Original Article

Expected Population Impacts of Discontinued Prostate-Specific Antigen Screening

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BACKGROUND: Prostate-specific antigen (PSA) screening for prostate cancer has high risks of overdiagnosis, particularly among older men, and reports from screening trials indicate that it saves few lives after 11 to 13 years of follow-up. New clinical guidelines recommend against PSA screening for all men or for men aged >70 years, but, to the authors' knowledge, the expected population effects of these guidelines have not been studied to date. **METHODS:** Two models of prostate cancer natural history and diagnosis were previously developed using reconstructed PSA screening patterns and prostate cancer incidence in the United States. Assuming a survival benefit of PSA screening consistent with the screening trials, the authors used the models to predict incidence and mortality rates for the period from 2013 through 2025 under continued PSA screening and under discontinued PSA screening for all men or for men aged >70 years. **RESULTS:** The models predicted that continuation of recent screening rates will overdiagnose 710,000 to 1,120,000 men (range between models) but will avoid 36,000 to 57,000 cancer deaths over the period 2013 through 2025. Discontinued screening for all men eliminated 100% of overdiagnoses but failed to prevent 100% of avoidable cancer deaths. Continued screening for men aged <70 years eliminated 64% to 66% of overdiagnoses but failed to prevent 36% to 39% of avoidable cancer deaths. **CONCLUSIONS:** Discontinuing PSA screening for all men may generate many avoidable cancer deaths. Continuing PSA screening for men aged <70 years could prevent greater than one-half of these avoidable cancer deaths while dramatically reducing overdiagnoses compared with continued PSA screening for all ages. *Cancer* 2014;120:3519-26. *© 2014 American Cancer Society.*

KEYWORDS: mass screening, models, statistical, prostate-specific antigen, prostatic neoplasms, surveillance.

INTRODUCTION

Prostate cancer is the most common solid organ cancer in men in the United States, with an estimated 233,000 new cases and 29,480 deaths expected in 2014.[1] The high incidence of prostate cancer reflects a combination of the high latent prevalence of disease[2] and the effects of prostate-specific antigen (PSA) screening. Widespread adoption of PSA screening beginning in 1987 led to a doubling of incidence rates and significantly reduced the occurrence of metastatic cancer at the time of presentation.[3] However, the role of PSA screening in the 56% decrease in prostate cancer mortality rates noted since 1991[4] remains controversial. The US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial found no reduction in mortality after 13 years of follow-up.[5] In contrast, the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial found a significant 20% relative reduction in mortality after 11 years of follow-up, but this amounted to an absolute reduction of only 1 death per 1000 men screened.[6] Although the long-term mortality benefit of PSA screening is uncertain, it may exceed that reported for the trials to date.[7,8]

Counterbalancing mixed reports of benefit, the harms of PSA screening are significant. In the United States, 23% to 42% of PSA-detected cancers would never have been detected in the absence of screening[9]; by definition, treating these overdiagnosed cancers cannot improve patient outcomes and often leads to erectile, urinary, and bowel dysfunction.[10-12] Although cancers detected in young men with high PSA levels and a high Gleason score are unlikely to be overdiagnosed,[13] a majority of cancers are found in older men with low-risk characteristics.

Concerns regarding high rates of overdiagnosis and overtreatment and small absolute numbers of cancer deaths prevented by screening in trial reports led the US Preventive Services Task Force to recommend against routine PSA screening

for all men.[14] Other organizations, such as the American Cancer Society,[15] the American Urological Association,[16] and the American College of Physicians,[17] advise shared decision-making for men aged <70 years with at least a 10-year life expectancy. An upper age limit for screening was motivated partly by the age group found to benefit from screening in the ERSPC trial and partly because of higher risks of overdiagnosis and uncertain treatment benefit among older men.[18-21]

In this article, we quantified expected population effects of these new PSA screening guidelines using 2 models of prostate cancer natural history. The models are statistical representations of disease progression, detection, treatment, and survival that were previously developed to study the plausible roles of PSA screening[22] and changes in initial treatments[23] in prostate cancer mortality trends. Because the models separate prostate cancer natural history and nonscreen diagnosis from detection by PSA screening, they provide a coherent framework for predicting the plausible effects of discontinued screening. We consider perfect adherence to these new guidelines and the continuation of contemporary disease management patterns as a reasonable (albeit idealized) substrate for evaluating expected impacts on prostate cancer incidence and mortality patterns.

## MATERIALS AND METHODS
Prostate Cancer Natural History
The 2 models of prostate cancer natural history and diagnosis[24,25] used in the current study were independently developed as part of the Cancer Intervention and Surveillance Modeling Network (CISNET), a consortium of investigators using surveillance models to investigate drivers of national cancer trends. Numerous statistical models have produced various estimates of prostate cancer outcomes associated with PSA screening, but many do not readily generalize beyond the particular setting to which they were applied. The CISNET prostate cancer models were designed to use population-based data sources to disentangle disease natural history and nonscreen diagnosis from the effects of PSA screening. In this way, the estimated models represent a virtual laboratory for assessing the expected impacts of alternative screening PSA scenarios, such as discontinued screening. By using 2 models, we were able to examine the sensitivity of the results to natural history assumptions.

Figure 1 illustrates prostate cancer natural history (health states and transitions between states, representing the onset of a screen-detectable cancer, disease progression
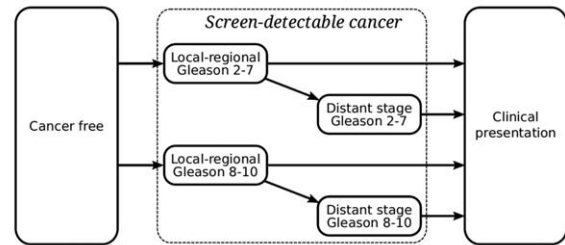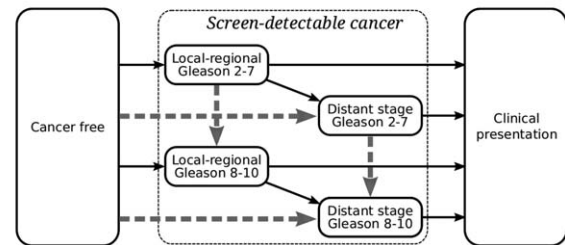
Figure 1. Health state transitions are shown in 2 models of prostate cancer natural history. Screen-detectable cancers in both models progress from locoregional to distant stage. In the University of Michigan model, cancer can also progress to distant-stage disease before becoming screen detectable (horizontal dashed gray arrows). Tumor grade (Gleason score of 2-7 or 8-10) is fixed in the Fred Hutchinson Cancer Research Center model but lower-grade disease can progress to higher grade in the University of Michigan model (vertical dashed gray arrows).

through stages and/or grades, and clinical presentation) in the 2 models. In the Fred Hutchinson Cancer Research Center (FHCRC) model, cancers are localized at onset and may be either low grade (Gleason score of 2-7) or high grade (Gleason score of 8-10). Risks of metastasis and diagnosis depend on patient age, time since onset, and tumor stage and grade and are correlated with individual PSA levels. In the University of Michigan (UMICH) model, cancers can be localized or metastatic and low grade or high grade at onset, and risks of stage and grade progression and diagnosis depend on patient age, year, time since onset, and tumor stage and grade (see online supporting information for detailed model descriptions). Screening according to reconstructed PSA screening patterns in the United States[26] is superimposed on each model to produce screen-detected and non–screen-detected cases diagnosed each year.

The models were informed with the same prostate cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER) program. The FHCRC model also used PSA test results from the control arm of the Prostate Cancer Prevention Trial[27] to estimate PSA growth rates and data regarding biopsy practice patterns[25,28] to model disease detection when the PSA level

exceeds 4 ng/mL, whereas the UMICH model estimated effective test sensitivity using SEER incidence and US screening patterns. Risks of disease onset, progression, and nonscreen diagnosis were estimated so that the models reproduced prostate cancer incidence rates in the SEER program by age (50-84 years), calendar year (1975-2000), stage of disease (locoregional or distant), and tumor grade (Gleason score of 2-7 or 8-10). Estimation details are provided in the online supporting information.

Treatment Benefit and Prostate Cancer Survival

To project prostate cancer survival after diagnosis, the models used frequencies of conservative management, radical prostatectomy, and radiotherapy from SEER and frequencies of androgen deprivation therapy (ADT) from the Cancer of the Prostate Strategic Urologic Research Endeavor[29] database.

In the absence of screening, patients assigned to conservative management or ADT monotherapy were assumed to have baseline prostate cancer survival similar to that for untreated cases in SEER from 1983 through 1986, just before PSA screening began. We assumed that contemporary patients who were not detected by screening and who receive active surveillance have similar survival. To the best of our knowledge, there are no randomized trials to date comparing the main primary treatment options; based on a recent observational study,[30] we assumed that radical prostatectomy and radiotherapy with ADT are similarly efficacious and that these treatments are more efficacious than radiotherapy alone. Patients assigned to radical prostatectomy (or radiotherapy with ADT) had improved survival based on the Scandinavian trial of radical prostatectomy versus watchful waiting (hazard ratio [HR], 0.62)[31] and consistent with the US-based Prostate Cancer Intervention Versus Observation Trial.[32] Patients assigned to radiation monotherapy had survival that improved during the early 1990s (HR of 0.9 before 1990, linear improvement to an HR of 0.7 in 1995, and constant thereafter)[23] to reflect the increase in radiation dose intensity over time.

Screening Benefit

A patient who is diagnosed by screening and would have died of the disease in the absence of screening was assumed to have prostate cancer survival and initial treatment corresponding to the earlier age of the patient, stage of disease, and/or tumor grade at the time of screen detection. This "stage-shift" effect of screening was previously shown to be consistent with the mortality reduction observed in the ERSPC trial after 11 years of follow-up using the FHCRC model.[33]

In this study, both models used flexible representations of the stage-shift effect. Instead of giving a full stage-shift to all cancers detected early by screening, a parameter controls the scale of the benefit, with cancers that are detected later in their natural history receiving less benefit. Flexible stage-shift effects and parameter estimation details are given in the online supporting information.

Predicted effects of PSA screening on prostate cancer mortality are based on applying estimated stage-shift effects to prostate cancer survival over a lifetime horizon for the US population. In practice, the models independently generate prostate cancer survival (with any early detection and treatment benefit) and other-cause survival from US life tables.[34] Actual survival is the shorter of these competing survival times, with cause of death assigned accordingly.

Discontinued Versus Age-Restricted Screening

To quantify the expected effects of the new PSA screening guidelines, we predicted prostate cancer incidence, including overdiagnoses and distant-stage cancers, and mortality under 3 scenarios: a continuation of recent screening patterns (continued), a continuation of recent screening patterns restricted to men aged <70 years (age-restricted), and discontinued screening for all ages (discontinued). Recent PSA screening patterns are based on a reconstruction using SEER-Medicare and National Health Interview Survey data in 2000[26] and updated using National Health Interview Survey data in 2005 and 2010. The incidence of overdiagnosis reflects patients diagnosed by PSA screening who would not have been diagnosed in the absence of screening (ie, who would have died of other causes before clinical presentation). Prostate cancer mortality after 2010 assumes that the distribution of initial therapies remains constant as observed in 2010. Predictions are for men aged 50 to 84 years between January 1, 2013, and December 31, 2025.

To inflate predictions for the SEER population to the US population, incidence and mortality rates were multiplied by US Census projections by 5-year age group and calendar year.[35]

Model Validations

As a partial validation of the natural history models, we compared predicted and observed incidence counts from SEER in the year 2010 (ie, a decade later than the data used to estimate the models). General agreement would suggest that 1) the models reflect reasonable approximations to natural history and 2) there have not been
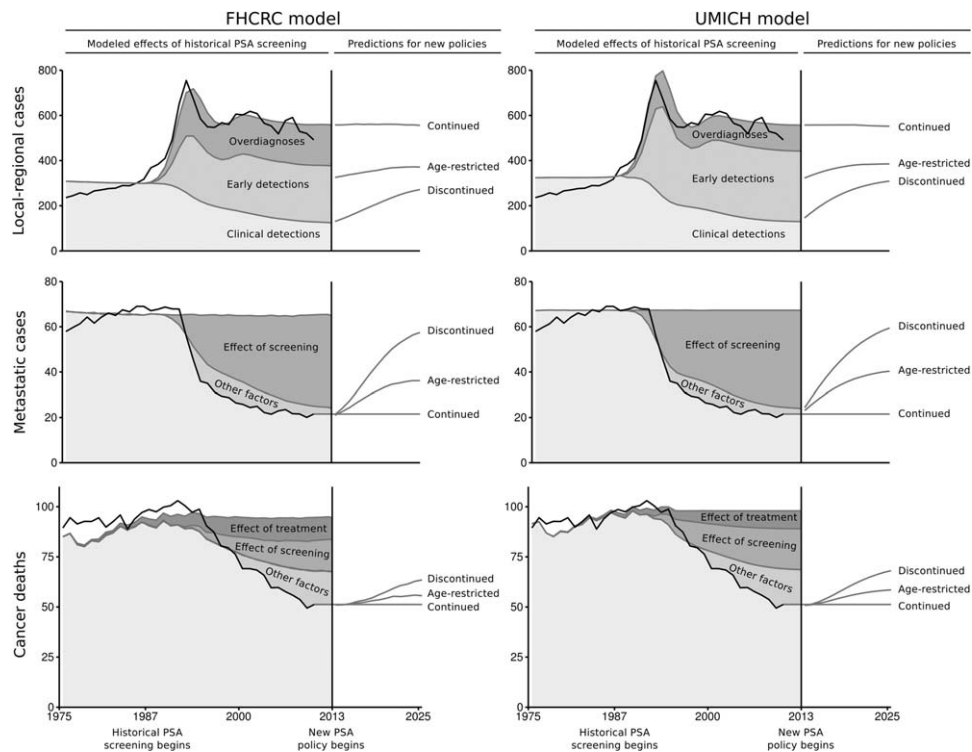
Figure 2. Historical prostate cancer incidence and mortality rates, modeled effects of historical prostate-specific antigen (PSA) screening, and model predictions are shown under 3 PSA screening policies: A) continuation of recent PSA screening patterns (continued); B) continuation of recent PSA screening patterns restricted to men aged <70 years (age-restricted); and C) discontinued PSA screening for all men (discontinued). Rates are age-standardized per 100,000 men aged 50 to 84 years. FHCRC indicates Fred Hutchinson Cancer Research Center; UMICH, University of Michigan.

significant changes in prostate cancer epidemiology or practices related to prostate cancer diagnosis since the year 2000.

As a partial validation of the survival benefit of early detection and treatment, we compared predicted and observed *absolute* mortality reductions in simulations of the ERSPC trial through 11 years of follow-up based on stage-shift effects calibrated to match *relative* mortality reductions. General agreement would suggest that the models reflect reasonable approximations to prostate cancer survival, benefits of early detection and treatment, and competing risks of other-cause death.

Sensitivity Analysis

Because some have argued that the lack of screening benefit reported in the PLCO trial reflects at best a more modest impact of early detection in the United States,[36,37] we also predicted the effects of screening on prostate cancer mortality assuming reduced efficacy. The models recalibrated stage-shift effects of screening to yield a 15% mortality reduction compared with no screening after 11 years of follow-up in simulated ERSPC trials, which is approxi-

mately one-half of the 29% reduction reported after correction for noncompliance.[6] The models then projected mortality rates under continued, age-restricted, and discontinued PSA screening assuming this reduced benefit.

RESULTS

Model Validations

Figure 2 illustrates prostate cancer incidence rates reported in SEER and projected by the models for the calibration (1975-2000) and validation (2001-2010) years (see online supporting information for comparisons by patient age and stage of disease). The models closely approximate observed trends in locoregional and metastatic incidence before and after the introduction of PSA screening through 2010. Figure 2 also shows corresponding mortality rates; the models project constant mortality in the absence of screening or changes in initial treatments and similar reductions due to these interventions.

Table 1 presents a snapshot of localized cases, metastatic cases, and prostate cancer deaths reported in SEER and projected by the models in 2010. Both models over-projected localized cases, although discrepancies were

TABLE 1. Prostate Cancer Cases and Deaths Extrapolated From SEER and Effects of Historical PSA Screening Predicted by 2 Models in 2010[a]

	SEER	FHCRC	UMICH
Localized cases			
Screen detections			
Overdiagnoses	—	65,500	41,300
Early detections	—	104,900	126,100
Clinical detections	—	51,000	53,700
Total	202,500	221,400	221,100
Metastatic cases			
Prediction under no screening	—	24,300	25,100
Effect of screening	—	−14,600	−15,400
Effect of other factors (not modeled)	—	−1,400	−1,400
Total	8,300	8,300	8,300
Prostate cancer deaths			
Prediction under no screening or treatment	—	33,600	34,800
Effect of treatment	—	−4,000	−3,100
Effect of screening	—	−5,400	−7,100
Effect of other factors (not modeled)	—	−6,100	−6,500
Total	18,100	18,100	18,100

Abbreviations: FHCRC, Fred Hutchinson Cancer Research Center model; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology, and End Results program registries; UMICH, University of Michigan model.
[a] Counts are for US men aged 50 to 84 years.

relatively modest (2.0% for FHCRC vs 2.3% for UMICH) over the period 2005 through 2010. The models estimated that 3 out of 4 cases were detected by PSA screening in 2010, of which 25% to 38% (range between models) were overdiagnosed. The models agreed that screening explains nearly all of the decrease in metastatic cases, and the calibrated stage-shift effects of screening explain 48% to 52% of the observed drop in prostate cancer deaths compared with no screening.

In simulated ERSPC trials after 11 years of follow-up, both models approximated the relative mortality reduction of 29% after correction for nonattendance estimated by trial investigators[6] (29% for FHCRC vs 28% for UMICH) and modestly overprojected the observed absolute mortality reduction of 1.1 per 1000 men screened (1.7 for FHCRC vs 1.5 for UMICH),[6] most likely because they did not account for nonattendance or contamination in the actual trial.[38]

Overall, the correspondence between model projections and empirical data supports using the models to investigate the plausible effects of new PSA screening policies. However, to account for factors not in the models that contributed to the declines in distant-stage incidence and mortality, we quantified the unexplained portions of the declines in 2010 and subtracted these differences from model projections in subsequent years. In other words, we assumed that other factors that contributed to the

observed declines in 2010 would remain constant into the future.

Primary Analysis

Figure 2 also illustrates prostate cancer incidence and mortality rates predicted by the models under continued, age-restricted, and discontinued PSA screening for the period 2013 through 2025. The models predicted immediate declines in localized incidence rates under age-restricted and discontinued screening, with steady increases accumulating over this period. In both models, incidence rates nearly returned to pre-PSA levels by the year 2025 under discontinued screening. Mortality rates also increased under age-restricted and discontinued screening, with significantly faster increases noted under discontinued screening. However, mortality rates did not return to pre-PSA levels due to the continuation of contemporary patterns of initial treatments and other factors contributing to the observed decline in mortality by 2010.

Table 2 reports localized cases, metastatic cases, and prostate cancer deaths under each PSA screening scenario for the period 2013 through 2025. Under continued screening, the models projected 710,000 to 1,120,000 overdiagnosed cases and approximately 130,000 metastatic cases at the time of presentation. Age-restricted screening was found to prevent 470,000 to 720,000 overdiagnoses (64%-66% decrease) but added 58,000 to 73,000 metastatic cases at the time of presentation (46%-57% increase). In contrast, discontinued screening was found to eliminate all overdiagnoses but more than doubled metastatic cases at the time of presentation. The models project >280,000 prostate cancer deaths through 2025 under continued screening. Age-restricted screening added 13,000 to 22,000 prostate cancer deaths (5%-8% increase) whereas discontinued screening added 36,000 to 57,000 prostate cancer deaths (13%-20% increase).

In summary, the models concurred that age-restricted screening appears to substantially reduce overdiagnoses while preventing a majority of the additional metastatic cases at the time of presentation and prostate cancer deaths predicted under discontinued screening.

Sensitivity Analysis

Under reduced PSA screening efficacy, age-restricted screening added 6,000 to 14,000 prostate cancer deaths (2%-5% increase), whereas discontinued screening added 18,000 to 35,000 prostate cancer deaths (6%-12% increase). As in the primary analysis, age-restricted screening was found to prevent a majority of the additional

TABLE 2. Prostate Cancer Cases and Deaths Predicted by 2 Models Under 3 PSA Screening Policies: A) Continuation of Recent PSA Screening Patterns (Continued), B) Continuation of Recent PSA Screening Patterns Restricted to Men Aged <70 Years (Age-Restricted), and C) Discontinued PSA Screening for All Men (Discontinued) for the Period 2013 Through 2025[a]

	Continued (A)		Age-Restricted (B)		Discontinued (C)		Percent Relative Effects of Age-Restricted Versus Discontinued Screening 100×(A-B)/(A-C)	
	FHCRC	UMICH	FHCRC	UMICH	FHCRC	UMICH	FHCRC	UMICH
Localized cases								
Screen detections								
Overdiagnoses	1,122,900	705,200	399,700	237,100	0	0	64.4	66.4
Early detections	1,763,600	2,071,400	1,130,000	1,163,900	0	0	35.9	43.8
Clinical detections	795,600	890,900	1,008,800	1,216,900	1,372,400	1,679,500	37.0	41.3
Total	3,682,100	3,667,400	2,538,400	2,617,800	1,372,400	1,679,500	49.5	52.8
Metastatic cases	127,900	129,300	186,200	202,600	271,100	291,300	40.7	45.3
Prostate cancer deaths								
Base case PSA efficacy	283,500	284,600	296,400	306,900	319,400	342,000	35.9	38.9
Reduced PSA efficacy	284,300	285,400	290,300	299,400	301,800	320,700	33.9	39.6

Abbreviations: FHCRC, Fred Hutchinson Cancer Research Center model; PSA, prostate-specific antigen; UMICH, University of Michigan model.
[a] Counts are for US men aged 50 to 84 years.

prostate cancer deaths predicted under discontinued screening.

DISCUSSION

In the last 2 years, there have been major revisions to prostate cancer screening policy recommendations by influential US guidelines panels, most notably the US Preventive Services Task Force.[14,39] Motivated largely by the results of the PLCO and ERSPC trials, the new recommendations are generally conservative and advocate the cessation of routine PSA screening for all men or for men aged >70 years or those with a limited life expectancy. The response to these recommendations in terms of clinical practice is evolving, but screening rates could decline dramatically. The results of the current analysis suggest that discontinued screening could have profound consequences for prostate cancer deaths and advanced disease in the United States.

The continuation of current screening is expected to overdiagnose as many as 1 million US men but prevent large numbers of metastatic cases at the time of presentation and prostate cancer deaths by 2025. Discontinued screening indiscriminately eliminates both the harms and benefits of screening; for example, it eliminates the overdiagnosis and overtreatment of men with low-risk prostate cancer but at great cost. Restricting screening to men aged <70 years eliminates a majority of overdiagnosed cases and preserves >50% of the metastatic cases avoided and

lives saved with contemporary screening patterns; this finding is insensitive to whether screening efficacy is similar to or lower than that reported in the ERSPC trial.

The models confirm that PSA screening generates substantial numbers of overdiagnosed cases, but the estimates are below other reported figures,[40] which were based on coarse approximations with limited accounting for patient age or period effects.[41] The wide range for the absolute number of overdiagnoses predicted by the 2 models is not unexpected given that this harm is not directly observable and estimates are sensitive to unknown aspects of prostate cancer natural history. In particular, the UMICH model estimated fewer overdiagnoses and more early detections than the FHCRC model because its allowance for faster cancer progression during the screen-detectable window implies shorter lead times.[42] Nonetheless, the reduction in overdiagnoses expected under age-restricted PSA screening relative to discontinued PSA screening is highly consistent between models.

The current study results confirmed that if screening improves survival by a "stage-shift" effect, then PSA screening appears to have played an important role in the observed decline in prostate cancer mortality. However, screening and changes in primary treatments do not explain the entire observed decline in prostate cancer mortality. Other factors, such as increasing obesity rates[43] or decreasing smoking rates,[44] or other interventions such as

treatment at the time of biochemical recurrence[45] might have reduced mortality. The results of the current study assumed the unexplained contribution of these factors to the decline in mortality in 2010 will remain constant. Provided these factors do not interact with the effects of screening, they should not affect our main results.

The status quo of widespread relatively late screening[46] irrespective of life expectancy[47] and nearly universal treatment[29] clearly is far from optimal. Nevertheless, as the current analysis demonstrated, wholesale abandonment of screening efforts may be a costly solution. Although an age-restricted policy is a compelling improvement, it does not account for life expectancy or screening history; a 66-year-old healthy man with no prior PSA exposure faces a very different risk profile than a counterpart with multiple comorbidities and multiple prior PSA levels <1 ng/mL.[48,49] Other screening strategies may yield more favorable harm-benefit tradeoffs,[33] particularly when combined with the greater use of active surveillance.[50]

We accounted for key sources of uncertainty by using 2 models of prostate cancer natural history and a sensitivity analysis to screening benefit. Nonetheless, other sources of uncertainty remain. Despite relying on population-based data sets and conditioning effects of interventions on patient and tumor characteristics, the varied populations and settings in certain data sources may not be perfectly compatible with each other or representative of the general US setting. Restriction to coarse grade categories (Gleason scores 2-7 vs 8-10) was necessary to avoid bias due to upward grade migration over time. We also did not incorporate life expectancy when selecting men to be screened in the models, but it is likely that men who choose to be screened for prostate cancer are healthier than the general population. Therefore, our estimates of overdiagnoses under screening may be modestly inflated. Finally, we previously demonstrated that, due to widespread contamination and lower-than-expected mortality, the stage-shift effect of screening is neither supported nor contradicted by results from the PLCO trial.[51] Nevertheless, the screening benefit in our primary analysis has not been confirmed over the long-term.

Recently revised screening guidelines are poised to yield a significant shift in prostate cancer epidemiology, reducing overdiagnosis and overall incidence at the expense of increasing the burden of prostate cancer metastasis and mortality. The current study projections indicate that discontinuing screening may significantly erode observed reductions in prostate cancer mortality over a relatively short time frame. Continuing screening but restricting it to men aged <70 years is one approach that could preserve many of the benefits of contemporary patterns of screening while still reducing harms. Rather than abandoning screening entirely, the results of the current study support finding ways to continue screening that mitigate harm while preserving as much of the benefit as possible.

CONFLICT OF INTEREST DISCLOSURES

Dr. Cooperberg received personal fees from Dendreon, Amgen, AbbVie, Astellas, GenomeDx, Genomic Health, Myriad, and Janssen for work performed outside of the current study.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9-29.
2. Etzioni R, Cha R, Feuer EJ, Davidov O. Asymptomatic incidence and duration of prostate cancer. *Am J Epidemiol*. 1998;148:775-785.
3. Etzioni R, Gulati R, Falcon S, Penson D. Impact of PSA screening on the incidence of advanced stage prostate cancer in the US: a surveillance modeling approach. *Med Decis Making*. 2008;28:323-331.
4. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Mortality-All COD, Aggregated with State, Total US (1969-2010) <Katrina/Rita Population Adjustment>. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2013. Underlying mortality data provided by National Center for Health Statistics (cdc.gov/nchs).
5. Andriole GL, Crawford ED, Grubb RL 3rd; PLCO Project Team. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012;104:125-132.
6. Schroder FH, Hugosson J, Roobol MJ, et al; ERSPC Investigators. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med*. 2012;366:981-990.
7. Gulati R, Mariotto AB, Chen S, Gore JL, Etzioni R. Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. *J Clin Epidemiol*. 2011;64:1412-1417.
8. Hanley JA. Measuring mortality reductions in cancer screening trials. *Epidemiol Rev*. 2011;33:36-45.
9. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst*. 2009;101:374-383.
10. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008;358:1250-1261.
11. Huang GJ, Sadetsky N, Penson DF. Health related quality of life for men treated for localized prostate cancer with long-term followup. *J Urol*. 2010;183:2206-2212.

12. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med*. 2013;368:436-445.

13. Gulati R, Inoue LY, Gore JL, Katcher J, Etzioni R. Individualized estimates of overdiagnosis in screen-detected prostate cancer. *J Natl Cancer Inst*. 2014;106:djt367.

14. Moyer VA; U.S. Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157:120-134.

15. Wolf AM. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin*. 2010; 60:70-98.

16. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. *J Urol*. 2013;190:419-426.

17. Qaseem A, Barry MJ, Denberg TD, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Screening for prostate cancer: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2013;158:761-769.

18. Ross KS, Guess HA, Carter HB. Estimation of treatment benefits when PSA screening for prostate cancer is discontinued at different ages. *Urology*. 2005;66:1038-1042.

19. Schaeffer EM, Carter HB, Kettermann A, et al. Prostate specific antigen testing among the elderly--when to stop? *J Urol*. 2009;181: 1606-1614; discussion 1613-1614.

20. Sun L, Caire AA, Robertson CN, et al. Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras. *J Urol*. 2009;182:2242-2248.

21. Vickers A, Bennette C, Steineck G, et al. Individualized estimation of the benefit of radical prostatectomy from the Scandinavian Prostate Cancer Group randomized trial. *Eur Urol*. 2012;62: 204-209.

22. Etzioni R, Tsodikov A, Mariotto A, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control*. 2008;19:175-181.

23. Etzioni R, Gulati R, Tsodikov A, et al. The prostate cancer conundrum revisited: treatment changes and prostate cancer mortality declines. *Cancer*. 2012;118:5955-5963.

24. Tsodikov A, Szabo A, Wegelin J. A population model of prostate cancer incidence. *Stat Med*. 2006;25:2846-2866.

25. Gulati R, Inoue L, Katcher J, Hazelton W, Etzioni R. Calibrating disease progression models using population data: a critical precursor to policy development in cancer control. *Biostatistics*. 2010;11:707-719.

26. Mariotto A, Etzioni R, Krapcho M, Feuer EJ. Reconstructing PSA testing patterns among black and white men in the US from Medicare claims and the National Health Interview Survey. *Cancer*. 2007; 109:1877-1886.

27. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215-224.

28. Pinsky PF, Andriole GL, Kramer BS, Hayes RB, Prorok PC, Gohagan JK; Prostate, Lung, Colorectal and Ovarian Project Team. Prostate biopsy following a positive screen in the Prostate, Lung, Colorectal and Ovarian cancer screening trial. *J Urol*. 2005;173:746-750; discussion 750-751.

29. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol*. 2010;28:1117-1123.

30. Boorjian SA, Thompson RH, Tollefson MK, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. *Eur Urol*. 2011;59:893-899.

31. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2011;364:1708-1717.

32. Wilt T, Brawer MK, Jones K, Barry M. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012; 367:203-213.

33. Gulati R, Gore JL, Etzioni R. Comparative effectiveness of alternative prostate-specific antigen-based prostate cancer screening strategies: model estimates of potential benefits and harms. *Ann Intern Med*. 2013;158:145-153.

34. National Center for Health Statistics. Vital Statistics of the United States, 1993. Volume II: Mortality, Part A. Hyattsville, MD: National Center for Health Statistics; 2002.

35. United States Census Bureau. 2004 Interim National Population Projections. Washington, DC: Population Division, United States Census Bureau; 2004.

36. Chou R, LeFevre ML. Prostate cancer screening--the evidence, the recommendations, and the clinical implications. *JAMA*. 2011;306: 2721-2722.

37. Miller AB. New data on prostate-cancer mortality after PSA screening. *N Engl J Med*. 2012;366:1047-1048.

38. Roobol MJ, Kerkhof M, Schroder FH, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol*. 2009; 56:584-591.

39. Tasian GE, Cooperberg MR, Cowan JE, et al. Prostate specific antigen screening for prostate cancer: knowledge of, attitudes towards, and utilization among primary care physicians. *Urol Oncol*. 2012;30: 155-160.

40. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. *J Natl Cancer Inst*. 2009;101:1325-1329.

41. Etzioni R, Gulati R, Mallinger L, Mandelblatt J. Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening. *Ann Intern Med*. 2013;158:831-838.

42. Gulati R, Wever EM, Tsodikov A, et al. What if I don't treat my PSA-detected prostate cancer? Answers from three natural history models. *Cancer Epidemiol Biomarkers Prev*. 2011;20:740-750.

43. Fesinmeyer MD, Gulati R, Zeliadt S, Weiss N, Kristal AR, Etzioni R. Effect of population trends in body mass index on prostate cancer incidence and mortality in the United States. *Cancer Epidemiol Biomarkers Prev*. 2009;18:808-815.

44. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. *JAMA*. 2011;305:2548-2555.

45. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA*. 2008;299: 2760-2769.

46. Drazer MW, Huo D, Schonberg MA, Razmaria A, Eggener SE. Population-based patterns and predictors of prostate-specific antigen screening among older men in the United States. *J Clin Oncol*. 2011;29:1736-1743.

47. Walter LC, Bertenthal D, Lindquist K, Konety BR. PSA screening among elderly men with limited life expectancies. *JAMA*. 2006;296: 2336-2342.

48. Vickers AJ, Cronin AM, Bjork T, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. *BMJ*. 2010;341:c4521.

49. Grenabo Bergdahl A, Holmberg E, Moss S, Hugosson J. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. *Eur Urol*. 2013;64:703-709.

50. Ganz PA, Barry JM, Burke W, et al. National Institutes of Health State-of-the-Science Conference: role of active surveillance in the management of men with localized prostate cancer. *Ann Intern Med*. 2012;156:591-595.

51. Gulati R, Tsodikov A, Wever EM, et al. The impact of PLCO control arm contamination on perceived PSA screening efficacy. *Cancer Causes Control*. 2012;23:827-835.