DOI: 10.32481/djph.2017.06.009

Screening for Prostate Cancer:

Making sense of the US Preventative Services Task Force 2017 Draft Recommendation Statement

David M. Bercaw, MD

In April, 2017, the United States Preventive Service Task Force (USPSTF) issued a draft recommendation statement on screening for prostate cancer.[1] This draft recommendation reflects an update of the 2012 recommendations.[2] This article will examine the proposed changes in the new recommendations, the rationale behind the changes, and offer guidance for their implementation by practicing clinicians.

Background

The Centers for Disease Control and Prevention estimates that more than 2.5 million US men were diagnosed and living with prostate cancer in 2013.[3] During that same year, 176,000 US men were diagnosed with prostate cancer, and nearly 28,000 died from prostate cancer.[4] Most men with prostate cancer are asymptomatic. Autopsy studies of men who died from other causes have demonstrated greater than 20% incidence in men 50-59 years of age, and greater than 30% of men 75 years of age and older.[5] However, prostate cancer may be both symptomatic and aggressive, accounting for the death in 25,000 men in 2016.[3] Ideally, screening for prostate cancer should identify early, localized disease which is high-risk and can be successfully treated to prevent morbidity and mortality from metastatic disease.

Measurement of the level of prostate-specific antigen (PSA) is the most common form of screening for prostate cancer. Elevations of PSA can occur in prostate cancer, but elevations may also occur as false positives—usually from benign prostatic hyperplasia or prostatitis. Diagnosis of prostate cancer relies upon an invasive procedure, transrectal ultrasound-guided core- needle biopsy. Currently there is no definitive method for distinguishing between those prostate cancers which will become progressive and/or metastatic and those which will remain indolent and asymptomatic.

2012 USPSTF Recommendations

In 2012, the USPSTF recommended against PSA- based screening for prostate cancer, giving it a grade D recommendation ("There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.").[2] The 2012 recommendations were based largely upon two major trials of PSA screening: the U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC). The U.S. trial failed to demonstrate reduction in prostate cancer mortality,[6] while the European trail demonstrated a reduction in prostate cancer deaths of approximately 1 death per 1000 men screened in the 55 to 69 year old subgroup.[7]

In the 2012 recommendations, the USPSTF considered the potential harms related to screening for prostate cancer. They cited the high incidence of false positive PSA results (approximately 80% when cutoffs between 2.5 and 4.0 μg/L are used).[7] False positive results may cause unnecessary negative psychological impact as well as unnecessary invasive procedures such as

DOI: 10.32481/djph.2017.06.009

prostate biopsy. One third of men who undergo prostate biopsy report having to seek follow-up care for significant pain, fever, hematuria, UTI, or transient dysuria or hesitancy.[8]

The 2012 USPSTF recommendations also considered the potential harm related to treating prostate cancer detected by PSA screening. Approximately 3 to 5 in 1000 men who undergo prostate cancer surgery will die within 1 month of the procedure, and between 10 and 70 men in 1000 will have serious post-operative complications requiring intervention. Between 200 and 300 in 1000 post-prostatectomy men will experience long-term urinary incontinence and/or erectile dysfunction.[9,10] Radical prostatectomy is associated with a 20% incidence of long-term urinary incontinence requiring regular use of pads, and with long-term erectile dysfunction in two out of three men.[9,10] Radiation therapy is associated with long-term erectile dysfunction in more than half of subjects, and with bothersome bowel symptoms (bowel urgency and fecal incontinence) in one out of six men. Androgen deprivation therapy is associated with a 40% incidence of erectile dysfunction, and has not demonstrated improved survival in localized prostate cancer.[9,10]

Additionally, the recommendations noted that substantial over-diagnosis of prostate cancer will identify men who would have had an indolent form of cancer which would never have caused symptoms and would not have contributed to their death. Since our ability to distinguish indolent cancers from aggressive cancers is modest, at best, many of these men will elect to undergo unnecessary treatment.

The USPSTF concluded in 2012 that "…there is convincing evidence that PSA-based screening for prostate cancer results in considerable overtreatment and its associated harms."[2] The USPSTF concluded that "there is moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh the harms."[2]

2017 USPSTF Draft Recommendations

The proposed summary statement regarding screening for prostate cancer reads:

> *The decision about whether to be screened for prostate cancer should be an individual one. The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of PSA-based screening for prostate cancer. Screening offers a small potential benefit of reducing the chance of dying of prostate cancer. However, many men will experience potential harms of screening, including false- positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and impotence. The USPSTF recommends individualized decision-making about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision. (C recommendation: "Clinicians may provide this service to selected patients depending on individual circumstances. However, for most persons without signs or symptoms there is likely to be only a small benefit from this service.")*[1]

DOI: 10.32481/djph.2017.06.009

The change from a D to a C recommendation is based upon additional studies which have been published since the 2012 recommendations. Three factors are largely responsible for the USPSTF recommendations change:

- The largest ongoing trial to demonstrate the benefit of screening (ERSPC), published the results of 13 years of follow-up in Lancet in 2014. The study demonstrated an ongoing reduction in prostate cancer mortality of slightly more than one man per 1000 screened (RR, 0.79 [95% CI, 0.69-0.91]).[11]
- ERSPC offered additional new data suggesting that 3.1 men per 1000 screened would avoid metastatic prostate cancer (RR, 0.70 [95% CI, 0.60-0.82]).[12]
- There has been a significant increase in "active surveillance" since the 2012 recommendations, allaying some of the previous concerns about the harms of screening. Active surveillance offers men with a lower-risk prostate cancer (based upon clinical stage, tumor grade, and PSA level) the option of monitoring, via more frequent PSA testing and/or repeat biopsy, rather than proceeding directly to treatment interventions. Under this approach, treatment can be reserved for those men whose cancer appears to be progressing while under surveillance.

Cooperberg and Carroll documented that in the United States, active surveillance increased from a rate of about 10% of men diagnosed with lower-risk prostate cancer from 2005-2009, to a rate of about 40% from 2010-2013.13 The USPSTF acknowledged that more longer-term follow-up studies are needed in order to assure that active surveillance in this select population is as effective as intervention with radiation and/or surgery, since one study has reported an increase in metastatic disease compared to the intervention group.[1]

The USPSTF 2017 draft recommendation concludes, with moderate certainty, that:

> …overall, the potential benefits and harms of PSA-based screening for prostate cancer in men ages 55-69 years are closely balanced. Each man's individual values and preferences will determine whether he feels that the overall balance of potential benefits and harms is positive or negative.[1]

The USPSTF 2017 draft recommendations again advise clinicians about the potential harms of over-diagnosis (identifying asymptomatic cancers which would never have contributed to death). In addition to causing unnecessary anxiety over a diagnosis of prostate cancer, over-diagnosis exposes men to unnecessary active surveillance (with repeat PSA measurements and possible repeat prostate biopsies) and/or unnecessary treatment (surgery, radiation, and/ or antiandrogen therapy). While it is impossible to conclusively determine the over-diagnosis rate, decision analysis models suggest that 21% of screen-detected cancers in the PLCO trial and 50% in the ERSPC trial were overdiagnosed.[13]

The USPSTF 2017 draft recommendation acknowledges that there are two groups of men who are underrepresented in the prostate cancer screening trials: African American men and men who have a family history of prostate cancer.

Regarding African American men:

- Despite the 12.6% African American makeup of the US population, only 4% of the participants in the PLCO trial were African American.

DOI: 10.32481/djph.2017.06.009

- Unfortunately, African American males have double the incidence of prostate cancer compared with white men (203.5 vs. 121.9 cases per 100,000 men).[3] They are also more likely to die of prostate cancer (44.1 vs. 19.1 deaths per 100,000 men).[3]
- One caveat which the USPSTF offers (which is not based upon randomized controlled trials, but upon decision analysis models) is that given the higher rates of aggressive prostate cancer in African American men, PSA-based screening may provide greater benefit to African American men than the general population.[3]
- Until further studies suggest otherwise, the USPSTF advises that there is insufficient evidence to guide more specific screening recommendations for African American men, so this group has also been included in the C recommendation.[1]

Regarding men with a family history of prostate cancer:

- Data from the Finnish arm of the ERSPC trial suggest that men with a first degree relative with prostate cancer are 30% more likely to be diagnosed with prostate cancer than men without a family history.[14]
- The PLCO trial included 7% of its subjects reporting a family history of prostate cancer. This subset had a lower rate of prostate cancer-specific mortality when screened with PSA compared with controls, but the difference was not statistically significant and may have been under-powered (hazard ratio, 0.49 [95% CI, 0.22 to 1.10]; $p = 0.08$).[15]
- Screening may increase the potential for harm, especially among men with a family history of indolent and less aggressive prostate cancers.[1]
- Until further studies suggest otherwise, the USPSTF advises that there is insufficient evidence to guide more specific screening recommendations for men with a family history of prostate cancer, so this group has also been included in the C recommendation.[1]

The USPSTF draft recommendations did not revise their 2012 recommendations regarding men 70 years and older:

- The USPSTF has retained its previous D recommendation for its proposed guidelines. There is adequate evidence from randomized controlled trials demonstrating no mortality benefit for men in this age group.[1]

The Way Forward: Implementing the Proposed 2017 Guidelines

The newly proposed C recommendation from the USPSTF emphasizes that "the balance of benefits and harms in men remains close," so the decision to screen for prostate cancer in men ages 55 to 69 years of age must be individualized.[1] This shared decision-making model requires clinicians to educate their patients about the potential benefits and harms of screening, and then base the mutual decision upon the patient's individual values and preferences.

Some men may value finding and treating prostate cancer so highly that they are readily willing to assume the risks of prostate biopsy, radiation therapy, surgery, and/or androgen deprivation therapy—if those interventions will provide the highest level of assurance that they will not

DOI: 10.32481/djph.2017.06.009

suffer from the morbidity or mortality of metastatic prostate cancer. Others may be more comfortable not being screened, given the very close balance of benefit versus harm. It is likely that a majority of men (and their clinicians) will struggle with the decision, knowing that the body of knowledge is incomplete, that the net benefit is small, and that the interventions have the potential to cause more harm than good.

To make an informed decision about prostate cancer screening, men must be informed about the risks of over-diagnosis and over-treatment. Clinicians should emphasize that ordering a PSA test is not "just a blood test." If the PSA result is a true positive, having ordered that test was a potential invitation to prevent morbidity and mortality from prostate cancer—yet at the same time, is also an invitation to unintended morbidity and mortality from over-diagnosis and overtreatment. If the PSA result is a false positive, having ordered that test was an invitation to unnecessary anxiety, further invasive testing (including prostate biopsy), and unnecessary repeat PSA screening (possibly leading to repeat biopsies).

A meaningful discussion with a patient about screening for prostate cancer includes not only informing them about the pros and cons of PSA testing, but also delving into that patient's personal values and preferences. This discussion typically occurs during a busy office visit which also focuses upon acute and/ or chronic illnesses, other preventive health concerns, and the myriad of quality metrics which must be addressed. Doing justice to the commitment to a quality discussion about shared decision-making is a potentially daunting task.

As is often the case with medical evidence, we have access to improved guidelines based on new and better information. The USPSTF has provided professional (see Table 1)[1] and patient education material (see Figure 1)[1] to assist the clinician in this endeavor.

Table 1. Estimated Effects After 13 Years of Inviting U.S. Men Ages 55 to 69 Years to PSA-Based Screening for Prostate Cancer*

	Number of Men Affected
Men invited to screening	1,000
Men who receive at least 1 positive PSA test result	240
Men who have 1 or more transrectal prostate biopsies	220†
Men hospitalized for a biopsy complication	2
Men diagnosed with prostate cancer	100
Men who initially receive active treatment with radical prostatectomy or radiation therapy	65
Men who initially receive active surveillance	30
Men who initially receive active surveillance who go on to receive active treatment with radical prostatectomy or radiation therapy	15
Men with sexual dysfunction who received initial or deferred treatment	60
Men with urinary incontinence who received initial or deferred treatment	15

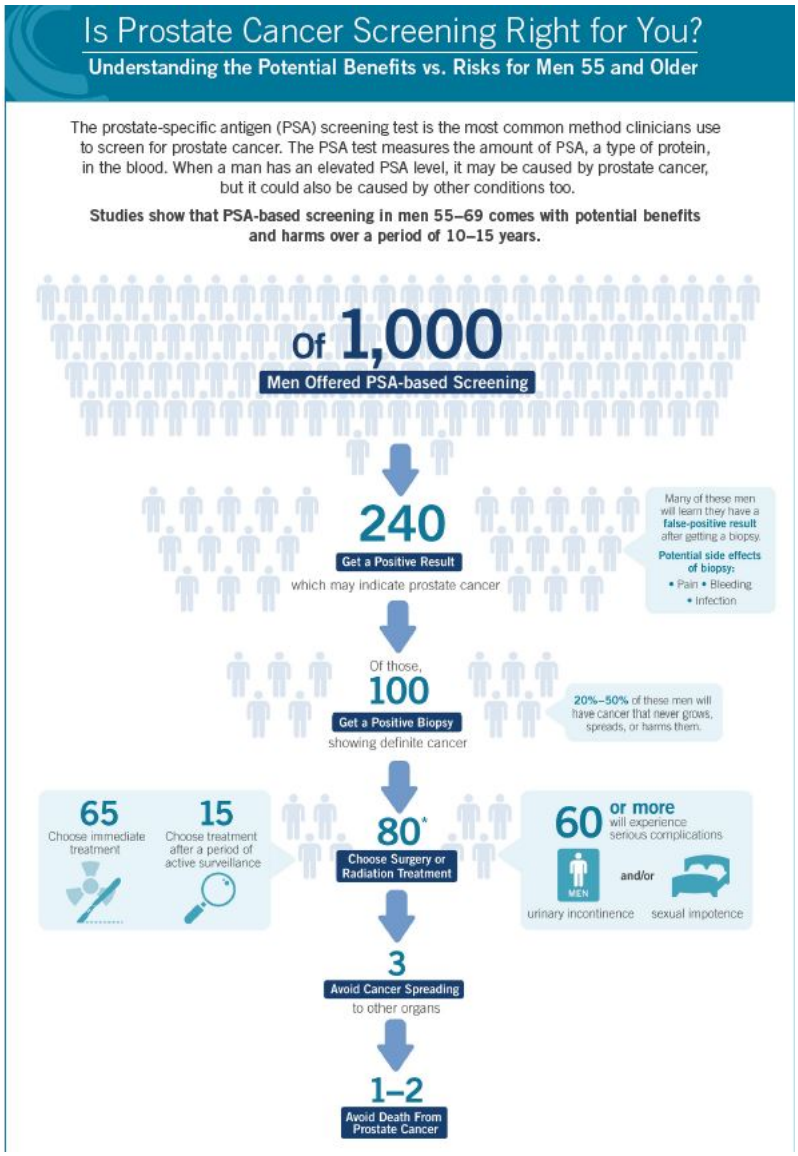
DOI: 10.32481/djph.2017.06.009

Men who avoid metastatic prostate cancer	3
Men who die of causes other than prostate cancer	200
Men who die of prostate cancer despite screening, diagnosis, and treatment	5
Men who avoid dying of prostate cancer	1 to 2

*Estimates based on benefits observed in the ERSPC trial for men ages 55 to 69 years.

†Result based on biopsy rate in the ERSPC trial. Current practice in the United States will likely result in fewer biopsies. The potential effect of fewer biopsies on other outcomes, including reductions in prostate cancer diagnosis and mortality, are not clear.

Figure 1. Patient Education Material



There is still no ‘one size fits all’ approach; primary care providers and specialists will need ongoing partnership with their shared patients to make optimal decisions.

DOI: 10.32481/djph.2017.06.009

References:

1. US Preventive Services Task Force (USPSTF) Screening for prostate cancer website. (2017). Retrieved from: http://www.screeningforprostatecancer.org
2. Moyer, V. A., & the U.S. Preventive Services Task Force. (2012, July 17). Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*, *157*(2), 120–134. PubMed https://doi.org/10.7326/0003-4819-157-2-201207170-00459
3. National Cancer Institute. (2017, Mar 2). Cancer stat facts: prostate cancer. Retrieved from: https://seer.cancer.gov/statfacts/html/prost.html
4. Ryerson, A. B., Eheman, C. R., Altekruse, S. F., Ward, J. W., Jemal, A., Sherman, R. L., . . . Kohler, B. A. (2016, May 1). Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer*, *122*(9), 1312–1337. PubMed https://doi.org/10.1002/cncr.29936
5. Jahn, J. L., Giovannucci, E. L., & Stampfer, M. J. (2015, December 15). The high prevalence of undiagnosed prostate cancer at autopsy: Implications for epidemiology and treatment of prostate cancer in the Prostate-specific Antigen-era. *International Journal of Cancer*, *137*(12), 2795–2802. PubMed https://doi.org/10.1002/ijc.29408
6. Miller, A. B. (2012, March 15). New data on prostate-cancer mortality after PSA screening. [PMID: 12824459]. *The New England Journal of Medicine*, *366*(11), 1047–1048. PubMed https://doi.org/10.1056/NEJMe1200185
7. Schröder, F. H., Hugosson, J., Roobol, M. J., Tammela, T. L., Ciatto, S., Nelen, V., ... Auvinen, A., & the ERSPC Investigators. (2009, March 26). Screening and prostate-cancer mortality in a randomized European study. [PMID: 19297566]. *The New England Journal of Medicine, 360*(13), 1320–1328. PubMed
8. Rosario, D. J., Lane, J. A., Metcalfe, C., Donovan, J. L., Doble, A., Goodwin, L., . . . Hamdy, F. C. (2012, January 9). Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: Prospective evaluation within ProtecT study. [PMID: 22232535]. *BMJ (Clinical Research Ed.)*, *344*, d7894. PubMed https://doi.org/10.1136/bmj.d7894
9. Chou, R., Croswell, J. M., Dana, T., Bougatsos, C., Blazina, I., Fu, R., . . . Lin, K. (2011, December 6). Screening for prostate cancer: A review of the evidence for the U.S. Preventive Services Task Force. [PMID: 21984740]. *Annals of Internal Medicine*, *155*(11), 762–771. PubMed https://doi.org/10.7326/0003-4819-155-11-201112060-00375
10. Chou, R., Dana, T., Bougatsos, C., Fu, R., Blazina, I., Gleitsmann, K., & Rugge, J. B. (2011). Treatments for localized prostate cancer: Systematic review to update the 2002 U.S. Preventive Services Task Force recommendation. Evidence Synthesis no. 91. AHRQ Publication no. 12-05161-EF-2. Rockville, MD: Agency for Healthcare Research and Quality.
11. Schröder, F. H., Hugosson, J., Roobol, M. J., Tammela, T. L. J., Zappa, M., Nelen, V., ... Auvinen, A., & the ERSPC Investigators. (2014, December 6). Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet, 384*(9959), 2027–2035. PubMed

DOI: 10.32481/djph.2017.06.009

12. Schröder, F. H., Hugosson, J., Carlsson, S., Tammela, T., Määttänen, L., Auvinen, A., . . . Roobol, M. J. (2012, November). Screening for prostate cancer decreases the risk of developing metastatic disease: Findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). *European Urology*, *62*(5), 745–752. PubMed https://doi.org/10.1016/j.eururo.2012.05.068

13. Fenton, J. J., Weyrich, M. S., Durbin, S., Liu, Y., Bang, H., & Melnikow, J. (2017). Prostate-specific antigen-based screening for prostate cancer: A systematic evidence review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 154. AHRQ Publication No. 17-05229-EF-1. Rockville, MD: Agency for Healthcare Research and Quality.

14. Saarimäki, L., Tammela, T. L., Määttänen, L., Taari, K., Kujala, P. M., Raitanen, J., & Auvinen, A. (2015, May 1). Family history in the Finnish Prostate Cancer Screening Trial. *International Journal of Cancer*, *136*(9), 2172–2177. PubMed https://doi.org/10.1002/ijc.29243

15. Liss, M. A., Chen, H., Hemal, S., Krane, S., Kane, C. J., Xu, J., & Kader, A. K. (2015, January). Impact of family history on prostate cancer mortality in white men undergoing prostate specific antigen based screening. *The Journal of Urology*, *193*(1), 75–79. PubMed https://doi.org/10.1016/j.juro.2014.07.085

Copyright (c) 2017 Delaware Academy of Medicine / Delaware Public Health Association.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.