Prostate cancer screening

In 2017 an estimated 161,360 prostate cancer cases will be diagnosed, and approximately 26,730 men will die from prostate cancer in the United States [1]. Prostate cancer mortality has decreased in the past decade, attributed by many to the widespread use of prostate-specific antigen (PSA)-based detection strategies. However, the dilemma of managing prostate cancer is that while 1 in 7 men will eventually be diagnosed, and the disease remains the second leading cause of male cancer deaths, only 1 man in 30 with prostate cancer will die of his disease [1]. Balancing the early detection of potentially lethal prostate cancer that may benefit from treatment with over treating low-risk screen detected cancers that suffer complications from unnecessary treatment continues to be the controversy regarding prostate cancer screening.

The risk of being diagnosed with prostate cancer increases twofold if one first-degree relative is diagnosed and by a factor of four if 2 or more relatives are affected [2]. Hereditary prostate cancer is estimated to occur in 40% of early-onset and 10% of all prostate cancers. BRCA1/2 mutations increase the likelihood of being diagnosed with prostate cancer [3]. The relative risk of being diagnosed with prostate cancer by age <65 years is estimated at 1.8 to 4.5 fold for *BRCA1* carriers and at 2.5 to 8.6 fold for *BRCA2* carriers [3]. Numerous retrospective studies report that *BRCA2* carriers are diagnosed with prostate cancer at a younger age, with higher-risk disease, have increased rates of lymph node metastases and/or distant metastasis at diagnosis, and a higher mortality rate from prostate cancer than noncarriers. Ethnicity also impacts the likelihood that a man will be diagnosed with prostate cancer [1,4]. Matched for age, African-American men have a higher chance of being diagnosed with prostate cancer, having higher risk disease at diagnosis, and more worrisome histologic features in the radical prostatectomy specimen than white men [4].

Autopsy-detected prostate cancers prevalence is similar worldwide but the incidence of clinically identified disease varies. As such, dietary and environmental factors have been suggested to play a role in prostate cancer growth and progression. Consumption of a diet high in fat content is believed to increase risk. The risk of being diagnosed with prostate cancer in Asian men living in Asia is low but this risk increases substantially if the man moves to Western countries. Factors suggested as being protective include consumption of the isoflavonoid genistein (which inhibits 5α-reductase) found in many legumes, cruciferous vegetables, lycopene found in tomatoes, and inhibitors of cholesterol biosynthesis (statin drugs). The development of prostate cancer is a multistep process. One early change is hypermethylation of genes including GSTP1, which leads to loss of function of a gene that detoxifies carcinogens. Many prostate cancers develop adjacent to a lesion termed PIA (proliferative inflammatory atrophy) suggests a role for inflammation in the etiology of the disease [5].

The decision to undergo testing to detect prostate cancer is based on the individual's estimated life expectancy and, separately, the probability that a clinically significant cancer may be present. Screening for prostate cancer includes digital rectal examination (DRE), or, more typically, a change in or an elevated serum PSA. The DRE focuses on prostate size and consistency. Many cancers occur in the peripheral zone and can be palpated on DRE. Carcinomas are characteristically hard, nodular, and irregular. Overall, about 25% of men with an abnormal DRE have cancer.

PROSTATE-SPECIFIC ANTIGEN

PSA is a kallikrein-related serine protease (kallikrein-related peptidase 3; *KLK3*) that liquefies the seminal coagulum. PSA is made by both nonmalignant and malignant epithelial cells and, as such, is prostate-specific, not prostate cancer-specific. Serum PSA levels may increase from a variety of causes including prostatitis and benign prostatic hyperplasia. Serum levels may increase slightly after a DRE but the performance of cystoscopy or prostate biopsy may increase PSA levels as much as tenfold for up to

10 weeks.

PSA circulating in the blood is inactive and mainly occurs as a complex with the protease inhibitor α_1-antichymotrypsin; the formation of complexes between PSA, α_2-macroglobulin, or other protease inhibitors is less significant. The remainder circulates as free (unbound) PSA which is rapidly eliminated from the blood by glomerular filtration with an estimated half-life of 12–18 hours. Elimination of PSA bound to protease inhibitors is slow (estimated half-life of 1–2 weeks) as it too is largely cleared by the kidneys. Following radical prostatectomy PSA levels should become undetectable after about 6 weeks if the prostate has been completely removed (radical prostatectomy).

PSA testing was approved by the U.S. Food and Drug Administration in 1994 for the early detection of prostate cancer. Widespread use of the PSA test markedly increased the proportion of men diagnosed with early-stage cancers with more than 80% of newly diagnosed cancers being clinically organ confined. Serum PSA is strongly correlated with the risk and outcome of prostate cancer. A single PSA measured at age 60 is associated (area under the curve=0.90) with a man's lifetime risk of death from prostate cancer [6]. Most prostate cancer deaths (90%) occur among men with PSA levels in the top quartile (>2 ng/mL), although only a minority of men with PSA >2 ng/mL will develop lethal prostate cancer [6]. Despite this and mortality rate reductions reported from large randomized prostate cancer screening trials, routine use of the test remains controversial.

In 2017, the U.S. Preventive Services Task Force issued an updated guideline for prostate cancer screening [7]. A "C" recommendation was given for men aged 55–69 years meaning these men should be informed about the benefits and harms of screening for prostate cancer, and offered PSA testing if they choose it. For men aged ≥70 years, the recommendation remains "D", or "do not screen" concluding that "there is moderate or high certainty that this service has no net benefit or that the harms outweigh the benefits." The American Urological Association recommends shared decision-making for men age 55 to 69 years considering PSA-based screening, a target age group for whom benefits may outweigh harms. Outside this age range, PSA-based screening as a routine was not recommended. The entire guideline is available at www.AUAnet.org/education/guidelines/prostate-cancer-detection.cfm.

Several lines of evidence suggest that implementation of the following 3 guidelines would improve PSA screening outcomes. First, avoid PSA tests in men with little to gain from screening. There is no rationale for recommending PSA screening in asymptomatic men with a short life expectancy. Therefore a man older than age 75 years should only be tested in special circumstances, such as previous testing showing higher than median PSA levels that are measured before age 70 or excellent overall health (life expectancy greater than 10 years). In addition, because a baseline PSA is a strong predictor of the future risk of lethal prostate cancer, men with low PSA levels, for example a PSA less than 1 ng/mL at age 45 years, should undergo less frequent testing, perhaps every 5 years. Should the PSA level remain less than 1-ng/mL screening could potentially be stopped after age 60. Men with PSAs above age median but below biopsy thresholds can be counseled about their elevated risk and actively encouraged to return for regular screening and more comprehensive risk assessment. Second, do not treat those who do not need treatment. Many men with screen-detected prostate cancer are considered to be low-risk and do not require immediate intervention. These men can be managed by active surveillance (observation with selective delayed treatment). Third, men who do need treatment should be referred to high-volume centers. Although it is clearly not feasible to restrict treatment exclusively to high-volume centers, shifting treatment trends so that more patients are treated by high-volume providers will improve cancer control and decrease complications. The goal of prostate cancer screening should be to maximize the benefits of PSA testing and minimize its harms. Following the 3 rules outlined here should improve the ratio of benefit to harm from PSA screening.

SECOND-LINE SCREENING TESTS

PSA criteria used to recommend further diagnostic testing have evolved over time. However, based on the commonly used cut-point for prostate biopsy (a total PSA≥4 mg/mL), most men undergoing prostate cancer screening do not have histologic evidence of prostate cancer at biopsy. In addition, some men with PSA levels below this cut point harbor cancer cells in their prostate. Information from the Prostate Cancer Prevention Trial demonstrates that there is no PSA below which the risk of prostate cancer is zero. Thus, the PSA level establishes the likelihood that a man will harbor cancer if he undergoes a prostate biopsy. The goal is to increase the sensitivity of the test for younger men more likely to die of the disease and to reduce the frequency of detecting cancers of low malignant potential in elderly men more likely to die of other causes.

The 4Kscore test measures 4 prostate-specific kallikreins. The results are combined with clinical information in an

algorithm that estimates an individual's percent risk for aggressive prostate cancer should that individual opt for a prostate biopsy. The 4Kscore test has also been shown to identify the likelihood than an individual will develop aggressive prostate cancer, defined as high grade prostate cancer pathology and/or poor prostate cancer clinical outcomes, within 20 years.

Prostate Health Index (PHI) is a blood test that estimates the risk of having prostate cancer. The PHI test is a combination of the free PSA, total PSA, and the [-2] proPSA isoform of free PSA. These 3 tests are combined in a formula that calculates the PHI score. The PHI score is a better predictor of prostate cancer than the total PSA test alone or the free PSA test alone.

Unlike other solid organ cancers in which imaging studies select the patient for a biopsy, the diagnosis of prostate cancer is typically made when a man with an elevated PSA test undergoes a non-imaging-directed ("blind") transrectal ultrasound-guided biopsy. A pathway with imaging to decide which men with an elevated PSA go on to biopsy should reduce unnecessary biopsy and improve diagnostic accuracy. There is some evidence that multiparametric prostate magnetic resonance imaging (MRI) tends to detect higher risk disease and systematically overlooks low-risk disease, which makes it attractive as a potential triage test. Whether or not this will become standard-of-care is yet to be determined. Concerns regarding the availability of appropriate equipment, availability of expert radiologists, and patient inconvenience (relative to a blood test like the 4Kscore Test or PHI) may limit the broad use of MRI in this setting.

A diagnosis of cancer is established by an image-guided (usually transrectal ultrasound-guided) needle biopsy. Contemporary schemas advise an extended-pattern 12-core biopsy that includes sampling from the peripheral zone as well as a lesion-directed palpable nodule or suspicious image-guided sampling. Because a prostate biopsy is subject to sampling error, men with an abnormal PSA and negative biopsy are frequently advised to undergo additional testing which may include a 4Kscore Test, PHI, prostate MRI, and/or repeat biopsy.

CONFLICTS OF INTEREST

The author has nothing to disclose.

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