Comparative Efficiency of Prostate-Specific Antigen Screening Strategies for Prostate Cancer Detection

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Context Despite widespread use of serum prostate-specific antigen (PSA) testing to detect prostate cancer, the relative effectiveness of different PSA screening strategies is unknown.

Objective To compare prostate cancer mortality, PSA testing rates, and biopsy rates using various PSA screening strategies, including the standard strategy of annually testing men aged 50 through 75 years.

Design and Setting A Monte-Carlo simulation based on a Markov model was used to simulate the natural history of prostate cancer using different starting ages, testing intervals, and PSA thresholds for prostate biopsy. Age-specific PSA levels and prostate biopsy detection probabilities were determined from population data and surgical series.

Main Outcome Measures Numbers of prevented prostate cancer deaths, PSA tests, and prostate biopsies per 1000 men aged 40 through 80 years, compared among 7 different strategies vs no screening.

Results Compared with annual PSA testing beginning at age 50 years, the strategy of PSA testing at ages 40 and 45 years followed by biennial testing beginning at age 50 years was estimated to simultaneously reduce prostate cancer mortality and number of PSA tests and biopsies performed per 1000 men. Specifically, compared with no screening, the standard strategy prevents 3.2 deaths, with an additional 10500 PSA tests and 600 prostate biopsies, while the earlier but less frequent strategy prevents 3.3 deaths, with an additional 7500 PSA tests and 450 prostate biopsies. Strategies that lowered the PSA threshold for prostate biopsy to below 4.0 ng/mL or strategies that used age-specific PSA levels were not more efficient than use of a PSA threshold of 4.0 ng/mL. These 2 findings remained true under all sensitivity analyses performed to test assumptions of the model.

Conclusion Recognizing that the efficacy of PSA screening is unproved, the standard strategy of annual PSA screening beginning at age 50 years appears to be less effective and more resource intensive compared with a strategy that begins earlier but screens biennially instead of annually.

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IDENTIFICATION OF EFFICIENT SERUM prostate-specific antigen (PSA) screening strategies is increasingly important now that PSA testing is widely used to screen for prostate cancer. Although a common approach to PSA testing in clinical practice is to offer annual PSA measurements beginning at age 50 years for men at normal risk with more than a 10-year life expectancy,[1] this approach may not be the most efficient strategy.

Randomized screening trials are in progress both in the United States and in Europe to address the relationship between screening and prostate cancer mortality.[2] However, these trials cannot test the efficiency of multiple screening strategies that vary the test threshold, age to start screening, and screening intervals in a trial designed to address mortality reductions with screening compared with no screening.

There are many potential screening strategies that could vary by the age to start PSA testing, the PSA threshold that would prompt further evaluation (prostate biopsy), and the PSA testing intervals. Monte-Carlo simulations that model the natural history of a cancer are one approach to identifying screening strategies that efficiently reduce cancer deaths and limit unnecessary testing, and such models have been used to evaluate screening strategies for cervical,[3] ovarian,[4] and prostate[5,6] cancer. Recognizing that the benefits of prostate cancer screening have not been proved, we used a Markov model of the natural history of prostate cancer to compare the efficiency of various PSA screening strategies with the standard strategy of

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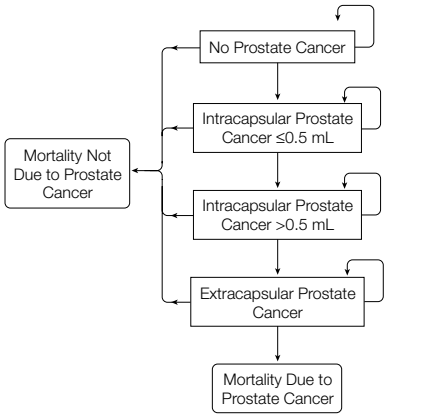
Figure 1. Schematic Outline of Model Structure



Each year men may progress from their current state along any of the transitions indicated by arrows.

annual PSA testing among men aged 50 through 75 years.

METHODS

A Monte-Carlo simulation based on a Markov model was used to simulate prostate cancer detection in men for 40 years, starting at age 40 years, under different strategies for screening using PSA. We simulated 100 populations of 1 million men each, and mean results were recorded; all models were also run using 100 000 runs of 1000 men each, and the mean values of all outcome variables were unchanged. The program was written using Version 6.12 of the SAS programming language (SAS Institute Inc, Cary, NC).

Model Structure

Men were classified in 1 of 4 groups: no prostate cancer, organ-confined prostate cancer volume of 0.5 mL or less, organ-confined prostate cancer volume of greater than 0.5 mL, or non–organ-confined prostate cancer. Each year, beginning at the age of 40 years, men could remain in the same state, progress to the next prostate cancer state, or die from other causes (FIGURE 1). Death rates from other causes were assumed to be unaffected by prostate cancer status, although sensitivity analyses were conducted altering this assumption.

Biopsy detection probabilities were based on the prostate cancer state,[7] with greater probability of detecting larger cancers, and it was assumed that biopsies would be negative in the absence of cancer. No more than 3 biopsy sessions were performed on any single man unless his serum PSA level exceeded 10.0 ng/mL. Men whose organ-confined prostate cancer was 0.5 mL or less were considered cured by surgery. Men whose organ-confined cancer volume was greater than 0.5 mL were given a 90% probability of being cured by surgery.[8] In both cases, mortality from surgical treatment was set at 0.5%.[9] Men in whom non–organ-confined prostate cancer was discovered could still die from prostate cancer or from other causes. In the base case analysis, their natural history was assumed to be unaffected by the cancer detection.

Model Inputs and Outputs

Age-specific prevalence of different prostate cancer states was determined based on an Office of Technology Assessment study combining data from 8 US hospital-based autopsy studies.[10] These data gave prevalence by age decade, so they were interpolated separately for each prostate cancer state using a fourth-order polynomial to yield age-specific prevalence. Cancer grade was not included because insufficient data are available on the rate at which tumor grade changes over time and the association between tumor grade and PSA level or tumor volume. Age-specific prostate cancer mortality was interpolated similarly from Surveillance, Epidemiology, and End Results (SEER) data from the National Cancer Institute from the pre-PSA era,[11] and all-cause mortality was taken from 1996 life tables from the National Center for Health Statistics.[12] Once age-specific death rates and prevalence of each prostate cancer state were determined, age-specific transition probabilities between states were calculated as follows: transitions among states were assumed to take place in annual increments (Figure 1), and then the transition probabilities were computed by setting the rate of entry into each state equal to the rate of exit from the state at 1 year older, where *exit* may refer either to prostate cancer progression or noncancer mortality.

Paired values of PSA from an individual in 2 successive years were assumed to follow a bivariate log-normal distribution. For men with no cancer or an organ-confined prostate cancer volume of 0.5 mL or less, the age-specific mean PSA value and the variance in log PSA were taken from a community-based sample of men in Olmsted County, Minnesota.[13] For men with an organ-confined prostate cancer volume of more than 0.5 mL and non–organ-confined prostate cancer, age-specific mean PSA level at each age was based on extensive Johns Hopkins surgical series data,[14,15] and variance was based on data from the Baltimore Longitudinal Study of Aging.[16] These data were also used to calculate the correlation between log PSA values in successive years for all men.

Outputs included prostate cancer deaths prevented (compared with no screening), person-years of life saved, the number of PSA tests administered, and the number of prostate biopsies. Person-years of life saved were calculated by allowing men who had been successfully treated to progress as if they had not been treated, monitoring whether they would have progressed to prostate cancer mortality, and then calculating each successfully treated man's life expectancy at the age at which death from prostate cancer would have occurred. All results were discounted by 3% annually, so that PSA tests, biopsies, person-years lived, and deaths which occurred at a young age were valued more than those which occurred later in life. This was done to enable resources used and health outcomes realized to be compared on a common basis across time even though they occur in different years.

Screening Strategies

Strategies were evaluated by varying the PSA threshold for prostate biopsy (the PSA level at which a prostate biopsy is performed), PSA testing intervals, and the start age for PSA testing, since these factors affect the efficiency of screening.

We evaluated a lower PSA threshold for taking a biopsy because of evidence suggesting that the prostate cancer detection rate is similar for men whose PSA levels are between 2.5 ng/mL and 4.0 ng/mL compared with men whose PSA levels are between 4.0 ng/mL and 10.0 ng/mL and because of the suggestion that detection of cancer at lower thresholds may improve cure rates.[17] We varied PSA testing intervals because there is evidence that yearly PSA testing may not be the most efficient strategy for screening.[5,6,14] Finally, we chose to evaluate screening strategies before age 50 years because younger men are more likely to be diagnosed with curable cancer compared with older men with similar pretreatment PSA levels.[15]

Sensitivity Analyses

Sensitivity analyses were run to test all major assumptions of the model (TABLE 1). First, models were run after both increasing and decreasing all prostate cancer prevalences by 20%. Second, a model was run using recent prostate cancer death rates (1989-1994)[11] instead of rates from the pre-PSA era. Models were also run varying prostate cancer death rates by 20%. Third, a model was run in which the noncancer death rate increased by 10% for men with intracapsular cancer volume greater than 0.5 mL and by 20% for men with extracapsular cancer, based on a previously observed 14% overall elevation.[18] Fourth, instead of a bivariate log normal with an age-specific mean, a model was considered whereby each successive year's PSA was log normally distributed with a mean that was 3.2% greater than current PSA level for men without cancer or with small intracapsular cancer, and 17.5% greater for men with large intracapsular cancer or extracapsular cancer.[19] Additional models were also run with increasing and decreasing PSA variance and the correlation between successive PSA values by 20%. Fifth, biopsy detection rates for the 3 prostate cancer states were raised so that the false-negative rate fell by 50% since urologists are beginning to alter biopsy strategies to reduce the false-negative rate of prostate biopsy.[20] A model was also run with decreased biopsy detection rates. Sixth, models were run with increased and decreased cure rates for each prostate cancer state. Seventh, operative mortality due to prostatectomy was set at 0% and at 2%. Eighth, the limit on the number of biopsies was altered so that no more than 3 could be performed unless the PSA level was more than 6 ng/mL, and another model was run with no limit on the number of biopsies. Finally, the simulation was run without a discount rate and with a 5% discount rate.

In addition, to verify the integrity of the model structure, we compared the age-specific prevalence of each prostate cancer state in the model with expected prevalence based on the Office of Technology Assessment combined autopsy data, and we compared age-specific prostate cancer death rates to expected rates based on SEER data. In all cases, values from the model were within 10% of their expected values.

Incremental Cost-effectiveness Ratios

Because this analysis compares screening strategies both in terms of health outcomes (prostate cancer deaths prevented and person-years of

Table 1. Assumptions and Parameters Used in Simulation

Assumption	Base-Case Assumption	Sensitivity Analyses
Prostate cancer prevalence, % (age, y)		
Intracapsular, ≤0.5 mL	6 (40) Through 34 (80),[10] varying continuously by age	5 (40) Through 27 (80)-7 (40) through 41 (80)
Intracapsular, >0.5 mL	3 (40) Through 16 (80)[10]	2 (40) Through 13 (80)-4 (40) through 19 (80)
Extracapsular	1 (40) Through 6 (80)[10]	1 (40) Through 5 (80)-1 (40) through 7 (80)
Prostate cancer death rate (age, y) per 100 000	0.1 (40) Through 325.9 (80)[11]	0.1 (40) Through 324.8 (80)[11]*
Nonprostate cancer death rates, age-specific	Unaffected by prostate cancer status[12]	Increased by 10% in men with intracapsular cancer >0.5 mL, by 20% in men with extracapsular prostate cancer[18]
PSA levels, age-specific	Bivariate log-normal, with mean value based on age and prostate cancer status[13-16]	Value at age 40 years based on age and cancer status, then annual increases based on cancer status[13,19]†
Biopsy detection rates, by cancer type, %		
Intracapsular ≤0.5 mL	32[7]	20-68
Intracapsular >0.5 mL	83[7]	75-91
Extracapsular	86	79-93
Treatment result, cure rate by cancer type, %		
Intracapsular ≤0.5 mL	100	90
Intracapsular >0.5 mL	90[8]	80-100
Extracapsular	No effect	20
Operative mortality from prostatectomy, %	0.5	0-2
Maximum number of biopsies	3 Unless PSA >10 ng/mL	3 Unless PSA >6 ng/mL-no limit
Discount rate, %	3	0-5

*Sensitivity analyses increasing and decreasing prostate cancer death rates by 20% were also performed.
†Sensitivity analyses varying the correlation between successive prostate-specific antigen (PSA) values and the variance of a given year's PSA were also performed.

life saved) and resources (PSA tests and prostate biopsies), we have reported the results in the format recommended for cost-effectiveness analyses.[21,22(pp276-303)] The number of prostate cancer deaths prevented relative to the no screening strategy was used as the primary effectiveness measure. We ranked the screening strategies in order of increasing effectiveness, beginning with the no-screening strategy. Each subsequent strategy was compared with the next most effective strategy not dominated by other strategies. A dominated strategy is one that is both less effective and uses more resources than some other strategy or linear combination of strategies. The incremental cost-effectiveness ratio is the number of additional PSA tests or prostate biopsies required to prevent 1 additional prostate cancer death with the new strategy compared with the next most effective nondominated strategy.[22(p399)]

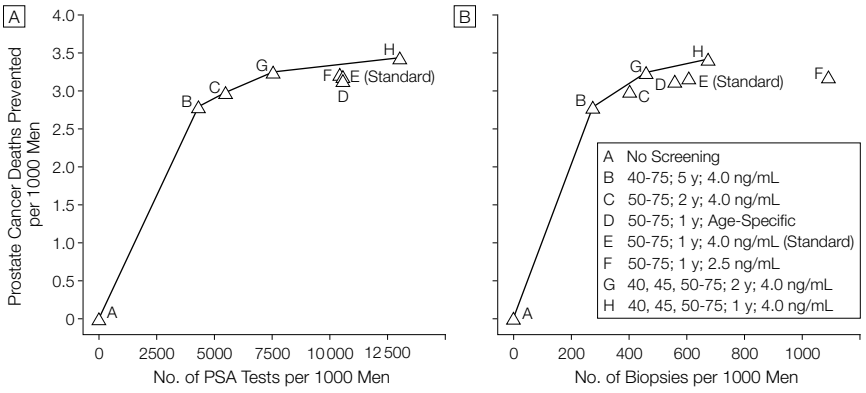
RESULTS

The relationships between prostate cancer deaths prevented and number of PSA tests administered and between prostate cancer deaths prevented and number of prostate biopsies results are shown in FIGURE 2A (for PSA tests) and Figure 2B (for biopsies), discounted 3% annually. In each graph resources are plotted on the horizontal axis and prostate cancer deaths, relative to the strategy of no screening, are plotted on the vertical axis. The strategies are ranked in order of increasing number of prostate cancer deaths prevented, beginning with the strategy of no screening. The point representing each nondominated strategy is connected by a straight line to the next most effective strategy not dominated by other strategies (see the "Methods" sections). The incremental cost-effectiveness ratio, expressed as the additional number of PSA tests administered or biopsies performed per 1000 men required to prevent 1 additional prostate cancer death per 1000 men, is graphically represented by the inverse of the slope of the line connecting 2 adjacent points. In these graphs the dominated strategies lie below the concave outline of nondominated strategies[22(pp276-303)] that are connected by the line.

The standard strategy (E) of annual PSA testing among men between the ages of 50 and 75 years with a 4.0 ng/mL PSA threshold for prostate biopsy is dominated by the strategy of earlier but less frequent PSA testing (G) both in terms of PSA tests (Figure 2A) and prostate biopsies performed (Figure 2B). Lowering the PSA threshold for taking a prostate biopsy to 2.5 ng/mL also results in a dominated strategy (F), as does use of age-specific PSA thresholds (D).

TABLE 2 shows the results in tabular form, again ranking the strategies in order of increasing prostate cancer deaths prevented relative to the strategy of no screening. Based on these simulations, the standard strategy (E) of men aged 50 through 75 years undergoing an annual screening is estimated to require 3300 PSA tests and 190 biopsies per prostate cancer death prevented. The incremental cost-effectiveness ratios are presented comparing each strategy with the next most effective nondominated strategy. Relative to the strategy of no screening, a strategy of screening men aged 40 through 75 years every 5 years requires an additional 1500 PSA tests and performing 100 prostate biopsies for each prostate cancer death prevented per 1000 men (strategy B). A strategy of screening men aged 50 through 75 years every 2 years (strategy C) requires that 6000 PSA tests be performed for each further prostate cancer death prevented per 1000 men. In terms of biopsies per prostate cancer death prevented, screening every 2 years is dominated by the combination of screening every 5 years and early but less frequent screening. This may be seen in Figure 2B by the fact that a straight line connecting the points representing strategies B and G lies above the point representing strategy C. A strategy (G) of screening with PSA tests at age 40 and 45 years when PSA levels remain below 2.0 ng/mL, and biennial PSA testing after age 50 years (or earlier if a PSA level is 2.0 ng/mL or higher), requires an additional 7500 PSA tests per prostate cancer death prevented compared with strategy C, which is the next most effective nondominated strategy in terms of PSA tests and deaths prevented. Strategy G also requires that an additional 400 prostate biopsies be performed for each additional prostate cancer death prevented compared with strategy B, which is the next most effective

Figure 2. Comparison of Different Screening Strategies



Compares 7 strategies with the standard strategy of annual serum prostate-specific antigen (PSA) testing of men aged 50 through 75 years using a PSA threshold of 4.0 ng/mL for prostate biopsy. The number of prostate cancer deaths prevented and PSA tests (A) and biopsies performed (B). Descriptions of strategies follow the format: age range in years for PSA testing, except for strategies G and H, which test at age 40 and 45 years and bienially (strategy G) or annually (strategy H) from ages 50 through 75 years; testing interval; and PSA threshold for biopsy. PSA threshold for biopsy is 4.0 ng/mL except where otherwise noted. Age-specific PSA thresholds are 3.5 ng/mL for men aged 50 through 59 years, 4.5 ng/mL aged 60 through 69 years, and 6.5 ng/mL aged 70 through 75 years.

nondominated strategy in terms of biopsies and prostate cancer deaths prevented. Increasing the screening intensity to annual PSA screening (strategy H) requires an additional 30 500 PSA tests and 1200 prostate biopsies for each additional prostate cancer death prevented.

The standard strategy (E) of annual screening of men aged 50 through 75 years prevents fewer prostate cancer deaths and requires more PSA tests and more biopsies than the strategy of earlier but less frequent PSA testing (G). Annual age-specific screening (D) and annual testing with the biopsy threshold lowered to 2.5 ng/mL were also dominated by earlier but less frequent testing (G). Two other strategies were considered and were found to be dominated (results not shown): biennial screening between the ages of 40 and 75 years, and early but less frequent screening using a PSA cutoff of 2.5 ng/mL at age 40 and 45 years, and 4.0 ng/mL at age 50 years and above.

Relative tradeoffs between strategies were similar for all sensitivity analyses. The absolute number of prostate cancer deaths, PSA tests, and biopsies varied; however, for all sensitivity analyses, the age-specific strategy (D), the standard strategy (E), and a strategy using a lower PSA threshold for biopsy (F) were dominated by the strategy of earlier but less frequent testing (G). Compared with the standard strategy, the savings in PSA tests using the strategy of early but less frequent screening ranged from 2900 to 3100 and the reduction in prostate cancer deaths ranged from 0.04 to 0.14 per 1000 men and discounted 3%. The reduction in biopsies varied between 140 and 151, except when no limit was imposed on the number of biopsies that could be performed on any one man, in which case the reduction in testing was even larger. Although relative differences between strategies did not change, the absolute number of biopsies performed was fairly sensitive to the variance in log-PSA used for men without prostate cancer: increasing the variance by 40% led to increases of 30% to 35% in the number of biopsies performed under various screening strategies.

When the simulation was run without screening, the age-specific mortality for men aged 65 to 69 years was 77 per 100 000 compared with 79 per 100 000 based on SEER data.[11] At all ages between 40 and 80 years the simulation output was similar to SEER data with respect to mortality. Average survival after progression to non–organ-confined prostate cancer in our model was 8.3 years. This is consistent with a median time to metastases of 8 years from the time of a detectable PSA in men who are not cured with radical prostatectomy and obviously had non–organ-confined prostatic cancer at the time of surgery.[23] We found that the number of biopsies performed per prostate cancer detected was 7.1. This is similar to 5 biopsies per cancer detected among 10 523 men aged 55 to 74 years in the European Randomized Study of Screening for Prostate Cancer.[24]

COMMENT

In this study, we have used a Monte-Carlo simulation based on a Markov model to compare the projected benefits and resource implications of different prostate cancer screening strategies. The approach of comparing only nondominated strategies enables one to avoid strategies predicted to prevent

Table 2. Simulated Outcomes (Mean of 100 Simulations of 1 Million Men) of Different Prostate Specific-Antigen (PSA) Screening Strategies Compared With No Screening*

	PSA Screening Strategies						
	B	C	D	E (Standard)	F	G	H
Screening strategy							
Age range for PSA testing, y	40-75	50-75	50-75	50-75	50-75	40,45,50-75	40, 45, 50-75
PSA triggering a biopsy, ng/mL	4.0	4.0	3.5, 4.5, 6.5†	4.0	2.5	4.0	4.0
PSA level to begin regular screens early, ng/mL	. . .	. . .	. . .	. . .	. . .	2.0‡	2.0‡
Testing interval, y	5	2	1	1	1	2	1
Simulated outcomes							
Prostate cancer deaths prevented	2.8	3.0	3.1	3.2	3.2	3.3	3.4
Person-years of life saved, y	35	36	38	38	38	40	43
No. of PSA tests	4300	5400	10 500	10 500	10 400	7500	13 000
No. of prostatic biopsies	270	400	550	600	1080	450	670
Cost-effectiveness ratios							
PSA tests per death prevented vs no screening	1500	1800	3300	3300	3200	2300	3800
Biopsies per death prevented vs no screening	100	130	180	190	340	140	190
Incremental PSA tests per death prevented§	1500	6000	Dominated	Dominated	Dominated	7500	30 500
Incremental biopsies per death prevented§	100	Dominated	Dominated	Dominated	Dominated	400	1200

*All values are mean results per 1000 men (aged 40-80 years) over the entire course of the simulation, with a 3% annual discount rate. Results were rounded to reflect their precision. Numbers that differ have nonoverlapping 95% confidence intervals. Strategies G and H include PSA test at age 40 and 45 years followed by annual testing of men aged 50 through 75 years. Ellipses indicate not applicable.
†Age-specific PSA threshold for prostate biopsy: 3.5 ng/mL for men aged 50 through 59 years; 4.5 ng/mL for men aged 60 through 69 years; and 6.5 ng/mL for men aged 70 through 75 years.
‡If the PSA level is 2.0 ng/mL or more at age 40 or 45 years, then biennial screening (strategy G) or annual screening (strategy H) begins at that point.
§Incremental ratios represent the cost-effectiveness of a strategy compared with the next most effective strategy in the Table (ie, the nearest nondominated strategy to the left).

fewer prostate cancer deaths while requiring more tests and more biopsies. One may view all nondominated strategies (including no screening) as rational in the sense that each represents the most prostate cancer deaths prevented for a given number of PSA tests administered and a given level of prostate biopsies performed among all strategies considered. The approach of incremental cost-effectiveness ratios, using numbers of PSA tests and prostate biopsies instead of monetary costs, provides a conceptual framework for comparing screening strategies with different starting ages for PSA testing, different PSA testing intervals, and different PSA thresholds for prostate biopsy. In this way one can successively estimate how many additional tests and biopsies per additional prostate cancer death prevented would be required for each increase in screening intensity.

The findings indicate—for the first time—that screening men at age 40 and 45 years with a 2-year testing interval after age 50 years (or before if the PSA level is more than 2.0 ng/mL), while holding the PSA threshold for a prostate biopsy at 4.0 ng/mL, may be more efficient than the current strategy of annual PSA screening from the ages of 50 through 75 years, because it is predicted to lower prostate cancer deaths slightly while simultaneously reducing the number of PSA tests administered and biopsies performed. The additional PSA tests at age 40 and 45 years provide the opportunity for early detection in younger men at the cost of performing only 2 additional PSA tests per man. This is more than compensated for by the reduced overall number of PSA tests and biopsies resulting from biennial rather than annual screening. Although the prevalence of prostate cancer is lower in 40- through 50-year-old men compared with older men, younger men with PSA-detected prostate cancers are more likely to have curable disease compared with older men whose cancers are detected by PSA tests.[15] This is reflected in our finding that starting earlier but testing less often does not increase and may actually decrease prostate cancer mortality. Our model may have underestimated the mortality decrease, because it did not reflect recently published evidence that younger men who undergo aggressive treatment for prostate cancer have lower mortality and morbidity compared with older men.[25]

Our findings also suggest that younger men (aged 40-50 years) with PSA levels of 2.0 ng/mL or more may benefit from biennial surveillance. In the 4th decade of life, 2.0 ng/mL is approximately the 95th percentile for serum PSA for age.[13] Furthermore, Gann et al[26] demonstrated with a somewhat older population that men with PSA levels above 2.0 ng/mL are more than 12 times as likely to be diagnosed with prostate cancer within the next decade compared with men with PSA levels below 1.0 ng/mL. These data support the rationale for increased surveillance of young men with "normal" PSA levels of 2.0 ng/mL or more, while continuing to use 4.0 ng/mL as the cutoff for taking a biopsy.

Our results suggest that lowering PSA thresholds for taking a biopsy to 2.5 ng/mL may not meaningfully reduce prostate cancer deaths, despite greatly increasing biopsies performed. This is consistent with previous findings from a surgical series of PSA-detected cancers demonstrating that when PSA levels were 4.0 ng/mL or less, 94% of tumors were curable and 69% were small, but when the PSA level was 4.1 to 5.0 ng/mL, 89% of the cancers were still curable, and only 33% of tumors were small.[14] Thus, a biopsy threshold of 4.0 ng/mL appears to detect potentially curable cancers with a reduced risk of detecting smaller, potentially unimportant tumors. The increase in biopsies with a lower PSA threshold predicted by our model is not surprising since the percentage of men in screened populations with PSA levels between 2.6 and 3.0 ng/mL is almost double the percentage of men with PSA levels between 4.1 and 5.0 ng/mL.[27] Thus, lowering the PSA threshold is estimated to increase the burden of PSA testing by nearly doubling the percentage of men who undergo prostate biopsies. Although this might be acceptable if cancer mortality were substantially reduced, our results suggest that it would not be.

Several other computer models have been used to examine prostate cancer screening, and it is worthwhile to compare the results of these studies to those of our simulation. When our simulation was used to model onetime screens at age 65 and 75 years, it predicted benefits per person screened of 13 and 4 days, respectively. In comparison, a model by Krahn et al[28] found 1 to 2 days, a model by Barry et al[29] found 17 days and 6 days, respectively, and a model by Etzioni et al[5] found 17 days for both ages. Our model thus appears to be slightly more conservative than those of Barry et al and Etzioni et al, while less conservative than that of Krahn et al. At these same ages, our model predicted benefits per person treated of 270 and 47 days, again more conservative than the model of Barry et al, which estimated 588 and 177 days, and that of Etzioni et al,[5] which estimated 453 and 139 days.

The study by Etzioni et al[5] also evaluated several strategies for serial prostate cancer screening. Their model predicted that biennial screening with a PSA level of 4.0 ng/mL reduced the number of screens while retaining 93% of the years of life saved. These authors created a stage-driven model, whereas our model is based on tumor volumes from surgical and autopsy series. Despite these differences in model construction, the results are remarkably similar. For example, their model estimated that annual screening of men aged 50 through 75 years with a cutoff of 4.0 ng/mL saved 0.16 person-years per man screened,[5] whereas our model was slightly more conservative in predicting 0.11 person-years. The similarities in outcome despite the differences in model construction support the validity of this approach in the evaluation of screening strategies.

Several limitations of our study deserve mention. First, our findings are based on a model of the natural history of prostate cancer and are only accurate to the extent that our model accurately represents the disease. Second, we recognize that our analysis is based on as-

sumptions of long-term treatment effectiveness that have not yet been established by randomized clinical trials. However, sensitivity analyses showed similar results when changes were made in assumptions or model inputs. Third, we evaluated PSA testing strategies without regard to the effect of digital rectal examination (DRE) on prostate cancer outcomes. This could have led to an underestimation of prostate cancer deaths prevented if DRE in combination with PSA testing prevents death from prostate cancer. In addition, failure to account for DRE findings in our model could have led to underestimation of the number of prostate biopsies performed since an abnormal DRE is considered an indication for taking a prostate biopsy. However, our results in terms of biopsies per cancer detected are similar to those from a large screening trial.[24] Fourth, our model does not take into account the ability of PSA criteria such as PSA velocity, PSA density, or free PSA to assess the risk that prostate cancer is present. These criteria could potentially reduce the percentage of men undergoing prostate biopsies, and failure to account for these in our model could have led to overestimation of the number of biopsies performed relative to cancer deaths prevented. Fifth, our results may not apply to black men since PSA levels in this study were obtained from a primarily white population,[13] and it is known that black men have higher PSA levels than whites. Finally, our model did not take into account the morbidity from prostate cancer treatment and the effects of diagnosis and treatment on quality of life, nor the full costs associated with detection and management of prostate cancer.[30] Thus, this cannot be considered a formal cost-effectiveness analysis of prostate cancer screening.

In summary, this study suggests that if screening for prostate cancer is beneficial, a screening strategy at age 40 and 45 years with a 2-year testing interval after age 50 years may be both more effective and require less testing than the standard strategy of annual PSA testng beginning at age 50 years. The approach of starting earlier but screening less often is predicted to reduce substantially PSA testing and biopsies while still yielding slightly lower prostate cancer mortality rates than the current annual screening strategy. Although the value of any PSA screening has yet to be proved, the incremental cost-effectiveness ratios suggest that the current standard of annual PSA testing after age 50 years may not be the best choice because it is both less effective and more resource intensive than another strategy.

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REFERENCES

1. Potter SR, Partin AW. NCCN practice guidelines for early detection of prostate cancer. *Oncology*. 1999; 13:99-115.
2. Auvinen A, Rietbergen JB, Denis LJ, Schroder FH, Prorok PC. Prospective evaluation plan for randomized trials of prostate cancer screening, for the International Prostate Cancer Screening Trial Evaluation Group. *J Med Screen*. 1996;3:97-104.
3. Zhang YS, Miller AB, Sherman GJ. Optimising the age, number of tests, and test interval for cervical screening in Canada. *J Epidemiol Community Health*. 1982;36:1-10.
4. Skates SJ, Singer DE. Quantifying the potential benefit of CA 125 screening for ovarian cancer. *J Clin Epidemiol*. 1991;44:365-380.
5. Etzioni RA, Cha R, Cowen ME. Serial prostate-specific antigen screening for prostate cancer: a computer model evaluates competing strategies. *J Urol*. 1999;162:741-748.
6. Ross KS, Pearson JD, Guess HA, Epstein JI, Carter HB. Rational PSA screening strategies for prostate cancer: computer simulations of age ranges, PSA cutoffs, and testing intervals [abstract]. *J Urol*. 1999;161:210.
7. Epstein JI, Walsh PC, Sauvageot J, Carter HB. Use of repeat sextant and transition zone biopsies for assessing extent of prostate cancer. *J Urol*. 1997;158: 1886-1890.
8. Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy: patterns of recurrence and cancer control. *Urol Clin North Am*. 1997;24:395-406.
9. Mark DH. Mortality of patients after radical prostatectomy: analysis of recent Medicare claims. *J Urol*. 1994;152:896-898.
10. US Congress, Office of Technology Assessment. *Cost and Effectiveness of Prostate Cancer Screening in Elderly Men*. Washington, DC: US Government Printing Office; May 1995. Publication OTA-BP-H-145.
11. Ries LAG, Kosary CL, Hankey BF, Miller BA, Edwards BK, eds. *SEER Cancer Statistics Review, 1973-1995*. Bethesda, Md: National Cancer Institute; 1998.
12. *US Abbreviated Life Tables for 1996*. Vol 1, No 1. Hyattsville, Md: National Center for Health Statistics; 1999.
13. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men: establishment of age-specific reference ranges. *JAMA*. 1993;270:860-864.
14. Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate-specific antigen testing intervals for detection of curable prostate cancer. *JAMA*. 1997;277:1456-1460.
15. Carter HB, Epstein JI, Partin AW. The influence of age and prostate specific antigen on the chance of curable prostate cancer among men with nonpalpable disease. *Urology*. 1999;53:126-130.
16. Guess HA, Pearson JD, Carter HB, Brant LJ, Fozard JL. Receiver operating characteristic curves for subjects with a previously normal test: prostate-specific antigen testing. *J Epidemiol Biostat*. 1997;2:161-169.
17. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination: enhancement of specificity with free PSA measurements. *JAMA*. 1997;277:1452-1455.
18. Brown BW, Brauner C, Minnotte MC. Noncancer deaths in white adult cancer patients. *J Natl Cancer Inst*. 1993;85:979-987.
19. Whittemore AS, Lele C, Friedman GD, Stamey T, Vogelman JH, Orentreich N. Prostate-specific antigen as predictor of prostate cancer in black men and white men. *J Natl Cancer Inst*. 1995;87:354-360.
20. Klein EA, Zippe CD. Transrectal ultrasound guided prostate biopsy: defining a new standard. *J Urol*. 2000; 163:179-180.
21. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses, for the Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996;276:1339-1341.
22. Siegel JE, Weinstein MC, Torrance GW. Reporting cost-effectiveness studies and results. In: Gold MR, Russell LB, Siegel JE, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996:276-303.
23. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999;281:1591-1597.
24. Schroder FH, van der Cruijsen-Koeter I, de Koning HJ, Vis AN, Hoedemaeker RF, Kranse R. Prostate cancer detection at low prostate specific antigen. *J Urol*. 2000;163:806-812.
25. Lu-Yao GL, Albertsen P, Warren J, Yao SL. Effect of age and surgical approach on complications and short-term mortality after radical prostatectomy: a population-based study. *Urology*. 1999;54:301-307.
26. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA*. 1995; 273:289-294.
27. Labrie F, Dupont A, Suburu R, et al. Serum prostate specific antigen as pre-screening test for prostate cancer. *J Urol*. 1992;147:846-852.
28. Krahn MD, Mahoney JE, Eckman MH, Trachtenberg J, Pauker SG, Detsky AS. Screening for prostate cancer: a decision analytic view. *JAMA*. 1994;272: 773-780.
29. Barry MJ, Fleming C, Coley CM, Wasson JH, Fahs MC, Oesterling JE. Should Medicare provide reimbursement for prostate-specific antigen testing for early detection of prostate cancer, IV: estimating the risks and benefits of an early detection program. *Urology*. 1995;46:445-461.
30. Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer. *JAMA*. 2000;283:354-360.