EDITORIAL AND COMMENT

Changes in Prostate Cancer Presentation Following the 2012 USPSTF Screening Statement: Observational Study in a Multispecialty Group Practice

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In this issue of the *Journal of General Internal Medicine*, Presti and colleagues present an analysis of the incidence of PSA testing, prostate biopsy, any prostate cancer, and first presentations with metastatic disease among men in the Kaiser Permanente of Northern California Health Plan.¹ The analysis was planned to examine the effect of the 2012 US Preventive Task Force “D” recommendation against PSA screening on these rates.² No data on prostate cancer mortality are presented. Reasonably, their primary comparisons were the population-based incidence for these parameters between 2010–2011 (pre-guideline) and 2014–2015 (post-guideline). The years 2012–2013 were considered “transition years.” In this large population of men, between the two key time intervals, the paper reports PSA screening rates dropped about 23%, biopsy rates dropped 64%, incident prostate cancer rates dropped 54%, and initial presentations with metastatic cancer increased 37%. Because of the sample size, confidence intervals around these point estimates are tight.

So can we reasonably conclude the 2012 Task Force guideline was responsible for these trends, and that with time, as the authors suggest, increased prostate cancer mortality rates will follow? And if so, was the 2012 Task Force recommendation erroneous, at least in retrospect?

One methodologic concern is that the study used first presentations with metastatic disease as a proxy for the “true” population-based metastatic rate. Rates of first presentation with metastatic disease underestimate the true rates of metastases, and more so when PSA screening rates are higher, a form of lead-time bias. Men are reported to tumor registries when they are first diagnosed with prostate cancer, along with their stage at diagnosis. If a man is detected early with nonmetastatic disease due to a screening PSA test, but later develops metastatic disease, he is not re-reported. The fact that the European Randomized Study of Prostate Cancer (ERSPC) screening, the one “positive” randomized trial of PSA screening, showed about a 20% mortality reduction suggests that

most men destined to develop metastatic disease and die of prostate cancer will do so despite screening.^{3, 4} Therefore, the effect of this bias may be large, with many men developing metastatic disease subsequent to initial diagnosis with a PSA test. True rates of metastatic disease might have been estimated by adding the number of male health plan members in the target age group who presented with metastatic disease on a bone scan or advanced imaging test or who developed a PSA level > 100 ng/mL (the definition of metastatic disease used in the ERSPC)⁵ to the men who were reported as presenting with metastatic disease during each key time interval. The men with evidence of metastases but who did not initially present with metastases would presumably have been reported at some previous time (even before the interval of interest) with nonmetastatic disease. One would expect that comparing true rates of metastatic prostate cancer would mitigate the differences noted in first presentations with metastatic disease between the two key time intervals that may have been due to stage shift given the dramatically different screening rates observed.

A second interesting observation addresses the attribution of causation. The USPSTF recommendation addresses PSA screening, not subsequent evaluation including prostate biopsy. The reduction in rates of biopsies and incident prostate cancer seems considerably out of proportion to the observed decreases in PSA screening rates. Were men less likely to be biopsied at any given PSA level, and if so, was the change in threshold driven by decreases in primary care referrals or increases in the threshold for biopsy among urologists once patients were referred? The relatively stable level of median PSA at biopsy does not suggest this different threshold was attributable to referring men for or performing biopsies only at higher PSA levels in 2014–2015. As the authors note, the large decrease in biopsy rates in this population is greater than that in other studies. The reasons remain obscure and are unlikely to be simply due to changes in Task Force recommendations regarding screening.

What if time does show an uptick in the mortality rate for prostate cancer in this population or in the US population in general? This endpoint would be less susceptible to bias, although previous studies have shown that cause of death assignments on death certificates are influenced by whether

men were treated aggressively for prostate cancer,⁶ which tends to happen when screening is more intense and men are more likely to be diagnosed with clinically localized disease. Setting bias aside, would not this observation prove the 2012 Task Force recommendation was erroneous? A thought experiment may be helpful. Imagine that rather than the widespread dissemination of the PSA test for screening in the early 1990s, a policy had been introduced requiring mandatory radical prostatectomy for all men at say, age 55 (just a thought experiment, remember!). Over the next 25 years, As the cohort of men without a prostate grew in number and aged, rates of incident prostate cancer would have steadily fallen, followed by true rates of metastatic disease and then prostate cancer mortality, all eventually to very low levels. Then let us say the policy was discontinued. With time, these trends would reverse and prostate cancer deaths would increase. Does that mean “prophylactic radical prostatectomy” would have been a good preventive policy? Of course not! Decisions on preventive policies for reducing the morbidity and mortality of disease need to consider the harms as well as the benefits of any proposed intervention, and the harms of this intervention would have been judged completely unacceptable.

The Task Force makes recommendations on preventive interventions, including screening tests, based on evidence-based judgments about net benefits of interventions; that is, an estimate of the benefits minus the harms. The evidence suggests many more men are harmed than benefit through a higher risk of getting a prostate cancer diagnosis, and the subsequent harms of treatment. In the ERSPC, at 11 years, after organized screening had ended for most participants in the intervention arms, the ratio of additional incident cases of prostate cancer to each averted prostate cancer death was 37 to one.³ Though this ratio dropped with further follow-up,^{4, 7} organized screening had ended, which should have resulted in cumulative incidence curves coming together over time. In the present study, male Kaiser plan members had about twice the incidence of prostate cancer in 2010–2011 than in 2014–2015, and a prostate cancer diagnosis is *not* a good thing. Even if first presentations of metastatic disease are accepted as a relevant outcome, the ratio of additional diagnoses per case of first presentation with metastatic disease avoided was estimated at 25 to one. No information is provided on how many of the men in this study were treated with surgery, radiation, or androgen deprivation or on their outcomes including treatment complications. Without that information, estimating net benefit of more versus less intensive screening among the men in this study is simply not possible.

The authors of this study correctly indicate that in 2018 the USPSTF changed the recommendation on PSA screening to a grade “C” for men age 55–69, which they describe as “No recommendation for or against routine provision of this service.” That description actually better fits the current definition of a USPSTF “I” statement, when there is insufficient evidence to assess the balance of benefits and harms of the preventive service. The current definition of a “C”

recommendation is, “The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty the net benefit is small.”⁸

The authors of this paper conclude that the findings of this study, “...may be valuable in the shared decision-making process around prostate cancer screening.” The editorialist is skeptical about this claim, absent data on true rates of metastatic disease and a more in-depth analysis of screening and treatment harms. However, further research on this natural experiment should be able to address these issues, and perhaps support the claim with time. The best evidence on the benefits and harms of screening, of course, comes from randomized trials, including the ERSPC that has already reported that screening reduced the occurrence of metastases by about 3 cases per 1000 men screened after 12 years of follow-up.⁵ The USPSTF has produced an infographic accompanying their 2018 revised recommendation that summarize these data to assist clinicians and patients in shared decision-making discussions about prostate cancer screening.⁸

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Compliance with Ethical Standards:

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