Point-Counterpoint

Cancer Epidemiology, Biomarkers & Prevention

The United States Preventive Services Task Force Recommendation against Prostate-Specific Antigen Screening—Counterpoint

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As a prostate cancer expert, I am disturbed by the recent U.S. Preventive Services Task Force (USPSTF) draft recommendation against prostate cancer screening in asymptomatic men (1) and hope to clarify information from recent studies on this issue.

Implementation of the USPSTF draft recommendation has the potential to cause great harm. Prostate cancer is a leading cause of cancer death, and countless men would unnecessarily suffer and die from prostate cancer if this draft is accepted.

To support its recommendation, the USPSTF highlighted 3 randomized clinical trials (RCT): the European Randomized Study of Prostate Cancer Screening (ERSPC; ref. 2), the Goteborg trial (Sweden; ref. 3), and the Prostate, Lung, Colorectal, Ovarian trial (PLCO; ref. 4). However, they gave little weight to the 2 trials that showed substantial reduction of prostate cancer mortality: (ERSPC; ref. 2) and Goteborg (3).

Flawed Analyses in RCT of Prostate Cancer Screening

The **Goteborg** trial (3) is the best conceived and executed RCT. Its greatest advantages are the inclusion of younger men and the longer follow-up. Of the men in the screening arm, 76% were screened, and the contamination rate (i.e., screening of controls) was only 3% when it began, since screening was far less prevalent in Europe. This figure contrasts with 15% contamination in ERSPC (2) and 52% in PLCO (4). Lower prostate-specific antigen (PSA) cutoff values were used during the study. Biopsy was conducted for an abnormal screening test in 93% and 77% had 14 years of follow-up. In the screening arm, 64% more prostate cancer cases were diagnosed; advanced cases were fewer; and the prostate cancer mortality rate was 44% lower. The number needed to treat to prevent one prostate cancer death (NNT) was 12, comparable with breast cancer screening.

Although Goteborg is a stand-alone trial, designed and initiated before and independently of the ERSPC, the USPSTF discounted it as an independently confirmatory study because the Goteborg researchers contributed 60% of their subjects to ERSPC (2, 3, 5).

ERSPC (2) has the largest sample size of the RCTs to test the impact of PSA testing on prostate cancer mortality. It included 162,243 men from 7 countries in the prespecified core age group of 55 to 69 years. The larger sample size and younger population are among the reasons that ERSPC is more informative than PLCO. Another strength is the substantially lower rates of pre- and intratrial screening of controls.

At 9 years of follow-up in ERSPC (2), the screening arm had a 71% higher prostate cancer detection rate; a significantly lower proportion with high-risk tumors; a 41% lower rate of metastatic disease at diagnosis; and a statistically significant 20% lower prostate cancer mortality rate—observed largely in men younger than 70 years. In reviewing ERSPC, the USPSTF included results from countries that enrolled men outside ERSPC's prespecified age range and then claimed that those figures statistically negated the prostate cancer mortality benefit (5).

PLCO studied 76,685 men aged 55 to 74 years at 10 U.S. centers (4). Its flaws include pretrial PSA screening within 3 years of study entry in $\geq$43% of the study cohort (eliminating many life-threatening prostate cancers from the study population) and screening of $\geq$52% of controls during the study (further reducing the power to detect a mortality difference). PLCO's protocol did not include a biopsy recommendation for men with abnormal results, and about 60% of such men did not undergo biopsy within 1 year (potentially compromising early detection and treatment). PLCO enrolled men up to 74 years old who are less likely to have a screening benefit.

With 7 to 10 years follow-up, PLCO reported a nonsignificantly higher prostate cancer mortality in its screening arm and information suggesting harm from screening. Nevertheless, prostate cancer mortality was 25% lower among men who had undergone $\geq$2 PSA tests at baseline than in those who had not been tested (5).

PLCO reported a subset analysis in which subjects with minimal comorbidity had a 44% lower prostate cancer mortality with an NNT of 5 (6). The USPSTF ignored this report (6).

PLCO updated the results with up to 13-year follow-up in which the screening arm, despite having proportionately less high-stage and high-grade disease, inexplicably had a 9% higher prostate cancer mortality rate (not significant; ref. 7). PLCO also reexamined the prostate cancer

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mortality rates by age, comorbidity, and pretrial PSA testing. In the update, they changed the definition of comorbidity to exclude many important conditions that affect clinical decisions and overall mortality. Using the new definition, they reported no prostate cancer mortality benefit in any of the subgroups. However, using their more complete definition of comorbidity from their first subset analysis (6), there remained a significant 27% lower prostate cancer mortality rate in subjects with minimal comorbidity undergoing screening (7).

ERSPC (2) and Goteborg (3) provide valid level 1 evidence of a PSA screening prostate cancer mortality benefit, whereas PLCO is essentially non-informative on this issue (4, 6, 7). The lack of a significant difference in the screening behavior between 2 arms of PLCO probably accounts for the absence of a mortality benefit.

Flawed Meta-analyses of RCT

The epitome of evidence-based medicine on screening is meta-analyses of well-designed RCTs; however, the USPSTF relied upon 2 flawed meta-analyses that combined low-quality RCTs showing little or no benefit with higher quality trials showing substantial benefits (5, 8, 9). The panel gave more weight to PLCO (4) than to ERSPC (2), despite the fact PLCO is more flawed, and they conclude that the mortality benefit from screening is "small to none (5)." Data from the low-quality RCTs should not be combined in meta-analyses with data from 2 higher quality RCTs that showed substantial prostate cancer mortality benefits (10). Combining the data from heterogeneous trials dilutes of the mortality benefits in the higher quality trials. In summarizing the results of the RCTs, Allan and colleagues (11) commented "We believe these meta-analyses obscure, not enhance, the issue of prostate cancer screening's effect on cancer-specific mortality..." and concluded "The best evidence demonstrates prostate cancer screening will reduce prostate cancer mortality. It is time for the debate to move beyond this issue..."

USPSTF Ignored Epidemiologic Data

A 75% reduction in the rate of advanced prostate cancer at diagnosis and a 40% reduction of age-adjusted prostate cancer mortality in the United States have occurred during the PSA era (12), and similar patterns have occurred in countries where PSA screening is widespread (13). Two NCI modeling teams estimated that 45% and 70%, respectively, of this benefit is directly attributable to PSA screening (14). However, the USPSTF panel largely disregarded epidemiologic data on prostate cancer stage migration and mortality during the PSA era (5).

Potential Effect on Patients from USPSTF Recommendations

Prostate cancer mortality is the primary endpoint of most RCTs; however, the prevention of metastases is also important. The USPSTF did not take into account the NNT to prevent one case of metastatic disease, which would lead to an incalculable reduction in human suffering (2, 3, 5).

Screening has not been adequately studied in high-risk populations such as men with a strong family history of prostate cancer and men of African descent who have 50% higher prostate cancer incidence and 200% higher mortality rates. Epidemiologic data show that African-American men also have decreasing prostate cancer mortality rates during the PSA era (13), yet high-risk men are included in the USPSTF draft recommendation against PSA screening (1).

The imperfections of the PSA test are well known. Not only are there falsely positive and negative results but also the results can be inconclusive. Some patients undergo repeated testing, scans, and biopsies, leading to so-called "PSA anxiety (15)."

The USPSTF incorrectly stated that none of the RCTs provided information related to psychologic harms from screening. However, the Goteborg trial reported no anxiety associated with biopsy in 45%, whereas only 6% experienced high levels of anxiety (15).

The composition of the USPSTF panel is disconcerting, as it included no urologist, radiation oncologist, or medical oncologist. This make-up may explain why many currently used prostate cancer risk assessment tools for decision making are absent from the rationale for the draft recommendation. The PSA screening as conducted in the RCTs is not representative of how it is conducted in clinical practice today (16).

The potential complications of treatment are also well known, but the true rates of overdiagnosis and overtreatment are unknown. Surgical pathology data suggest that prostate cancer is still diagnosed too late (25%–30%) more often than too early (17, 18).

The USPSTF overestimated the risks associated with radical prostatectomy and radiation therapy based on outdated studies. Moreover, side effects of treatment are less in younger men currently treated by experienced physicians and will continue to decrease with ongoing improvements in patient management (19). However, the USPSTF largely ignored the evolution of treatment, concluding that the extent to which they might affect estimates of benefits relative to harms is yet to be determined (5).

Early diagnosis finds the cancer when it is still curable. By recommending against screening asymptomatic men, the USPSTF recommends against diagnosing curable prostate cancer.

The USPSTF recommendation polarizes the medical community and confuses patients. Nearly all urologists and most internists support PSA screening (20). However, because of the extensive media coverage the USPSTF recommendations have received, a change in clinical practice is likely and fewer patients will opt to be tested.

PSA is the best screening test we have for the early diagnosis of prostate cancer. For now, no other way to identify prostate cancer in its curable stages exists. To

deny men the opportunity for informed decision making, needlessly places many patients with prostate cancer in positions of being denied a cure. To implement that denial based upon flawed science would be unconscionable.

The USPSTF's draft recommendation to downgrade PSA testing to level "D" is unfounded and irresponsible.

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