SOUNDING BOARD

Reconsidering the Trade-offs of Prostate Cancer Screening

Jonathan E. Shoag, M.D., Yaw A. Nyame, M.D., M.B.A., Roman Gulati, M.S., Ruth Etzioni, Ph.D., and Jim C. Hu, M.D., M.P.H.

After the widespread adoption of prostate-specific antigen (PSA) screening in the early 1990s, prostate cancer diagnoses increased rapidly while death rates halved over the course of the next quarter century.[1] Initial results from randomized trials and recommendations against screening from professional societies, which were recently moderated, probably contributed to screening's falling out of favor over the past decade.[2-4] Decreased screening has been associated with a sustained fall in prostate cancer diagnoses.[1] Although not necessarily reflective of a change in the number of men in whom metastatic disease will ultimately develop, some evidence suggests that the incidence of metastatic disease at diagnosis, which had been decreasing until 2010, may now be rising.[1,5-8] The decline in PSA screening has a number of contributing factors but appears to have been precipitated in part by misinterpretation of existing randomized data and lack of attention to follow-up time when the calculus of harms and benefits is evaluated. Here, we present a reevaluation of the plausible long-term effects of PSA screening using the most up-to-date data available.

A prevailing opinion regarding PSA screening is that "two large, randomized, controlled trials of PSA screening showed equivocal or no benefit."[9] This view is problematic. One of these trials — the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial — was not useful for evaluating the efficacy of screening relative to no screening, because nearly 90% of the men in the control group had undergone PSA testing.[10-13] The other widely cited trial of screening is the European Randomized Study of Screening for Prostate Cancer (ERSPC), in which the rate of screening in the control group was substantially lower than the rate in the control group of the PLCO trial.[14] The most recent update of the ERSPC estimated that 570 men from 55 to 69 years of age would need to be screened to prevent one death from prostate cancer with 16 years of follow-up.[15,16] This benefit is qualitatively similar to recommendations supporting breast cancer screening, with the need to screen 1250 women from 50 to 59 years of age, 476 women from 60 to 69 years of age, and 769 women from 70 to 74 years of age to prevent one death from breast cancer at 10 years.[17]

Given the natural history of prostate cancer, 16 years of follow-up from randomization may not provide a sufficient time horizon to examine the mortality benefit from screening, because men often begin screening in their 50s and the median age at death from prostate cancer is 80 years.[1] Conflation of the long-term benefits of screening that are needed to inform policy and patient decisions and the short-term results available from clinical trials is highly problematic. Among men with clinically detected prostate cancer (usually a more advanced form than screening-detected cancer) who were followed for 21 years, mortality from prostate cancer tripled from 15 per 1000 person-years during the first 15 years to 44 per 1000 person-years thereafter.[18] Thus, the absolute benefit of screening over the longer term may be greater than that observed over the 16-year horizon in the ERSPC as deaths from prostate cancer continue to accrue.

The benefits of screening cannot be measured only in mortality reduction and should also reflect the diminished morbidity from avoidance of advanced disease. Metastatic prostate cancer is incurable and, if symptomatic, can be painful and debilitating. Its treatment (i.e., androgen deprivation and chemotherapy) is costly and associated with long-term toxic effects. Relatively short-term (12-year) data from four centers participating in the ERSPC have shown that screening results in an absolute risk reduction of metastatic disease of 3.1 per 1000 men who

Table 1. Estimates of the Number Needed to Screen and the Number of Excess Prostate Cancer Diagnoses to Prevent One Death from Prostate Cancer during the Indicated Follow-up Interval.*

Variable	No. Needed to Screen (95% CI)	No. of Excess Diagnoses (95% CI)
16 Yr of follow-up: empirical estimate from ERSPC	570 (380–1137)	18 (12–35)
25 Yr of follow-up: conservative model estimate	385 (273–687)	11 (8–20)

* Model estimates are based on extrapolation of deaths from prostate cancer among men who received a diagnosis of prostate cancer during the first 16 years of follow-up of the European Randomized Study of Screening for Prostate Cancer (ERSPC), under the assumption that the relative mortality reduction would continue with additional follow-up. Confidence intervals are based on 95% confidence limits of the 16-year empirical estimates of mortality. (For model assumptions and details, see the Supplementary Appendix.) ERSPC protocols varied among sites. Men underwent randomization between the ages of 55 and 69 years and at most centers were screened every 4 years, with referral to biopsy when prostate-specific antigen levels were more than 3.0 ng per milliliter. The stopping age varied from 67 to 78 years of age.

underwent randomization.[19] The Prostate Testing for Cancer and Treatment (ProtecT) trial, which compared monitoring, surgery, and radiotherapy for localized, largely low-risk prostate cancer, also clearly showed a reduction in prostate cancer metastases with definitive treatment at 10 years of follow-up.[8]

In light of the oncologic benefits of screening, patients, providers, and policymakers need to weigh the value of these benefits against the harms of screening. Perhaps the greatest of these harms is the detection of cancers that would not cause deaths or complications in a patient's lifetime ("overdetection") and consequent treatment-related long-term adverse effects. Although screening is certainly associated with excess detection, many prostate cancers that would present clinically may simply be found earlier with screening. For instance, the cumulative incidence of prostate cancer in the ERSPC was 13.3% among men in the screening group and 10.3% among men in the control group at 16 years, and the relative risk of prostate cancer diagnosis in the screening group as compared with the control group diminished with longer follow-up time.[16] Thus, this discrepancy in rates probably represents the upper limit of excess detection associated with screening, because the control group may continue to "catch up" to the screening group with additional follow-up.

Since many policymakers now advocate for "shared decision making" regarding PSA screening, it is imperative for patients and providers to have a clear understanding of the harm–benefit calculus for screening. Available decision aids for prostate cancer screening, such as those developed by the U.S. Preventive Services Task Force and the American Academy of Family Physicians,[20,21] are limited by their reliance on relatively short-term follow-up (i.e., 13 years) in their calculations of the benefit of screening. This reliance on short-term follow-up is rooted in an unsupported presumption that additional benefit will not continue to accrue over a man's lifetime. The presentation of data in the above decision aids also implies that only lethal prostate cancer would be diagnosed in the absence of PSA screening. The resultant suggestion is that screening prevents one death from prostate cancer per 1000 men screened at the expense of diagnosing 100 cancers.

Using a formal, transparent model, we provide alternative estimates of the long-term effects of PSA screening (Table 1). The model projections are based on long-term survival of patients with prostate cancer and competing mortality in the United States. The projections assume that the relative mortality reductions observed in clinical trials continue to hold, as deaths resulting from cases diagnosed during the first 16 years of follow-up continue to accrue (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The model projects that 11 additional cases need to be diagnosed to prevent one death from prostate cancer at 25 years in the United States. Although the preservation of the relative reduction in mortality among men in whom prostate cancer was diagnosed over 16 years of screening in the ERSPC is uncertain, other assumptions that underpin these projections are conservative (see the Supplementary Appendix). Even though other screening programs are likely to have different magnitudes of harms and benefits,[22] limited data on other programs are available from randomized trials. We believe that these projections provide a more complete picture of the plausible long-term effects of PSA screening.

Important considerations are not reflected in these estimates. These include the benefit of preventing advanced prostate cancers, associated costs of screening and detection, as well as the ways in which detection and a cancer diagnosis

affect a man's quality of life. Perhaps chief among these quality-of-life concerns is that screen detection exposes men to the risks of treatment, which can have long-lasting effects on urinary and sexual function. Contemporary data on these treatment-related side effects show that the burden of erectile dysfunction and urinary incontinence caused by treatment is of somewhat similar magnitude as the modeled prostate cancer–specific mortality benefit presented here.[23-26] For instance, the ProtecT trial showed that treating 4 men with prostatectomy or 8 with radiotherapy rather than active monitoring would cause one additional case of erectile dysfunction at 2 years. Similarly, treating 5 men with prostatectomy or 143 men with radiotherapy would cause one additional case of urinary incontinence.[25] These data also show that, in contrast to metastatic prostate cancer, these therapies do not affect overall health-related quality of life, with no clinically significant declines in physical functioning or emotional well-being or worsening in energy or fatigue scores.[23,27,28] It must be acknowledged, though, that these patient-reported outcomes may not reflect the full effect of treatment on these men's lives.

Also not included in our analysis are more recent changes to prostate cancer diagnosis and management strategies that have the potential, albeit as yet unproven, to refine screening for the better. Previous work has suggested that the trade-offs of screening can potentially be improved by stopping testing or testing less frequently, and using more conservative biopsy criteria, in older men and by using longer screening intervals for men with low PSA levels.[22] Magnetic resonance imaging (MRI) continues to be evaluated as a triage tool before biopsy, with the PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) trial indicating that more than a quarter of men with an elevated PSA level may safely avoid prostate biopsy by undergoing a prebiopsy MRI.[29,30] Although the data are not yet mature, supplemental biomarkers and polygenic risk scores also show promise in further risk stratification of patients.[31,32] The harms of overdetection have also been attenuated in the United States in recent years by divorcing radical therapy from detection. Almost 50% of U.S. men who receive a diagnosis of low-risk prostate cancer now opt for active surveillance, in which cancers are closely monitored rather than immediately treated.[33-35] If U.S. practice patterns follow those observed in the U.K. ProtecT trial, more than 50% of men on active surveillance will ultimately cross over to definitive therapy.[36] Although surveillance has harms, it avoids or delays the risk of erectile dysfunction, which affects many aging men at baseline.[37]

Evidence from randomized trials shows that PSA screening reduces prostate cancer mortality and prevents metastatic disease. Overdetection and associated treatment-related complications remain substantial disincentives. Greater acceptance and adoption of active surveillance and newer diagnostic pathways may already be mitigating some of these harms. It is nevertheless true that despite three decades of PSA screening in the United States, the long-term magnitude of benefit balanced against the harms of screening remains uncertain. Here, we integrate relevant data under transparent assumptions to evaluate the trade-offs of PSA screening. As clinicians who screen, diagnose, and treat patients with prostate cancer and as statisticians who are devoted to understanding the effects of cancer screening, we suggest that the balance of benefits and harms of screening may be more favorable than is generally appreciated.

Supported by grants from the Wallace Fund (to Drs. Shoag and Hu), a Damon Runyon Cancer Research Foundation Physician-Scientist Training Award (to Dr. Shoag), a grant from the Department of Defense (CDMRP W81XWH1910577, to Dr. Nyame), and grants from the National Institutes of Health (R50 CA221836, to Mr. Gulati, and U01 CA199338, to Dr. Etzioni).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Drs. Shoag and Nyame contributed equally to this article.

From the Department of Urology, Weill Cornell Medicine, New York (J.E.S., J.C.H.); and the Department of Urology, University of Washington (Y.A.N.), and the Division of Public Health Sciences, Fred Hutchinson Cancer Research Center (Y.A.N., R.G., R.E.) — both in Seattle.

1. Analysis data. Surveillance, Epidemiology, and End Results Program, National Cancer Institute (https://seer.cancer.gov/seerstat/analysis.html).

2. US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA 2018;319:1901-13.

3. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;157:120-34.

4. Lee DJ, Mallin K, Graves AJ, et al. Recent changes in prostate cancer screening practices and epidemiology. J Urol 2017;198:1230-40.

5. Welch HG, Kramer BS, Black WC. Epidemiologic signatures in cancer. N Engl J Med 2019;381:1378-86.

6. Hu JC, Nguyen P, Mao J, et al. Increase in prostate cancer

distant metastases at diagnosis in the United States. JAMA Oncol 2017;3:705-7.
7. Li J, Siegel DA, King JB. Stage-specific incidence rates and trends of prostate cancer by age, race, and ethnicity, United States, 2004-2014. Ann Epidemiol 2018;28:328-30.
8. Dalela D, Sun M, Diaz M, et al. Contemporary trends in the incidence of metastatic prostate cancer among US men: results from nationwide analyses. Eur Urol Focus 2019;5:77-80.
9. Aronowitz R, Greene JA. Contingent knowledge and looping effects — a 66-year-old man with PSA-detected prostate cancer and regrets. N Engl J Med 2019;381:1093-6.
10. Shoag JE, Mittal S, Hu JC. More on reevaluating PSA testing rates in the PLCO trial. N Engl J Med 2016;375:1500-1.
11. Shoag JE, Mittal S, Hu JC. Reevaluating PSA testing rates in the PLCO trial. N Engl J Med 2016;374:1795-6.
12. Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017;123:592-9.
13. Pinsky PF, Miller E, Prorok P, Grubb R, Crawford ED, Andriole G. Extended follow-up for prostate cancer incidence and mortality among participants in the Prostate, Lung, Colorectal and Ovarian randomized cancer screening trial. BJU Int 2019; 123:854-60.
14. Tsodikov A, Gulati R, Heijnsdijk EAM, et al. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. Ann Intern Med 2017;167:449-55.
15. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384:2027-35.
16. Hugosson J, Roobol MJ, Månsson M, et al. A 16-yr follow-up of the European Randomized Study of Screening for Prostate Cancer. Eur Urol 2019;76:43-51.
17. Siu AL. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2016; 164:279-96.
18. Johansson JE, Andrén O, Andersson SO, et al. Natural history of early, localized prostate cancer. JAMA 2004;291:2713-9.
19. Schröder FH, Hugosson J, Carlsson S, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012;62:745-52.
20. Is prostate cancer screening right for you? Understanding the potential benefits vs. harms for men 55–69. U.S. Preventive Services Task Force (https://www.uspreventiveservicestaskforce.org/Home/GetFileByID/3795).
21. Clinical Preventative Services Recommendation: Prostate Cancer. PSA-based prostate cancer screening in men aged 55-69. American Academy of Family Physicians (www.aafp.org/patient-care/clinical-recommendations/all/prostate-cancer.html).
22. 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;158:145-53.
23. Barocas DA, Alvarez J, Resnick MJ, et al. Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years. JAMA 2017;317:1126-40.
24. Chen RC, Basak R, Meyer AM, et al. Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. JAMA 2017; 317:1141-50.
25. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2016;375:1425-37.
26. Hoffman KE, Penson DF, Zhao Z, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. JAMA 2020; 323:149-63.
27. Litwin MS, Saigal CS, Lubeck DP, Li YP, Henning JM, Carroll PR. Health-related quality of life in men with metastatic prostate cancer: the misleading effect of lead-time bias. BJU Int 2003;91: 9-13.
28. Downing A, Wright P, Hounsome L, et al. Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. Lancet Oncol 2019;20:436-47.
29. Auvinen A, Rannikko A, Taari K, et al. A randomized trial of early detection of clinically significant prostate cancer (ProScreen): study design and rationale. Eur J Epidemiol 2017;32: 521-7.
30. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767-77.
31. Seibert TM, Fan CC, Wang Y, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts. BMJ 2018;360:j5757.
32. Loeb S, Lilja H, Vickers A. Beyond prostate-specific antigen: utilizing novel strategies to screen men for prostate cancer. Curr Opin Urol 2016;26:459-65.
33. Loeb S, Byrne N, Makarov DV, Lepor H, Walter D. Use of conservative management for low-risk prostate cancer in the Veterans Affairs integrated health care system from 2005-2015. JAMA 2018;319:2231-3.
34. Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990-2013. JAMA 2015; 314:80-2.
35. Womble PR, Montie JE, Ye Z, Linsell SM, Lane BR, Miller DC. Contemporary use of initial active surveillance among men in Michigan with low-risk prostate cancer. Eur Urol 2015;67:44-50.
36. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415-24.
37. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med 2007;357: 762-74.

DOI: 10.1056/NEJMsb2000250