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Comparative Effectiveness of Alternative Prostate-Specific Antigen–Based Prostate Cancer Screening Strategies

Model Estimates of Potential Benefits and Harms

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Background: The U.S. Preventive Services Task Force recently concluded that the harms of existing prostate-specific antigen (PSA) screening strategies outweigh the benefits.

Objective: To evaluate comparative effectiveness of alternative PSA screening strategies.

Design: Microsimulation model of prostate cancer incidence and mortality quantifying harms and lives saved for alternative PSA screening strategies.

Data Sources: National and trial data on PSA growth, screening and biopsy patterns, incidence, treatment distributions, treatment efficacy, and mortality.

Target Population: A contemporary cohort of U.S. men.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: 35 screening strategies that vary by start and stop ages, screening intervals, and thresholds for biopsy referral.

Outcome Measures: PSA tests, false-positive test results, cancer detected, overdiagnoses, prostate cancer deaths, lives saved, and months of life saved.

Results of Base-Case Analysis: Without screening, the risk for prostate cancer death is 2.86%. A reference strategy that screens men aged 50 to 74 years annually with a PSA threshold for biopsy referral of 4 μg/L reduces the risk for prostate cancer death to 2.15%, with risk for overdiagnosis of 3.3%. A strategy that uses higher PSA thresholds for biopsy referral in older men achieves a similar risk for prostate cancer death (2.23%) but reduces the risk for overdiagnosis to 2.3%. A strategy that screens biennially with longer screening intervals for men with low PSA levels achieves similar risks for prostate cancer death (2.27%) and overdiagnosis (2.4%), but reduces total tests by 59% and false-positive results by 50%.

Results of Sensitivity Analysis: Varying incidence inputs or reducing the survival improvement due to screening did not change conclusions.

Limitation: The model is a simplification of the natural history of prostate cancer, and improvement in survival due to screening is uncertain.

Conclusion: Compared with standard screening, PSA screening strategies that use higher thresholds for biopsy referral for older men and that screen men with low PSA levels less frequently can reduce harms while preserving lives.

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Prostate cancer screening is one of the most controversial topics in public health policy. Although prostate-specific antigen (PSA) testing is ubiquitous in the United States, there has always been uncertainty about its efficacy and effectiveness. Sustained decreases in prostate cancer mortality since the first wave of screening in the early 1990s suggest benefit but are not conclusive because improvements in prostate cancer treatment may also explain the decrease.

Results from randomized screening trials done in Europe and the United States have only stoked the controversy. The PLCO (Prostate, Lung, Colorectal, and Ovarian) cancer screening trial in the United States showed no difference between prostate cancer mortality rates in intervention and control groups (1), whereas the ERSPC (European Randomized Study of Screening for Prostate Cancer) showed a significant mortality reduction but documented a high frequency of overdiagnosis per life saved (2). Updated results from both studies confirmed their original findings (3, 4), with fewer overdiagnoses per life saved in the ERSPC under additional follow-up. The trial results have been extensively debated, and it is now clear that the PLCO results reflect a comparison of organized annual screening versus opportunistic screening rather than screening versus no screening (3, 5). Still, largely on the basis of these trial results, the U.S. Preventive Services Task Force (USPSTF) recently recommended against routine PSA-based screening (6).

Other organizations have updated or are in the process of updating their guidelines in light of the trial results. To date, no other published guideline recommends against PSA screening, and many encourage informed decision making at an individual level. However, Welch (7) points out that this carries an enormous burden and argues that strategies that make the harm–benefit tradeoff more favorable are urgently needed.

The USPSTF recommendation also identifies the need for additional research to "evaluate the benefits and harms

See also:

Print

Editorial comment. 211
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Context

Few data exist to help clinicians have nuanced conversations with patients about whether and how to have prostate cancer screening.

Contribution

This modeling study compared 35 screening strategies that differed by ages to start and stop screening, screening intervals, and thresholds for biopsy. Compared with standard screening, using higher thresholds for biopsy referral for older men and screening men with initially low prostate-specific antigen levels less frequently seems to reduce harms of screening while preserving lives.

Caution

The model did not incorporate men's preferences for outcomes.

Implication

Strategies exist that likely improve the tradeoffs of prostate cancer screening. Data from this model may inform conversations that clinicians have with men about whether and how they should be screened.

—The Editors

of modifications of the use of existing prostate cancer screening tools" and "optimize the benefits while minimizing the harms" (6). In this article, we take up that challenge and address the following question: Can we identify strategies that reduce the harms of screening while preserving its effect on detection and survival? In other words, can we screen smarter for prostate cancer?

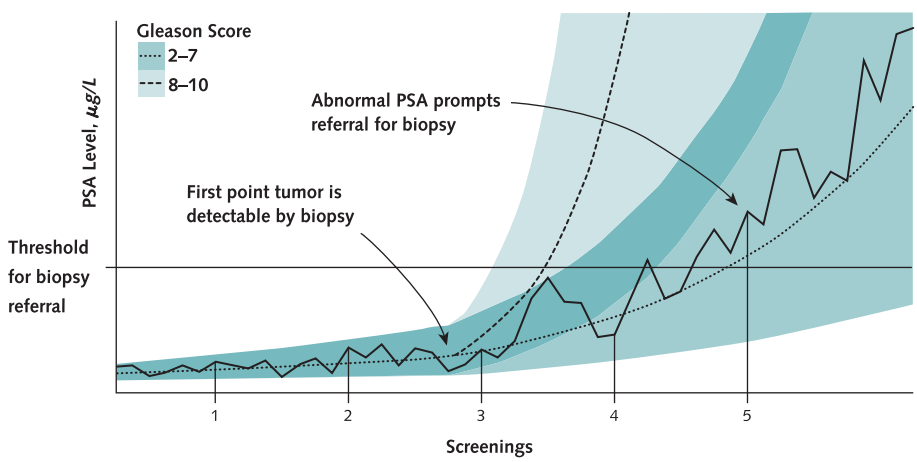
METHODS

There are many potential avenues to smarter screening because many variables define a screening strategy: ages to start and stop screening, the screening interval, and the threshold for biopsy referral (and all but the starting age may depend on previous results). All variables have been topics of debate, but it is unlikely that novel combinations will be explored in a prospective randomized setting (8, 9). An alternative is to model disease incidence and mortality under observed screening practices, then study model-projected outcomes under alternative screening strategies.

The Fred Hutchinson Cancer Research Center microsimulation model of prostate cancer was developed as part of the Cancer Intervention and Surveillance Modeling Network (http://cisnet.cancer.gov), a consortium of investigators whose goal is to use modeling to understand the roles of different interventions in explaining trends in cancer incidence and mortality.

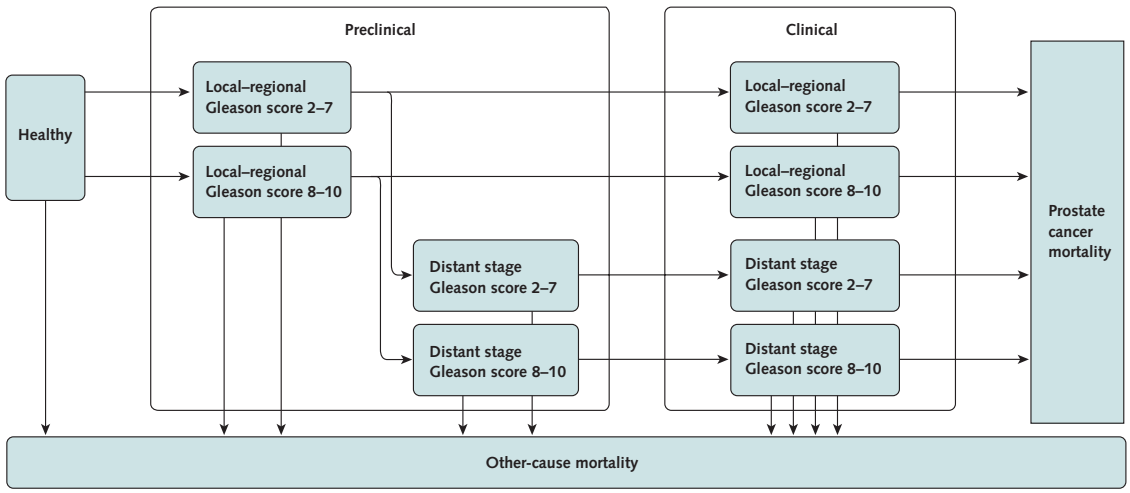
The incidence component of the model consists of 2 linked parts: PSA growth and disease progression. Prostate-specific antigen growth is based on data from the control group of the Prostate Cancer Prevention Trial (**Figure 1**). Disease progression consists of tumor onset, metastasis, and clinical diagnosis that would occur in the absence of PSA screening, with the risks for events after onset indicated by PSA levels (**Figure 2**). To calibrate the model, we superimposed PSA screening according to observed U.S. screening patterns and obtained model-projected disease incidence. We then identified rates of onset, metastasis, and clinical diagnosis so that model-projected incidence and observed incidence matched (10, 11). The calibrated

Figure 1. **Fred Hutchinson Cancer Research Center prostate cancer incidence model: underlying PSA growth before and after onset of tumors with a Gleason score of 2 through 7 and 8 through 10.**



The dashed and dotted lines are PSA trajectories by age for the 2 categories of Gleason score. Shaded bands around those lines illustrate between-person variability in PSA values based on interquartile ranges. The jagged line illustrates an example PSA trajectory for a man who develops a tumor with a Gleason score of 2 through 7. In this example, PSA exceeds the threshold for biopsy referral on the fifth test of a schematic screening strategy. PSA = prostate-specific antigen.

Figure 2. **Fred Hutchinson Cancer Research Center prostate cancer incidence model: healthy, preclinical, clinical, prostate cancer mortality, and other-cause mortality states in the absence of screening.**



model closely replicated observed age-adjusted incidence rates by stage and grade.

The mortality component of the model consists of disease-specific and other-cause survival. Disease-specific survival depends on age, stage (local–regional or distant), and grade (Gleason score 2 through 7 or 8 through 10) at diagnosis. For local–regional cases, disease-specific survival also depends on primary treatment (radiation or surgery), which is assumed to be administered according to patterns observed in the 9 core areas of the SEER (Surveillance, Epidemiology, and End Results) program in 2005. The **Appendix Table** (available at www.annals.org) shows additional details of the model incidence and mortality components and data sources used to estimate the model.

Screening that identifies nonoverdiagnosed disease before clinical diagnosis results in identification of earlier-stage tumors than might be identified without screening, leading to a reduction in prostate cancer mortality (**Appendix Figure 1**, available at www.annals.org). We refer to this as a "stage-shift model" for the effect of screening on prostate cancer mortality.

The candidate screening strategies we consider are 32 combinations of 2 ages to start (40 or 50 years) and stop (69 or 74 years) screening, 2 screening intervals (annual or biennial), and 4 thresholds for biopsy referral (PSA level of 4.0 μg/L; PSA level of 2.5 μg/L; PSA level of 4.0 μg/L or PSA velocity of 0.35 μg/L per year; or PSA level > 95th percentile for age [2.5, 3.5, 4.5, and 6.5 μg/L for ages 40 to 49, 50 to 59, 60 to 69, and 70 to 74 years, respectively]). The strategies are motivated by contemporary controversies. Some studies advocate lowering the age at which to start screening from 50 to 40 years, and others argue for lowering the PSA threshold for biopsy (12–14). Some studies suggest reducing the frequency of screening for men with low PSA levels (14); we operationalize this idea by evaluating an adaptive strategy (8) that screens biennially but increases the screening interval to 5 years if PSA is below its age-specific median (15). The original suggestion for the adaptive strategy (8) terminates screening at age 60 years for men with PSA levels less than 1.0 μg/L, but our implementation of this strategy continues screening to age 74 years to facilitate comparisons with other strategies.

We also evaluated strategies that have been recommended by guidelines groups. On the basis of recommendations from the American Cancer Society, we evaluated a strategy that changes the screening interval from annual to biennial if the PSA level is less than 2.5 μg/L (16). On the basis of recommendations from the National Comprehensive Cancer Network (17), we evaluated a strategy with annual screening starting at age 40 years but that expands to 5-year intervals if the baseline PSA level is less than 1.0 μg/L, changes to annual screening at age 50 years, and refers to biopsy if the PSA level is higher than 2.5 μg/L or PSA velocity is higher than 0.35 μg/L per year. We did not include a strategy from the American Urological Association because they recommend starting screening at age 40 years but do not indicate a screening interval or biopsy threshold. Our reference strategy was annual screening for patients aged 50 to 74 years with a PSA threshold of 4.0 μg/L for biopsy referral.

For each candidate screening strategy, we projected a range of negative outcomes (number of tests, false-positive results, overdiagnoses, and prostate cancer deaths) and positive outcomes (cancer detected, lives saved, and months of life saved). Because unnecessary biopsy- and treatment-

Table. **Lifetime Harms and Benefits Projected for a Man Aged 40 Years Under Alternative PSA Screening Strategies***

Policy	Screening Age, *y*	Screening Interval	Criterion for Biopsy Referral	Mean Screenings, *n*	Mean FP Results, *n*
1 (based on NCCN)	40–74	Annual (quinquennial if age <50 y and PSA level <1 μg/L)	PSA level >2.5 μg/L or PSA velocity >0.35 μg/L per year	21.8	3.4
2	40–74	Annual	PSA level >4.0 μg/L or PSA velocity >0.35 μg/L per year	29.5	3.0
3	50–74	Annual	PSA level >4.0 μg/L or PSA velocity >0.35 μg/L per year	20.0	2.7
4	40–74	Annual	PSA level >2.5 μg/L	29.7	2.8
5	50–74	Annual	PSA level >2.5 μg/L	20.1	2.8
6	40–74	Annual	PSA level >4.0 μg/L	30.0	1.7
7	40–74	Biennial	PSA level >2.5 μg/L	15.4	1.5
8	50–74	Annual	PSA level >4.0 μg/L	20.3	1.6
9 (based on ACS)	50–74	Annual (biennial if PSA level <2.5 μg/L)	PSA level >4.0 μg/L	12.1	1.6
10	40–74	Biennial	PSA level >4.0 μg/L or PSA velocity >0.35 μg/L per year	15.4	1.1
11	50–74	Biennial	PSA level >2.5 μg/L	10.6	1.4
12	40–69	Annual	PSA level >4.0 μg/L or PSA velocity >0.35 μg/L per year	26.6	2.1
13	50–74	Biennial	PSA level >4.0 μg/L or PSA velocity >0.35 μg/L per year	10.6	1.0
14	50–69	Annual	PSA level >4.0 μg/L or PSA velocity >0.35 μg/L per year	17.0	1.9
15	40–74	Annual	PSA level >95th percentile for age	30.0	1.2
16	40–74	Biennial	PSA level >4.0 μg/L	15.5	0.9
17	40–69	Annual	PSA level >2.5 μg/L	26.8	1.9
18	50–74	Biennial	PSA level >4.0 μg/L	10.6	0.8
19	50–74	Biennial	PSA level >4.0 μg/L	10.6	0.8
20	50–74	Annual	PSA level >95th percentile for age	20.4	1.2
21	50–69	Annual	PSA level >2.5 μg/L	17.1	1.8
22 (based on Vickers and Lilja [8])	45–74	Biennial (quinquennial if PSA level < median for age)	PSA level >4.0 μg/L	8.3	0.8
23	40–69	Annual	PSA level >4.0 μg/L	27.0	1.0
24	40–74	Biennial	PSA level >95th percentile for age	15.5	0.6
25	40–69	Biennial	PSA level >2.5 μg/L	13.6	0.9
26	50–69	Annual	PSA level >4.0 μg/L	17.3	1.0
27	50–74	Biennial	PSA level >95th percentile for age	10.6	0.6
28	40–69	Annual	PSA level >95th percentile for age	27.0	0.9
29	40–69	Biennial	PSA level >4.0 μg/L or PSA velocity >0.35 μg/L per year	13.6	0.7
30	50–69	Biennial	PSA level >2.5 μg/L	8.7	0.9
31	50–69	Annual	PSA level >95th percentile for age	17.3	0.8
32	50–69	Biennial	PSA level >4.0 μg/L or PSA velocity >0.35 μg/L per year	8.7	0.6
33	40–69	Biennial	PSA level >4.0 μg/L	13.6	0.5
34	40–69	Biennial	PSA level >95th percentile for age	13.6	0.5
35	50–69	Biennial	PSA level >4.0 μg/L	8.7	0.5

ACS = American Cancer Society; FP = false-positive; NCCN = National Comprehensive Cancer Network; NND = number needed to detect; PSA = prostate-specific antigen.

* Median PSA values are 0.7, 1.0, 1.4, and 2.0 μg/L and 95th-percentile PSA values are 2.5, 3.5, 4.5, and 6.5 μg/L for ages 40–49, 50–59, 60–69, and 70–74 y, respectively (15). NND by screening to save 1 life is overdiagnoses divided by lives saved. Probability of life saved and mean months of life saved are based on the model assumption that a patient whose stage was shifted from distant to local–regional by screening receives a corresponding survival benefit. Strategies are sorted by the probability of life saved. For comparison, in the absence of screening, the model projects 12.0% probability of cancer detection and 2.86% probability of cancer death.

related complications represent fixed fractions of false-positive results and overdiagnoses, we do not present these outcomes separately. Projected outcomes are presented for a contemporary man aged 40 years based on a simulated cohort of 100 million men for each screening strategy. Outcomes are reported as the mean number of events or the lifetime probability of each outcome. We also calculated the additional number needed to detect (NND) to prevent 1 prostate cancer death, which represents overdiagnoses per life saved and has become established as a summary measure of the harm–benefit tradeoff in prostate cancer screening (18, 19).

Model Validation

We previously calibrated the Fred Hutchinson Cancer Research Center prostate model using data through 2000 (10, 11). To validate the incidence component of the model, we compared observed and model-projected age-adjusted incidence by stage through 2005. To validate the mortality component of our model, we simulated the ERSPC, which, based on the protocol at most ERSPC centers, screened men every 4 years and obtained a biopsy from 86% of men with a PSA level higher than 3.0 μg/L (4). Using this framework, we calculated model-projected rates of prostate cancer mortality for screened versus un-

Table—Continued

Probability of ≥1 FP Results, %	Probability of Cancer Detected, %	Probability of Overdiagnosis, %	Probability of Cancer Death, %	Probability of Life Saved, %	Mean Time of Life Saved, *mo*	NND
44	18.2	6.0	2.02	0.85	1.00	7.08
45	17.9	5.8	2.03	0.84	1.00	6.90
44	17.7	5.5	2.05	0.81	0.96	6.84
32	17.0	4.9	2.06	0.81	0.96	6.08
31	16.8	4.7	2.08	0.78	0.94	6.01
22	15.5	3.5	2.13	0.72	0.88	4.79
29	16.1	4.0	2.14	0.71	0.85	5.58
21	15.3	3.3	2.15	0.70	0.86	4.70
21	15.3	3.3	2.15	0.70	0.86	4.70
26	15.6	3.6	2.16	0.69	0.84	5.13
29	15.9	3.8	2.16	0.69	0.84	5.51
41	16.0	3.9	2.18	0.67	0.89	5.77
26	15.5	3.4	2.19	0.67	0.82	5.07
40	15.7	3.7	2.21	0.65	0.85	5.67
16	14.4	2.4	2.21	0.64	0.83	3.78
20	14.9	2.8	2.22	0.64	0.78	4.42
27	15.1	3.1	2.21	0.63	0.84	4.85
20	14.7	2.7	2.23	0.61	0.77	4.34
20	14.7	2.7	2.23	0.61	0.77	4.34
15	14.3	2.3	2.23	0.61	0.81	3.71
27	14.9	2.9	2.24	0.61	0.82	4.75
19	14.4	2.4	2.27	0.58	0.75	4.09
17	14.0	2.0	2.30	0.54	0.75	3.66
14	13.8	1.8	2.31	0.54	0.73	3.39
24	14.2	2.2	2.33	0.52	0.72	4.20
17	13.8	1.8	2.32	0.51	0.73	3.58
14	13.7	1.7	2.33	0.51	0.70	3.32
15	13.7	1.7	2.33	0.51	0.73	3.29
21	13.9	1.9	2.34	0.50	0.71	3.90
23	14.0	2.0	2.35	0.49	0.70	4.12
14	13.5	1.5	2.35	0.48	0.71	3.20
20	13.8	1.8	2.37	0.47	0.67	3.85
15	13.4	1.4	2.41	0.43	0.64	3.18
13	13.2	1.3	2.42	0.42	0.63	2.99
14	13.3	1.3	2.43	0.41	0.61	3.11

screened cohort participants aged 55 to 69 years after 11 years of follow-up and compared the projected absolute and relative mortality reductions with observed mortality reductions.

Sensitivity Analysis

Recognizing that the incidence and mortality model inputs are subject to uncertainty, we conducted a sensitivity analysis to determine the robustness of our findings across a range of plausible values. In this analysis, we focused on unobservable inputs, namely the rates of disease onset, metastasis, and clinical detection in the incidence model and the extent of screening effect in the mortality model. Our previous work calibrating the incidence model to U.S. prostate cancer incidence trends yielded a range of values for each model parameter, and we ran the model 100 times under each screening strategy, each time sampling the model parameters from their respective ranges to determine the variability in results that would be induced by varying these inputs. In addition, we ran all screening strategies under several settings for the survival effect of screening, ranging from no effect to the effect consistent with the stage-shift model (**Appendix Figure 1**).

Role of the Funding Source

This study was funded by the National Cancer Institute and the Centers for Disease Control and Prevention, which had no role in trial design, data analyses, manuscript preparation, or the decision to submit the manuscript for publication.

RESULTS

Under no screening, the model projects a lifetime chance of a prostate cancer diagnosis of 12.0% and a lifetime chance of dying of prostate cancer of 2.86%. The chance of diagnosis is higher than estimates from the pre-PSA era of 9% (20), but our projected probability of diagnosis assumes contemporary biopsy practices, which are more sensitive than pre-PSA protocols (21).

Model Validation

Model-projected, age-adjusted incidence closely matches observed incidence through 2005 (**Appendix Figure 2**, available at www.annals.org), indicating that, without any change in model parameters, the model predicts incidence reasonably well beyond its years of calibration (1975–2000). The simulation of the ERSPC projects that screening reduces mortality by 28% after 11 years of follow-up, close to the reduction of 29% estimated by trial investigators after correcting for noncompliance (4). It also projects an absolute mortality reduction of 2.08 per 1000 men enrolled after 11 years of follow-up, higher than the 1.07 per 1000 men enrolled observed in the trial (4). At least part of the discrepancy probably resulted from crossover to screening in the control group of the trial (22).

The **Table** summarizes lifetime outcomes projected under all 35 screening strategies, numbered in descending order by probability of life saved; the reference strategy (annual screening for men aged 50 to 74 years with a PSA threshold for biopsy referral of 4.0 μg/L) ranks eighth. **Appendix Figure 3** (available at www.annals.org) shows how outcomes of reference strategies change when any of the strategy's variables (screening ages, screening interval, PSA level threshold, PSA velocity threshold) changes.

The reference strategy yields a 15.3% lifetime chance of diagnosis; 3.3% lifetime chance of overdiagnosis; and 2.15% lifetime chance of prostate cancer death, which is a relative reduction of 24.8% compared with the 2.86% chance of prostate cancer death with no screening. Under this reference strategy, the lifetime chance of a false-positive result is 21% and the NND is 4.7, which is similar to other long-term estimates (23, 24). Unless otherwise stated, all results are presented relative to this strategy.

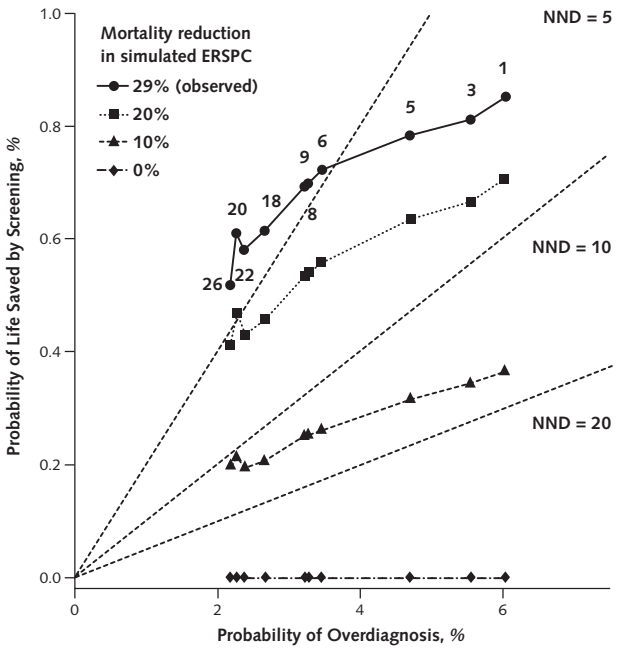
The National Comprehensive Cancer Network strategy (strategy 1) saves the most lives. However, the lifetime risks for a false-positive result and overdiagnosis are nearly twice that of the reference strategy. In general, lowering the PSA threshold or adding a velocity threshold generates substantial harms relative to incremental lives saved (strategies 3 and 5).

Varying ages to start and stop screening has a substantial effect on lives saved and overdiagnoses. Lowering the starting age to 40 years (strategy 6) increases the probability of life saved and overdiagnosis and substantially increases the number of PSA tests. Lowering the stopping age to 69 years (strategy 26) leads to a relative reduction of the probability of life saved by 27%, but the probability of overdiagnosis is decreased by nearly half and the probability of a false-positive PSA test result decreases by nearly 20%. The latter finding reflects the fact that a sizeable proportion of men diagnosed with fatal prostate cancer in the absence of screening are older than 70 years, and cancer in these men has the potential to be detected early; however, many more men in this age group have cancer that would not have affected their life expectancy, so screening this age group substantially increases the number of overdiagnoses. Screening men up to age 74 years but increasing the threshold for biopsy referral by an age-dependent PSA cutoff (strategy 20) reduces overdiagnoses by one third (to 2.3%) while only slightly altering the lives saved (to 2.23%). Therefore, 1 approach to preserve the effect of screening on mortality while controlling overdiagnosis may be to screen older men more conservatively (stopping at age 69 years or increasing the PSA threshold for biopsy referral for ages 70 to 74 years).

The performance of the American Cancer Society strategy (strategy 9) exactly parallels the reference strategy with no difference in overdiagnoses and lives saved. The only effect of this strategy relative to the reference strategy is that it reduces the number of tests conducted. This suggests that, by keeping the starting age and PSA threshold fixed, if the PSA level is low the interval between PSA assessments can be increased to biennial examinations without affecting other outcomes. Screening every 5 years rather than every 2 years when the PSA level is lower than the median for PSA within 10-year age groups (strategy 22) decreases the average number of tests by one third and overdiagnoses by one quarter relative to a biennial strategy while only reducing the chance of life saved by a relative 17%.

Figure 3 illustrates the tradeoffs between the probability of overdiagnosis (X value) and probability of life saved (Y value) for selected screening strategies. Projections under the base-case survival effect correspond to the 29% mortality reduction observed in the ERSPC after 11 years of follow-up (corrected for noncompliance) and are connected by the darkest line at the top. The NND for each strategy is the ratio X:Y, and the dashed lines from the origin (representing no screening) illustrate fixed NND values of 5, 10, and 20 for reference. Strategies 1, 3, and 5 have NNDs between 5 and 10 because they fall between the radiating lines "NND = 5" and "NND = 10"; remaining strategies under the 29% mortality reduction assumption all have NND less than 5. **Figure 3** shows that, relative to stopping screening at age 69 years (strategy 26), continuing screening through age 74 years but with age-dependent PSA thresholds for biopsy (strategy 20) increases probability of life saved (absolute increase, 0.1%) much more than it increases overdiagnosis (absolute increase, 0.05%). **Figure 3** also shows results obtained in analyses of sensitivity to the survival effect (that is, for mortality reductions of 20%, 10%, and 0%).

Figure 3. **Tradeoff between lifetime probabilities of life saved by screening and overdiagnosis for selected screening strategies.**



Each point represents the tradeoff for 10 of the 35 screening strategies examined in this study: the reference strategy (strategy 8); strategies that differ from the reference by a single screening variable (strategies 3, 5, 6, 9, 18, 20, and 26 [**Appendix Figure 3**]); and strategies based on recommendations by the National Comprehensive Cancer Network (strategy 1), the American Cancer Society (strategy 9), and Vickers and Lilja (strategy 22) (8) (see the **Table** for strategy details). The assumed effects of screening on prostate cancer survival correspond to mortality reductions of 29% (the reduction observed in the ERSPC trial after correction for noncompliance), 20%, 10%, and 0% projected in a simulated version of the ERSPC after 11 years of follow-up. Probability of life saved by screening corresponding to a mortality reduction of 29% is based on the assumption that a patient whose stage was shifted from distant to local–regional by screening receives the survival of the earlier stage. Probability of life saved by screening corresponding to mortality reductions of 20%, 10%, and 0% in the simulated version of the ERSPC are based on a generalization of this stage-shift assumption that projects prostate cancer survival on a continuum between no effect for patients with short lead times and the full stage shift for patients with long lead times. Probability of overdiagnosis is based on model-projected competing risks for prostate cancer detection and other-cause mortality. Lines connect projections under the same mortality reduction. The additional NND to prevent 1 prostate cancer death is an established summary measure of the harm–benefit tradeoff in prostate cancer screening compared with no screening, defined as the overdiagnoses divided by lives saved by screening. The NND corresponding to any point in the figure is obtained as the ratio of the probability of overdiagnosis to the probability of life saved. For reference, dashed lines radiating from the origin (representing no screening) illustrate fixed NND values of 5, 10, and 20. For a given probability of overdiagnosis, as the probability of life saved by screening decreases, the corresponding NND increases. For the mortality reduction of 29%, NNDs range from 7.1 (strategy 1) to 3.6 (strategy 26), and for the mortality reduction of 10%, NNDs range from 16.5 (strategy 1) to 9.9 (strategy 26). A strategy that falls between 2 NND lines (for example, "NND = 5" and "NND = 10") has an NND between those NND values. Different strategies will be preferred depending on relative weighting of the probabilities of life saved and overdiagnosis. Among the strategies considered, strategy 1 maximizes the probability of life saved and will be the preferred strategy if survival is the highest priority. Strategy 26 minimizes the probability of overdiagnosis and will be preferred if the morbidity associated with treatment is the greatest concern. For priorities between these extremes, the preferred strategy will be based on the most favorable balance between probabilities of life saved and overdiagnosis. For example, assuming the mortality reduction of 29%, a target tradeoff of 5 or fewer overdiagnoses per life saved (that is, NND ≤5) would identify strategies above and to the left of the "NND = 5" line. Assuming a mortality reduction of 20%, a target tradeoff of 5 or fewer overdiagnoses per life saved identifies strategy 20 as the only option. No strategy satisfies a target tradeoff of NND ≤3. No strategy satisfies a target tradeoff constraint of NND ≤10 under a mortality reduction assumption of 10%. ERSPC = European Randomized Study of Screening for Prostate Cancer; NND = number needed to detect.

Sensitivity Analysis

Varying the incidence model inputs produces very little variation in absolute model-projected outcomes (results not shown). Further, overall conclusions about tradeoffs across candidate strategies are robust to our sensitivity analysis on assumed survival effect. Less-intensive strategies (that is, those with fewer screens or higher thresholds for biopsy referral among older men) generally have lower risk for overdiagnosis with modest effects on relative rankings of disease-specific deaths or lives saved (**Figure 3**).

DISCUSSION

Since the advent of PSA screening, there has been uncertainty about screening benefit and concern about screening harms. The recent USPSTF recommendation against PSA screening for prostate cancer has raised awareness of the harms of existing screening strategies. In response, we sought to identify smarter screening strategies using microsimulation modeling.

The use of modeling in policy development is becoming more accepted (25, 26). The USPSTF relied on modeling to determine strategies for breast (27) and colorectal cancer (28) screening. Many models have been developed to study prostate cancer screening (29–34). Indeed, a recent publication considered 6 strategies for prostate cancer screening (24). However, like other prostate screening models, it did not conceptualize the disease process in a way that permits comprehensive evaluation of all screening strategy variables. Our model is unique in that it not only represents individual PSA over time but also explicitly links PSA growth with disease progression, which is linked with mortality. As a consequence, we can explore the outcomes of varying PSA thresholds for biopsy referral as well as variations in screening ages and intervals, which may change dynamically depending on PSA levels. By quantifying the likelihood of a false-positive result, overdiagnosis, or lives saved associated with a broad range of screening strategies, we can identify strategies that reduce harms but preserve the effect of early detection on prostate cancer mortality.

Our results yield several important conclusions. First, we find that aggressive screening strategies, particularly those that lower the PSA threshold for biopsy, do reduce

prostate cancer mortality relative to the reference strategy. However, the harms of unnecessary biopsies, diagnoses, and treatments may be unacceptable. Quantifying the magnitude of these harms relative to potential gains in lives saved is critical for determining whether the projected harms are acceptable.

Second, we find substantial improvements in the harm–benefit tradeoff of PSA screening with less frequent testing and more conservative criteria for biopsy referral in older men. These approaches preserve the survival effect and markedly reduce screening harms compared with the reference strategy. In particular, using age-specific PSA thresholds for biopsy referral (strategy 20) reduces false-positive results by a relative 25% and overdiagnoses by 30% while preserving 87% of lives saved under the reference strategy. Alternatively, using longer screening intervals for men with low PSA levels (strategy 22) reduces false-positive results by a relative 50% and overdiagnoses by 27% while preserving 83% of lives saved under the reference strategy. These adaptive, personalized strategies represent prototypes for a smarter approach to screening.

When smarter screening strategies achieve similar absolute probabilities of life saved, the choice between them depends on relative weighting of overdiagnosis and other harms. Using these 2 prototype strategies as an example, strategy 22 reduces total tests by a relative 59% and false-positive results by 33% but increases overdiagnoses by 5% relative to strategy 20. In general, the relative weighting of harms, like the relative weighting of benefits and harms, may depend on whether one adopts an individual or a societal perspective. If an individual perspective is adopted, preferences may vary across the population.

Other investigators have recommended personalized strategies for PSA screening as a means to reduce harms while preserving benefit. Carter and colleagues (14) suggested that the screening interval should be lengthened in men with low PSA levels. The risk calculator from the Prostate Cancer Prevention Trial produces a personalized prediction of the risk for occult disease based on PSA, age, race, and family history (35). In principle, we could compare an approach based on this calculator with other personalized strategies, but this would require adding race and family history to the model, recalibrating the model accordingly, and determining a reasonable risk threshold for biopsy referral. This could be done but is beyond the scope of the present study.

Every model is necessarily a simplification of reality and limited by its assumptions. Our model is no exception. We allow the likelihood of developing high-grade disease to vary with age but do not model grade progression. Because of limitations in the SEER data used to calibrate the model, we are limited to 2 stages (SEER local–regional or distant stage) and 2 grades (Gleason score 2 through 7 or 8 through 10). We model survival benefit by a stage-shift mechanism, which is probably also a simplification. Yet, a close match between our calibrated model and observed incidence and absolute and relative mortality reductions in a simulated ERSPC give us confidence that we are producing a valid representation of the likely tradeoffs in screening for a complex heterogeneous disease. Our model also does not incorporate utilities or produce quality-adjusted estimates of the effect of screening on survival. However, existing data on utilities associated with prostate cancer screening and postdiagnosis health states are extremely limited (36) and we do not believe that they are sufficiently reliable for modeling at this time. Further versions of the model will include other elements that are missing in the present version, including utilities once adequate data become available, costs, and race-specific disease progression.

In his recent editorial, Welch (7) concludes, "In the case of the prostate, for the past two decades we've been looking too damn hard. That's what's led to so many biopsies and so much overdiagnosis." By screening smarter, we do not look as hard, particularly in older men at the highest risk for overdiagnosis. As shown in the PLCO trial and supported by our model results across a broad range of alternative strategies, there are diminishing returns to intensive screening. If we recognize that realistic screening strategies must achieve an acceptable balance of benefits and harms as opposed to unconditionally maximizing benefits, we can improve on the effectiveness of existing PSA-based screening for prostate cancer.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Mr. Gulati (e-mail, rgulati@fhcrc.org). A detailed model description is available at http://cisnet.cancer.gov/prostate/profiles.html.

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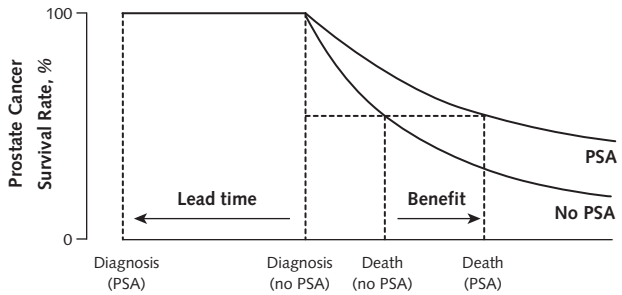
Appendix Table. **Summary of Model Components, Constituent Elements, Variables on Which Each Element Depends, and Data Sets Used to Estimate Each Element***

Element, by Component	Dependency	Data Set	Study, Year (Reference)
Incidence			
Preonset PSA growth	Age	PCPT	Gulati et al, 2010 (11)
Postonset PSA growth	Age, age at onset, grade	PCPT	Gulati et al, 2010 (11); Etzioni et al, 2012 (37)
Cancer onset	Age	SEER 9	Gulati et al, 2010 (11)
Cancer metastasis	PSA	SEER 9	Gulati et al, 2010 (11)
Clinical detection	PSA	SEER 9	Gulati et al, 2010 (11)
Mortality			
Treatment patterns	Age, year, stage, grade	SEER 9	Etzioni et al, 2012 (37)
Prostate cancer survival for unscreened, untreated patients	Age, stage, grade	SEER 9	Etzioni et al, 2012 (37)
Prostate cancer survival benefit for radical prostatectomy	(Local–regional stage only)	Published SPCG-4 trial results	Bill-Axelson et al, 2011 (38)
Prostate cancer survival benefit for radiotherapy	(Local–regional stage only)	Published CaPSURE study	Cooperberg et al, 2010 (39)
Prostate cancer survival benefit for early detection	Whether cancer detected in earlier stage	Published ERSPC protocol and results	Schröder et al, 2012 (4)
U.S. life tables	Age, year	Vital Statistics of the United States	National Center for Health Statistics, various years (40)
Additional data for calibration			
PSA screening patterns	Age, year	SEER-Medicare linked database, NHIS 2000	Mariotto et al, 2007 (41)
Biopsy frequency	Age, PSA	PLCO cancer screening trial	Pinsky et al, 2005 (42)
Biopsy sensitivity	Year	Literature review	Babaian et al, 2000 (43); Presti et al, 2000 (44); Eichler et al, 2006 (45)

CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; ERSPC = European Randomized Study of Screening for Prostate Cancer; NHIS 2000 = National Health Interview Survey 2000; PCPT = Prostate Cancer Prevention Trial; PLCO = Prostate, Lung, Colorectal, and Ovarian; PSA = prostate-specific antigen; SEER = Surveillance, Epidemiology, and End Results; SPCG-4 = Scandinavian Prostate Cancer Study Group 4.

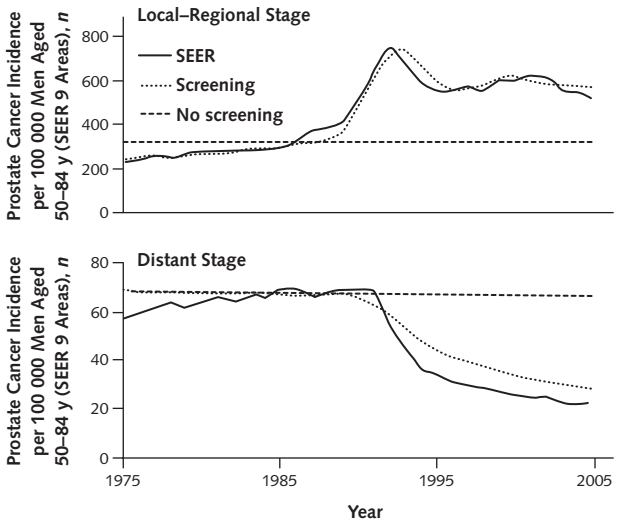
* The prostate cancer incidence component of the model was previously calibrated to reproduce prostate cancer incidence trends in the SEER 9 program by age (50–84 y), year (1975–2000), stage (local–regional vs. distant), and grade (Gleason score 2–7 vs. 8–10). The calibration used a simulated maximum likelihood algorithm to estimate incidence model parameters. At each iteration of the algorithm, the model simulated a population of patients under the current input parameter settings by the following steps: generate ages at onset of preclinical tumors from an age-dependent Weibull distribution; sample individual PSA growth trajectories, estimated separately for biopsy-confirmed cancer and noncancer patients using serial PSA data from the control group of the PCPT; generate ages at metastasis and clinical detection assuming the log of the times to these events have Weibull distributions with hazard functions proportional to PSA; and generate PSA screening schedules, indicators of compliance with biopsy referral after abnormal PSA results, and indicators of biopsy sensitivity to detect latent cancer. Using a Nelder–Mead algorithm, incidence model parameters that most closely matched observed incidence by age, year, stage, and grade were identified. After diagnosis, the mortality component of the model assigned initial treatments (radical prostatectomy, radiotherapy, or conservative management) to both screen and nonscreen patients based on SEER 9 treatment distributions from 2005, generated baseline prostate cancer survival from a Poisson regression model fit to untreated patients in SEER 9 in 1983–1986, improved prostate cancer survival using a hazard ratio of 0.62 for patients who received radical prostatectomy or radiotherapy (37–39), further improved prostate cancer survival for screen-detected local–regional stage patients who would have been diagnosed in distant stage in the absence of screening; and independently generated other-cause death from U.S. life tables. The final individual age at death was set to be the earlier of the age at prostate cancer death and the age at other-cause death.

Appendix Figure 1. **Effect of screening on prostate cancer survival based on the stage-shift model and a scheme for considering more modest effects in a sensitivity analysis.**



The effect of early detection on prostate cancer survival is assumed to follow a stage-shift model; that is, when nonoverdiagnosed patients are shifted from distant to local–regional stage at diagnosis, they receive a corresponding survival improvement. This figure represents a nonoverdiagnosed patient whose prostate cancer would have been detected in distant stage in the absence of PSA screening. His prostate cancer survival in the absence of PSA screening is represented by the curve labeled "no PSA." In the presence of PSA, his prostate cancer is detected in local–regional stage, and his prostate cancer survival follows a more favorable distribution, namely that for local–regional stage cases. This prostate cancer survival is represented by the curve labeled "PSA." The new survival begins at his original date of clinical diagnosis because, as a nonoverdiagnosed patient, by definition he cannot die during his lead time. In a sensitivity analysis, we considered a more modest effect of screening on prostate cancer survival. To implement this, the age at prostate cancer death consists of a weighted average of the age at prostate cancer death in the absence of screening and the age at prostate cancer death in the presence of screening: [Death (actual)] = $w \times$ [Death (no PSA)] + $(1 - w) \times$ [Death (PSA)], where the weight ($w = e^{-\alpha\lambda}$) depends on lead time λ = [Diagnosis (no PSA)] − [Diagnosis (PSA)] and on a variable reflecting the effect of screening on survival α. Consequently, when α is small, the weight is approximately 1, and the actual age at prostate cancer death is the same as that projected in the absence of screening. In contrast, when α is large, the weight is approximately 0, and the actual age at prostate cancer death is the same as that projected in the presence of screening. For values of α between these extremes, weight depends on the lead time, with longer lead times leading to more weight being placed on age at prostate cancer death in the presence of screening. We use 4 values of α to achieve mortality reductions due to screening, ranging from 0 to the full effect expected under the stage-shift model. PSA = prostate-specific antigen.

Appendix Figure 2. **Observed and projected age-adjusted prostate cancer incidence rates per 100 000 men aged 50 to 84 years, by stage at diagnosis.**



In the absence of PSA screening, the model projects constant prostate cancer incidence at approximately the level observed in the core 9 catchment areas of SEER in 1985. In the presence of observed PSA screening (39), the model projects prostate cancer incidence that closely replicates the observed rapid increase and subsequent stabilization in local–regional stage incidence and much of the observed decline in distant stage incidence because of early detection. PSA = prostate-specific antigen; SEER = Surveillance, Epidemiology, and End Results.

Appendix Figure 3. **Effect of varying individual screening strategy components on projected lifetime harms and benefits relative to the reference strategy.**

Variable	Screening Strategy							
Screening strategy number	3	5	6	**8**	9	18	20	26
Screening ages, *y*	50–74	50–74	**40–74**	**50–74**	50–74	50–74	50–74	**50–69**
Interscreening interval	Annual	Annual	Annual	**Annual**	**PSA-based**	**Biennual**	Annual	Annual
PSA level threshold, *μg/L*	4.0	**2.5**	4.0	**4.0**	4.0	4.0	**Age-based**	4.0
PSA velocity threshold, *μg/L per year*	**0.35**	NA	NA	**NA**	NA	NA	NA	NA
Harms and benefits								
Mean PSA tests, *n*	20.0	20.1	30.0	20.3	12.1	10.6	20.4	17.3
False-positive results, *n*	2.7	2.7	1.7	1.6	1.6	0.8	1.2	1.0
Probability of ≥ 1 false-positive result, %	43.7	31.3	21.8	21.4	21.1	19.7	15.4	16.8
Probability of cancer diagnosis, %	17.7	16.8	15.5	15.3	15.3	14.7	14.3	13.8
Probability of overdiagnosis, %	5.5	4.7	3.5	3.3	3.2	2.7	2.3	1.8
Probability of overtreatment, %	4.5	3.8	2.7	2.6	2.6	2.1	1.8	1.5
Probability of cancer death, %	2.1	2.1	2.1	2.2	2.2	2.2	2.2	2.3
Probability of life saved, %	0.8	0.8	0.7	0.7	0.7	0.6	0.6	0.5
Mean time of life saved, *mo*	1.0	0.9	0.9	0.9	0.9	0.8	0.8	0.7

Only the reference strategy (strategy 8) and strategies that differ from the reference strategy in a single variable are shown. Strategies are identified by the strategy number shown in the **Table**, and varied screening strategy components are in bold. In strategy 9, the screening interval is biennial if the PSA level is <2.5 μg/L and annual if the PSA level is ≥2.5 μg/L. In strategy 20, the threshold for biopsy referral is a PSA level of 3.5, 4.5, and 6.5 μg/L for ages 50–59, 60–69, and 70–74 y, respectively (21). Strategies are sorted in decreasing order by probability of life saved. NA = not applicable; PSA = prostate-specific antigen.