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Is prostate cancer screening cost-effective? A microsimulation model of prostate-specific antigen-based screening for British Columbia, Canada

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Prostate-specific antigen (PSA) screening for prostate cancer may reduce mortality, but it incurs considerable risk of over diagnosis and potential harm to quality of life. Our objective was to evaluate the cost-effectiveness of PSA screening, with and without adjustment for quality of life, for the British Columbia (BC) population. We adapted an existing natural history model using BC incidence, treatment, cost and mortality patterns. The modeled mortality benefit of screening derives from a stage-shift mechanism, assuming mortality reduction consistent with the European Study of Randomized Screening for Prostate Cancer. The model projected outcomes for 40-year-old men under 14 combinations of screening ages and frequencies. Cost and utility estimates were explored with deterministic sensitivity analysis. The incremental cost-effectiveness of regular screening ranged from $36,300/LYG, for screening every four years from ages 55 to 69 years, to $588,300/LYG, for screening every two years from ages 40 to 74 years. The marginal benefits of increasing screening frequency to 2 years or starting screening at age 40 years were small and came at significant cost. After utility adjustment, all screening strategies resulted in a loss of quality-adjusted life years (QALYs); however, this result was very sensitive to utility estimates. Plausible outcomes under a range of screening strategies inform discussion of prostate cancer screening policy in BC and similar jurisdictions. Screening may be cost-effective, but the sensitivity of results to utility values suggests individual preferences for quality versus quantity of life should be a key consideration.

Key words: prostate cancer, PSA testing, screening, cost-effectiveness

Abbreviations: ADT: androgen deprivation therapy; BC: British Columbia; ERSPC: European Randomized Study of Screening for Prostate Cancer; FHCRC: Fred Hutchinson Cancer Research Center; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PSA: prostate-specific antigen; QALY: quality-adjusted life-year; UK NSC: United Kingdom National Screening Committee; USPSTF: United States Preventive Services Task Force

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Screening for prostate cancer with prostate-specific antigen (PSA) testing has divided the medical community. The objective of screening is to reduce prostate cancer mortality by identifying and treating early disease before progression occurs, but the PSA test alone has low predictive value, giving rise to many false-positive tests.[1–3] A further challenge is that prostate cancer is highly prevalent among older men and many cancers are low risk and will not cause death even if left untreated.[4] Both the UK National Screening Committee (UK NSC) and the US Preventive Services Task Force (USPSTF) recommend against routine prostate cancer screening, concluding that the harms associated with false-positive tests, unnecessary biopsies, over-diagnosis and overtreatment outweigh the potential mortality benefit from early detection.[5–7]

Two large clinical trials have produced conflicting results with respect to the effect of PSA screening on prostate cancer mortality.[8,9] The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, which offered annual screening for 6 years to men 55–74 years old, found no reduction

What's new?

Is screening for prostate cancer worth it? While screening can save lives, it also can lead to over-diagnosis and lower quality of life. In this study, the authors evaluated the cost-effectiveness of PSA screening. This study compared 14 different screening strategies, including different frequencies and ages at first screening. They found the screening programs to be cost-effective, but concluded that the reduction in quality of life outweighs the benefits in reduced mortality.

in mortality after 13 years of follow-up[8]; however, the trial has been criticized for high PSA testing rates in the control arm and inconsistent follow-up of men with abnormal PSA tests.[10–12] The European Randomized Study of Screening for Prostate Cancer (ERSPC) found a 21% reduction in prostate cancer mortality in the screened group (RR 0.79, 95% CI: 0.68–0.91) after 11 years of follow-up.[9]

Studies evaluating the cost-effectiveness of PSA screening have produced a wide range of results. A recent study estimated that screening cost US$262,758 per life-year gained (LYG), or over $5 million per death avoided.[13] A systematic review reported cost-effectiveness in the range of US$12,000/LYG to US$65,000/LYG, with screening being more cost-effective in men aged 50–69 years than in men over 70 years.[14] Krahn et al.[15] reported a range of $113,000/LYG to $729,000/LYG, but after utility adjustment all screening strategies showed a net loss in quality-adjusted life years (QALYs).

Given these varied and conflicting results, our objective was to evaluate the cost-effectiveness of PSA screening strategies in British Columbia (BC), Canada. Cost-effectiveness, expressed as cost per LYG, and cost-utility, expressed as cost per QALY, were the outcomes of interest.

Methods

We developed 14 screening strategies for analysis, with varying age ranges and frequency. Four minimal screening strategies were included, with single screens at age 50 years, 60 years or 70 years, or a screen at age 60 years followed by a second screen at age 65 years for men with PSA levels above the median. Most strategies had screening every 2 or 4 years, including one strategy with an adaptive screening frequency, where men with PSA levels above the median for their age are screened again in 2 years and the rest return in 4 years. Two strategies used an age-based PSA threshold, where men 70 years and older are subject to a positive PSA test threshold of 4.0 ng/ml, rather than base case of 3.0 ng/ml. A screening strategy representing the core group of the ERSPC trial—screening every 4 years, from ages 55 to 69 years—was also included. We evaluated these strategies using a microsimulation model of prostate cancer, developed at the Fred Hutchinson Cancer Research Centre (FHCRC) and adapted to the BC setting.

FHCRC model

The foundation of the FHCRC model is a natural history model of prostate cancer, with PSA growth (on the logarithmic scale) proportional to age and cancer growth proportional to PSA.[1,16] To reproduce the effect of PSA testing on prostate cancer incidence, simulated PSA screening histories[17] and observed biopsy compliance rates[18] were applied to the model to identify men with screen-detected cancers. Prostate cancer incidence from the model was calibrated to data from US Surveillance, Epidemiology and End Results (SEER) by age, stage and grade for ages 50–84 years in 1975–2000.[19]

Prostate cancer survival was modeled by applying treatment effects for the six treatment options in the model: radical prostatectomy, radiotherapy and conservative management, each with or without androgen deprivation therapy (ADT). The effect of PSA screening on prostate cancer mortality was incorporated using a stage shift mechanism, where a number of cancers that would have been diagnosed at a distant stage in the absence of screening are screen-detected and diagnosed at the locoregional stage, and consequently experience improved survival. This mechanism for the prostate cancer mortality reduction associated with screening is consistent with ERSPC results.[9,20,21] The model has been extensively validated with population incidence data and other natural history models.[19,22,23] Analysis of BC incidence data demonstrated that the FHCRC natural history model, when combined with plausible assumptions about pre-PSA detection patterns and screening dissemination in BC, could successfully reproduce historical prostate cancer incidence and mortality. However, natural history parameters estimated for the US setting were used in this analysis (see Supporting Information for further information). Parameters for treatment distribution and cost were based on observed BC data.

Costs

Costs used in the model are outlined in Table 1. The cost of a PSA test was provided by a local laboratory services provider. The cost of a biopsy was estimated using the average prostate biopsy case cost for Ontario[24] combined with professional costs for BC.[25]

For all men diagnosed with prostate cancer at any stage, we applied a fixed cost to account for urologist consults and other diagnostic tests, excluding biopsy.[25,26] We calculated the mean cost of radical prostatectomy, radiotherapy and ADT, by age and stage, for the first year following diagnosis using BC Cancer Agency treatment records for 2004–2008 combined with unit cost estimates[24,25] and actual cost, where available. For end-of-life costs, we calculated the cost of all

Table 1. Model cost and utility parameters

Model parameter	Estimate	
Screening costs	*Unit cost*	
PSA test	$30	
Biopsy	$880	
Prostate cancer costs	*Mean cost*	
Local-regional disease:		
Conservative management	$1,200	
Radical prostatectomy	$11,600	
Radiotherapy	$12,500	
Androgen deprivation therapy	$3,600	
Distant disease	$7,400	
End-of-life care	$9,600	
Health state	*Utility*	*Range*[1]
Healthy/screening	1.0	Not varied
Short-term treatment effects	0.88	0.861–0.919
Long-term treatment effects	0.90	0.879–0.926
Untreated symptomatic disease	0.90	0.879–0.926
Distant disease	0.85	0.845–0.855
End of life	0.50	0.42–0.58

[1]With the exception of the End-of-Life health state, ranges for sensitivity analysis were 95% confidence limits calculated by sampling from beta distributions generated from published mean and standard deviation values.

systemic therapy and radiotherapy received in the last year of life for men who died of prostate cancer and added an estimate of other end-of-life prostate cancer costs, including hospitalization, physician services and long-term care.[27]

Utilities

Utility is a broad measure of health and is expressed as a weight (on a scale of 0–1) representing the preferences individuals have for a particular health state or set of symptoms. The time spent in a given health state can be adjusted for quality of life by multiplying by the appropriate utility value, giving quality-adjusted life-years (QALY).[28]

In the model, time in each health state shown in Figure 1 is counted until transition out or death from any cause other than prostate cancer. The negative effects of prostate cancer treatment, specifically bowel, urinary and sexual dysfunction, have been found to persist over the long term.[29,30] The health state utilities are shown in Table 1.[31–33] Standard gamble utility values for short- and long-term treatment effects[31] were weighted for the treatment distribution in the model. The value for untreated symptomatic locoregional disease was estimated to be the same as for long-term treatment effects. With the exception of the end-of-life state, where we used the range reported by Earle et al.[33] for late metastatic disease, we calculated the 95% confidence limits for use in sensitivity analysis by sampling from beta distributions generated using the published mean and standard deviation.[34]

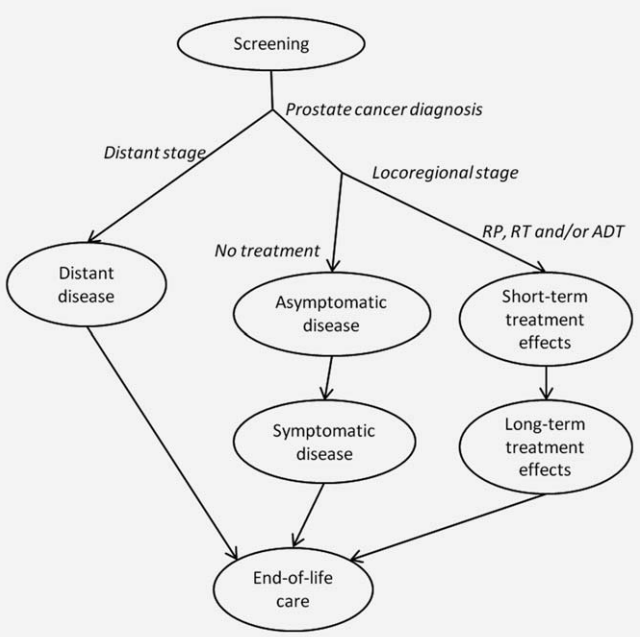

Figure 1. Health states. All men are in the screening health state until diagnosis of prostate cancer or death from a non-prostate cancer cause (not illustrated). Men diagnosed with locoregional disease who undergo initial treatment of any kind – radical prostatectomy (RP), radiotherapy (RT), or androgen deprivation therapy (ADT) – move through short-term treatment effect (first year post-treatment) and long-term treatment effect (>1 yr post-treatment) health states. Men with PSA-detected locoregional disease who do not undergo treatment remain in full health (asymptomatic disease state) until their disease manifests clinically (symptomatic disease state). The distant disease state includes only men diagnosed with distant disease, not those progressing from local-regional disease. All men who die of prostate cancer spend up to one year in the end-of-life care health state.

Analysis

We simulated a cohort of men aged 40 years in the year 2000, projecting forward 50 years to age 90 years. Our outcomes of interest were incremental cost-effectiveness, expressed as cost per LYG and cost-utility, expressed as cost per QALY gained. Incremental cost-effectiveness ratios (ICERs) were calculated to compare screening strategies.[28] The ICER describes the marginal cost of one strategy over another, relative to the marginal change in effectiveness:

$$\text{ICER} = \frac{\Delta\text{Cost}}{\Delta\text{Effectiveness}}$$

The sequence of strategies, from lowest cost to highest, that gives the lowest ICER values forms the cost-effectiveness frontier. All other strategies are said to be dominated by the strategies on the frontier, because the strategies on the frontier have relatively lower cost and/or higher effectiveness.[28]

Our analysis is from the perspective of the BC health system and costs are expressed in 2010 Canadian dollars. Costs and benefits were discounted at 3.5% per year, with sensitivity analysis at 6% and 0%.[35] We conducted sensitivity

analysis for cost by varying screening and biopsy costs by 25% and by varying treatment costs by 25%. To explore sensitivity to utilities, we created best and worst case scenarios: in the best case, we used the upper 95% confidence limit of the mean for locoregional disease states and the lower 95% confidence limit for distant disease and end-of-life states to maximize the potential effect. The opposite was done for the worst case scenario.

Results

Simulated per capita costs ranged from $438 with no screening to $1,445 with biennial screening beginning at age 40 years (Table 2). Cost-effectiveness values, relative to no screening, were between $27,000 and $54,000/LYG. Biennial screening from age 40 to 74 years was the most effective strategy but was also the least cost-effective strategy on the cost-effectiveness frontier, with an ICER of $588,300/LYG. Other strategies on the cost-effectiveness frontier were a single screen at age 60 years, screening every 4 years from 55 to 69 years, screening every 4 years from 50 to 74 years with an elevated PSA threshold for men over 70 years, and adaptive screening from 50 to 74 years (Fig. 2). Isolating the effect of starting age, ending age (including the age-based threshold) and screening frequency (Table 3) indicates that moving from adaptive screening to biennial screening, and from screening starting at age 50 years to starting at age 40 years are relatively cost-ineffective.

After utility adjustment, all screening strategies, regardless of age range or frequency, resulted in a loss of QALYs. Higher frequency screening strategies in older men resulted in the largest QALY losses: biennial screening from 60, 55 and 50 to 74 years, and the adaptive screening strategy all resulted in losses of over 0.01 QALYs. In sensitivity analysis for utility (Table 2 and Fig. 2), the worst-case scenario resulted in a loss of over 0.015 QALYs for most screening strategies; however, in the best case scenario, five strategies resulted in QALY gains. The most effective screening strategy was screening every 4 years from age 50 to 74 years with a PSA threshold of 4.0 ng/ml for men over 70 years, giving an additional 0.0013 QALYs over no screening. This strategy and a single screen at age 60 years, followed by a screen at age 65 years for men with PSA above the median, were the two most cost-effective strategies in the best case scenario, but both ICERs were over $300,000/QALY.

In the sensitivity analysis for cost-varying screening and treatment costs independently has little effect on overall costs and cost-effectiveness (Table 4). The results are sensitive to discounting, with higher discount rates giving higher ICERs.

With regular screening every 2–4 years, the model projected prostate cancer mortality reductions ranging from 12.4%, for screening every 4 years from 55 to 69 years, to 23.1%, for biennial screening from 40 to 74 years (Table 2). Over-diagnosis, expressed as a percent of all prostate cancers, ranged from 8.4% to 21.9% for those same strategies. The ratio of over-diagnoses to prostate cancer deaths avoided was lowest for the 55(4)69 strategy, at 3.0 (Supporting Information). Screening beyond age 70 years or with increased frequency greatly increased over-diagnosis. Of the minimal screening strategies, a single screen at age 60 years followed by a second test at age 65 years for those above the median provided the greatest mortality reduction, 8.1%, with over-diagnosis of 5.1% (Table 2). Additional outcomes, including number of cancers detected, over-diagnosed cases, prostate cancer deaths avoided, false positives and biopsies, are provided in the Supporting Information.

Discussion

If we consider results without utility adjustment, a number of PSA screening strategies may be cost-effective, depending on willingness-to-pay thresholds. At a threshold of $50,000/LYG, screening every 4 years from age 55 to 69 years would be considered cost-effective, and at a threshold of $80,000/LYG the adaptive screening strategy would be cost-effective. The marginal benefit from starting screening at age 40 years or from screening biennially is small; regular screening with lower frequency confers the greatest mortality benefit relative to cost. A recent estimate of the cost-effectiveness of PSA screening, based on an extrapolation of ERSPC results, was $262,758/LYG[13]—much higher than our results reported here. The reasons for this difference are twofold: the authors use unadjusted ERSPC results in their model, which likely underestimates effectiveness over the longer term,[20] and the authors use much higher prostate cancer treatment costs than we observe in Canadian settings.[27]

Relative to no screening, cost-effectiveness values were all under $54,000/LYG, but these results should be interpreted cautiously. The simulated no screening strategy acts as a counterfactual for this analysis and does not necessarily reflect current experience, where men have widespread access to screening despite the absence of organized programs. Marginal analysis using ICERs is a better tool for decision-making. ICERs take into account differences in cost and effectiveness across strategies, reflecting the fact that decision-makers in this situation must choose between many competing alternatives.[28]

After utility adjustment, all PSA screening strategies, regardless of intensity, resulted in a loss of QALYs. These findings support the conclusions of the USPSTF and the UK NSC,[5,6] that the detriment to quality of life exceeds the benefits of reduced prostate cancer mortality, but this result was sensitive to utility estimates. Recently, Heijnsdijk et al.[36] simulated PSA testing for men 55–69 years old and reported that 0.056 QALYs were gained with annual screening[36]; however, the utility values for long-term treatment effects used in the model were much higher than those used here, and the values for palliative care and metastatic disease were much lower, due to differences in the data sources used. The values in our base case most closely resemble the authors' "unfavorable" sensitivity analysis scenario, which resulted in a loss of 0.021 QALYs.[36] The authors also did not discount

Table 2. Cost-utility and cost-effectiveness of PSA -screening strategies, and sensitivity analysis for best and worst case utility values

Screening strategy name	Age range (years)	Interval	PSA threshold (ng/ml)	Mortality reduction[4] (%)	Over-diagnosis[5] (%)	Cost	Life-years gained (LYG)[6]	Cost-effectiveness ($/LYG)[6]	ICER ($/LYG)	With utility adjustment			
										Base case	*Worst case*[8]	*Best case*[8]	
										QALY[6]	QALY	QALY	ICER ($/QALY)
No screening	–	–	–	–	–	$438	–	–	–	–	–	–	–
50(1)	50	Single test	3.0	0.4	0.06	$469	0.0009	$35,000	Dominated[7]	−0.0004	−0.0006	−0.0003	Dominated[7]
60(1)	60	Single test	3.0	4.1	1.9	$559	0.0045	$27,000	$27,000	−0.0015	−0.0027	0.0000	Dominated
70(1)	70	Single test	3.0	6.1	7.1	$571	0.0034	$39,500	Dominated	−0.0012	−0.0023	0.0001	Dominated
60(1),65(A)	60,65	Adaptive, two tests[1]	3.0	8.3	5.1	$677	0.0077	$31,200	Dominated	−0.0026	−0.0050	0.0007	$340,300
55(4)69	55–69	4 years	3.0	12.4	8.4	$820	0.0117	$32,700	$36,300	−0.0043	−0.0077	0.0002	Dominated
50(4)74,4.0	50–74	4 years	3.0, 4.0[2]	14.7	10.7	$909	0.0134	$35,100	$51,000	−0.0040	−0.0081	0.0013	$371,100
50(4)74	50–74	4 years	3.0	18.2	17.2	$1,013	0.0148	$38,800	Dominated	−0.0060	−0.0106	0.0000	Dominated
60(2)74	60–74	2 years	3.0	21.1	20.7	$1,152	0.0151	$47,200	Dominated	−0.0103	−0.0159	−0.0031	Dominated
50(2)69	50–69	2 years	3.0	18.5	14.9	$1,166	0.0166	$43,800	Dominated	−0.0093	−0.0149	−0.0021	Dominated
55(2)74	55–74	2 years	3.0	21.2	19.4	$1,209	0.0170	$45,400	Dominated	−0.0105	−0.0165	−0.0028	Dominated
50(2)74,4.0	50–74	2 years	3.0, 4.0[2]	20.0	16.1	$1,216	0.0172	$45,100	Dominated	−0.0067	−0.0125	0.0007	Dominated
50(A)74	50–74	Adaptive[3]	3.0	22.5	21.0	$1,256	0.0184	$44,600	$70,500	−0.0104	−0.0169	−0.0022	Dominated
50(2)74	50–74	2 years	3.0	22.6	21.0	$1,309	0.0184	$47,300	Dominated	−0.0104	−0.0168	−0.0021	Dominated
40(2)74	40–74	2 years	3.0	23.1	21.9	$1,445	0.0187	$54,000	$588,300	−0.0096	−0.0162	−0.0011	Dominated

Abbreviations: LYG, life-years gained; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.
[1]All men are tested at age 60 years; men with PSA above the median are screened again at age 65 years.
[2]Threshold of 3.0 ng/ml up to age 69 years, and 4.0 ng/ml for men ≥70 years.
[3]Men with PSA above the median (by age) are screened again in 2 years, all others screened again in 4 years.
[4]Prostate cancer mortality reduction relative to no screening; absolute mortality reduction is available in the supplementary material.
[5]Over-diagnosis expressed as percent of all diagnosed prostate cancer cases; absolute diagnosis and over-diagnosis rates are available in the supplementary material.
[6]Expressed as gains/losses relative to no screening
[7]Dominated strategies are less cost-effective (i.e., they are less effective or have a higher ICER) than the next screening strategy in the table.
[8]In the worst case scenario, for distant disease and end of life health states the upper limit of utility values are used, and for all local-regional disease states the lower limit is used; the best case scenario is the opposite.

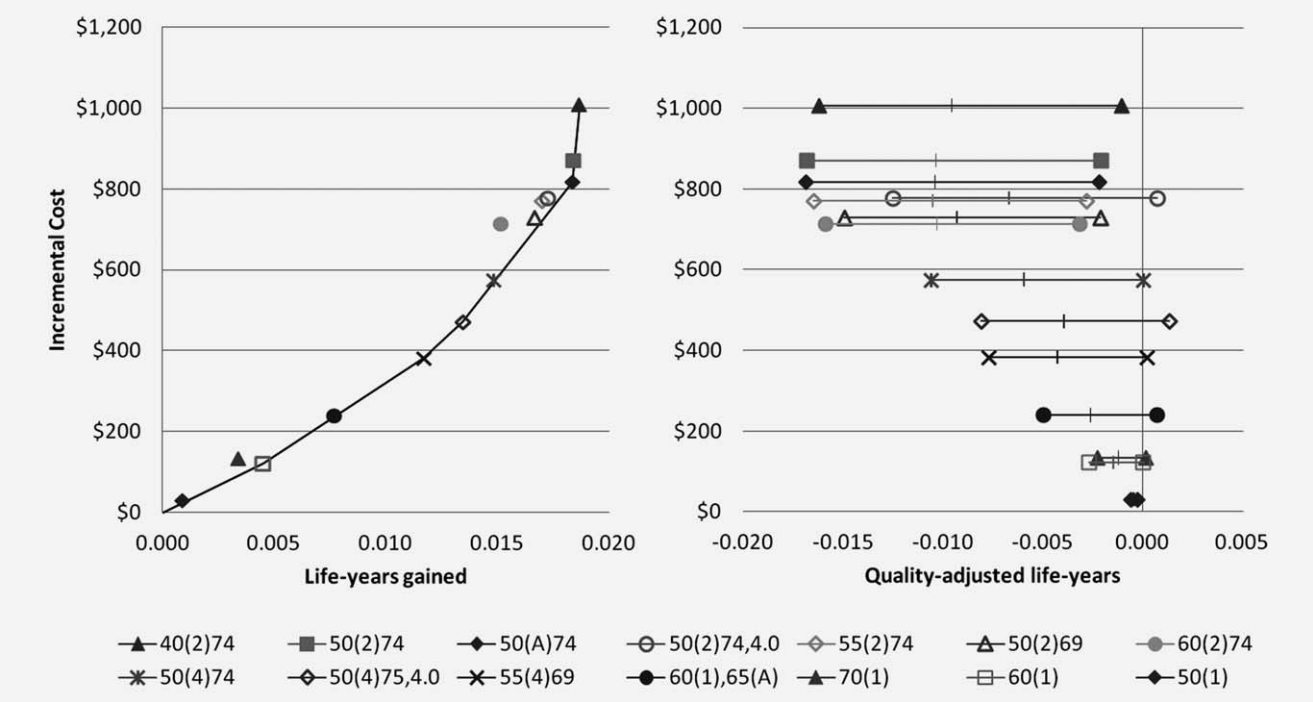

Figure 2. Cost-effectiveness planes for PSA screening strategies without utility adjustment (left) and with utility adjustment (right). In left panel, line indicates the cost-effectiveness frontier. In right panel, points at left indicate the "worst case" scenario (lower limit of utility for treatment effects and symptomatic disease; upper limit of utility for distant disease and end of life), and points to the right indicate the "best case" scenario. Marks in centre indicate base-case values Abbreviations: QALY, quality-adjusted life-year

Table 3. Effect of starting age, ending age and PSA threshold, and frequency on cost-effectiveness

Screening strategy	ICER ($/LYG)
Decreasing starting age	
60(2)74	–
55(2)74	$27,600
50(2)74	$80,900
40(2)74	$494,000
Increasing ending age & threshold	
50(2)69	–
50(2)74,4.0	Dominated[1]
50(2)74	$48,100
Increasing frequency	
50(4)74	–
50(A)74	$68,500
50(2)74	$1,150,000

Abbreviations: LYG, life-years gained; ICER, incremental cost-effectiveness ratio; see Table 2 for full screening strategy descriptions.
[1]Dominated strategies have a higher ICER (i.e., they are less cost-effective) than the next most effective strategy.

future utility; we provide comparable undiscounted results in the Supporting Information. It is clear from these models that the cost-effectiveness of PSA screening is highly dependent on the utility weights and health states used, due to the small mortality benefit of screening and the large impact of overtreatment and earlier treatment on quality of life.

In sensitivity analysis using results unadjusted for quality of life, we found that varying screening or treatment costs had little effect. A limitation of our analysis is that, due to the current model structure, we were unable to explore the effect of varying mortality reduction on cost-effectiveness. Reducing the effectiveness of screening would increase the ICER values, and other modeling work by the FHCRC group suggests that the position of the screening strategies relative to each other may be largely unchanged,[21] but the magnitude of the effect is unknown at this time.

Over-diagnosed cases, defined as prostate cancer cases detected on screening that would not have been clinically diagnosed in a patient's lifetime, made up 8.4–21.9% of all cancer diagnoses in our simulations of regular screening (every 2–4 years). The ERSPC reported the relative risk of cancer diagnosis in core screening group of 1.63; that is, 38.5% of cancers in the screening arm were potentially over-diagnosed cases based on the observed excess incidence.[9] The reasons for the lower over-diagnosis in the simulated screening strategies are due to differences in study design and population. First, following the initiation of screening, excess incidence is made up of both over-diagnosed cases and non-over-diagnosed cases detected from the collection of prevalent cancers.[37] With lead times for prostate cancer estimated at 5.4–6.9 years[22] and only 11 years of follow-up in the

Table 4. Sensitivity analysis for screening cost, treatment costs, and discount rate, for screening strategies on the cost-effectiveness frontier

	Screening costs (−25%, +25%)		Treatment costs (−25%, +25%)		Discount rate (0%, 6%)		
Screening strategy	Cost range[1]	ICER range ($/LYG)	Cost range[1]	ICER range ($/LYG)	Cost range[1]	LYG range	ICER range ($/LYG)
No screen	$438–$438	–	$328–$547	–	$1268–$221	–	–
60(1)	$550–$569	$24,900–$29,200	$429–$690	$22,400–$31,700	$1494–$300	0.0154–0.0020	$14,700–$39,800
60(1),65(A)	$659–$696	Dominated[2]–$39,700	$526–$828	$30,500–dominated	$1748–$369	0.0274–0.0033	$21,200–dominated
55(4)69	$783–$857	$32,500–$40,300	$652–$989	$31,400–$41,500	$2042–$458	0.0411–0.0051	$21,400–$51,200
50(4)75,4.0	$858–$960	$43,000–$59,100	$732–$1086	$46,300–$55,700	$2241–$512	0.0474–0.0058	$31,800–$71,400
50(A)74	$1161–$1350	$61,600–$79,400	$1036–$1475	$61,800–$79,200	$3076–$705	0.0663–0.0078	$44,300–$96,400
40(2)74	$1305–$1585	$447,400–$729,100	$1224–$1666	$582,100–$594,500	$3385–$855	0.0674–0.0080	$275,000–$980,900

Abbreviations: LYG, life-years gained; ICER, incremental cost-effectiveness ratio; see Table 2 for full screening strategy descriptions.
[1]Range of total costs (including screening and treatment) resulting from sensitivity analysis.
[2]Dominated strategies have a higher ICER (i.e., they are less cost-effective) than the next most effective strategy.

ERSPC, it is likely that the reported excess incidence is an overestimate of true over-diagnosis. Second, differences between the ERSPC study population and the simulated population contribute to the differences in over-diagnosis. The MISCAN (microsimulation screening analysis) model constructed using ERSPC Rotterdam parameters and population data from the Netherlands estimated over-diagnosis as a percent of all prostate cancers at 49.9%; calibrating the model to US SEER incidence estimated over-diagnosis at only 18.6%.[22] This difference has largely been attributed to higher biopsy compliance at ERSPC study sites than would be expected in general practice, leading to increased screening sensitivity and increased over-diagnosis.[22,37] The MISCAN model and the FHCRC model are two of three models that were developed independently using common data sources through the Cancer Intervention and Surveillance Modeling Network. Over-diagnosis among US men aged 50–84 years in 1985–2000 as predicted by the FHCRC model (11.9% of all prostate cancers diagnosed) was within the range of other two models (8.6% and 18.6%).[22]

A challenge we faced in this analysis is that little information is available about current screening practices in BC. PSA tests for asymptomatic men are not covered through the provincial insurance plan and therefore data are not routinely collected. Cross-sectional data from the Canadian Community Health Survey indicate that in 2003 approximately 18% of men aged 40–49 years and 50% of men aged 50–74 years in BC reported having had received a PSA test.[38] Of those, over 50% reported having been tested in the last year.[38] From this we can infer that a potentially large proportion of men are being tested at a frequency that is not cost-effective. Reducing the screening rate in this population may help to mitigate the detrimental effect of over-diagnosis on quality of life, while also improving the cost-effectiveness of health services provided.

The sharply contrasting results between the analyses with and without adjustment for quality of life suggest that the screening decision is not straightforward and is sensitive to utility weights. Published utilities vary widely due to the measurement methods used, the specific health states considered and the target populations. There is also significant heterogeneity between individuals' utility values. In our model, we used mean utilities that were elicited from prostate cancer patients using the standard gamble method.[31,32] Although the method itself is robust, using mean estimates does not reflect the heterogeneity in the population. Men may make different screening decisions depending on how they value the potential health outcomes and the relative importance they place on quality versus quantity of life. The use of decision support tools has been shown to successfully help men understand the potential consequences of PSA screening and make informed decisions that align with their values.[39–41]

In addition to improving the quality of individuals' decision-making, there may also be ways to mitigate the harms that arise as a consequence of screening. Introducing

age-based PSA thresholds could reduce the potential for harm to men who undergo screening. We found that with utility adjustment, the two strategies with the elevated PSA threshold of 4.0 ng/ml for men over 70 years performed relatively well compared with the other screening strategies, and the strategy with screening every 4 years with the age-based threshold gave the largest QALY gain in sensitivity analysis. Another critical option is wider adoption of active surveillance (AS) for low-risk disease, where men defer radical interventions and only receive treatment if subsequent PSA tests, digital rectal exams and biopsies show evidence of progression. AS has been found to successfully delay or prevent radical treatment without increasing prostate cancer mortality[42–44] and may also be cost-saving due to treatments avoided.[45] With an estimated 30–50% of patients eligible for AS,[46] the adverse effects related to radical treatment may be markedly reduced with increased AS uptake. Work is ongoing to incorporate AS into the FHCRC prostate cancer model.[47]

The FHCRC model is built on high-quality data and has been extensively validated against population data and other natural history models,[20,22,23] but it may not fully represent our experience in Canada and BC. However, prostate cancer mortality in the United States and Canada is very similar,[48] and differences in incidence are likely due to differences in PSA testing rates and nonscreen diagnostic intensity, and not to differences in the natural history of disease. By using local treatment distribution, resource use and cost data, we are confident that this analysis reflects local practice.

Our results demonstrate that screening for prostate cancer with low-frequency PSA testing may be cost-effective when quality of life is not considered, but all screening has a net negative effect on QALYs. The sensitivity of these results to utility adjustment is an important finding, suggesting that men's preferences for quality or quantity of life should directly inform their decision to be screened. Further work to investigate options that mitigate the harms of over-diagnosis and overtreatment would be of significant value.

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