event because follow-up data were not yet available beyond 2011. In addition to the (RPDB) and OCR, the following administrative databases were used: 1) the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) for information on inpatient hospitalizations, 2) the CIHI Same-Day Surgery database (SDS) for outpatient same-day surgeries, 3) the CIHI National Ambulatory Care Reporting System (NACRS) for emergency visits, 4) the Ontario Drug Benefit program database (ODB) for drugs, and 5) the OHIP Claims History Database for physician billing claims. Table 3 lists the data sources and codes used for each variable in the model.

Table 1: Number of Newly Diagnosed, Nonmetastatic Prostate Cancer Cases in Ontario, Overall and by Age Group, 2003–2010

Year	Total Cases	Age Group, Years					
		40–49	50–59	60–69	70–79	80–89	90+
2003	6,779	123	1,135	2,546	2,191	712	72
2004	7,275	158	1,393	2,615	2,322	718	69
2005	7,849	169	1,462	2,965	2,374	793	86
2006	8,319	183	1,715	3,143	2,429	767	82
2007	8,481	213	1,714	3,332	2,402	751	69
2008	7,984	202	1,654	3,052	2,279	733	64
2009	8,034	206	1,562	3,218	2,252	724	72
2010	8,031	205	1,559	3,213	2,248	733	73

Source: Data provided by the Institute for Clinical and Evaluative Sciences, November 18, 2013.

Table 2: Initial Treatment Distribution for Newly Diagnosed, Nonmetastatic Prostate Cancer Patients in Ontario, Overall and by Age Group, 2010

Treatment	Total Number of Patients	Proportion of Total, %	Age Group, Years					
			40–49	50–59	60–69	70–79	80–89	90+
AS	2,777	34.6	50	520	1,000	778	381	48
RP	2,540	31.6	130	843	1,341	225	<5	0
RT	1,503	18.7	25	194	624	596	64	0
ADT	589[a]	7.3	0	<5	70	266	231	21
RT + ADT[b]	563	7.0	0	< 5	138	370	55	< 5
RP + ADT[b]	54	0.7	0	0	40	13	<5	0
Total Patients	8,031[c]	100	205	1,559	3,213	2,248	733	73

Source: Data provided by the Institute for Clinical and Evaluative Sciences, November 18, 2013.

Abbreviations: ADT, androgen deprivation therapy; AS, active surveillance; RP, radical prostatectomy; RT, radiation therapy.

[a]Data were only available for men aged 65 years and older, so it was assumed that the proportion of men aged 60–64 years receiving pharmacological ADT was equal to that of men aged 65–69 years, yielding an additional 64 men on ADT (total number used in analysis was 653).

[b]ADT was being given as either adjuvant or neoadjuvant therapy.

[c]Numbers may not add up to 8,031 because categories with less than 5 patients are denoted as < 5 to protect patient confidentiality.

Table 3: Administrative Data Sources and Codes

Variable	Database	Code
Prostate cancer	OCR	ICD-10 – C61
Exclusion variables		
Metastases	DAD	ICD-10 C77.x, C78.x, C79.x, C80.x
Palliative care	DAD	Main patient service = 58 (palliative care unit)
	OHIP Claims History	OHIP fee codes A945, C945, C882, C982, K023, W882, W872, W972, W982
Chemotherapy	DAD, NACRS Oncology	CCP 13.55, CCI 1.ZZ.35, ICD-9 V66.2, V67.2, ICD10 Z511, Z542
	OHIP Claims History	OHIP fee codes G381, G281, G339, G345, G359, G075, G382, G390 associated with prostate cancer (ICD 185)
Treatment variables		
Pharmacological ADT[a]	ODB	Specific DINs (Canada) for LHRH agonists, estrogen, anti-androgens
Surgical ADT	DAD, SDS	CCP 74.31 (removal of both testes in same operative episode) or 74.32 (removal of remaining testis) or CCI 1.QM.89 (excision total testis) or 1.QM.91 (excision radical testis)
Radical prostatectomy	DAD	CCP 72.4 or CCI 1.QT.91
Radiation therapy	OHIP Claims History	OHIP fee codes X310, X311, X312, X313, X322

Abbreviations: ADT, androgen deprivation therapy; CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; DAD, Discharge Abstract Database; DIN, Drug Identification Number; ICD, International Classification of Diseases; LHRH, luteinizing-hormone releasing-hormone; NACRS, National Ambulatory Care Reporting System; OCR, Ontario Cancer Registry; ODB, Ontario Drug Benefit; OHIP, Ontario Health Insurance Plan; SDS, Same-Day Surgery.

[a]For men aged 65 years and older only; this information is only available for individuals covered under the provincial drug plan.

Resource Utilization

Resource utilization associated with screening, diagnosing, staging, and treatment were estimated, using data from several sources. Table 4 shows the values used to compute the total amount of each resource used for all screening strategies.

Screening, Diagnosis, and Staging

The proportion of men currently being screened in Ontario (opportunistic screening) was derived from the 2003 Canadian Community Health Survey, which contains the most recent Ontario-specific data. (4) We assumed that screening patterns did not change significantly between 2003 and 2010 because the incidence of nonmetastatic PC has remained similar over time (Table 1). Information on the uptake of a population-based PC screening program was not available, so the proportion of men who would be screened was assumed to be the average of the uptake of breast, cervical, and colorectal population-based screening programs, reported in a systematic review. (30) We used data from the American PLCO trial to approximate the proportion of the screened population who would have a PSA reading above the accepted threshold (> 4 ng/mL), the proportion of these men who would be biopsied, the proportion who would be diagnosed with PC, and the proportion of cancers that would be considered high risk (Gleason score > 6). (9;31;32) (The Gleason score is often used to evaluate the prognosis of men with PC. It grades the cancer from 2 to 10 based on its microscopic appearance; cancers with higher scores are more aggressive and have a poorer prognosis.)

We assumed that the trial population is similar to that of Ontario and that data from the trial could be applied to the Ontario context. (*Personal communication, clinical expert, November 13, 2013*) The PLCO trial used age groups that were slightly different than those in our analysis, so we assumed that the proportion of men aged 40 to 54 years in our analysis with a PSA level greater than 4 ng/mL was equal to that of men aged 55 to 59 years in the trial. Similarly, we assumed that the proportion of men aged 75 years and older in our analysis with a PSA level greater than 4 ng/mL was equal to that of men aged 70 to 74 years in the trial. Based on information from the Cancer Quality Council of Ontario, we were able to determine the proportion of men with PC in Ontario who received a computed tomography (CT) scan of their abdomen/pelvis. (33) These data were not available for bone scintigraphy (bone scanning) so we assumed that only patients with high-risk PC received that procedure. (*Personal communication, clinical expert, November 13, 2013*)

We used Statistics Canada data to determine the number of males in each age group, (34) and we used the following formulas to estimate the resources that would be used under each strategy:

(a) Number of PSA Tests = (Number of Males in Specified Age Group in Ontario) x (Proportion Screened)

(b) Number of Urologist Visits = (a) x (Proportion With PSA > 4 ng/mL)

(c) Number of Biopsies = (b) x (Proportion Biopsied)

(d) Number of Bone Scans = (c) x (Proportion Diagnosed With PC) x (Proportion High-Risk PC)

(e) Number of CT Scans (Abdomen/Pelvis) = (c) x (Proportion Diagnosed With PC) x (Proportion CT Abdomen/Pelvis in Ontario)

The number of newly diagnosed, nonmetastatic PC cases in each age group was assumed to be equal to the number of screen-detected PC cases diagnosed in 1 year under the current opportunistic screening approach in Ontario. We also assumed that nonmetastatic incident

cases were detected through PSA screening rather than through PSA testing as follow-up to a previous diagnosis or because of suspected PC.

The number of screen-detected PC cases diagnosed in 1 year under a population-based screening program was estimated for each age group using the following formula:

Screen-Detected PC Cases (Population-Based Screening) = (Number of Males in Specified Age Group in Ontario) x (Proportion Screened) x (Proportion With PSA > 4 ng/mL) x (Proportion Biopsied) x (Proportion Diagnosed With PC)

Treatment

The proportion of Ontario PC patients in each age group receiving each type of initial treatment (Table 2) was applied to the number of screen-detected PC cases in each age group, to determine the total number of men who would receive RT, RP, ADT, and AS under each screening strategy. We assumed that men receiving pharmacological ADT alone were on it for the full year. Similarly, we assumed that men on AS remained on it for a year. The costs of ADT for men receiving it as adjuvant or neo-adjuvant treatment to RT or RP (i.e., RT + ADT or RP + ADT) were excluded from the analysis because we could not determine how long they were receiving the therapy. Table 5 contains the total number of each resource used over 1 year under each screening strategy.

Table 4: Data Used to Estimate Resource Utilization in Screening, Diagnosis, Staging, and Treatment of Prostate Cancer in Ontario

Parameter	Value, %	Source
Proportion screened (opportunistic screening)		
All ages	27.2	CCHS (4)
Age 40–49	11.7	CCHS (4)
Age 50–59	35	CCHS (4)
Age 60–69	41.4	CCHS (4)
Age 70–79	36	CCHS (4)
Age 80+	29.9	CCHS (4)
Proportion screened (population-based screening)	52.2	Ferroni et al, 2012 (30)
Proportion with PSA > 4ng/mL		
All ages	7.9	PLCO trial (31)
Age 55–59	4.1	PLCO trial (31)
Age 60–64	7.2	PLCO trial (31)
Age 65–69	10.8	PLCO trial (31)
Age 70–79	14	PLCO trial (31)
Proportion biopsied	40.2	PLCO trial (32)
Proportion diagnosed with prostate cancer	44.5	PLCO trial (32)
Proportion with high-risk cancer (Gleason score > 6)	7.4	PLCO trial (31;32)
Proportion receiving CT abdomen/pelvis in Ontario	27	CQCO (33)

Abbreviations: CCHS, Canadian Community Health Survey; CT, computed tomography; CQCO, Cancer Quality Council of Ontario; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen.
Note: Due to unavailability of data, proportions not reported with age breakdown were assumed to be the same across all ages.

Table 5: Total Resource Utilization Over 1 Year Under Each Screening Strategy

Resource	Total Units/Cases (1 Year)		
	Opportunistic Screening (Ages 40+ Years)	Opportunistic Screening (Ages 50–74 Years)	Population-Based Screening
PSA test, units	569,152	472,045	654,973
Urologist visit, units	44,894	34,066	46,416
Biopsy, cases	18,047	13,694	18,659
Bone scintigraphy, units	592	449	612
CT abdomen/pelvis, units	2,168	1,645	2,242
Radical prostatectomy, cases	2,593	2,444	3,321
Radiation therapy, cases	2,066	1,511	2,058
Androgen deprivation therapy, cases	653	236	318
Active surveillance, cases	2,777	1,965	2,685

Abbreviations: CT, computed tomography; PSA, prostate-specific antigen.

Costs

The cost of a PSA test in Ontario was obtained from the Canadian Medical Laboratories price list. (35) The cost of an urologist visit in Ontario was retrieved from the Ontario Physician Schedule of Benefits. (36) The average costs of a hospital visit for a prostate biopsy (including complications), for a CT scan of the abdomen/pelvis, and for bone scintigraphy in Ontario were obtained from the Ontario Case Costing Initiative (OCCI). (37) These numbers include direct medical costs (i.e., procedure, pathology, physician, nursing, diagnostic imaging, pharmacy, and laboratory) and hospital overhead costs (e.g., administration, finance, human resources, plant operations). Costs associated with increased physician visits due to anxiety experienced by men who receive an abnormal PSA or biopsy result were not included in this analysis.

All treatment costs were obtained from a study by Krahn et al, (38) whereby the authors used ICES administrative data to determine the total health care costs (including direct medical and hospital overhead costs) associated with each of the different health states experienced by men diagnosed with PC in Ontario. Patients all began in a nonmetastatic, nontreatment state (AS) and could either remain in that state or transition into a treatment state (RP, RT, or ADT). The authors explained that the costs for RT could be an underestimation because they assumed that patients received conventional 4-field RT, which is significantly less expensive than conformal RT, a newer type of RT more frequently used today. Costs for patients initially on RT and RP included costs up to 182 days before the start of treatment and 1 year after treatment, with a maximum of 18 months of observation time. There was no maximum observation time for costs of patients on ADT or AS. Costs were reported per 100 days, and adjustment factors for patient characteristics were reported, allowing us to adjust the costs to our patient population and apply them to a 1-year period. Costs reported were total costs incurred by the health care system for each patient, so this number was adjusted to reflect PC-attributable costs only, based on another study by Krahn et al (39) which found that 72% of the total costs in the 12-month period after diagnosis are attributable to PC. Since the provincial government pays for pharmacological ADT only for men aged 65 years and older, the cost of ADT for men aged 40 to 64 years includes non-drug costs only which Krahn et al (38) found make up 59% of the total cost of ADT.

To calculate the total costs associated with the PSA test itself in the opportunistic screening strategies, we multiplied the total number of PSA tests by the proportion of males in Ontario who are at high risk for PC based on their history (i.e., African ancestry or PC in the family), and we assumed that proportion to be 10% of the population, based on the PLCO trial. (9) We took this approach because the ministry pays for opportunistic screening only for high-risk men.

Table 6 presents the cost of each resource used in this analysis. When 2012 costs were not available, we used the health care component of the Statistics Canada Consumer Price Index for Ontario to adjust all costs to 2012 Canadian dollars. (40)

Table 6: Cost of Each Resource Used in Screening, Diagnosis, Staging, and Treatment of Prostate Cancer in Ontario

Resource	Cost, $[a]	Source
PSA test	30	CML Healthcare (35)
Urologist visit	80	Schedule of Benefits[b] (36)
Biopsy (with complications)	1,270	OCCI[c] (37)
Bone scintigraphy	610	OCCI[c] (37)
CT abdomen/pelvis	614	OCCI[c] (37)
Radical prostatectomy (1 year)	20,650	Krahn et al (38)
Radiation therapy (1 year)	7,016	Krahn et al (38)
ADT: ages 40–64 years (1 year)	4,361	Krahn et al (38)
ADT: ages 65+ years (1 year)	7,392	Krahn et al (38)
Active surveillance (1 year)	6,015	Krahn et al (38)

Abbreviations: PSA, Prostate-specific antigen; CML, Canadian Medical Laboratories; OCCI, Ontario case costing initiative; CT, computed tomography; ADT, androgen deprivation therapy.

[a]Costs are reported in 2012 Canadian dollars.

[b]Using fee code A355, for a general consultation with an urologist.

[c]Using Canadian Classification for Health Interventions (CCI) codes for biopsy of the prostate (2.QT.71.BA, 2.QT.71.HA, and 2QT.71.LA), CT abdomen/pelvis (3.OT.20.WA, 3.OT.20.WC, and 3.OT.20.WE), and bone scintigraphy (3.WZ.70.CA).

Validation

Estimates were validated using the Ontario PC incidence data from ICES (Table 1). The number of screen-detected PC cases under the opportunistic screening strategies was estimated using the same method of estimation used for the population-based screening strategy (i.e., using data from the PLCO trial). These numbers were then compared to the actual incidence observed in the ICES data, and formulas were adjusted accordingly to correspond to the population of Ontario.

Sensitivity Analysis

The method of estimation used in this analysis is subject to significant uncertainty because it relies on several assumptions and data from a variety of sources. Because we took a conservative approach with our base case estimates, we tested all uncertain parameters in one-way sensitivity analyses using extreme values. We varied the following parameters: the proportion of men screened under the population-based strategy; the proportion of screen-detected cases under the opportunistic screening strategies the proportion of pharmacological ADT use in men aged 40 to 59 years and 65 to 69 years; the proportion of men aged 40 to 54 years and aged 75 years and older with a PSA greater than 4ng/mL; the number of individuals who received ADT (excluding adjuvant or neo-adjuvant treatment); and the cost of RP and RT.

Results of Primary Economic Evaluation

Base Case Analysis

The total 1-year cost associated with opportunistic PSA screening of men aged 40 years and older in Ontario—the amount, we estimate, that is currently being spent annually by the health care system for PSA screening in this province—is approximately $119.2 million. Of that amount, screening of men aged 50 to 74 years (the target age group for a population-based screening program) costs approximately $97.3 million. The Ontario government is currently spending $22 million in 1 year on PSA screening of men younger than 50 and older than 74 years.

If a population-based PSA screening program for men aged 50 to 74 years were introduced in Ontario, the program would cost approximately $149.4 million in the first year, assuming that 52% of Ontario males in that age group participated. This amounts to an additional annual expenditure of $30.1 million over current practice. If the PSA test were no longer to be used for screening purposes (i.e., if it were only used in men who have been diagnosed with PC and are receiving treatment or are being followed after treatment for the disease), a potential savings of approximately $119.2 million would be realized. Table 7 displays the results of the base case analysis.

Table 7: Results of Base Case Analysis

Strategy	Total Cost, $[a]	Incremental Cost, $[a]
Opportunistic PSA screening (ages 40+ years)	119,235,088	Reference
Opportunistic PSA screening (ages 50–74 years)	97,263,991	–21,971,097
Population-based PSA screening (ages 50–74 years)	149,374,169	30,139,081
No PSA screening	0	–119,235,088

Abbreviation: PSA, prostate-specific antigen.
[a]Costs are reported in 2012 Canadian dollars.

Sensitivity Analysis

Sensitivity analyses are described below with results reported in Table 8. The impact of each sensitivity analysis can be seen by comparing its results with the base case results (reported in the first row of Table 8).

Proportion screened under population-based screening: When uptake of the population-based screening program was set to be 100%, the total cost of introducing such a program in Ontario increased to $286.6 million, resulting in an incremental cost of $167.4 million for population-based screening over opportunistic screening of men aged 40 years and older.

Screen-detected cancers under opportunistic screening: When the number of screen-detected cancers, under the strategy of opportunistic screening of men aged 40 years and older, was set to equal the estimated number of all incident PC cases in Ontario for 2013 (9,600 cases, as forecast in the 2013 Canadian Cancer Statistics Report (1)), the cost of this strategy increased to $142.5 million. This translated into an incremental cost of almost $7 million for population-based screening over opportunistic screening of men aged 40 years and older.

Proportion of pharmacological ADT use in men aged 40 to 59 years: When the proportion of pharmacological ADT use in men aged 40 to 59 years was set to equal that of men aged 65 to 69 years (4.1%), the cost of each strategy increased by less than $420,000, resulting in minor changes to the incremental cost difference between strategies.

Proportion of pharmacological ADT use in men aged 60 to 64 years: When the proportion of pharmacological ADT use in men aged 60 to 64 years was set to equal 0, the cost of each strategy decreased by less than $355,000, resulting in minor changes to the incremental cost difference between strategies.

Proportion of men aged 40 to 49 years with a PSA level greater than 4ng/mL: According to data from the PLCO trial, the proportion of men with a PSA greater than 4ng/mL increases by around 3% with each 5-year increase in age. (31) For men aged 55 to 59 years, this proportion is 4.1%, so if we were to extrapolate backwards, this number would get very small. We therefore chose 0.1% as the smallest proportion in men aged 40 to 49 years. This resulted in a minor decrease of almost $575,000 in the cost of opportunistic screening of men aged 40 years and older. Due to a lack of data, this assumption could not be tested for the age group 50 to 54 years.

Proportion of men aged 75 years and older with a PSA level greater than 4ng/mL: Based on the same trend described above (a 3% increase for every 5-year advance in age, beginning at 14% for men aged 70 to 74 years and ending at 29% for men aged 99 years), we used the maximum proportion of men aged 75 years and older with a PSA level greater than 4 ng/mL. This increased the cost of opportunistic screening of men aged 40 years and older by $5.3 million, amounting to an incremental cost of almost $25 million for the population-based screening strategy over screening men aged 40 years and older.

Number of patients on ADT: When we included the 553 men who received ADT as adjuvant or neo-adjuvant therapy under the ADT category (in addition to including them under the respective RT or RP categories), the cost of each strategy increased by more than $3 million. The incremental cost of population-based screening over screening of men aged 40 years and older decreased to $28.1 million.

Cost of radical prostatectomy: Based on evidence that the cost of RP and RT are similar (41), we set the cost of RP to be that of RT. This resulted in a considerable decrease in the cost of each strategy. The incremental cost of population-based screening over screening of men aged 40 years and older decreased to $20.2 million dollars.

Cost of radiation therapy: When we set the cost of RT to equal that of RP, the cost of each strategy increased considerably. The incremental cost of population-based screening over opportunistic screening of men aged 40 years and older remained almost unchanged at $30 million.

Table 8: Results of One-Way Sensitivity Analyses

Parameter	Base Case Value	Sensitivity Analysis Value	Cost, $[a]			
			Opportunistic (Ages 40+ Years)	Opportunistic (Ages 50–74 Years)	Population-Based	Incremental (Population-Based vs. Opportunistic 40+)
Base case results			**119,235,088**	**97,263,991**	**149,374,169**	**30,139,081**
Proportion screened (population-based), %	52.2	100	No change	No change	286,648,877	167,413,789
Number of screen-detected cancers (opportunistic 40+)	8,095	9,600	142,529,802	116,266,258	No Change	6,844,389
Proportion of pADT use in men age 40–59 yrs, %	0	4.1	119,551,639	97,543,755	149,791,979	30,240,340
Proportion of pADT use in men age 60–64 yrs, %	4.1	0	118,954,965	96,983,869	149,020,659	30,065,694
Proportion of men age 40–49 yrs with PSA > 4 ng/mL,(%	4.1	0.1	118,660,386	No change	No change	30,713,783
Proportion of men age 75+ yrs with PSA > 4 ng/mL, %	14	29	124,567,505	No change	No change	24,806,664
Number of patients on ADT	653	1,206	124,486,157	100,844,443	152,583,226	28,097,069
Cost of RP, $	20,650	7,016	83,922,280	63,941,790	104,090,005	20,167,725
Cost of RT, $	7,016	20,650	147,403,529	117,856,402	177,427,559	30,024,030

Abbreviations: pADT, pharmacological androgen deprivation therapy; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; vs, versus; yr, year.
[a]All costs are in 2012 Canadian dollars.

Limitations

To estimate resource utilization and costs associated with each strategy, we made many assumptions and used data from a variety of sources. Both can introduce considerable uncertainty into the analysis. Inherent in this process is the synthesis of data based on heterogeneous populations or populations that are different from the target population of the analysis. A major assumption underlying this analysis is that the population in the PLCO trial is similar to the population of Ontario. Although this may be true based on demographics, we cannot say that individuals in the two populations would behave in the same way under a PSA screening program. On the other hand, we know that treatment patterns differ between Canadian and American populations, which is why the use of administrative data specific to Ontario was a major strength of this analysis.

Without information about ADT use in younger men and by excluding the costs associated with adjuvant and neo-adjuvant use of ADT, we may have underestimated the costs associated with the treatment of PC. Additionally, for the proportion of patients currently being screened in Ontario, we used 2003 data from the Canadian Community Health Survey. Although it may be safe to assume that screening patterns have not changed in the past decade, we based that assumption on the fairly consistent incidence of nonmetastatic PC in Ontario, which could be due to other, unknown factors. For the proportion of men screened under the population-based program, we used an average based on other cancer screening programs (two were for female cancers); experience from those programs may not be representative of the uptake of a PSA screening program.

It has been shown that most men cope well with the diagnostic uncertainty of an abnormal screening or biopsy result, but a small number of men may experience severe anxiety, potentially leading to increased visits to the physician. (42;43) We did not include the costs associated with these increased visits. In accordance with the perspective of the ministry, we also did not include indirect costs relating to patients' lost income and the impact of treatment on the families and informal caregivers. Furthermore, the side-effects of the various treatments for PC can decrease a patient's functional status and quality of life, leading to significant social costs.

This analysis was designed to estimate the 1-year cost of current opportunistic screening in Ontario and the first-year cost if a population-based screening program were introduced in the province. We did not include downstream cost offsets, which may fall with more intensive screening and rise with less screening. The introduction of a population-based screening program would likely lead to fewer cases of advanced or metastatic PC and any associated complications, resulting in a potential cost savings to the health care system. In contrast, if screening were eliminated completely, the health care system would see more cases of advanced and metastatic PC, resulting in increased expenditures to treat these patients. Moreover, due to the 1-year time horizon of our analysis, we could not capture the decrease in costs resulting from a decrease in cancer detection rates with subsequent screening. Taking into account these additional factors, a screening program is likely to result in a large, short-term increase in health care expenditures but a smaller one in the long term.

CONCLUSIONS

Since 1998, only 7 studies (12-18) have evaluated the economic impact of population-based PSA screening for the detection of PC, by considering the costs of screening, diagnosis, staging, and treatment of screen-detected cancers. These studies show mixed results. Overall, PSA screening was found to be expensive and cost-ineffective but may be cost-effective in select patient populations. Only one study, published in 1999, was directly relevant to the Ontario context (18) and showed that the cost of opportunistic screening of men aged 40 to 74 years was $17.4 million in Ontario in 1995 ($45 million for all of Canada). The authors forecasted the first-year cost of introducing a population-based screening program in Canada in 2005, but not specifically for Ontario.

This analysis is the first economic evaluation of a hypothetical population-based PSA screening program in Ontario, or all of Canada, in almost 15 years. We estimate that the provincial government is currently spending $119 million on opportunistic PSA screening in 1 year, including $22 million for men outside the target age group for a population-based screening program. If Ontario were to introduce a population-based screening program for men aged 50 to 74 years, an added expenditure of $30 million would be required for the first year alone. If PSA screening were eliminated completely, a savings of close to $113 million could be realized. The forecasts for both expenditures and savings are probably overstated in the long-term, as they only capture the impact of screening over 1 year, not over the full course of the disease or over subsequent years of a screening program.

Sensitivity analyses showed that the results are highly sensitive to uptake of the population-based screening program. Depending on how many men participate, a population-based PSA screening program in Ontario could cost up to $287 million in the first year, or $167 million above our base case forecast. The results were also sensitive to the costs of radical prostatectomy and radiation therapy. By varying the costs of these treatments, we found that the cost of a population-based screening program could range from $104 million to $177 million.

This analysis evaluated the economic impact of PSA screening at the population-level in Ontario over 1 year, based on the observation that screening is not effective population-wide. At the individual level, the decision to be screened is highly sensitive to patients' preferences with respect to the balance between benefits and harms. (44;45) To understand the true impact of introducing a population-based screening program, future research in this area would need to attempt to incorporate individual patient preferences about screening, as well as downstream costs and effects of screening. Decision-analytical methods can be useful in assessing the balance of benefits and harms associated with screening and in helping to identify specific situations or patient populations in which screening may be appropriate, while providing a systematic way of forecasting the downstream costs and effects associated with screening.

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APPENDICES

Appendix 1: Literature Search Strategies

1) Database(s): Ovid MEDLINE(R) 1946 to October Week 1 2013, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 21, 2013

#	Searches	Results
1	exp Prostatic Neoplasms/	94715
2	(prostat* adj2 (cancer* or neoplas* or tumo?r*)).ti,ab.	82676
3	1 or 2	111264
4	exp Prostate-Specific Antigen/	19351
5	(prostate specific antigen* or PSA or kallikrein or semenogelase or gamma seminoprotein or seminin).ti,ab.	38308
6	4 or 5	42305
7	exp Mass Screening/	101662
8	exp "Early Detection of Cancer"/	7290
9	screen*.ti,ab.	475238
10	7 or 8 or 9	512375
11	Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. or Congresses.pt.	2880547
12	3 and 6 and 10	4674
13	12 not 11	4170
14	Cost-benefit analysis/ or costs.tw. or cost effective.tw.	203159
15	(letter or editorial or historical article).pt.	1465230
16	Animals/ not (Animals/ and Humans/)	3957893
17	13 and 14	192
18	17 not 15	191
19	18 not 16	191
20	remove duplicates from 19	180
21	limit 20 to english language	160

2) Database(s): Ovid EMBASE

#	Searches	Results
1	exp prostate tumor/	0
2	(prostat* adj2 (cancer* or neoplas* or tumo?r*)).ti,ab.	82676
3	1 or 2	82676
4	exp prostate specific antigen/	19351
5	(prostate specific antigen* or PSA or kallikrein or semenogelase or gamma seminoprotein or seminin).ti,ab.	38308
6	4 or 5	42305
7	exp early diagnosis/	20080
8	exp screening/	101662
9	screen*.ti,ab.	475238
10	7 and 8 and 9	2517
11	Case Report/ or Comment/ or Editorial/ or Letter/ or conference abstract.pt.	2821118
12	10 not 11	2287
13	(Cost adj effectiveness).ab. or (Cost adj effectiveness).ti. or (Life adj years).ab. or (Life adj year).ab. or Qaly.ab. or ((Cost or costs).ab. and Controlled Study/) or (Cost and costs).ab.	75794
14	(health economics/ or exp economic evaluation/ or exp health care cost/ or exp pharmacoeconomics/ or (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. or (expenditure$ not energy).ti,ab. or (value adj2 money).ti,ab. or budget$.ti,ab.) not ((metabolic adj cost) or ((energy or oxygen) adj cost) or ((energy or oxygen) adj expenditure)).ti,ab.	510608
15	13 and 14	73938
16	12 and 15	133
17	Animals/ not (Animals/ and Humans/)	3957893
18	16 not 17	133
19	limit 18 to english language	123

3) Database(s): Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, NHS Economic Evaluation Database

ID	Search	Hits
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees	3027
#2	prostat* near/2 (cancer* or neoplas* or tumo?r*):ti,ab,kw (Word variations have been searched)	4081
#3	#1 or #2	4081
#4	MeSH descriptor: [Prostate-Specific Antigen] explode all trees	898
#5	prostate specific antigen* or PSA or kallikrein or semenogelase or gamma seminoprotein or seminin:ti,ab,kw (Word variations have been searched)	2057
#6	#4 or #5	2057
#7	MeSH descriptor: [Mass Screening] explode all trees	4548
#8	MeSH descriptor: [Early Detection of Cancer] explode all trees	347
#9	screen*:ti,ab,kw (Word variations have been searched)	16725
#10	#7 or #8 or #9	17072
#11	MeSH descriptor: [Case Reports] explode all trees	1
#12	Comment:pt (Word variations have been searched)	1831
#13	Editorial:pt (Word variations have been searched)	321
#14	Letter:pt (Word variations have been searched)	5498
#15	Congresses:pt (Word variations have been searched)	45
#16	#11 or #12 or #13 or #14 or #15	6271
#17	#3 and #6 and #10	310
#18	#17 not #16	310
#19	MeSH descriptor: [Costs and Cost Analysis] explode all trees	20266
#20	MeSH descriptor: [Costs and Cost Analysis] explode all trees	20266
#21	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	14344
#22	MeSH descriptor: [Health Care Costs] explode all trees	6101
#23	Cost* or cost benefit analys* or health care costs:ti,ab,kw (Word variations have been searched)	35234
#24	#19 or #20 or #21 or #22 or #23	35277
#25	letter or editorial or historical article:pt (Word variations have been searched)	5891
#26	#24 not #25	35201
#27	MeSH descriptor: [Animals] explode all trees	6200
#28	MeSH descriptor: [Humans] explode all trees	952
#29	#27 not (#27 and #28)	5248
#30	#26 not #29	35066
#31	#18 and #30	33

Appendix 2: Summary of Studies Included in Literature Review

Study, Year	Study Details	Population	Interventions/ Comparators	Health Outcomes[a]	Costs[a]	Cost-Effectiveness
Martin et al, 2013 (12)	**Type of economic analysis:** CUA **Study design:** Decision-analytic model **Perspective:** Payer; Australia **Time horizon:** Lifetime	Males in the general population **Age:** 50 years and older	1) No screening 2) Screen all men with PSA every 4 years	**Primary outcome:** QALYs **Total QALYs:** NR	**Currency, cost year:** A$, 2012 **Total costs:** NR **Discount rate:** 5%	**ICER, $/QALY[b]:** Average risk: 291,817 High risk: 110,726 Very high risk: 30,572
Holmberg et al, 1998 (15)	**Type of economic analysis:** CEA **Study design:** Decision-analytic model **Perspective:** Payer; Sweden **Time horizon:** 10 years	Males in the general population **Age:** 50–69 years	1) No screening 2) Screen men at 3-year intervals for 4 rounds – first 2 with DRE, last 2 with DRE and PSA	**Primary outcome:** PC cases detected, localized cases detected, and cases treated curatively **Total:** NR	**Currency, cost year:** Sk, 1996 **Total costs:** NR **Discount rate:** NR	**ICER:** 158,000 Sk/extra cancer case detected 167,000 Sk/extra localized cancer case detected 249,000 Sk/extra cancer case treated curatively
Sennfalt et al, 2004 (16)	**Type of economic analysis:** CEA **Study design:** Decision-analytic model **Perspective:** Payer; Sweden **Time horizon:** 15 years	Males in the general population **Age:** 50–69 years	1) No screening 2) Screen men at 3-year intervals for 4 rounds – first 2 with DRE, last 2 with DRE and PSA	**Primary outcome:** Localized PC cases detected and cases treated curatively **Total number of localized PC cases detected:** 1) 343 2) 94	**Currency, cost year:** Sk, 1999 **Total costs:** NR **Discount rate:** NR	**ICER:** 168,000 Sk/extra localized cancer case detected 356,000 Sk/extra cancer case treated curatively
Hamashima and Yoshida, 2000 (14)	**Type of economic analysis:** CEA **Study design:** Decision-analytic model **Perspective:** Payer; Japan **Time horizon:** Lifetime	Males in the general population **Age:** 40–69 years	1) No screening 2) Screen all men with DRE 3) Screen all men with PSA 4) Screen all men with DRE and PSA	**Primary outcome:** LYs gained for cured cases **Total LYs gained for cured cases[c]:** 1) 65–1,057 2) 81–1,317 3) 103–1,668 4) 113–1,829	**Currency, cost year:** $, 1999 **Total costs, $ 1,000, range[c]:** 1) 182–5,945 2) 1,374–6,914 3) 1,426–7,790 4) 3,786–8,392 **Discount rate:** 5%	**ICER, $/LY[c]:** 1) Reference 2) 74,200–3,700 3) 32,900–3,000 4) 75,500–3,200

Study, Year	Study Details	Population	Interventions/ Comparators	Health Outcomes[a]	Costs[a]	Cost-Effectiveness
Benoit et al, 2001 (13)	**Type of economic analysis:** CEA **Study design:** Decision-analytic model **Perspective:** Payer; United States **Time horizon:** Lifetime	Males in the general population with at least a 10-year life expectancy **Age:** 50–70 years	1) Screen men aged 50–70 years with PSA 2) Screen men aged 50–59 years with PSA and DRE 3) Screen men aged 50–69 years with PSA and DRE 4) Screen men aged 60–69 years with PSA and DRE	**Primary outcome:** LYs **Total LYs:** 1) 11,542 2) 22,926 3) 23,364 4) 27,377	**Currency, cost year:** $, NR **Total costs, $ million, range:** 1) 44–57 2) 54–69 3) 83–108 4) 107–139 **Discount rate:** 10% (costs only)	**ICER, $/LY**: 1) Reference 2) 878–1,054 3) 66,210–89,041 4) 5,981–7,725
Krahn et al, 1999 (18)	**Type of economic analysis:** Cost analysis **Perspective:** Payer; Canada **Time horizon:** One year	Males in the general population	1) Opportunistic PSA screening of men aged 40–74 years in 1995 2) Screen all men aged 50–74 years with PSA in 1995 3) Screen all men aged 50–74 years with PSA in 2005	NA	**Currency, cost year:** Can$, 1999 **Total costs, $ million (range):** 1) 45 (40–84) 2) 317 (356–691)[d] 3) 219 (208–412) **Discount rate:** NA	NA
Heijnsdijk et al, 2009 (17)	**Type of economic analysis:** Cost analysis **Study design:** Decision-analytic model **Perspective:** Payer; Netherlands **Time horizon:** 25 years	Males in the general population	1) No screening 2) Screen every 4 years from age 50–70 years with PSA 3) Screen every year from age 55–70 years with PSA 4) Screen every 2 years from age 55–70 years 5) Screen every 4 years from age 55–75 years	NA	**Currency, cost year:** €, 2008 **Total costs, € million:** 1) 30.3 2) 60.7 3) 76.1 4) 70.5 5) 83.4 **Discount rate:** NR	NA

Abbreviations: CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DRE, digital rectal exam; ICER, incremental cost-effectiveness ratio; PC, prostate cancer; PSA, prostate-specific antigen; NA, not applicable; NR, not reported; LY, life-years; QALYs, quality-adjusted life-years.

[a]Total costs and health benefits are reported as a total cost for all patients in the analysis, unless otherwise stated.

[b]Model was run 3 times, once for each risk group (average, high and very high risk for prostate cancer).

[c]Model was run 3 times, once for each age group (40–49, 50–59, and 60–69 years); results are presented as a range from the 40–49-year age group to the 60–69-year age group.

[d]Range as reported.

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