

## Effects of USPSTF guidelines on patterns of screening and treatment outcomes for prostate cancer

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and prompted the physicians to initiate conversation of informed screening. Younger patients were inclined towards aggressive treatment and older patients opted towards watchful waiting both with emphasis on the importance of evidence-based information provided by the physician. Decision aids were useful in making informed decisions and could be used to educate patients on screening purposes and treatment options. However, even with well-created decision aids and physician influence, patients' own belief system played a major part in healthcare decision making in either screening or treatment for prostate cancer.

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**Key words:** Prostate cancer screening; United States Preventive Services Task Force guidelines; Prostate cancer treatment outcomes

### Abstract

The updated United States Preventive Services Task Force (USPSTF) for prostate cancer in 2012 recommends against prostate-specific antigen (PSA) based screening for men of all ages. Prostate cancer is the second most common and second most deadly cancer in American men. PSA screening for prostate cancer has been present since 1994 leading to an over diagnosis and over treatment of low volume disease. There is an overall agreement of men towards the guidelines but even with the understanding of the USPSTF, these men tend to follow more personal beliefs that have been influenced by their knowledge of the disease process and physician influence. Physicians also followed the directions of the patients and opted not to change their current practice of PSA screening despite the new guidelines. Time, legal, and ethical issues were some of the barriers that physicians faced in tailoring their practice towards screening. The importance of informed consent is highlighted by both the patients and the physicians and clearly more effective when the patient was pre-informed of the disease process

**Core tip:** Prostate cancer screening has never been more controversial since publication of large randomized trials showing conflicting results with some demonstrating beneficial mortality effects from the European trials but the American screening trial showing no mortality benefit. At the core of the prostate cancer screening debate is not only the overdiagnosis, but rather over-treatment of men with low-risk prostate cancer. This review explores the literature regarding these patterns of screening especially post publication of the United States Preventive Services Task Force guidelines. The use of enhanced risk-adapted approach, perhaps with decision aids, may serve as useful tools to help in the decision for continued screening for men who would benefit.

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## INTRODUCTION

In May 2012, the United States Preventive Services Task Force (USPSTF) presented new guidelines for prostate cancer screening with recommendation against prostate-specific antigen (PSA) based screening for men of all ages<sup>[1]</sup>. This was a Grade D recommendation which suggests that there was no net benefit from screening or that harm outweighs the benefit from PSA screening. The new guidelines comes 4 years after the previous guideline in August 2008 which recommended against PSA screening for men mainly 75 years or older and concluding that there is insufficient data to assess the benefit *vs* harm in PSA screening in men younger than 75 years<sup>[2]</sup>. Prostate cancer is the second most common cancer in American men with American Cancer Society estimating 233000 new cases being diagnosed in 2014 and 29480 men dying of prostate cancer<sup>[3]</sup>. The average age for diagnosis is about 67 years of age and about 1 out of 6 men will be diagnosed with prostate cancer in their lifetime. Prostate cancer is the second leading cause of cancer death in American men with 1 in 36 men who will die of their disease<sup>[3]</sup>. Screening for prostate cancer in men 50 years or older by PSA testing and digital rectal exam were approved by The Food and Drug Administration in 1994. Since then, there has been an increase in diagnosed cases of prostate cancer especially those with low risk and low volume disease. There has been a corresponding decline in mortality from prostate cancer which can be attributed to newer therapies and not entirely due to screening alone. However, PSA screening has been faced with controversy regarding over-diagnosis and over-treatment<sup>[4]</sup>. Given the ambiguity of PSA screening, many organizations have recommended “informed decision making” where the patient is allowed to make the decision to undergo the test or not with knowledge gathered from physician, social, as well as cultural input. The American Urological Association (AUA) has also supported informed decision making until May 2013 when the new guidelines from the AUA presented that PSA screening is recommended against in men ages 40-54 and 70 years or older. They continued to recommend informed decision making for men 55-69 years which is the core group that would benefit from screening<sup>[5]</sup>. This review will focus on how the new guidelines presented by USPSTF for screening for prostate cancer has affected the decision making in choosing to screen for prostate cancer and treatment outcomes with men diagnosed with prostate cancer with exploration into new biomarkers used in disease diagnosis and progression. A literature review was performed using MEDLINE and Pubmed using key words: prostate cancer screening; USPSTF guidelines; informed decision making; decision aids for screening; prostate cancer treatment outcomes. The time frame was set at 2000-2014 and focused on studies done in United States.

## DECISION MAKING IN PSA SCREENING

The response of men to the new guideline was looked

into by Squiers *et al*<sup>[6]</sup> in a study where 1089 males were inquired about decision making about PSA testing with regard to the new changes from 2012. These were non-institutionalized men between the ages of 40-74, residing in the United States, who have never been diagnosed with prostate cancer. The men were given questionnaires assessing their knowledge about the PSA testing, their opinions on the new recommendations and whether or not they would follow the guidelines. Forty-four percent of the men in the study group have had a PSA test done in the preceding two years while 70% of the subjects responded that they had not discussed the benefits and potential harms with their healthcare providers. The study also revealed that the majority of the men were not aware of USPSTF but when explained, 69% reported that they felt confident that the recommendation was based on latest research. After the introduction of the new guidelines, 62% of the men stated that they agreed with the guidelines. However, among those who agreed with the guidelines, 54% intended to not follow them in the future. Most of these men tended to be African-Americans, income over > \$100000 and have had previous PSA testing. The younger men (40-49 years) tended to agree more with recommendations and were less worried about getting the disease compared to men aged 50-59 years of age. Overall, 61% of the men stated that the new recommendation did not affect their decision on getting PSA testing in the future. The study cites Pollack *et al*<sup>[7]</sup> where primary care physicians were surveyed on the effect of the new recommendations on their practice. Not surprisingly, only 2% of the physicians would no longer order routine PSAs and 38% indicated that they would not change their practice. These studies shed some light into the fact that even after the presentation of the new guidelines, informed decision making would still continue on with input from both the physicians’ practice and patients’ beliefs.

It is important to assess the informed decision making in the view of the physicians as well. Wilkes *et al*<sup>[8]</sup> focused on primary care physicians’ ability to educate or activate patients’ informed decision about routine PSA testing. It has been established that factors such as legal fears, lack of time educating the patient, and difficulty understanding each patient’s personal belief system were among the barriers physicians usually face in choosing to follow the guidelines as stated. The study group consisted of 120 California-based primary care physicians and 712 of their male patients were between ages of 55 to 65 years, who have no history of cancer. Majority (80%) of the patients had undergone a PSA test in the past 2 years and had expressed strong preferences in being involved in their health decision making. Among the parameters investigated in the study, was the response from the physician about PSA testing when prompted by the patient. Majority of the physicians opted towards education and screening when prompted by these patients and had long term sustained education even beyond the 3 mo after prompting by the patient. According to the authors, this

method might be more effective and sustainable than using continued medical education for physicians. It is to be noted that a major limitation that is mentioned in the study is that the patient population were of higher education and socioeconomic status and therefore it would be unclear if these results could be extrapolated to patients who are from a lower socioeconomic status. Even though physicians were more stimulated when the discussion about decision making was initiated by the patient, the patients themselves were educated on prostate cancer and screening prior to the physician encounter. Therefore, the patient initiation of the discussion is dependent on the patient's knowledge and his willingness to bring the discussion to the physician.

Some populations were more affected by the new guidelines than others. In Cohn *et al.*<sup>[9]</sup>'s study, a population of men chosen before and after the USPSTF recommendation were brought in and analyzed how the new recommendations impacted the decision making of PSA screening by their primary care physicians. The number of men chose to undergo testing post recommendation was statistically significantly ( $P < 0.0001$ ) less (7.6%) than men who tested prior to the recommendations (8.6%). Some factors that influenced decision making included patients who have had prior benign prostatic hyperplasia (BPH), had previous PSA status and time since previous testing. Men with BPH had increased screening even post recommendations and men were more likely to continue testing if they had done so previously. In contrast, the study also resulted in increased PSA testing in men who had never undergone a PSA (5.1% *vs* 4.5%,  $P = 0.03$ ). The study observed an abrupt decrease in testing in the group of men who had previous PSA values  $> 4.0$  ng/mL. Men in this population were of mostly ages 70-79 years and could reflect decrease due to chronically elevated PSA. The changes in frequency of PSA screening also differed with the age of the population. Men 70-79 years had an increase in frequency of testing up until 2008, when more research was presented that showed less benefit in testing in this age population. Men ages 50-69 years, followed an overall general trend. The ER-SPC study (Table 1) suggested that men in this age range are more likely to receive mortality benefit with PSA screening<sup>[10]</sup>. The younger population of men 40-49 years had a plateau in 2010 and a significant decrease in 2012. The NCCN clinical practice guidelines in oncology suggest discussion of PSA screening at age 40. Even though younger men are choosing to opt out of PSA screening, the long term effect of decreased screening is unknown. The overall decrease in testing shown in the study corresponds to Veterans Health Administration (VHA) Pacific Northwest Network and the linked Surveillance, Epidemiology and End Results-Medicare databases looking at the influence of new USPSTF recommendations. Interestingly, the study states that independent of previous PSA screening or age, African American men tend to receive less PSA testing. African American men tend to have more aggressive tumors and would benefit

from regular screening. Given the social notion of "over-screening" in the general population, this concept seems to result in "under-screening" of African-American men.

Aslani *et al.*<sup>[4]</sup> used retrospective data from health care systems in northeastern Ohio from January 2008 to December 2013 to assess the outcome changes given the new guidelines. The study indicated that the PSA screening has been significantly increasing from the beginning of the research period up until March of 2009 and slightly declined up until May 2012, when the guidelines were published. The decline since March 2009 is attributed by the authors to the PLCO trials (Prostate, Lung, Colorectal and Ovarian cancer screening trial) indicating no difference in mortality with the control group in PSA screening. The rate of testing declined, mentioned a statically insignificant by the author from May 2012 to end of research period. With regard to the age, the most significant decrease in testing was observed in men older than 60 years. Similar results were presented by Zeliadt *et al.*<sup>[11]</sup> where a 3% decline in PSA testing among men of all ages was seen after the PLCO trial. The data from Zeliadt *et al.*<sup>[11]</sup> ranged from August 2004 to March 2010 in practices from the Veterans Health administration Pacific Northwest network.

## EFFECT OF TREATMENT OUTCOMES FOR PROSTATE CANCER

In Xu *et al.*<sup>[12]</sup>'s study, the main focus was on the perspective of men when choosing their prostate cancer treatment. Men who were younger than 75 years who were recently diagnosed with prostate cancer were given information about the different options of treatment and was interviewed on their decision making process. The study included 21 men who consisted of both Caucasian and African American males. Compared to the other studies in the review, this study focused on the emotional perspective rather than evidence or system-based information, that goes towards discussing newly diagnosed cancer and choosing treatment. Younger men opted towards more aggressive treatment and there were few men who initially chose surgery but decided on radiation or watchful waiting after adverse effects of surgery was mentioned. Majority of the men appreciated the depth of resources provided by the physician and wanted the physician to give a personalized recommendation on the treatment type. The patients felt more secure if the physician provided an evidence based treatment option for them to consider. It is important to note that many personal, emotional factors go into decision making for these patients and even distrust of physicians in a small number of patients. However, the decisions were based on a foundation set forth by the physician using evidence-based recommendations.

Similar results were shown in Holmboe *et al.*<sup>[13]</sup> where men were asked about their prostate cancer treatment decisions. Most men cited popular data and good research



**Table 1** Comparison between the prostate, lung, colorectal and ovarian and European randomized study of screening for prostate cancer trials

Participants	PLCO		ERSPC	
	Screening	Control	Screening	Control
Age	55-74 yr		55-69 yr	
Contamination rates	40% (1 <sup>st</sup> year) to 52% (subsequent years)		15%	
Total	38343	38350	72890	89353
Cancer incidence	3452 (9%)	2974 (7.75%)	5990 (8.2%)	4307 (4.8%)
Cancer mortality	92	82	214	326

PLCO: Prostate, lung, colorectal and ovarian; ERSPC: European randomized study of screening for prostate cancer.

as a decision factor. It is possible that the ultimate decisions were influenced by the physicians, yet confirmed by the patient's own beliefs. This sets the standard for the physicians to provide latest and most pertinent data for the patients given the strong influence they have on the decision process.

Another aspect of the new recommendations is the treatment outcomes of men who have already been diagnosed with prostate cancer. The PIVOT trial (Prostate cancer Intervention Versus Observation) found no disease specific survival benefit for radical prostatectomy at 12 years compared to watchful waiting<sup>[14]</sup>. However, one of the thought processes brought about in this trial is that most of these cases of prostate cancer, which was clinically non-apparent, would not have been diagnosed with the previous thoughts about PSA screenings and majority of men were older for whom contemporary recommendation would probably dictate active surveillance rather than surgery. There is no optimal treatment for prostate cancer especially at early stages and the radical surgical treatments are not without adverse outcomes. It is important for the physician to guide the patient to make informed decisions<sup>[15]</sup>.

A systemic review done to analyze the decision making of men with prostate cancer showed that controlling cancer was one of the major decision factors in choosing the treatment. This was either defined as extending survival or preserving the quality of life, depending on the patient values. However, efficacy of the treatment was not given gravity in the decision making process. Relying on published research varied among the patients and avoiding adverse effects were more commonly cited by those who chose watchful waiting. It appears that the decision making mostly relied on the content and information provided to them by their provider over the patient's own belief system. In addition, psychological factors play a role where younger men's perception of early stage of cancer would warrant more aggressive treatment. The decision for over-diagnosis or over-treatment rests partly in the hands of physicians. Therefore, shared decision-making may help since majority of men would report no major physician-patient interactions regarding PSA screening<sup>[16]</sup>.

However, lack of physical, social support and misinformation often resulted in patients choosing more aggressive treatment over more non-invasive treatments. One method of providing proper, balanced information is the use of decision making aids<sup>[17]</sup>.

## USING DECISION AIDS IN THE PROCESS OF PSA SCREENING AND PROSTATE CANCER TREATMENT

Given the ambiguity in the benefit of PSA screening for prostate cancer, the decision making to undergo screening is at times left at the discretion of the patient. Evans *et al*<sup>[18]</sup> reviewed aids that served to assist patients in deciding to undergo the screening based on input from the patient including the patient's health status in the era prior to the published USPSTF guidelines. The study utilized 7 decision aids where 2 were specified for men over 50 years with others presented to the general population of men in United States and Canada. Presence of prostate cancer and/or urological symptoms varied among the sample populations. The decision aids were from Cancer Information Services, NHS Centre for Reviews and Dissemination, Foundation for Informed Medical Decision-Making, Minneapolis VA Medical Center, prostate-specific antigen information script, Cancer Research United Kingdom and American Institute for Cancer Research. The decision aids included knowledge assessing about PSA testing, screening guidelines, test interpretation and prostate cancer disease process. The aids also gave information about treatment options including surgery, radiation and watchful waiting. The results concluded an overall 3.5% absolute reduction in the number of patients who had a PSA test 12 or 18 mo following the decision aid intervention. The knowledge of prostate cancer and PSA screening was also tested in these trials. The results indicated that there was a short term increase of 19.5% more correct answers compared with control group at 2 wk after the intervention. This was less prominent in long term knowledge retention at a year or more with only a difference of 3.4% more correctly answered questions. However, the relationship of the knowledge about prostate cancer and screening and the outcome of decision making to undergo PSA screening were not clearly stated. There were personal values, linguistic and cultural influences that affected the decision making that the authors considered a limitation to the study.

Fagerlin *et al*<sup>[19]</sup> analyzed patient information aids that were supplied to prostate cancer patient and found that only 44 out of 546 had all the treatment options provided (surgery, radiation therapy, hormone therapy and watchful waiting). Only about half of the aids described surgery and radiation therapy in full detail and about one third discussed the risks and benefits of each type of treatment. Most aids had a biased towards one specific type of treatment or overall biased towards the more aggressive treatment options. Patients who received well

prepared decision aids were more likely to select watchful waiting over active treatment [relative risk ratio (RR) = 1.53, 95% confidence interval (CI) = 1.31 to 1.77]. Several online decision aids are currently available and Knight presented key characteristics that offer guidance in the delivery of these decision aids<sup>[20]</sup>. A limitation to these aids is the fact that watchful waiting is written in the same connotation as palliative approach at times and this leads the patients to select inappropriate treatment. As a result, older men tend to opt for inappropriate hormonal therapy and younger men with low risk disease attempted invasive curative therapy. In addition, the clinical utility of decision aids resides in its ability to increase patients' involvement, improve knowledge and realistic perception of outcomes. However, it remains uncertain whether it is truly cost-effective or would work in patients with lower health literacy<sup>[21]</sup>.

## USING EMERGENT BIOMARKERS IN FURTHER REFINING PSA SCREENING AND DIAGNOSIS

The topic of PSA screening has also brought about an upsurge of techniques to better refine the use of a biomarker other than the PSA for improvement in PSA screening or diagnosis. To this end, several promising biomarkers have emerged in the market and while a comprehensive discussion can be found elsewhere<sup>[22]</sup>, recent discovery and commercial availability of a few may illustrate these points. Traditional serum biomarkers such as the PSA has long been heralded as the mainstay of screening biomarker but some would advocate that instead of seeking a new and better marker, a more prudent approach may be to use a panel that incorporates already existing features which led to the development of the PHI or prostate health index which comprises of analyses of the PSA, free PSA (fPSA), and [-2]proPSA<sup>[23-26]</sup>, the latter showing increased specificity for aggressive prostate cancer detection<sup>[27]</sup>. Instead of serum biomarkers, a promising approach could be the use of molecular signatures such as the fusion product TMPRSS2-ERG which makes biological sense since TMPRSS2 is androgen-regulated and coming under control of the transcription factor ETS family would be a driver for prostate cancer growth and it is prevalent in prostate cancers<sup>[28]</sup>. Perhaps a search for a more economical and sensitive way of diagnosing prostate cancer but ultimately distinguishing the benign from aggressive ones in a single or combination of tests<sup>[29]</sup>, could impact the screening landscape for this disease.

## DISCUSSION

Prostate cancer is the second most common cancer seen in American men. The 2012 USPSTF guidelines recommended against PSA screening for all men. Patients tend to agree with the new USPSTF guidelines for PSA

screening. However, the ultimate decision was not solely based on the guidelines and was more focused around their medical or social beliefs. Patients who were older, with previous prostate pathology continued to follow their regular screening despite agreeing with the guidelines. Same outcomes were seen from the physicians' point of view. Most physicians agreed to the guidelines but opted not to change their routine PSA testing given legal, time and knowledge constraints. The populations that saw a decrease in the PSA screening were younger men, with no prior prostate disease and who have a low risk of prostate cancer. The treatment outcomes for prostate cancer were based on personal expectations and physician recommendations. Using new research and guidelines were part of the decision making but not the sole determining factor. There is also the potential utility for the use of decision aids that provides information about prostate cancer disease process, different treatment options and the benefit/risk of each option. The decision aids overall improved the knowledge of the patients and assisted in the decision making process for treatment options. However, the choice of treatment could be affected by any biases presented in the aids and whether a certain treatment is written in a positive or negative connotation.

## CONCLUSION

Patients had a general trend of continuing their regular screening for prostate cancer despite the new USPSTF guidelines although certainly, time will tell whether the uptake in the community with both physicians and patients alike, would ultimately show the trend towards decreased overall screening. The use of decision aids can be used to improve the patients' knowledge of the patient on the disease process and treatment options but ultimately patients tend to put forth personal belief and personal outcome expectations as more determining factors in choosing treatment.

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