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Prostate Cancer Screening and the Goldilocks Principle: How Much Is Just Right?

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Introduction

As the debate continues on the merits of prostate cancer (PCa) early detection, primary care providers (PCPs), urologists, and specialists are left struggling to balance benefits from early detection and treatment of lethal PCa that justify the inherent risks of overtreatment. The 2012 U.S. Preventive Services Task Force (USPSTF) recommendation against prostate-specific antigen (PSA)–based screening highlighted the limitations in the historical implementation of screening.[1] Given the low specificity of PSA for clinically significant PCa in the screening setting, it is not surprising in retrospect that population-wide application with a threshold of 4.0 ng/mL defining a positive result led to overdiagnosis and overtreatment as well as many missed cancers when PSA is used alone. The longstanding underuse of active surveillance (AS) in low-risk disease and the associated harms of treatment factored strongly into these recommendations. More recent AS data suggest that the trend has shifted markedly,[2-5] with increasing evidence now showing that patients can be safely monitored over a long period.[6]

Although a screen none/treat none approach avoids the risks, abandoning screening altogether would probably contribute to reversal of the stage migration and the reduction in PCa mortality rates over the past 20 years (Fig 1A).[7-10] This risks a potential reversion to the pre-PSA era in terms of underdiagnosis, undertreatment, and more advanced-stage disease (Fig 1B), leading to higher morbidity and mortality. Recently, the USPSTF proposed a draft recommendation to change the PSA screening grade from D to C, supporting shared physician/patient decision making regarding benefits and risks of screening.[11] This update was drafted in the context of increasing evidence that early detection has at least partially driven the observed PCa mortality reduction over time.[11] The timing is therefore appropriate to ask, given the changing landscape of PCa early detection and management of localized PCa, is there a sweet spot for evidence-based population screening to detect clinically significant PCa?

In this position statement, we highlight the need for a balanced approach to PCa early detection, emphasizing shared decision making (SDM), precision-based strategies, and appropriate risk-based management for men diagnosed with PCa. Furthermore, it is critical to enhance investment in research on strategies to optimize screening protocols and to encourage physicians to have an informed individualized conversation regarding screening. Our hope is that the recent draft recommendation will bring us closer to an appropriate balance that minimizes harms, while maximizing survival and quality of life, and reducing disease-related morbidity and mortality.

Start of the Controversy

The publications of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial[12] and the European Randomized Study of Screening for Prostate Cancer[13] represented a key inflection point in the screening debate (Appendix Table A1, online only). In addition to the planned analyses, data from these trials have been used in many secondary analyses to better understand their clinical implications. Critically, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial was shown to be underpowered to detect a mortality difference in light of the high (91%) PSA screening rate in the control arm.[14] With many other issues surfacing,[15,16] the authors concluded that this trial should be viewed as one showing no difference between organized screening and opportunistic screening, rather than informing the question of screening versus no screening.[17]

Conversely, the European Randomized Study of Screening for Prostate Cancer demonstrated a small statistically significant mortality advantage associated with screening in the core age group, with a number needed to diagnose down to 27 patients to prevent one PCa death. Although not powered for subgroup analyses by age, screening was associated with benefit only in the 65 to 69–years age group.[18] Interestingly, a recent simulation study suggested that adjusting for mean lead time, as reflected in the timing and intensity of PSA testing in both arms, translated to lower risk of PCa death in the more intensely screened groups (25% *v* 31% and 27% *v* 32%, respectively) in both trials, although further validation is required because of the novel methodologic approach.[19] Despite the uncertainties in the data, the USPSTF issued a grade D recommendation in 2012, concluding that "The harms of PSA-based screening for prostate cancer include a high rate of false-positive results and accompanying negative psychological effects, high rate of complications associated with diagnostic

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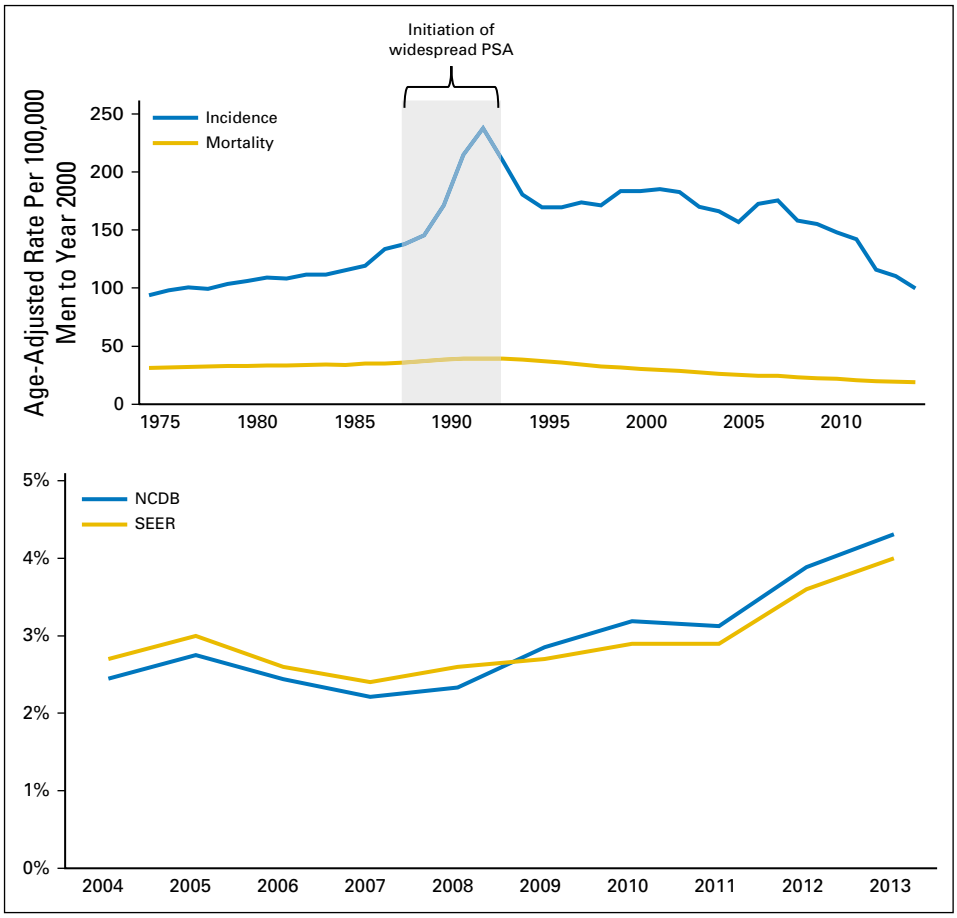

Fig 1. (A) Age-adjusted incidence and mortality of prostate cancer on the basis of SEER.[9] PSA, prostate-specific antigen. (B) Percent of men diagnosed with prostate cancer presenting with metastatic disease. (Data from Hu et al[10] and Weiner et al.[52]) NCDB, National Cancer Data Base.

biopsy, and—most important—a risk for overdiagnosis coupled with overtreatment."[1] Following this decision, updated guidelines were published by most major societies.[2,20-23] Although there is disagreement on details such as initiating and stopping screening or PSA cutoffs to trigger biopsy, SDM remains the cornerstone of most of these guidelines.[3]

Meanwhile, the landscape of PCa early detection approach and management continues to evolve. The greater understanding of the value of PSA isoforms, as well as other molecular and imaging biomarkers, has led to the reduction in number of prostate biopsies (PBx) while still detecting the vast majority of Gleason score ≥ 7 cancers.[24-28] Although the relative performance of these tools in the screening space is not yet fully established, they have been incorporated into national guidelines.[20,29-31] In addition, there has been increasing recognition of the safety of AS in low-risk PCa; thus AS rates have increased dramatically. Before 2009, AS rates ranged between 6.7% and 14.3% of low-risk patients compared with 40% to 50% after 2010 to 2013.[3,5,32] Updated guidelines from American Urological Association/American Society for Therapeutic Radiology and Oncology/Society of Urologic Oncology[2] and ASCO[33] now consider AS to be the preferred management approach for most men with low-risk disease. Novel strategies have been implemented to help standardize appropriate use of AS.[34] In addition, there are a number of tissue-based molecular classifiers now available to assist with risk stratification of patients with newly diagnosed PCa, and these may help increase the pool of patients eligible for AS.[35-37]

Impact of 2012 Recommendation

PSA screening has declined sharply since 2012, with parallel drops across all age strata.[38-40] In a recent survey, 75% of PCPs changed their practice by reducing PSA testing,[41] and there has been a decrease in testing from 27.3% to 16.7% ($P < .001$) since the USPSTF recommendation.[42] A decrease in the biopsy rate has also been observed in both community[43] and academic settings,[44,45] with one study showing a 21.7% overall decrease in PBx in a large community practice.[43] In addition, during this same time period, an increase in secondary testing before biopsy has been observed.[46] Although the proportion of high-risk PCa detection has increased compared with low-risk cancer (adjusted relative risk, 1.25; 95% CI, 1.02 to 1.52),[44] there has been a concomitant decrease in the overall detection of high-risk PCa, which implies underdiagnosis of an important group of patients.[44,45,47,48] Importantly, there was a similar decrease among all age groups, suggesting a missed opportunity to detect and cure young, healthy men with clinically significant PCa.

A clear temporal association has been established showing a decrease in the overall incidence of PCa since the USPSTF recommendation.[39,40,45,47,49] Age-adjusted incidence rates of PCa have now fallen to levels not seen since the mid-1980s.[50] Although incidence rate is not a metric for harm or mortality, it is unclear what percentage of undetected high-risk patients will ultimately develop metastatic disease. More importantly, however, the subgroup of high-risk patients with imminently lethal disease represents

a substantial proportion of men diagnosed with PCa. Hoffman et al have shown an age-adjusted increase in incidence of distant disease in younger men ages 50 to 69 years from 2004 to 2012 (annual percentage change, 1.7%; 95% CI, 0.2% to 3.2%).[51] In addition, Jemal et al[49] have shown an increase in incidence of distant disease in men older than the age of 75 years as well. This changing pattern is potentially associated with the change in recommendations for PSA screening by the USPSTF. However, other analyses have demonstrated increasing rates of metastatic disease at diagnosis over time starting in the prior decade, suggesting that factors unrelated to screening are increasing the burden of metastatic disease.[52] With recent developments, we now have the opportunity to correct the course to appropriately balance early detection and overdetection.

Future Directions

The USPSTF draft C recommendation is a big step in the right direction. This change creates an opportunity to ensure that decreases in overdetection and overtreatment are sustained as we look toward the future. There are still many areas of research where ongoing efforts to optimize patient selection for PBx and to consider AS rather than primary therapy will probably pay dividends.

We must maximize efforts for biomarker discovery and validation. The importance of independent validation and head-to-head comparison cannot be understated. Second, we must continue to better educate both PCPs and PCa clinicians regarding the art and science of PCa early detection and risk-adapted management. This is especially important for the PCPs who perform most PCa screening. The recent draft recommendation is not a license for blanket screening, but rather for individually justified early detection. More importantly, we hope that it will help support PCPs to engage in conversations regarding screening that are individualized and centered on SDM. Going forward, ensuring proper SDM will lay the foundations for a successful screening program.

Furthermore, it is important to underscore that although mortality is an important outcome, it is not the only metric to consider in relation to PSA screening. Morbidity of advanced disease as the result of delayed diagnosis is an important measure that must be considered relative to early detection and treatment. PCa is a chronic disease that may cause significant morbidity from local and metastatic progression for a prolonged period before death, and treatment is becoming physically and financially costly. Although seminal studies have now demonstrated statistically significant survival advantages with the use of docetaxel or abiraterone in hormone-sensitive metastatic disease, these treatment strategies have numerous toxicities and are not curative.[53-56] A number of modeling studies have used quality of life as the key metric and concluded that screening practices should include minimizing PSA testing in elderly men, selective biopsy indications (ie, not every PSA elevation is biopsied), AS for low-risk tumors, and treatment in a high-volume center.[57] Perhaps another strategy is baseline PSA testing at a younger age, which was found to predict risk of lethal PCa; this may help us better stratify who should be screened further at an older age.[58,59] Thus, for the majority of the population with low baseline PSA levels, subsequent testing could be deferred for many years, whereas those at risk for PCa mortality could be identified earlier and more likely within the window of opportunity for cure.

The emerging data on somatic and germline mutations in PCa have provided additional insights into the importance of identifying patients who may be carrying germline defects that predispose to aggressive PCa. A simple question regarding family history of cancer may be life-saving. It is no longer only first-degree relatives with PCa, but now includes close relatives with breast, ovarian, colon, and pancreatic cancer. Men with mutations in BRCA1 or BRCA2 and those with Lynch syndrome probably need a tailored early-detection program.[60-62] Whether these germline defects should have an impact on treatment decisions in low-risk disease remains to be determined.[63] Recognizing that African American populations experience both a higher incidence of PCa and higher mortality from PCa once diagnosed should also be considered in our screening algorithms.[64,65]

The data stress the continued need for smarter individualized screening strategies that incorporate information about family history and race, as well as additional assessments to more clearly define personal risk, such as imaging, urine, and blood markers; germline DNA information; and baseline PSA testing at a younger age in the 21st century. We strongly encourage investment in these important questions, as our hope is that emerging consensus will finally put this controversy to rest.

In conclusion, the goal of this report is to highlight knowledge gaps that may improve patient outcomes while minimizing potential harms. Although the elimination of overdiagnosis is not feasible, the management of an elevated PSA is changing markedly, with increased use of ancillary testing before biopsy decisions. There is no one-size-fits-all solution. Therefore, individualized screening with SDM is the foundation on which to build a successful program of diagnosis and treatment. The USPSTF's recent draft recommendation is a critical step toward finding a more balanced strategy. With an improved understanding of risk stratification and patient management both before and after diagnosis, we are increasingly convinced that a "just right" approach on the basis of personalized SDM is entirely possible. This will ultimately allow us to realize the goal of reduced death and suffering from PCa.

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Appendix

Table A1. Prostate Cancer Screening Trials Characteristics

Characteristic	PLCO	ERSPC	Goteborg
Size (No. of patients)	76,693	162,243	19,904
Age, years	55-74	55-69	50-69
PSA cutoff (ng/mL)	4	2.5-4	3
Screening interval	Annually	2-4 years	2 years
Follow up	15 years	13 years	14 years
Contamination	91%[14]	52%	Low
Compliance			
PSA	85%	83%	76%
Biopsy	24%-31%[16]	86%	93%
Reduction in PCSM	NA	0.79 RR	0.56 RR
NNS	NA	781	293
NNT	NA	27	12

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; NA, not available; NNS, number needed to screen; NNT, number needed to treat; PCSM, prostate cancer–specific mortality; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; RR, relative risk.