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The Ethical Dilemma Surrounding Prostate Specific Antigen (PSA) Screening

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Abstract

The Food and Drug Administration approved testing for prostate cancer screening in 1994. Today over four decades have passed since the Prostate-Specific Antigen (PSA) was first discovered. Yet enormous uncertainty governs the effectiveness of PSA testing as well as the appropriate strategy to best detect early prostate cancer. Many groups including the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), the American Urological Association (AUA) and the US Preventative Services Task Force (USPSTF), have issued a series of clinical guidelines for prostate cancer screening with inconsistent recommendations. Research shows that prostate cancer screening with PSA resulting in a false-positive screen occurs among 80 percent of men, while 20 percent of men have false-negative results. Recently changes to existing recommendations were suggested by the USPSTF due to concerns of negative effects of PSA testing on patient outcomes. While the evidence underlying prostate cancer screening recommendations is continuously in flux, it is important to understand implications of the debate for clinicians and men. In this paper we examine ensuing ethical considerations of PSA screening for prostate cancer.

Keywords: Prostate cancer; Prostate specific antigen; Multiparametric MRI; Ethics

Background

The American Cancer Society (ACS) estimates a total of 1,665,540 new cancer cases and 585,720 cancer deaths to occur in the United States in 2014 [1]. An estimated 233,000 new cases of prostate cancer are expected to be diagnosed in 2014 and 29,480 are expected to die of prostate cancer [2]. Excluding skin cancer, prostate cancer is the most commonly diagnosed cancer among men in the United States and the second most common cause of cancer death among men. About 1 in 6 men in the United States will be diagnosed with prostate cancer during their lifetime and 1 in 36 will eventually die from prostate cancer [3]. Despite the important burden of prostate cancer cases and deaths, and extensive research on its causes, prevention, early detection, and treatment, uncertainties abound with respect to prostate cancer prevention, screening, and treatment.

Current strategies for reducing the burden of prostate cancer are primarily aimed at early detection of clinically significant cancers and determining which prostate cancers are likely to be clinically insignificant. This is substantiated by scientific literature that suggests that early detection can play a vital role in detecting clinically important prostate cancers, and distinguish these cancers from those that are unlikely to be clinically relevant during ones life [4]. Despite the large expanse of medical literature on early detection, differences of opinion abound on frequency of screening, appropriate age to initiate screening (if ever), interpretation of Prostate-Specific Antigen (PSA) results, and appropriate follow-up and treatment of men with proven prostate cancer. The enduring controversy is whether PSA screening should be recommended because of psychological and medical costs associated with PSA testing [5-7]. There are many persons and organizations who do not support population-based screening with PSA testing, based on concerns that present screening methods increase morbidity without affecting all-cause mortality [8].

Prostate cancer screening tools

Most clinically relevant as well as clinically insignificant prostate cancers are diagnosed through PSA screening, while a minority of new prostate cancers are diagnosed by Digital Rectal Examination (DRE) [9]. Early prostate cancer usually has no symptoms. With more advanced prostate cancers, men may experience weak or interrupted urine flow; inability to urinate or difficulty starting or stopping the urine flow; the need to urinate frequently, especially at night; blood in the urine; or pain or burning with urination. However, these symptoms occur frequently as a result of non-cancerous conditions, including prostate enlargement or prostate infection. Advanced prostate cancer commonly spreads to the bones, which can cause pain in the hips, spine, ribs, or other areas.

It has been suggested that PSA screening can detect prostate cancer years earlier than it would be detected by a DRE or development of symptoms, although the overwhelming majority of these cancers are not likely to be clinically significant [10]. Potential errors in diagnosis can be attributed to the many limitations of PSA screening. Although there is no absolute cutoff between a normal and an abnormal PSA level, prostate cancer screening programs initially considered >4 ng/mL as a positive PSA screening test. Many men who do not have prostate cancer will screen positive and require a biopsy for diagnosis (potentially due to benign prostate hyperplasia, prostatitis, urinary tract infections or prostate biopsies/surgery), and some men with prostate cancer many not have elevated PSA levels. Most importantly, PSA testing does not differentiate between low and high risk cancers. Because many prostate cancers grow so slowly that they never threaten a patient's life, overtreatment of prostate cancer with radical prostatectomy or radiation therapy is common. This is a particularly important issue since treatment for prostate cancer with radiation or surgery is associated with significant side effects.

The evidence

For years studies have tried to establish the benefits of PSA as a screening tool for prostate cancer. Results from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial have not shown convincing evidence that Prostate Specific Antigen (PSA) screening reduces prostate cancer mortality as the screened arm showed a higher rate of mortality than the control arm [6]. Doggett et al. examined whether annual PSA screening from age 50 to 75 reduced the number of prostate cancer deaths. However, they found a loss of 0.08 Quality Adjusted Life Years (QALY) or 30 days per person screened which implies that screening lowers quality of life compared to not screening [7]. Crawford et al. assessed the chances of an initially normal PSA rising to a level >4 ng/mL over 5 years of screening. Their results indicated that 98.7% of men with a PSA <1 ng/ml at baseline would remain negative (i.e., PSA ≤ 4ng/ml) after 5 subsequent years of annual PSA testing, and that 99% of men with a baseline PSA of 1-2 ng/ml would have a negative PSA test (i.e., PSA ≤ 4 ng/ml) the following year [11]. These results suggest that most men do not advance to a significant cancer but instead, their cancer diagnosis potentially leads to unnecessary overtreatment and results in excessive cost as well as risk of adverse consequences.

While evidence from the United States' study exists that PSA screening is not associated with a reduction in prostate cancer mortality, evidence from a large European prostate cancer screening study suggests otherwise. The European screening trial involving about 182,000 men between the ages of 50 and 74 years at entry concluded that PSA screening reduced the rate of death from prostate cancer by about a fifth at 13 years of follow-up. This has however, been questioned [12]. Screening did not affect all-cause mortality, and in order to prevent one death from prostate cancer, 781 men would need to be invited for screening and 27 cancers would need to be detected and treated. Given potential harms associated with overdiagnosis in screening (estimated by the authors to include 40% to 50% of screen-detected cases) and resultant overtreatment, the authors concluded that population-based screening should not be recommended [13,14].

The recommendations

Results from numerous studies conducted on PSA testing has led to considerable difference is screening guidelines issued by various entities [15]. The American Urological Association and the American Cancer Society recommend a shared decision making approach to offering annual PSA testing and DRE beginning at the age of 50 years to men with a normal risk of prostate cancer and beginning at an earlier age to men at high risk [16-22]. The National Comprehensive Cancer Network recommends a risk-based screening algorithm, including family history, race, and age [23]. The NCCN and the AUA recommend prostate biopsy for men with a high PSA velocity (rate of change of PSA level)-greater than 0.35 or 0.4 ng mL-1 y-1-stating that this PSA threshold may improve prostate cancer detection for men despite low PSA levels. In 2002, the USPSTF concluded that there was no direct evidence to demonstrate the reduction in mortality as a result of early screening. In 2008, the U.S. Preventive Services Task Force concluded that there was insufficient evidence in men under the age of 75 years to assess the balance between benefits and side effects associated with screening, and the panel recommended against screening men over the age of 75 years [24,25]. In 2010, Vickers et al., found no evidence to support the recommendation that men with high PSA velocity should be biopsied in the absence of other indications [26]. The 2011 US Preventative Services Task Force (USPSTF) policy

graded prostate cancer screening as "(D)- do not discuss with patients" [25]. In 2012, USPSTF released new recommendations advising against routine PSA testing for all men, based on reviews of 5 screening trials, stating that the harms of PSA testing outweigh the benefits [20,25]. However, the issue of prostate cancer remains important because 68% of prostate cancer mortality takes place under the age of 75 (the average life expectancy for men in the US).

Ethical considerations

Ethical considerations regarding prostate cancer screening are primarily related to PSA testing. Some researchers cite a decline in mortality post-PSA introduction; however, due to the low sensitivity and specificity as well recent considerations of increased mortality associated with PSA screening, using PSA as a marker for early prostate cancer detection continues to be controversial [27-37].

Today, over four decades have passed since PSA was first approved by the FDA as a tool for early detection of prostate cancer. Yet, enormous uncertainty continues to govern the effectiveness of PSA testing as well as the appropriate strategy to detect clinically significant early stage prostate cancers [38,39]. As shown above, many groups have attempted issuing guidelines for prostate cancer screening with inconsistent results [15-25]. The effect of these screening practices on clinical outcomes is not well documented. Nevertheless an educated guess regarding the chaos in practice can easily be made. Moreover due to the discovery of new evidence that over 25% of the time the control group was screened in the PLCO trial in the United States, the label of a true screening trial is likely to be inaccurate [40]. Presently evidence from the large prostate cancer screening trials in the United States and Europe are consistently updated to determine whether the clinical findings stand up as the data mature.

Many physicians and scientists argue that PSA screening of asymptomatic men does not improve prostate cancer survival statistics, and exposes many men to unnecessary radiation or surgical treatments [8]. However, when faced with a man asking for a PSA test, saying no for a clinician is a tough decision to make. Consenting to the request not only serves as a means of protection against malpractice complaints but early diagnosis of clinically relevant prostate cancers can save lives. Most patients are concerned about missing a diagnosis of prostate cancer (clinically significant or clinically insignificant) and argue that it is not ethical to ignore requests for PSA testing by men who might actually die from prostate cancer, despite the very large risks of overtreatment or anxiety among men who opt for active surveillance following a prostate cancer diagnosis made by biopsy.

Due to these concerns, most clinical guidelines for early detection of prostate cancer stress the importance of informed decisions; asymptomatic men should undergo PSA testing only after receiving adequate information about benefits, risks and uncertainties associated with undergoing this screening test. But what is a truly informed decision? Given the complexity of PSA testing and decisions that need to be made after detecting increased PSA levels, transferring responsibility for decisions from clinicians to men can be envisaged by some as a mean of avoiding legal responsibility.

Conclusion

Solution to the problems encountered with PSA testing is not yet in sight. In the absence of cost-effective screening techniques, scientists and researchers alike have been exploring modifications of the PSA for aiding in diagnosis. Several modifications have been suggested such as

the free versus total PSA, PSA density of the transition zone, age-specific PSA, PSA velocity and PSA doubling time, serial PSA and Pro-PSA [41-43]. Among these PSA velocity, or the study of PSA dynamics over time, has generated yet another controversy. While Catalona et al. argue the importance of PSA screening and suggest that PSA velocity is strongly associated with aggressive prostate cancer, Vickers and colleagues argue conversely [44-46].

A potential avenue of avoiding PSA testing is the research into new markers and the development of refined prostate imaging techniques such as multiparametric MRI among men who have an elevated PSA [47-49]. Multiparametric MRI is a non-invasive imaging technique for detection and staging of prostate cancer. Preliminary results suggest promising results in reducing overdiagnosis and improving detection of clinically significant cancer and active surveillance of low grade cancers [50-53]. In addition, multiparametric MRI represents cutting edge technology and is expensive resulting in a compromise on other health needs. Therefore long-term studies are required to accurately isolate the optimal potential of MRI for prostate cancer patients.

PSA testing more often than not results in detecting cancers that are unlikely to be clinically significant. Active surveillance is an attempt to avoid overtreatment of low risk prostate cancer, and, at the same time, this approach hopes to offer curative treatment for men who may have high risk prostate cancer. But how to know when to intervene, and upon which men? Prostate biopsies may be falsely negative, and complication risks increase along with the number of repeat biopsies.

The lid of the box has been lifted up with respect to routine PSA testing and the contents of the box are indeed perplexing. Until precise and affordable means of detecting high risk prostate cancer are developed and tested, the lid will most likely remain open and overtreatment of clinically significant prostate cancers will persist.

Acknowledgement

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