VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Prostate Cancer Screening: Facts, Statistics, and Interpretation in Response to the US Preventive Services Task Force Review

Sigrid Carlsson, *Memorial Sloan-Kettering Cancer Center, New York, NY; Sahlgrenska Academy at Göteborg University, Göteborg, Sweden*
Andrew J. Vickers, *Memorial Sloan-Kettering Cancer Center, New York, NY*
Monique Roobol, *Erasmus Medical Center, Rotterdam, the Netherlands*
James Eastham and Peter Scardino, *Memorial Sloan-Kettering Cancer Center, New York, NY*
Hans Lilja, *Memorial Sloan-Kettering Cancer Center, New York, NY; Lund University, Malmö, Sweden; and Institute of Biomedical Technology, University of Tampere, Tampere, Finland*
Jonas Hugosson, *Sahlgrenska Academy at Göteborg University, Göteborg, Sweden*

Recently, the US Preventive Services Task Force (USPSTF) published a review of the evidence for screening for prostate cancer[1] and made a clear recommendation against screening. By giving a grade of "D" in the recommendation statement that was based on this review, the USPSTF concluded that "there is moderate or high certainty that this service has no net benefit or that the harms outweigh the benefits." [2(p3)]

Whether these harms of screening, overdiagnosis and overtreatment, are justified by the benefits in terms of reduced prostate cancer mortality is open to reasonable doubt. As such, we can understand why a guideline group might recommend against prostate-specific antigen (PSA) screening, particularly the way in which it is currently practiced in the United States. That said, the USPSTF report contained a number of important errors of fact, interpretation, and statistics.

Definitive conclusions based on incomplete data. When the review was published, the largest active prospective trial of PSA screening, the European Randomized study of Screening for Prostate Cancer (ERSPC), had not yet reported at its prespecified main follow-up time. The results from the ERSPC, which were used as a basis by the USPSTF, report on an interim analysis at a median follow-up of only 9 years.[3] To draw the conclusion that screening results "in small or no reduction in prostate cancer–specific mortality"[1(p762)] would suggest that definitive conclusions of no benefit can be drawn from an ongoing trial with equivocal results at interim follow-up. Also, the recent analysis of the ERSPC trial that used 2 additional years of follow-up (11 years) consolidated the previous findings that PSA screening significantly reduces prostate cancer mortality (relative risk, 0.79; 95% CI, 0.68 to 0.91; $P = .001$).[4]

Overall mortality, cancer-specific mortality, and statistical power. One of the key questions addressed in the USPSTF report is whether "PSA-based screening decrease(s)… all-cause mortality."[1(p764)] It is a basic misunderstanding to believe that the screening trials such as ERSPC or the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) trial could address the question of whether screening affects all-cause mortality. This is because it has much lower power than cancer-specific mortality as a result of the statistical noise of deaths from other causes. As an illustration, imagine a trial that is designed to have 80% power to detect a decrease in cancer deaths at 10 years from 1% to 0.5%. Also assume that the intervention had precisely the effect hypothesized without increasing deaths from other causes, which occurred in approximately 20% of participants in each group. The *P* values for such a trial would be less than .01 for cancer-specific mortality but .5 for overall mortality; indeed, the trial would have less than 10% power to detect differences in all-cause mortality. These numbers are approximately those reported in the Göteborg trial.[5]

Combining data from incompatible trials. The USPSTF authors state that "our summary of the evidence [is that] most trials [of PSA screening] found no statistically significant effect on prostate cancer-specific mortality."[1(p767)] They also cite two recent meta-analyses[6,7] and report the conclusions as "no pooled effect of screening."[1(p767)] But combining PSA screening trials, whether formally or informally, involves treating different types of studies as comparable. The meta-analysis by Djulbegovic et al[6] and the updated Cochrane review[7] included two trials, the Quebec and the Norrköping trials, that have well-known, serious methodologic weaknesses. Of the remaining fair-quality trials, two demonstrated significant reductions in prostate cancer mortality: 20% after 9 years of follow-up and 44% after 14 years of follow-up in the ERSPC[3] and the Göteborg[5] trials. The third trial, PLCO,[8] did not demonstrate a protective effect of screening on prostate cancer mortality at a short follow-up (7 to 10 years). After the USPSTF report, the PLCO trial investigators reported on 10 to 13 years of follow-up with no statistically significant difference in risk at 13 years between the arms (risk ratio, 1.09; 95% CI, 0.87 to 1.36).[9]

The results of these three trials should not have been combined in the meta-analysis because the European and US trials did not address the same scientific question. The PLCO trial was conducted in the United States, where PSA testing was already widespread; this is in contrast to the ERSPC, which was conducted in Europe, where the background rates of PSA testing were very low. In the first year of the PLCO trial, 40% of men in the control arm underwent PSA testing,

with contamination reaching 52% by year six.[8] Contamination in the European trial was no more than 15%.[10]

Comparison of confidence intervals. The USPSTF authors claim that "chance could also explain the apparent discrepancy between the two trials [ERSPC and PLCO] because the risk estimate confidence intervals overlapped."[1(p767)] This demonstrates a critical misunderstanding of confidence intervals. To understand whether two values differ, we look at the confidence interval for the difference, not the confidence interval for each value separately.

Biologically implausible inference. The USPSTF writes "the PLCO trial evaluated a shorter screening interval (annual [in PLCO] versus every 4 years [in ERSPC]), suggesting that more conservative screening and treatment strategies might be more effective than more aggressive ones."[1(p767)] Less frequent screening may reduce the risk of overdiagnosis, but there is simply no plausible mechanism by which a much longer rescreening interval would improve cancer outcomes. There are numerous differences between the PLCO and ERSPC trials that might affect outcome, and the screening interval is only one factor.[10] The high rate of screening among controls in the PLCO trial[11] is the most likely explanation for the divergent results of PLCO and ERSPC, a phenomenon that reduces any differences between groups.

Failure to address the time-to-event nature of the data. The USPSTF authors state that "48 men received treatment for every prostate cancer–specific death prevented."[1(p767)] This is false: the number was calculated from the number of men diagnosed, not the number treated. In Göteborg, for example, approximately 25% of men who were diagnosed with cancer were still on surveillance at last follow-up.[5] Moreover, this statistic depends on the length of follow-up. Models have estimated the number needed to diagnose for prostate cancer screening to decrease to approximately 20 at 12 years of follow-up in the ERSPC,[12] as a whole, and to decrease to approximately nine at 25 years of follow-up.[13] The empirical estimate from ERSPC at 11 years of follow-up is 37,[4] and that from the Göteborg randomized trial with 14 years of follow-up is 12.[5]

Factual errors about the ERSPC reports. The USPSTF writes: "None of the RCTs [randomized controlled trials] of PSA-based screening provided information on potential psychological harms, such as anxiety or adverse effects on health-related quality of life."[1(p765)] This is not true. Three randomized PSA screening trials have reported no detrimental effect on men's anxiety levels or generic health status.[14-17]

Overestimation of the risk of radical prostatectomy. The USPSTF claims that the 30-day perioperative mortality rate after radical prostatectomy is 0.5%. This is based on a study of Medicare claims from 1991 to 1994,[18] that is, older patients who were treated nearly 20 years ago. If this figure were accurate, it would imply, for example, that a typical high-volume center such as Memorial Sloan-Kettering Cancer Center or Johns Hopkins would experience four or five deaths per year. This is nowhere near the case; this is, at least in part, because risk increases with age,[19,20] and because men older than age 65 years constitute a small minority of radical prostatectomy series. Contemporary estimates of perioperative mortality that are based on all men treated are close to 0.1%.[21]

In conclusion, the best trials that are available to date, which are currently still in progress, have demonstrated that screening can reduce prostate cancer death by 20% to 44%.[3-5] To recommend against screening on the basis of "moderate or high certainty"[2(p3)] of no benefit is one of a series of critical errors of fact, interpretation, or statistics that characterize the USPSTF report.

On the basis of the evidence of a benefit from the largest trial (ERSPC), some authors recently suggested that this best supports a grade C recommendation, rather than D, for men 55 to 69 years. This would imply recommending "against routinely providing the service"[22(p1952)] while indicating that "there may be considerations that support providing the service in an individual patient." [22(p1952)]

Nevertheless, we consider it reasonable to recommend against the way that PSA screening and associated treatments are currently implemented in the US, which causes unnecessary imbalances between the harms versus benefits of screening on a population level. First, PSA screening is often used in men who are unlikely to benefit from early detection because of short life expectancy and competing mortality; PSA tests are given to one third of men older than age 70 years with a greater than 50% risk of death within 5 years[23] and 15% of men older than age 65 years with advanced lung or GI tract cancers.[24] Current guidelines[25] also recommend a biopsy of the prostate for a wide variety of indications.[25] For example, men with a low PSA are recommended to have a biopsy if they have a positive digital rectal exam, although this is insufficiently informative in a screening setting,[26] and a high PSA velocity, which is similarly of limited benefit.[27]

The potential negative consequences from PSA screening, including psychological effects, false positives, and biopsy complications, might reasonably be regarded as acceptable for the individual man[28] if it were not for the burden of adverse effects from treatment for screen-detected tumors. Perhaps the most harmful consequence of PSA testing in the United States is that patients are almost always advised by their doctors to undergo curative treatment even if their risk of eventual death from prostate cancer is low. Surveys show that 99% of urologists and radiation oncologists would recommend treatment to a 65-year-old man with low-risk prostate cancer[29]; empirical studies show that fewer than 10% of men with low-risk disease are offered active surveillance.[30] This management of PSA-detected tumors needs to be reconsidered and individualized. Compounding this problem, much treatment is given by low-volume providers,[31] increasing the risk of treatment-related complications[32] and decreasing treatment effectiveness.[33,34]

We believe that implementation of the following three simple guidelines would immediately improve PSA screening outcomes in the United States. We also believe that these rules of thumb will have a greater practical impact than the USPSTF's blanket rejection of the PSA test, something which is unlikely to influence practice.

First, avoid PSA tests in men with little to gain. There is no justification for recommending PSA screening in asymptomatic men with a short life expectancy. Hence, men older than age 70 years should only be tested in special circumstances, such as higher than median PSAs that are measured before age 70 or excellent overall health. Moreover, because a baseline PSA is strongly predictive of the future risk of aggressive prostate cancer,[35,36] men with low PSAs (eg, less than 1 ng/mL) can undergo testing less frequently, such as every 7 to 8 years,[37] with screening possibly ending at age 60 if the PSA remains at 1 ng/mL or less.[36] Men with PSAs that are above age median but below biopsy thresholds can be counseled about their elevated risk and actively encouraged to return for regular screening and more comprehensive risk assessment.[38]

Second, do not treat those who do not need treatment. A high proportion of men with screen-detected prostate cancer do not need

immediate treatment and can be managed by active surveillance.[39] Indeed, some would argue that most screen-detected cancers do not need immediate curative treatment: men with low-risk prostate cancer such as Gleason 6 at biopsy and clinical stage T1 or T2a have a low risk of death as a result of prostate cancer.[40]

Third, refer men who do need treatment to high-volume centers. Although it is clearly not feasible to restrict treatment exclusively to high-volume centers, shifting treatment trends so that more patients are treated by high-volume providers will improve cancer control and decrease complications.[41]

PSA testing is not likely to go away, and on the basis of the ERSPC results—which do indicate reductions in mortality—this is perhaps a good thing. Our goal should therefore be to maximize the benefits of PSA testing and minimize its harms. Following the three rules outlined here could dramatically improve the ratio of harms to benefits from PSA screening.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Peter Scardino, OPKO Health (C) **Stock Ownership:** Peter Scardino, OPKO Health; Hans Lilja, OPKO Health **Honoraria:** Jonas Hugosson, Astellas Pharma **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** Andrew J. Vickers and Hans Lilja, patent applied for (for a statistical method to predict the result of prostate biopsy based on molecular markers); Hans Lilja, patents for free PSA, hK2, and intact PSA assays

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Chou R, Croswell JM, Dana T, et al: Screening for prostate cancer: A review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 155:762-771, 2011

2. Moyer VA, US Preventive Services Task Force: Screening for prostate cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med [epub ahead of print on May 21, 2012]

3. Schröder FH, Hugosson J, Roobol MJ, et al: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 360:1320-1328, 2009

4. Schröder FH, Hugosson J, Roobol MJ, et al: Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 366:981-990, 2012

5. Hugosson J, Carlsson S, Aus G, et al: Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 11: 725-732, 2010

6. Djulbegovic M, Beyth RJ, Neuberger MM, et al: Screening for prostate cancer: Systematic review and meta-analysis of randomised controlled trials. BMJ 341:c4543, 2010

7. Ilic D, O'Connor D, Green S, et al: Screening for prostate cancer: An updated Cochrane systematic review. BJU Int 107:882-891, 2011

8. Andriole GL, Crawford ED, Grubb RL 3rd, et al: Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 360:1310-1319, 2009

9. Andriole GL, Crawford ED, Grubb RL 3rd, et al: 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 104:125-132, 2012

10. Schröder FH, Roobol MJ: ERSPC and PLCO prostate cancer screening studies: What are the differences? Eur Urol 58:46-52, 2010

11. Pinsky PF, Blacka A, Kramer BS, et al: Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Clin Trials 7:303-311, 2010

12. Loeb S, Vonesh EF, Metter EJ, et al: What is the true number needed to screen and treat to save a life with prostate-specific antigen testing? J Clin Oncol 29:464-467, 2011

13. Gulati R, Mariotto AB, Chen S, et al: Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. J Clin Epidemiol 64:1412-1417, 2011

14. Macefield RC, Lane JA, Metcalfe C, et al: Do the risk factors of age, family history of prostate cancer or a higher prostate specific antigen level raise anxiety at prostate biopsy? Eur J Cancer 45:2569-2573, 2009

15. Carlsson S, Aus G, Wessman C, et al: Anxiety associated with prostate cancer screening with special reference to men with a positive screening test (elevated PSA): Results from a prospective, population-based, randomised study. Eur J Cancer 43:2109-2116, 2007

16. Essink-Bot ML, de Koning HJ, Nijs HG, et al: Short-term effects of population-based screening for prostate cancer on health-related quality of life. J Natl Cancer Inst 90:925-931, 1998

17. Brindle LA, Oliver SE, Dedman D, et al: Measuring the psychosocial impact of population-based prostate-specific antigen testing for prostate cancer in the UK. BJU Int 98:777-782, 2006

18. Yao SL, Lu-Yao G: Population-based study of relationships between hospital volume of prostatectomies, patient outcomes, and length of hospital stay. J Natl Cancer Inst 91:1950-1956, 1999

19. Lu-Yao GL, Albertsen P, Warren J, et al: Effect of age and surgical approach on complications and short-term mortality after radical prostatectomy: A population-based study. Urology 54:301-307, 1999

20. Lu-Yao GL, McLerran D, Wasson J, et al: An assessment of radical prostatectomy: Time trends, geographic variation, and outcomes—The Prostate Patient Outcomes Research Team. JAMA 269:2633-2636, 1993

21. Carlsson S, Adolfsson J, Bratt O, et al: Nationwide population-based study on 30-day mortality after radical prostatectomy in Sweden. Scand J Urol Nephrol 43:350-356, 2009

22. McNaughton-Collins MF, Barry MJ: One man at a time: Resolving the PSA controversy. N Engl J Med 365:1951-1953, 2011

23. Drazer MW, Huo D, Schonberg MA, et al: Population-based patterns and predictors of prostate-specific antigen screening among older men in the United States. J Clin Oncol 29:1736-1743, 2011

24. Sima CS, Panageas KS, Schrag D: Cancer screening among patients with advanced cancer. JAMA 304:1584-1591, 2010

25. Kawachi MH, Bahnson RR, Barry M, et al: NCCN clinical practice guidelines in oncology: Prostate cancer early detection. J Natl Compr Canc Netw 8:240-262, 2010

26. Schröder FH, Roobol-Bouts M, Vis AN, et al: Prostate-specific antigen-based early detection of prostate cancer: Validation of screening without rectal examination. Urology 57:83-90, 2001

27. Vickers AJ, Till C, Tangen CM, et al: An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. J Natl Cancer Inst 103:462-469, 2011

28. Carlsson S: Prostate cancer screening with PSA: A study of potential negative consequences. Gothenburg, Sweden, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, 2010. http://hdl.handle.net/2077/21922

29. Fowler FJ Jr, McNaughton Collins M, Albertsen PC, et al: Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. JAMA 283:3217-3222, 2000

30. Cooperberg MR, Broering JM, Kantoff PW, et al: Contemporary trends in low risk prostate cancer: Risk assessment and treatment. J Urol 178:S14–S19, 2007

31. Savage CJ, Vickers AJ: Low annual caseloads of United States surgeons conducting radical prostatectomy. J Urol 182:2677-2679, 2009

32. Begg CB, Riedel ER, Bach PB, et al: Variations in morbidity after radical prostatectomy. N Engl J Med 346:1138-1144, 2002

33. Vickers AJ, Bianco FJ, Serio AM, et al: The surgical learning curve for prostate cancer control after radical prostatectomy. J Natl Cancer Inst 99:1171-1177, 2007

34. Zietman AL, DeSilvio ML, Slater JD, et al: Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. JAMA 294:1233-1239, 2005

35. Lilja H, Cronin AM, Dahlin A, et al: Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. Cancer 117:1210-1219, 2011

36. 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 341:c4521, 2010

37. Roobol MJ, Roobol DW, Schröder FH: Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology 65:343-346, 2005

38. Memorial Sloan-Kettering Cancer Center: Screening guidelines: Prostate cancer. http://www.mskcc.org/cancer-care/screening-guidelines/screening-guidelines-prostate

39. Klotz L, Zhang L, Lam A, et al: Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 28:126-131, 2010

40. Lu-Yao GL, Albertsen PC, Moore DF, et al: Outcomes of localized prostate cancer following conservative management. JAMA 302:1202-1209, 2009

41. Eastham JA: Do high-volume hospitals and surgeons provide better care in urologic oncology? Urol Oncol 27:417-421, 2009

DOI: 10.1200/JCO.2011.40.4327; published online ahead of print at www.jco.org on June 18, 2012

