Original Investigation

Economic Analysis of Prostate-Specific Antigen Screening and Selective Treatment Strategies

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IMPORTANCE Prostate-specific antigen (PSA) screening for prostate cancer is controversial. Experts have suggested more personalized or more conservative strategies to improve benefit-risk tradeoffs, but the value of these strategies—particularly when combined with increased conservative management for low-risk cases—is uncertain.

OBJECTIVES To evaluate the potential cost-effectiveness of plausible PSA screening strategies and to assess the value added by increased use of conservative management among low-risk, screen-detected cases.

DESIGN, SETTING, AND PARTICIPANTS A microsimulation model of prostate cancer incidence and mortality was created. A simulated contemporary cohort of US men beginning at 40 years of age underwent 18 strategies for PSA screening. Treatment strategies included (1) contemporary treatment practices based on age and cancer stage and grade observed in the Surveillance, Epidemiology, and End Results program in 2010 or (2) selective treatment practices whereby cases with a Gleason score lower than 7 and clinical T2a stage cancer or lower are treated only after clinical progression, and all other cases undergo contemporary treatment practices. National and trial data on PSA growth, screening and biopsy patterns, incidence of prostate cancer, treatment distributions, treatment efficacy, mortality, health-related quality of life, and direct medical expenditure were analyzed. Data were collected from March 18, 2009, to August 15, 2014, and analyzed from November 20, 2012, to December 11, 2015.

INTERVENTIONS Eighteen screening strategies that vary by start and stop age, screening interval, and criteria for biopsy referral and contemporary or selective treatment practices.

MAIN OUTCOMES AND MEASURES Life-years (LYs), quality-adjusted life-years (QALYs), direct medical expenditure, and cost per LY and QALY gained.

RESULTS All 18 screening strategies were associated with increased LYs (range, 0.03-0.06) and costs ($263-$1371) compared with no screening, with the cost ranging from $7335 to $21 649 per LY. With contemporary treatment, only strategies with biopsy referral for PSA levels higher than 10.0 ng/mL or age-dependent thresholds were associated with increased QALYs (0.002-0.004), and only quadrennial screening of patients aged 55 to 69 years was potentially cost-effective in terms of cost per QALY (incremental cost-effectiveness ratio, $92 446). With selective treatment, all strategies were associated with increased QALYs (0.002-0.004), and several strategies were potentially cost-effective in terms of cost per QALY (incremental cost-effectiveness ratio, $70 831-$136 332).

CONCLUSIONS AND RELEVANCE For PSA screening to be cost-effective, it needs to be used conservatively and ideally in combination with a conservative management approach for low-risk disease.

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With the US Preventive Services Task Force recommendation against routine prostate-specific antigen (PSA) screening for prostate cancer[1] and conservative guidance from other national panels,[2-4] the future of PSA screening is uncertain. The recently updated guidelines relied heavily on results from 2 large trials conducted in the United States and Europe.[5-7] These results have been interpreted by some as demonstrating that PSA screening provides at most modest benefit, with unacceptable costs in terms of overdiagnosis and overtreatment.[8,9] However, for a long-term horizon, the number of lives saved by screening is likely to be considerably higher and the fraction of overdiagnosed patients is likely to be considerably lower compared with those of the trials.[10-13] Rather than rejecting screening, additional studies[13,14] have recommended seeking more personalized (or "smarter") screening strategies that preserve benefit while reducing harm. Unfortunately, these strategies are unlikely to be evaluated in randomized clinical trials owing to resource and logistic constraints. Therefore, we have used modeling to conduct simulated comparisons of candidate screening approaches.

In a recent study, Gulati et al[15] projected outcomes for a contemporary cohort of US men using 35 screening strategies that varied by screening ages, screening intervals, and criteria for biopsy referral. The authors identified several strategies that reduced screening harms by more than half yet retained most of the lives saved relative to a reference annual screening strategy for men aged 50 to 74 years. These smarter strategies used longer intervals between screening and more conservative criteria for biopsy referral in older men. Other investigators have proposed screening policies with similar objectives, including stopping screening at 60 years of age if the PSA level is lower than 1.0 ng/mL (to convert to micrograms per liter, multiply by 1.0),[16] using baseline PSA levels at ages 45 to 50 years to identify men appropriate for less frequent screening,[17] and referring patients for biopsy only when PSA levels exceed 10.0 ng/mL.[9] However, no studies to date have evaluated how these strategies alter the benefit-risk balance of PSA screening or whether they represent high-value alternatives to no screening.[18]

Beyond smarter screening strategies, support is growing for more selective treatment strategies. Active surveillance, which manages newly diagnosed prostate cancer conservatively with serial biopsies, is an increasingly common approach[19-21] for treating low-risk cases—which constitute most newly diagnosed prostate cancers. However, few studies have projected screening outcomes under alternative treatment practices.

The primary objective of this modeling study is to investigate whether smarter PSA prostate cancer screening strategies have the potential to be effective and cost-effective relative to no screening. In addition, we investigate the potential added value of combining screening and treatment strategies by projecting outcomes under selective treatment practices with increased use of conservative management among men with screen-detected, low-risk disease.

Key Points

Question: Can prostate-specific antigen (PSA) screening for prostate cancer be cost-effective?

Finding: Simulation modeling indicated that more conservative strategies with less frequent screening and higher PSA level thresholds for biopsy referral tended to be more cost-effective than less conservative strategies. No strategy was likely to be of high value under contemporary treatment patterns, but a selection of strategies was likely to be of at least moderate value (cost per quality-adjusted life-year, $70 831-$136 332) with increased use of conservative management for low-risk, screen-detected cancers.

Meaning: For PSA screening to be cost-effective, it must be used conservatively and ideally in combination with conservative management.

Methods

Overview

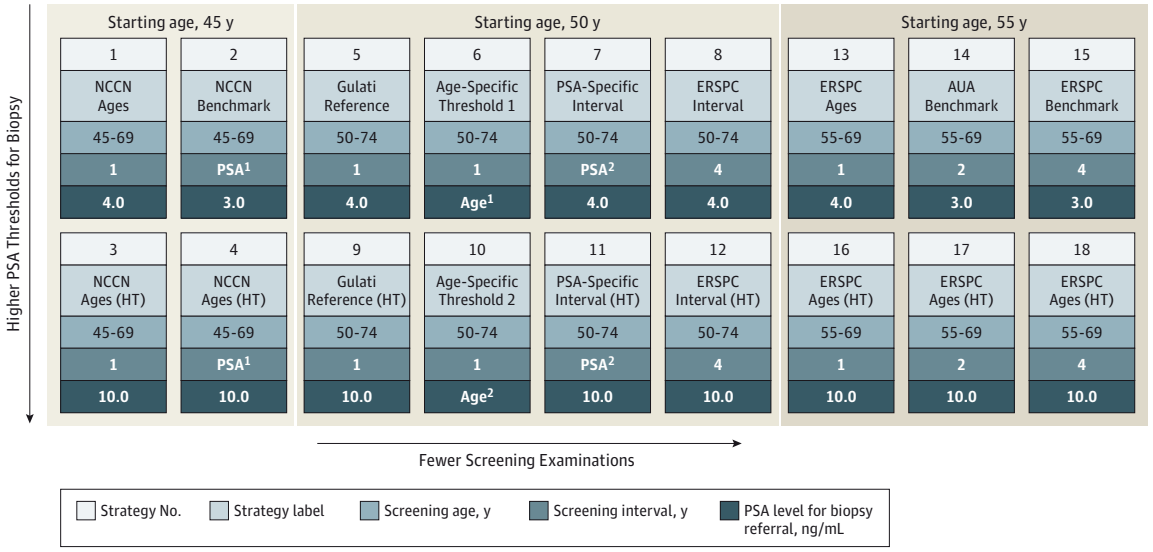
The Fred Hutchinson Cancer Research Center (FHCRC) microsimulation model of prostate cancer (summarized in eMethods in the Supplement) was developed as part of the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network Prostate Cancer Working Group.[22] The model is unique among prostate cancer models because it explicitly links cancer progression with individual PSA growth. This link is critical for evaluating screening strategies with PSA-dependent criteria for biopsy referral, screening intervals, and/or early screening cessation. The model has been fit to US incidence data (eFigure 1 in the Supplement) and has been used to study population incidence and mortality trends[23] and to evaluate the comparative effectiveness of alternative PSA screening policies.[15]

We expanded the FHCRC model to estimate quality-adjusted survival and costs for coordinated screening and treatment strategies from a US health care payer perspective. For each strategy, the model simulated a cohort of men beginning at age 40 and projected prostate cancer outcomes over a lifetime horizon. We calculated outcomes using health state utility and cost weights applied to the person-years tallied in the healthy state and the postdiagnosis states (eFigure 2 in the Supplement). Costs and survival outcomes were discounted at 3% per year in the base case, and cost outcomes are presented in 2014 US dollars. Data were collected from March 18, 2009, to August 15, 2014. The institutional review board of the FHCRC determined that this study, which used only deidentified and previously collected data, was exempt from human subjects review.

Screening Strategies

The strategies in our analysis (**Figure 1**) reflect promising strategies from a prior comparative effectiveness evaluation[15] and approximations to the National Comprehensive Cancer Network recommendations (strategy 2),[24] the American Urological Association guidelines statement (strategy 14),[2] and the most common protocol used in the European Randomised Study of Screening for Prostate Cancer (strategy 15).[25] We also

Figure 1. Candidate Prostate-Specific Antigen (PSA) Screening Strategies



Strategies were suggested by published screening studies, approximation to a trial protocol, approximation to a clinical recommendation statement from a national organization, or a combination of sources. All strategies are compared with no screening. Age[1] indicates age-dependent PSA thresholds for biopsy referral are 3.5, 4.5, and 6.5 ng/mL for ages 50 to 59, 60 to 69, and 70 to 74 years, respectively; Age[2], age-dependent PSA thresholds for biopsy referral are 4.5, 5.5, and 8.5 ng/mL for ages 50 to 59, 60 to 69, and 70 to 74 years, respectively.

PSA[1] indicates PSA-dependent screening interval is every 1 year if the PSA level is higher than 3.0 ng/mL and every 2 years otherwise; PSA[2], PSA-dependent screening interval is every 2 years if the PSA level is higher than 1.0 ng/mL and every 4 years otherwise. Strategies labeled *Gulati reference* are based on the reference strategy in Gulati et al.[15] AUA indicates American Urological Association; ERSPC, European Randomised Study of Screening for Prostate Cancer; HT, high threshold; and NCCN, National Comprehensive Cancer Network.

consider strategies that use a high PSA threshold (ie, 10.0 ng/mL) for referral to biopsy (strategies 3, 4, 9-12, and 16-18), a value that would mandate a biopsy recommendation. To supplement this selection, we also evaluated the cost-effectiveness of the superset of screening strategies that consists of all 150 combinations of starting ages 45, 50, and 55 years; cessation ages 69 and 74 years; screening intervals of 1, 2, and 4 years or 2 PSA-dependent intervals (explained in eMethods in the Supplement); and PSA thresholds 3.0, 4.0, and 10.0 ng/mL or 2 age-dependent PSA thresholds (explained in eMethods in the Supplement).

Survival Model

In the absence of screening and curative treatment, prostate cancer survival is based on observed survival for untreated cases diagnosed in the Surveillance, Epidemiology, and End Results (SEER) database in 1983 to 1986, just before the PSA era. Frequencies of curative surgery and/or radiotherapy are based on SEER trends by age and cancer stage and grade at diagnosis, and frequencies of use of adjuvant hormone therapy are based on patterns observed in the Cancer of the Prostate Strategic Urologic Research Endeavor database.[26] Effects of curative treatment are based on the Scandinavian randomized trial of prostatectomy vs watchful waiting (hazard ratio, 0.62)[27] and assuming similar efficacy for contemporary radiotherapy.[28,29]

The model represents the effect of early detection on prostate cancer survival by assuming that would-be metastatic cases detected by screening at a locoregional stage have their survival changed to that associated with detection at the earlier stage. Previous studies[14,15] showed that this effect is consistent with the published 21% mortality reduction reported in the European Randomized Study of Screening for Prostate Cancer. Although the results of the US Prostate, Lung, Colorectal, and Ovarian Cancer screening trial[12,14,30] did not show a reduction in the screening arm, the extensive contamination of the control arm suggests that a mortality benefit of this magnitude cannot be ruled out.[30]

In the present study, the model was extended to track time spent in the prediagnosis and postdiagnosis states, including short- and long-term disease management states after receipt of curative treatment, a state of no curative treatment, and a 2-year end-of-life state for men who die of prostate cancer. Cases with low-risk disease detected by screening may defer therapy until they progress to a point at which the disease would have become clinically apparent in the absence of screening. The eMethods in the Supplement summarizes health state definitions and durations.

Contemporary and Selective Treatment Practices

We considered 2 initial treatment scenarios. Under *contemporary* treatment practices, all cases receive curative treatment (prostatectomy or radiotherapy, with or without androgen deprivation therapy) based on the frequencies of treatment observed in the SEER program in the year 2010 by age and cancer stage and grade. We do not model the small proportion of localized cases who receive androgen deprivation therapy alone. In contrast, under *selective* treatment practices, screen-detected cases with a Gleason score[31] lower than 7 and a clinical T2a cancer stage or lower initially receive conservative management, and all other cases receive the same treatments as

Table 1. Health State Utility and Direct Medical Expenditure Model Inputs

Variable[a]	Point Estimate (Value Range)	Distribution	Source
Direct medical expenditure inputs, $			
PSA test (per procedure)	27 (22-32)	Normal	CMS[33]
Biopsy (per procedure)	688 (550-826)	Normal	Hayes et al,[35] 2013
Conservative management (per year)[b]	476 (381-571)	Normal	CMS[33]
Prostatectomy (per procedure)	10 600 (6410-10 684)	Normal	Wang et al,[34] 2014
Radiotherapy (full course of treatment)	22 515 (18 012-27 018)	Normal	Wang et al,[34] 2014
Androgen deprivation therapy (per year)[c]	2267 (1814-2720)	Normal	Cooperberg et al,[28] 2013
Distant-stage initial treatment (full course of treatment)	15 773 (12 618-18 927)	Normal	Cooperberg et al,[28] 2013
Distant-stage management (per year)[d]	2212 (1106-4424)	Normal	Cooperberg et al,[28] 2013
End of life (last year)			
Prostate cancer	40 807 (20 404-81 614)	Normal	Cooperberg et al,[28] 2013
Other cause of death	5000 (4000-6000)	Normal	Mobley et al,[37] 2006
Surgical complication (per event)	709 (567-851)	Normal	Cooperberg et al,[28] 2013
Radiotherapy complication (per event)	230 (184-276)	Normal	Cooperberg et al,[28] 2013
Office visit[e]	80 (64-96)	Normal	CMS[33]
Health state utility value inputs			
Healthy	1.00 (0.90-1.00)	Beta	Assumption
Utility decrement			
Symptomatic	0.11 (0.05-0.17)	Beta	Stewart et al,[32] 2005
Surveillance	0.08 (0.02-0.14)	Beta	Stewart et al,[32] 2005
Short-term treatment	0.25 (0.19-0.31)	Beta	Stewart et al,[32] 2005
Long-term treatment	0.08 (0.02-0.14)	Beta	Stewart et al,[32] 2005
Distant stage	0.25 (0.22-0.28)	Beta	Stewart et al,[32] 2005
End of life	0.67 (0.57-0.77)	Beta	Stewart et al,[32] 2005

Abbreviations: CMS, Centers for Medicare & Medicaid Services; PSA, prostate-specific antigen.

[a] The expenditure values below are presented as reported in the original publications. All costs were analyzed in 2014 US dollars.

[b] Assumed to consist of an annual office visit, annual PSA testing, and a biennial biopsy.

[c] Men receiving initial curative treatment involving androgen deprivation therapy with prostatectomy or radiotherapy were assumed to receive 1 year of treatment.

[d] Indicates a 1-time cost of initial treatment applied to men diagnosed as having distant-stage disease. Cost reflects the ongoing cost of care in the distant-stage state and was applied to all years in that state.

[e] Indicates cost applied once annually in men without a diagnosis of prostate cancer.

under contemporary treatment practices. The eMethods in the Supplement describes extensions to the FHCRC model to identify cases eligible for conservative management; the eTable in the Supplement depicts the frequencies of immediate primary treatments.

We model a conservative management program in which curative treatment is offered once cases progress to the point of would-be clinical diagnosis in the absence of screening. Consequently, only those cases that are not overdiagnosed receive delayed curative treatment. This conservative version of active surveillance is modeled because no consensus exists about the appropriate conduct of active surveillance, and the timing of progression to treatment under active surveillance is therefore unclear. Further, the end point of would-be clinical diagnosis in the absence of screening is generated by the FHCRC model. We believe this end point represents a useful benchmark for comparison but acknowledge that under most contemporary active surveillance approaches, curative therapy would likely be offered at an earlier point.

Health-Related Quality of Life and Costs

Few studies have produced estimates of health state utilities for prostate cancer and its treatment. The health state utility for men without prostate cancer diagnosis was assumed to be 1.0 to represent full health. All other health state utilities were extracted from a prior US study of 162 men 60 years or older that used standard gamble to elicit preferences for 19 prostate cancer health states.[32] The short-term treatment health state utility decrement was applied for 1 year to localized cases undergoing prostatectomy or radiotherapy and reflects a weighted mean of patients with and without major adverse effects of treatment.

We obtained cost estimates related to PSA testing, office visits, and conservative management by microcosting resource use with the Centers for Medicare & Medicaid Services 2014 reimbursement schedule.[33] Costs for surgical treatment and radiotherapy episodes were derived from a prior SEER-Medicare analysis that calculated the mean procedure-attributable cost for patients receiving either type of treatment.[34] The costs of biopsy, one-time distant-stage initial treatment, long-term management, end of life, and treatment complications were derived from prior economic analyses in prostate cancer (**Table 1**).[28,35-37] Treatment complication costs were applied to 12.5% and 4.2% of men undergoing prostatectomy and radiotherapy, respectively, based on the rates of grades 3 and 4 complications in a prior analysis.[28] Cost inputs were adjusted using the medical care component of the Consumer Price Index to 2014 US dollars.[38]

Model Outcomes

Data were analyzed from November 20, 2012, to December 11, 2015. We used the model to calculate prostate cancer diagnosis, treatment, death, unadjusted life-years (LYs), quality-adjusted LYs (QALYs), and cost for each screening strategy. The incremental cost-effectiveness ratio was calculated as the ratio of the difference in costs between strategies to the difference in effects (eg, QALYs) between strategies.[38] We calcu-

Table 2. Results in the Contemporary and Selective Treatment Scenarios[a]

PSA Screening Strategy No.	Screening Age, y	Screening Interval, y	PSA Level Threshold for Biopsy Referral, ng/mL	Contemporary Treatment Scenario					Selective Treatment Scenario				
				Total			Cost, $		Total			Cost, $	
				LY	QALY	Cost, $	Per LY Gained	Per QALY Gained	LY	QALY	Cost, $	Per LY Gained	Per QALY Gained
None	NA	NA	NA	36.302	21.504	4708	Reference	Reference	36.302	21.504	4708	Reference	Reference
4	45-69	PSA[1b]	10.0	36.347	21.508	5391	15 344	184 074	NA	NA	NA	NA	NA
18	55-69	4	10.0	36.329	21.508	5022	11 977	92 446	NA	NA	NA	NA	NA
12	50-74	4	10.0	36.338	21.507	5246	15 123	170 195	NA	NA	NA	NA	NA
11	50-74	PSA[2c]	10.0	36.348	21.507	5357	14 209	209 338	NA	NA	NA	NA	NA
9	50-74	1	10.0	36.357	21.507	5698	18 160	330 065	NA	NA	NA	NA	NA
17	55-69	2	10.0	36.338	21.507	5197	13 734	170 981	NA	NA	NA	NA	NA
3	45-69	1	10.0	36.345	21.507	5590	20 761	326 292	NA	NA	NA	NA	NA
16	55-69	1	10.0	36.343	21.506	5371	16 347	300 884	NA	NA	NA	NA	NA
15	55-69	4	3.0	36.343	21.502	5315	14 977	Dominated[d]	36.338	21.508	4971	7335	70 831
8	50-74	4	4.0	36.348	21.502	5513	17 466	Dominated[d]	36.343	21.508	5062	8622	89 333
10	50-74	1	Age[2e]	36.361	21.502	5818	19 006	Dominated[d]	36.355	21.509	5329	11 838	124 564
1	45-69	1	4.0	36.361	21.499	5919	20 751	Dominated[d]	36.354	21.509	5404	13 409	163 214
7	50-74	PSA[2c]	4.0	36.359	21.499	5730	17 983	Dominated[d]	36.352	21.508	5160	9098	136 332
6	50-74	1	Age[1f]	36.363	21.498	5928	19 972	Dominated[d]	36.357	21.508	5364	11 906	166 784
13	55-69	1	4.0	36.355	21.498	5688	18 645	Dominated[d]	36.350	21.508	5187	9985	128 680
14	55-69	2	3.0	36.353	21.498	5597	17 390	Dominated[d]	36.349	21.508	5105	8600	120 952
5	50-74	1	4.0	36.366	21.494	6079	21 649	Dominated[d]	36.360	21.507	5411	12 293	243 768
2	45-69	PSA[1b]	3.0	36.360	21.494	5835	19 622	Dominated[d]	36.353	21.506	5269	11 028	313 214

Abbreviations: NA, not applicable; LY, life-year; PSA, prostate-specific antigen; QALY, quality-adjusted LY.

SI conversion factor: To convert PSA to micrograms per liter, multiply by 1.0.

[a] The PSA screening strategy results are listed in descending order of QALYs in the contemporary treatment scenario. We do not report results for strategies with a PSA threshold for biopsy of 10.0 ng/mL in the selective treatment scenario because cases detected by screening are unlikely candidates for conservative management with delayed curative treatment.

[b] Indicates PSA-dependent screening interval is every 1 year if PSA level is higher than 3.0 ng/mL and every 2 years otherwise.

[c] Indicates PSA-dependent screening interval is every 2 years if PSA level is higher than 1.0 ng/mL and every 4 years otherwise.

[d] Indicates the PSA screening strategy was less effective (fewer QALYs) and more costly compared with no screening.

[e] Indicates PSA level thresholds for biopsy referral are 4.5, 5.5, and 8.5 ng/mL for ages 50 to 59, 60 to 69, and 70 to 74 years, respectively.

[f] Indicates PSA level thresholds for biopsy referral are 3.5, 4.5, and 6.5 ng/mL for ages 50 to 59, 60 to 69, and 70 to 74 years, respectively.

lated probabilistic outcomes using a Monte Carlo simulation and conducted 1-way sensitivity analyses to determine the inputs with the greatest influence on incremental QALY and cost outcomes.[39] Cost-effectiveness was evaluated at willingness-to-pay thresholds ranging from $50 000 to $150 000 per QALY.[40-44] This range reflects the implied willingness to pay for cancer treatments in the United States and is consistent with values used in prior analyses.[40,44-46]

Results

Contemporary Treatment Practices

Table 2 displays the results under contemporary treatment practices. Among the 18 screening strategies evaluated, all increased costs (range, $314-$1371) and LYs (range, 0.03-0.06) compared with no screening, but only strategies with the biopsy threshold at a PSA level higher than 10.0 ng/mL increased QALYs (range, 0.002-0.004). Among this subset of strategies, cost ranged from $11 977 to $21 649 per LY. Only quadrennial screening of men aged 55 to 69 years with a biopsy threshold at a PSA level higher than 10.0 ng/mL (strategy 18) was potentially cost-effective in terms of cost per QALY ($92 446 per QALY).

Corresponding results for the superset of screening strategies show that our selection of promising and policy-relevant strategies is representative of the range of cost-effectiveness outcomes (eFigure 3 in the Supplement). In general, only a small number of conservative screening strategies (4% of the superset) similar to those presented in Table 2 were potentially cost-effective at a willingness to pay of $150 000 per QALY or less.

Selective Treatment Practices

Selective treatment practices were implemented only for strategies with PSA thresholds lower than 10.0 ng/mL because cases of prostate cancer diagnosed with PSA levels higher than 10.0 ng/mL would not typically qualify as low risk or as candidates for delayed curative treatment. Similar to strategies under contemporary treatments, all strategies increased costs (range, $263-$703); however, in contrast to many strategies under contemporary treatments, all strategies under selective treatment practices increased QALYs (range, 0.002-0.004). Among the 10 screening strategies

evaluated (Table 2), strategies 8, 14, and 15 compared most favorably with no screening, resulting in 0.041, 0.046, and 0.036 more LYs; 0.004, 0.003, and 0.004 more QALYs; and $353, $397, and $262 greater cost, respectively. All of these strategies have screening intervals of 2 to 4 years with PSA biopsy thresholds of 4.0, 3.0, and 3.0 ng/mL; the incremental cost-effectiveness ratios for these strategies were $8622, $8600, and $7335 per LY gained and $89 333, $120 952, and $70 831 per QALY gained, respectively. One strategy (strategy 7) with screening interval every 4 years but becoming every 2 years if PSA is higher than 1.0 ng/mL also compared favorably to no screening, with an incremental cost-effectiveness ratio of $136 332 per QALY gained.

Results for the superset of screening strategies with selective treatment practices, including those with a biopsy threshold at a PSA level higher than 10.0 ng/mL, show that a large proportion of the strategies are potentially cost-effective at willingness-to-pay levels of $100 000 per QALY (43% of the superset) and $150 000 per QALY (70% of the superset) (eFigure 3 in the Supplement). The most cost-effective strategies in the superset are similar to the most cost-effective strategies in Table 2.

Sensitivity Analysis

One-way sensitivity analyses focused on QALYs demonstrated that results were by far most sensitive to the health state utility in the conservative management state. One-way sensitivity analyses evaluating cost differences were most sensitive to the costs of death due to prostate cancer, radiotherapy, and PSA testing. All analyses were conditional on the assumed efficacy of curative treatment.

Under contemporary treatment practices, the probabilistic sensitivity analysis demonstrated a low probability of PSA screening cost-effectiveness at willingness-to-pay levels at or below $100 000 per QALY (**Figure 2**). Only quadrennial screening of men aged 55 to 69 years with a PSA biopsy threshold of 10.0 ng/mL had greater than a 50% probability of being potentially cost-effective at a willingness to pay of $100 000 and $150 000 per QALY (Figure 2).

Under selective treatment practices, the probabilistic sensitivity analysis demonstrated that no strategies had a greater than 50% probability of being cost-effective at a willingness to pay of $50 000 per QALY, and only quadrennial screening of men aged 55 to 69 years with a PSA biopsy threshold of 3.0 ng/mL (strategy 15) and quadrennial screening of men aged 50 to 74 years with a PSA biopsy threshold of 4.0 ng/mL (strategy 8) had greater than a 50% probability of being potentially cost-effective at a willingness to pay of $100 000 per QALY (Figure 2). Several other relatively conservative strategies (strategies 7, 10, 13, and 14) were potentially cost-effective at a willingness to pay of $150 000 per QALY (Figure 2).

Discussion

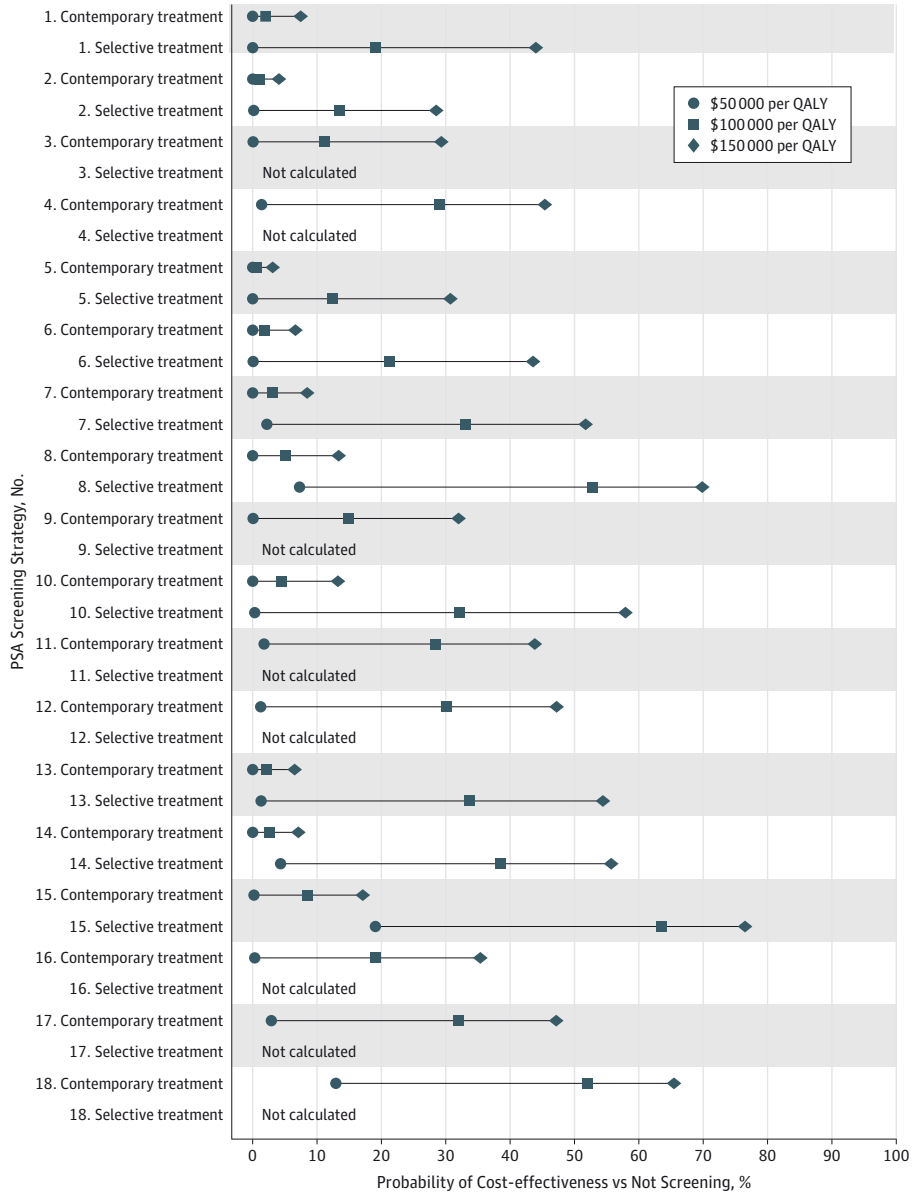
The value of PSA screening for prostate cancer is uncertain, as reflected by variable clinical guidelines. This study provides, to our knowledge, the first quantitative framework to evaluate the comparative effectiveness of PSA-based screening strategies and selective treatment approaches, and it addresses an urgent need for direction concerning the future of PSA screening in the United States. Our work indicates that strategies with a conservative screening frequency (eg, quadrennial) and/or a higher PSA biopsy threshold (eg, 4.0 ng/mL) are potentially cost-effective when combined with the increased use of conservative management for low-risk cases, but are unlikely to be cost-effective under contemporary treatment practices.

Our findings have clear implications for the future of PSA screening in the United States. Rather than stopping PSA screening, as recommended by the US Preventive Services Task Force, implementation of strategies that extend the screening interval and/or use higher PSA biopsy thresholds have the potential to preserve substantial benefit while controlling harm and costs. Although higher-threshold policies (eg, 10.0 ng/mL) are unlikely to be clinically appealing, they reinforce the general conclusion that conservative patterns of screening and biopsy referral are important directions to consider if PSA screening is to be clinically effective and cost-effective.

All strategies evaluated were potentially cost-effective in terms of cost per LY gained (range, $7335-$21 649). However, that metric ignores the important health-related quality-of-life impact of cancer diagnosis, treatment, and associated complications. For this reason, our primary analysis evaluated the impact of PSA screening in terms of cost per QALY gained. In analyses with contemporary treatment practices, we demonstrated that only strategies with highly conservative PSA biopsy thresholds (ie, 10.0 ng/mL) are expected to increase QALYs relative to no screening, and among those strategies only the most conservative (quadrennial screening at ages 55-69 years) was potentially cost-effective.

The contrasting cost-effectiveness results of the contemporary vs selective treatment practices demonstrate the importance of conservative management of low-risk prostate cancer and the potential for the increased use of active surveillance to make the benefit-risk tradeoffs and cost-effectiveness of screening acceptable. For example, quadrennial screening of men aged 55 to 69 years with a biopsy threshold at a PSA level of 3.0 ng/mL (strategy 15) and quadrennial screening of men aged 50 to 74 years with a biopsy threshold at a PSA level of 4.0 ng/mL (strategy 8) were dominated under contemporary treatment practices but had incremental cost-effectiveness ratios of $89 333 and $70 831 per QALY, respectively, under selective treatment practices. These favorable results in the selective treatment scenario are owing to men at low risk who underwent conservative management having better health-related quality of life, lower costs, and similar survival compared with men at low risk who received immediate curative treatment. In addition, our analysis of the superset of 150 screening strategies found that the high biopsy threshold (eg, PSA level of 10.0 ng/mL) that was favorable under contemporary treatments (eMethods in the Supplement) has a similar value under selective treatments because men diagnosed with high PSA levels are more promising candidates for immediate treatment[47] and are generally ineligible for surveillance programs.

Figure 2. Cost-effectiveness Acceptability Results for the Contemporary (CT) and Selective Treatment (ST) Scenarios



Cost-effectiveness is measured as willingness-to-pay levels of $50 000 to $150 000 per quality-adjusted life-year (QALY) gained. The strategy numbers relate to the strategies described in Table 2. The percentages describe the proportion of simulation runs in which the cost per QALY was less than or equal to the given willingness to pay. We do not report results for strategies with a prostate-specific antigen (PSA) threshold for biopsy referral of 10.0 ng/mL in the ST scenario because cases detected by screening are unlikely candidates for conservative management with delayed curative treatment.

The need for cost-effectiveness analyses exploring emerging PSA screening strategies has been discussed, but few such studies have been reported in the literature.[48,49] A recent study used another Cancer Intervention and Surveillance Modeling Network microsimulation model to evaluate the cost-effectiveness of a range of screening strategies in a European setting.[50] Their most cost-effective strategy screened men aged 55 to 59 years at 2-year intervals, which is consistent with our conclusions that conservative use of the test is imperative. The authors[50] concluded that shorter screening intervals are more cost-effective than longer intervals when they examined strategies with cessation of screening at about 60 years of age. In contrast, when they examined strategies with higher cessation ages, they found that longer screening intervals were more cost-effective. For example, quadrennial screening to age 69 or 74 years achieved much lower additional costs but similar QALYs gained compared with biennial or annual screening (in Figure 2B of their study). Their model reflects a European setting with very different costs for many services and with a lower frequency of curative treatments relative to the United States. In addition, several postdiagnosis utility values (eg, active surveillance, 0.97; 1 year after initial primary treatment, 0.95) were more favorable than ours (0.92 for both states). Despite these differences and differences in how the 2 models represent and estimate prostate cancer natural history,[51,52] their study and ours agree that only a highly conservative PSA screening strategy will be cost-effective.

This analysis has several limitations that should be noted. First, this microsimulation study uses the best available evidence to project the comparative effectiveness of PSA screening strategies vs no screening. Ideally, the comparative effectiveness of the PSA screening strategies would be evaluated head-to-head in real-world settings before implementation. However, such an evaluation is unlikely given the resource demands and complexity of designing studies to evaluate dozens of screening strategies. As a result, rigorously developed and validated disease models play an important role in projecting the comparative effectiveness of alternative PSA screening strategies. Nonetheless, our model evaluates a long-term time horizon, and uncertainty around model-projected results over time is likely to increase.

Few studies have elicited health state utilities for the PSA screening, making cost-effectiveness analyses challenging in this setting. As a result, we assume equivalence between several health states and those noted in prior studies (eg, our conservative management utility was assumed to be equivalent to that of patients with prostate cancer and a 20% chance of cancer spread who are not currently receiving treatment).[53] However, we allowed a fraction of those cases to later receive curative treatment, and their utilities are modified accordingly at that time. We do not model the health-related quality-of-life impact of biopsies, and we do not model the impact of an elevated PSA level (eg, 4.0 ng/mL) that is still below the threshold for biopsy referral (eg, 10.0 ng/mL) owing to a lack of data in this setting. Furthermore, our analysis does not reflect the substantial costs of several recently approved systemic treatments for advanced prostate cancer. To the extent that screening reduces metastasis and castrate resistance, inclusion of these new treatments could improve screening cost-effectiveness outcomes relative to those projected in this study. Previous studies have discussed other technical limitations of the FHCRC model.[15]

We recognize that the modeled conservative management program in the selective treatment scenario reflects a highly conservative approach to active surveillance. No standard protocol exists for active surveillance, but most contemporary programs would likely identify and treat progressive cases before they progressed to clinically detected disease (when cases are treated in the model). Thus, the selective treatment scenario results might underestimate survival and costs compared with contemporary active surveillance protocols.

Conclusions

Our work adds to a growing consensus[50,54,55] that highly conservative use of the PSA test and biopsy referral is necessary if PSA screening is to be cost-effective. Among the strategies considered, less frequent screening and more restrictive criteria for biopsy resulted in greater chances of PSA screening being cost-effective—particularly when combined with selective treatment strategies that do not immediately treat low-risk, screen-detected cases.

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Reproducible Research Statement: *Study Protocol:* Screening and treatment strategies available from Mr Gulati (e-mail, rgulati@fredhutch.org). *Statistical Code:* Cost-effectiveness analysis code available from Dr Roth (e-mail, jroth@fredhutch.org). *Data/Model:* Model source code (languages: C and R) available from Mr Gulati (e-mail, rgulati@fredhutch.org). A detailed model description is available at http://cisnet.cancer.gov/prostate/profiles.html, and a high-level overview of the model is available at https://resources.cisnet.cancer.gov/registry/packages/psapc-fhcrc.

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