Screening for prostate cancer

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INTRODUCTION

Prostate cancer is common and is among the main causes of cancer-related death. At the same time, in many cases, prostate cancer grows so slowly that it does not impact survival; hence, routine screening is controversial.

This topic reviews the efficacy of screening and recommendations regarding screening for prostate cancer.

Risk factors, clinical manifestations, and diagnosis of prostate cancer are discussed separately. (See "Risk factors for prostate cancer" and "Clinical presentation and diagnosis of prostate cancer".)

Genetic risk factors for prostate cancer, and screening of patients at high risk for prostate cancer due to genetic syndromes (*BRCA1*/*BRCA2*, Lynch syndrome), are described separately. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Management of male BRCA1/2 carriers without cancer' and "Genetic risk factors for prostate cancer" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

EPIDEMIOLOGY AND NATURAL HISTORY

- **Incidence** – Worldwide, there are an estimated 1,400,000 new cases of prostate cancer annually, making it the second most commonly diagnosed cancer in men [1]. Among men

in the United States, it is the leading cause of cancer, accounting for 27 percent of cancer diagnoses [2]. Surveillance, Epidemiology, and End Results (SEER) data indicate that between 2010 and 2015, the overall incidence of prostate cancer in the United States decreased, particularly for low-risk disease, while the incidence of metastatic disease (per 100,000) increased from 6.2 to 7.1 in men aged 50 to 74 and from 16.8 to 22.6 in men ≥75 years [3]. The declining incidence rate for low-risk disease was temporally associated with decreased prostate cancer screening following the 2012 US Preventive Services Task Force (USPSTF) recommendation against prostate cancer screening [4].

However, data from the US Cancer Statistics Public Use Research Database spanning 2005 to 2016 showed that the declining rate of low-risk disease had stabilized for men ≥75 years, and rates of regional-stage (annual percent change of 11.1) and distant-stage (annual percent change of 5.0) disease increased for men aged >50 years [5].

Similarly, analysis of SEER data from 2004 to 2018 also demonstrates an increase in the incidence of metastatic cancer. Among men 45 to 74 years of age, the incidence rate was stable during 2004 to 2010 and then increased significantly during 2010 to 2018 (annual percentage change 5.3 percent). In men aged 75 years or older, the incidence rate decreased from 2004 to 2011 and then increased from 2011 to 2018 (annual percentage change 6.5 percent) [6]. Analyses of longer-term data will be needed to determine whether changes in screening practices were associated with increased prostate cancer mortality rates. In 2018, the USPSTF issued a C recommendation for screening men ages 55 to 69, which may again alter screening practices and impact cancer incidence [7].

- **Natural history** – Without screening, many cases of prostate cancer do not ever become clinically evident. Data suggest that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced [8-10]. At autopsy of men who died of other causes, prostate cancer detection rates (approximately 30 percent for men in their fifties and up to 70 percent for men in their seventies), are higher than the lifetime incidence of diagnosed prostate cancer in the population [8-10].

  Prostate cancer survival is related to many factors, especially the extent of tumor at the time of diagnosis. The five-year relative survival among men with cancer confined to the prostate (localized) or with regional spread is 100 percent, compared with 31 percent among those diagnosed with distant metastases [11]. While men with distant-stage disease may benefit from palliative treatment, their cancers are generally not curable.

- **Declining mortality rates** – Prostate cancer mortality rates have declined in the United States between 1992 and 2017, decreasing from 39 to 19 per 100,000 persons (figure 1) [11]. Simulation models suggest that prostate-specific antigen (PSA) screening could account for 45 to 70 percent of the decline, mainly by decreasing the incidence of distant-stage disease [12]. Other factors that may explain the decline in mortality rates include advances in treatments for men with localized prostate cancer as well as for those with distant-stage disease. For example, the use of androgen deprivation therapy or other chemotherapies could allow men with advanced-stage disease to live long enough to die from a concomitant condition, rather than from prostate cancer.

BENEFITS AND HARMS OF SCREENING

For prostate cancer screening to be valuable, it must reduce disease-specific morbidity and/or mortality by detecting cancer at an early stage. However, detection at an early stage does not necessarily correlate with a clinically beneficial outcome (eg, decline in morbidity or mortality due to prostate cancer). Increased detection of prostate cancer subjects some patients to the risks associated with treatments that may not prolong life and that have risks of morbidity.

Effect on incidence — Screening increases the detection of prostate cancer among men. Prostate cancer incidence in the United States increased sharply during the initial years following the advent of prostate-specific antigen (PSA) testing and has returned to levels seen prior to the onset of testing as the rate of PSA testing has declined (figure 1) [11]. In a meta-analysis of four randomized trials including 675,232 participants, cancer was diagnosed more often in men who were screened (incidence rate ratio 1.23, 95% CI 1.03-1.48) compared with the control group [13]. The incidence rate ratio was higher for screen-detected localized prostate cancers (1.39, 95% CI 1.09-1.79).

Screening may reduce the risk for distant-stage prostate cancer. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), which enrolled 162,243 men ages 50 to 69 years, at a median follow-up of 12 years, the cumulative incidence rate of metastatic disease among those who were in the regular screening group was 0.67 percent compared with the incidence rate in the control group of 0.86 percent [14]. The relative reduction of metastatic disease was 30 percent in the intention to screen group (hazard ratio [HR] 0.70; 95% CI 0.60-0.82), with a relative reduction of 42 percent for men actually screened. The absolute risk reduction of metastatic disease was 3.1 per 1000 men randomized.

Effect on mortality — While prostate cancer mortality rates have declined since the advent of PSA testing, it is uncertain what proportion of this is due to PSA screening. (See 'Epidemiology

and natural history' above.)

The best available evidence from randomized trials found that screening has at most a small benefit in reducing prostate cancer mortality. Screening has no benefit in reducing overall mortality.

In a meta-analysis of five randomized trials with follow-up periods ranging from 10 to 20 years, a prostate cancer mortality reduction was not found (relative risk [RR] 0.96, 95% CI 0.85-1.08). In this meta-analysis of five trials, participants were randomized to control groups or to one-time or repeat screening that occurred at intervals ranging from one to four years [13]. However, the included studies each contained high or unclear risks of bias. The ERSPC trial found a small absolute survival benefit with PSA screening at nine years of follow-up, with an absolute risk reduction of 0.51 per 1000 men. By 16 years, the prostate cancer mortality rate in the screening group was 0.53 per 1000 person-years compared with 0.66 per 1000 person-years in the control group [15,16]. The absolute risk reduction of prostate cancer death was 1.76 per 1000 men, meaning that to avert one prostate cancer death, 570 men needed to be invited to screening, of whom 18 were expected to be diagnosed with cancer. While this trial was assessed to have the lowest risk of bias of those included in the meta-analysis, the risk of bias was unclear due to allocation concealment and completeness of outcome data. Another large trial included in the meta-analysis, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which enrolled 76,774 men ages 55 to 74 years, did not report a mortality benefit; however, the negative results have been largely discounted because so many patients randomized to the control group had screening as part of usual care [17,18].

Calculations that take into account not only years of survival, but also the value of each potential benefit and harm associated with screening, suggest that screening does not clearly improve quality-adjusted life years (QALYs), even if mortality is reduced. In a simulation modeling study that used ERSPC data, annual screening between ages 55 and 69 years was projected to result in nine fewer prostate cancer deaths per 1000 men followed for their lifetime, with a total of 73 life-years gained [19,20]. However, the simulation model using the same data to calculate QALYs showed a gain of only 56 QALYs with a 95% confidence interval that ranged from a loss of 21 QALYs to a gain of 97 QALYs.

Risks of prostate biopsy — Men with abnormal results of screening may have a prostate biopsy to determine if prostate cancer is present. Complications of prostate biopsy (eg, infection, pain, bleeding, urinary obstruction) occur in up to 2 percent of men [21]. Risks of prostate biopsy are described in detail separately. (See "Prostate biopsy", section on 'Complications'.)

Overdiagnosis of prostate cancer — Overdiagnosis refers to the detection by screening of a condition that would not have become clinically significant in the patient's lifetime. When screening finds cancer that would never have become clinically significant, patients have still been subjected to the risks of screening, confirmatory diagnostic testing, and potentially treatments that can result in side effects.

For prostate cancer screening, the potential for overdiagnosis appears to be substantial given the high prevalence of undiagnosed prostate cancer detected on autopsy series. Overdiagnosis is of particular concern because most men with screening-detected prostate cancers have early-stage disease and may be offered aggressive therapies that may produce long-lasting adverse effects (eg, impotence, urinary incontinence). However, the increased uptake of active surveillance rather than aggressive treatment may help to mitigate the treatment-related harms of overdiagnosis of prostate cancer [22].

Studies that applied computer-simulation models to study data from Surveillance, Epidemiology, and End Results (SEER) or ERSPC estimated that 23 to 50 percent of prostate cancer diagnoses were likely overdiagnosed [23-25]. The risk of overdiagnosis of prostate cancer appears to increase with increasing age [26]. A systematic review estimated that the percentages of screening detected cancers that were overdiagnosed was 20.7 percent in the PLCO and 50.4 percent in the ERSCP, respectively [27].

False-positive PSA — In addition to potential overdiagnosis, some abnormal PSA results are false positives; no cancer will be found on follow-up evaluation. While such patients don't incur risks of therapy, they may have anxiety about their test result and/or they may incur risks related to prostate biopsy. The false-positive rate depends in part on the patient's baseline risk as well as the threshold chosen for PSA interpretation. (See 'PSA interpretation' below.)

Anxiety — Receiving a diagnosis of prostate cancer is psychologically distressing, whether it is at an early stage or at an advanced stage. Anticipating treatments and their potential side effects, as well as dealing with the side effects if they occur, may lead to anxiety.

Even patients with a biopsy result that is negative for prostate cancer may develop anxiety, since a negative result cannot completely rule out prostate cancer due to the false-negative biopsy rate [28-30]. This is described separately. (See "Interpretation of prostate biopsy", section on 'Issues related to sampling error'.)

Risks of prostate cancer therapy — Screening that results in a diagnosis of prostate cancer may lead to therapy that carries substantial risks. For example, undergoing radical prostatectomy or radiation therapy has risks for immediate complications (eg, operative mortality, urinary symptoms) as well as for long-term sequelae (eg, urinary incontinence,

impotence, and bowel dysfunction); these adverse effects are common and are described in detail separately. (See "Radical prostatectomy for localized prostate cancer", section on 'Complications and quality of life' and "External beam radiation therapy for localized prostate cancer", section on 'Complications'.)

APPROACH TO SCREENING

Shared decision-making — We engage in shared decision-making about prostate cancer screening. Although the randomized trials of screening all have important methodological limitations, the best available evidence suggests that screening confers a small absolute benefit for reducing prostate cancer mortality and the risk of developing metastatic disease. However, the potential harms from screening that arise from false-positive tests (eg, prostate biopsy, anxiety, overdiagnosis, and treatment complications) are common. (See 'Benefits and harms of screening' above.)

We encourage shared decision-making because it is not appropriate for clinicians to determine how a patient should weigh these potential outcomes. Patients are encouraged to decide for themselves whether the benefits of screening outweigh the harms. Patients and clinicians should engage in shared decision-making when initially discussing screening as well as during subsequent screening discussions (whether the patient has agreed or declined to be screened in the past) [7,27,31-37]. (Related Pathway(s): Prostate cancer: Screening.)

For men at average risk, many clinicians do not specifically advise in favor of or against screening. Other experts may advise screening, particularly for men at higher risk for prostate cancer. Shared decision-making is essential with either approach.

Points that may be useful in shared decision-making discussions include [31,33,38]:

- Whether to have prostate cancer screening is a challenging decision for eligible men; there are both potential benefits and harms.
    - Prostate cancer is one of the most frequently diagnosed cancers and a leading cause of cancer death in men.
    - Prostate cancer screening may reduce the chance of dying from prostate cancer. However, the absolute benefit is small. Most men who choose not to be screened with a prostate-specific antigen (PSA) test will not be diagnosed with prostate cancer and will die from some other cause. Although some of these unscreened men will die from

prostate cancer, the lifetime risk of death in the United States due to prostate cancer is <3 percent [11].

- Screening is done with a PSA test, which can be repeated every one to two years.
  - The PSA test is not a test specifically for cancer. It may be abnormal even if there is no prostate cancer, and it may be normal even if there is prostate cancer.
  - Sometimes, additional tests may be done to assess the likelihood that an elevated PSA is due to prostate cancer. If the tests suggest a low likelihood of prostate cancer, the man may choose to avoid having a biopsy and instead have periodic follow-up.
- A prostate biopsy is needed to determine whether prostate cancer is present.
  - Biopsies can rarely cause serious infections or other complications.
  - Even if a man has a prostate cancer, a prostate biopsy may miss finding it.
- Patients who choose to be screened with a PSA test are much more likely than those who decline PSA screening testing to be diagnosed with prostate cancer.
  - Many prostate cancers detected by screening are considered "overdiagnosed," meaning that they never would have caused problems during a man's lifetime. Most men with prostate cancer will die from other causes, not from prostate cancer.
  - No available tests can accurately determine which men with a prostate cancer found by screening have a cancer that is destined to cause health problems and would be most likely to benefit from aggressive treatment.
  - Surgery and radiation therapies are the treatments most commonly offered to try to cure prostate cancer. These treatments can lead to problems with urinary incontinence, sexual dysfunction (eg, impotence), and bowel problems (eg, diarrhea). (See 'Risks of prostate cancer therapy' above.)

Online patient decision aids are available at American Cancer Society (ACS), American Society of Clinical Oncology (ASCO), and US Centers for Disease Control and Prevention (CDC).

Decision aids may help patients to make informed decisions about whether to be screened for prostate cancer, but their use does not clearly impact screening rates [39-42]. Systematic reviews have concluded that decision aids improve patient knowledge, increase participation in decision-making, decrease decisional conflict about screening, and make patients more confident about their decisions [41,42]. One meta-analysis found that decision aids were

associated with a somewhat lower rate of screening (relative risk [RR] 0.88, 95% CI 0.81-0.97) [41], whereas a more recent analysis found that screening rates were similar with and without the use of these aids (RR 0.96, 95% CI 0.88-1.03) [42]. Most included studies used decision aids developed before publication of mortality results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trials and before guidelines routinely recommended active surveillance for men with a low-risk prostate cancer; thus, studies evaluating updated decision aids are needed [42].

The use of prostate cancer risk calculators is discussed elsewhere. (See "Risk factors for prostate cancer", section on 'Using risk factors to estimate prostate cancer risk'.)

Age to begin discussing screening — There is some variability in recommendations by expert groups about the age to begin discussing screening for prostate cancer with men.

Assessing risk for prostate cancer — We use race, age, and family history to identify whether a man is at higher or average risk for prostate cancer. (See "Risk factors for prostate cancer".)

We do not stratify risk by obtaining a one-time measurement of PSA in men younger than age 50 years, although some experts do

Risk-adjusted approach

- **Average-risk men** – We suggest initiating discussion of screening for prostate cancer at age 50 years for average-risk men as long as life expectancy is at least 10 years. (Related Pathway(s): Prostate cancer: Screening.)

  There is some variability in the age at which expert guidelines recommend initiating discussion about screening for prostate cancer, mostly at age 50 or 55 years or, less commonly, age 45 years [7,31,33,35-37,43].

- ***BRCA* carriers** – Men known or likely to carry *BRCA1 or BRCA2* genetic mutations are at increased risk. Discussing screening for prostate cancer may begin as early as age 40 years, depending in part on the specific mutation, although data on the effectiveness of early screening are limited. Recommendations vary and are discussed separately. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Management of male BRCA1/2 carriers without cancer'.)

- **Lynch syndrome (hereditary nonpolyposis colorectal cancer)** – Men with Lynch syndrome appear to be at increased risk for prostate cancer [44]. A screening study of men ages 40 to 69 found that *MSH2* and *MSH6* carriers had a higher incidence of prostate cancer than non-carrier controls [45]. Discussing screening for prostate cancer

may begin as early as age 40 years, depending in part on the specific mutation, although data on the effectiveness of early screening are limited. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

- **Other higher-risk men** – We suggest initiating discussion of screening at age 40 to 45 years with other men at higher risk for prostate cancer, including [31,46-48]:

  - Black men
  - Men with a family history of prostate cancer, particularly in a first-degree relative who was diagnosed at age <65 years

  Men at higher risk may be more likely to benefit from screening. However, there is relatively little evidence addressing this, and these men should be informed that the potential benefits and risks of early screening are uncertain. (See 'Shared decision-making' above.)

  Among professional organizations, ACS guidelines recommend beginning screening discussions at age 40 to 45 in patients at high risk of developing prostate cancer (eg, Black men and men with a first-degree relative with prostate cancer diagnosed before age 65) [31]. The US Preventive Services Task Force (USPSTF) concluded evidence was insufficient to make a specific recommendation regarding screening discussions for these higher-risk groups, and the American Urological Association (AUA) indicates that decisions should be individualized for higher-risk men ages 40 to 54 years [7,49].

Screening with prostate-specific antigen

PSA testing — For men who choose prostate cancer screening, we suggest screening with a PSA blood test alone. Digital rectal examination (DRE) is generally not used as a screening test for prostate cancer, either alone or in combination with a PSA test. (See 'Digital rectal examination' below.)

Studies have estimated that PSA elevations may precede clinical manifestations of prostate cancer by 5 to 10 or more years [25,50,51].

However, PSA may also be elevated in the absence of prostate cancer in men with ongoing benign conditions (eg, benign prostatic hyperplasia [BPH]) or transient conditions (eg, prostatitis) (table 1). (See "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia" and "Acute bacterial prostatitis".)

PSA testing is discussed in detail separately. (See "Measurement of prostate-specific antigen".)

Reasons to temporarily defer PSA testing — Certain factors may transiently elevate PSA enough to affect its performance as a screening test. In the presence of any of these factors, it is appropriate to temporarily defer PSA screening long enough for a transient PSA elevation to resolve [52]:

- Symptoms suggesting bacterial prostatitis; defer PSA testing until six to eight weeks after symptoms resolve
- Acute urinary retention or urethral instrumentation; defer PSA testing for at least two weeks
- Recent prostate biopsy or transurethral resection of the prostate (TURP); defer PSA testing for at least six weeks

  The relationship between a PSA result and each of these conditions is discussed separately. (See "Measurement of prostate-specific antigen".)

Additionally, a patient who is repeating a PSA test to evaluate a result that was close to a cutoff that could prompt urologic evaluation should abstain for at least 48 hours from activities that can transiently increase PSA levels (eg, ejaculation or bicycling).

If DRE was performed, PSA can be measured immediately afterwards because DRE leads to only minimal transient PSA elevations of 0.26 to 0.4 ng/mL [53,54].

In men with symptomatic benign prostatic hypertrophy, measurement of PSA does not need to be deferred while treatment is provided to improve BPH symptoms, unless the patient has had TURP within the past six weeks.

Frequency of PSA testing — For patients who choose to undergo PSA screening, some experts suggest repeating PSA testing every two years until it is appropriate to discontinue screening, whereas other experts repeat PSA testing annually. Studies that show a potential benefit of screening with PSA studied programs that screened regularly at intervals of one to a few years. A large study in the United Kingdom failed to show a mortality benefit for a one-time screening PSA test [55].

Compared with one-time screening, serial PSA testing increases the overall sensitivity. Serial screening also increases the likelihood that detected tumors will be clinically organ-confined and be moderately or well differentiated, thus more amenable to successful treatment [56-58]. As an example, in the ERSPC with a four-year screening interval, the proportion of clinical stage I and II cancers increased from 81.5 during the first round to 96.3 percent during the second round, and the proportion of poorly differentiated cancers decreased from 8.1 to 3.3 percent [57].

With each round of PSA testing, detection rates for prostate cancer and positive predictive values of a PSA test decline substantially [56,57,59,60]. With screening at a four-year interval in the ERSPC, the cancer detection rate for PSA decreased from 5.1 percent in the first round of screening to 4.4 percent in the second round, and the positive predictive value (PPV) for a PSA ≥3.0 ng/mL decreased from 29.2 to 19.9 percent [57].

Two- versus four-year screening intervals appeared to have similar efficacy in detecting potentially life-threatening cancers in one nonrandomized study. Although the overall 10-year incidence of prostate cancer was higher with a two-year versus a four-year interval (13.1 versus 8.4 percent), the cumulative rates of aggressive cancers were similar and low in both groups (0.11 versus 0.12 percent); follow-up was not long enough to compare mortality rates [61]. However, potentially important differences between the patients and screening methods at the two study centers limit the strength of this nonrandomized comparison of screening intervals.

An alternative strategy is to adjust the frequency of testing based on the prior PSA result, with less frequent retesting in men with lower initial PSA levels (eg, ≤1.0 ng/mL) and annual testing in those with higher PSA levels that are still below a cutoff for biopsy [62-64]. This strategy is supported by the observation that men with an initial PSA <1 ng/mL had low rates of conversion (0.9 to 1.5 percent) over five years to higher PSA rates (>3 to 4 ng/mL) in the PLCO and ERSPC studies [62,63]. Cancer detection rates over four to five years were also low (0.12 and 0.15 percent) in this subgroup. For the relatively few patients who did have cancer, the four-year screening interval was estimated to result in a delay in cancer diagnosis of 15.6 months [64]. The clinical consequences of delayed diagnosis on prostate cancer mortality and morbidity are unknown, although the majority of cancers detected after a four-year screening interval in the ERSPC were early-stage [15].

Expert guidelines vary as to screening interval recommendations. The AUA states that a screening interval of two years may be preferred to annual screening [48]. Some guidelines suggest that screening intervals be individualized based on a baseline PSA level. The range of adjustments varies among guidelines (from annual to every two, three, or four years) based on the prior PSA level [31,43].

Discontinuing screening — There is general agreement about not screening men who have substantial comorbidities that limit life expectancy to less than 10 years. There is less consensus about a precise age at which to discontinue screening.

- **Life expectancy** – We do not screen men for prostate cancer who have a life expectancy of <10 years. Screening is unlikely to benefit these men given the generally indolent course of prostate cancer.

Professional society guidelines generally recommend not screening men who have less than 10-year [31,34] or 10- to 15-year [33,49] life expectancy.

- **Age** – For men with a life expectancy of at least 10 years, most clinicians offer screening up to age 70 years; some may continue screening until age 75 years if the patient desires it. Among guidelines, the suggested age to discontinue screening for prostate cancer varies from 69 to 75 years [7,33,35,36,43,49]. Actuarial tables suggest that among men in average health, only those ages 75 and younger have a 10-year life expectancy.

  Other data suggest that stopping screening in individuals as young as 65 years may be appropriate. An analysis found that discontinuing PSA testing at age 65 for men with PSA levels 0.5 ng/mL or less would still identify all cancers that would have been detected by age 75 [65]. Further, a decision analysis using Medicare data found that aggressive treatment of prostate cancer in men age 70 years and older would decrease the quality-adjusted life expectancy [66].

INTERPRETATION AND FOLLOW-UP OF PSA RESULTS

Correction for 5-alpha reductase inhibitor — If the patient takes a 5-alpha reductase inhibitor (ARI]) such as finasteride or dutasteride, a correction factor must be applied to a prostate-specific antigen (PSA) result for accurate interpretation, because ARIs are known to lower PSA results. The Prostate Cancer Prevention Trial (PCPT) found that men with a rising PSA level while on a 5 mg dose of finasteride for more than five years were at increased risk, compared with those with a stable or decreasing level, for being diagnosed with high-grade (Gleason 7 to 10) prostate cancer [67]. Only 5.6 percent of cancers were high-grade and 80.2 percent were found by end-of-study biopsies among men who did not have elevated PSA levels or abnormal digital rectal examination (DRE). The Reduction by Dutasteride in Prostate Cancer Events (REDUCE) trial, which enrolled men following a negative prostate biopsy, found that men whose PSA increased from a nadir at six months were at increased risk for being diagnosed with a Gleason 8 to 10 prostate cancer [68]. However, the incidence of these high-risk cancers was only 0.9 percent, and many were found at the 48-month end-of-study biopsy. Risk began rising when PSA increased >0.5 ng/mL compared with men whose PSA did not increase. (See "Measurement of prostate-specific antigen", section on 'Medications'.)

PSA interpretation — We use a PSA value of ≥4.0 ng/mL on a screening test (after applying a correction factor of 2.0 to the PSA result if the patient is using an ARI) to determine if further evaluation for prostate cancer is warranted. (See "Measurement of prostate-specific antigen".)

A PSA of ≥4.0 ng/mL has been the most widely accepted standard to balance tradeoffs between sensitivity and specificity. However, there is no single PSA value that avoids missing important cancers at a curable stage, avoids false-positives and detection of clinically insignificant disease, and avoids subjecting men to unnecessary prostate biopsies. A systematic review estimated that the PSA cutoff of 4.0 ng/mL had a sensitivity of 21 percent with specificity of 91 percent for detection of any prostate cancer; for detection of a high-grade cancer, sensitivity was 51 percent [31]. The low sensitivity means that some men with PSA levels <4 ng/mL will have prostate cancer. In the PCPT, 15.2 percent of men with PSA levels <4 ng/mL annually for seven years were found to have prostate cancer on end-of-study biopsy; 1.6 percent had high-grade prostate cancer [69].

Lowering the PSA cutoff improves test sensitivity somewhat. A PSA cutoff of 3.0 ng/mL had a sensitivity of 32 percent for detection of any prostate cancer; for detection of a high-grade cancer, sensitivity was 68 percent [31]. Among those with PSA between 2.1 and 4.0 ng/mL, prostate cancer was found in 24.7 percent (167 of 675 men) and 3.5 percent (four men) had high-grade cancers. Even a PSA cutoff as low as 1.1 ng/mL would have missed 17 percent of cancers, including 5 percent of the high-grade cancers [70].

However, lowering the PSA cutoff worsens specificity and overdiagnosis. A PSA cutoff of 3.0 ng/mL has a specificity of about 85 percent for detection of any prostate cancer [31]. It has been projected that if the PSA cutoff was lowered to 2.5 ng/mL, the number of men whose PSA is defined as abnormal would double to up to six million in the United States [71]. Additionally, many of the cancers that would be detected at these lower PSA levels may never have become clinically evident, so detecting them by using a lower PSA cutoff would lead to overdiagnosis and overtreatment [72]. (See 'Overdiagnosis of prostate cancer' above.)

Raising the PSA cutoff value increases the positive predictive value (PPV) for prostate cancer but lowers the likelihood that the cancer is organ-confined, thus potentially curable. For any PSA >4.0 ng/mL, the overall PPV for prostate cancer is approximately 30 percent [31]. However, for a PSA of 4.0 to 10.0 ng/mL, just somewhat above the cutoff, PPV is approximately 25 percent and nearly 75 percent of cancers are organ-confined [73]. With a higher cutoff of PSA >10 ng/mL, PPV increases to 42 to 64 percent, but less than 50 percent of cancers are organ-confined.

Some experts use age-specific reference ranges for PSA, rather than using the same cutoff for all ages. PSA levels generally increase with age, in part because older men are more likely to have a benign enlarged prostate producing larger amounts of PSA. However, there are limited data to support exact reference values for age cohorts.

There are several limitations to determining the accuracy of PSA screening. Most men with normal PSA values have not undergone biopsy unless they had a DRE that was abnormal; this workup bias leads to overestimating sensitivity and underestimating specificity of PSA to detect prostate cancer. Another limitation is the lack of consensus about which cancers are clinically important; PSA detects clinically unimportant cancers as well as important ones. Additionally, the false-negative rate of biopsy may have been as high as 10 to 20 percent in studies with <12 samples per prostate biopsy [74,75].

Referral to urology — Indications for a urology referral include:

- **PSA ≥4.0 ng/mL** – We refer patients for urology evaluation if the PSA is ≥4.0 ng/mL. Prior to referral, if the PSA is between 4.0 and 7.0 ng/mL, we repeat the testing in six to eight weeks, because PSA may be transiently elevated by certain modifiable benign factors (and any identified factors should be addressed prior to repeating the PSA test) (see 'Reasons to temporarily defer PSA testing' above). Some experts refer patients if the PSA level is ≥4.0 ng/m without first repeating a modestly elevated PSA.

- **Rise in PSA while on 5-alpha reductase inhibitor** – A patient taking finasteride or dutasteride for benign prostatic hyperplasia (BPH) with a confirmed PSA level rise >0.5 ng/mL (over any time frame) should be considered for urology referral.

- **Abnormal DRE** – Although we do not suggest DRE for screening, if DRE is performed, men with nodules, induration, or asymmetry on prostate examination should be referred to a urologist for evaluation, regardless of the serum PSA level. However, symmetric enlargement and firmness of the prostate are frequent in men with BPH and do not typically warrant urologic evaluation unless the PSA is elevated or there are other concerns. (See "Risk factors for prostate cancer" and "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia".)

Referral for urologic evaluation will not necessarily result in a prostate biopsy. Other tests (eg, free to total PSA ratio [f/T PSA], PCA3, 4Kscore test, and/or magnetic resonance imaging [MRI]) may be done by the urologist to help determine the likelihood that the PSA is elevated due to prostate cancer, the PSA may be followed over time, or a biopsy may be performed. Relevant considerations include the patient's health status, clinical likelihood for harboring significant disease, and personal wishes. (See "Clinical presentation and diagnosis of prostate cancer", section on 'Urologic evaluation'.)

METHODS NOT GENERALLY USED FOR SCREENING

Digital rectal examination — We suggest not performing digital rectal examination (DRE) for prostate cancer screening either as an adjunct to prostate-specific antigen (PSA) testing or as a standalone test.

DRE has low sensitivity and specificity for detecting prostate cancer. In one meta-analysis, DRE performed by primary care clinicians had an estimated sensitivity of 51 percent, a specificity of 59 percent, and a calculated overall positive predictive value (PPV) of 41 percent [76]. However, the quality of evidence was very low and there was substantial heterogeneity across studies. Additionally, urologists have been found to have relatively low interrater agreement for detecting prostate abnormalities [77].

The low sensitivity is due in part to the fact that DRE only detects palpable abnormalities in the posterior and lateral aspects of the prostate gland. Although this is where the majority of cancers arise, other areas of the prostate where cancer occurs are not reachable by a finger examination. Furthermore, about a third of cancers detected by DRE alone are clinically or pathologically advanced [73,78] compared with less than 10 percent detected by PSA screening [79]. Stage T1c prostate cancers, the majority of screen-detected cancers, are nonpalpable by definition.

Although DRE and PSA are somewhat complementary and their combined use may increase the overall rate of cancer detection, DRE has limited utility as an adjunctive test. In a multicenter screening study of 6630 men, the prostate cancer detection rate was 3.2 percent for DRE, 4.6 percent for PSA, and 5.8 percent for the two methods combined [73,78]. Just 18 percent of cancers were detected only by DRE. In another study, the PPV of a suspicious DRE with a normal PSA level was 10 percent, whereas the PPV for a normal DRE with an elevated PSA level was 24 percent [80]. Among men with a normal PSA level, abnormalities on DRE appeared less likely to be from a cancer if the PSA concentration was below 1.0 ng/mL than if the PSA concentration was between 3.0 to 4.0 ng/mL.

Most specialty society guidelines do not suggest DRE for screening, although some [31,37,43] include DRE either to evaluate an elevated PSA, or as an option along with PSA testing.

Other tests — We do not routinely use any other testing or test interpretation strategies either for screening or for deciding which men to refer for urologic evaluation for an elevated PSA.

We do not use either the absolute change in PSA or the PSA velocity (ie, the rate of change of PSA over time) to determine whether to refer a patient who is not taking a 5-alpha reductase inhibitor (ARI) (see 'Referral to urology' above). PSA increases more rapidly in men with prostate cancer than in healthy men. However, PSA velocity adds little predictive information to PSA

alone [81-87]. (See "Clinical presentation and diagnosis of prostate cancer", section on 'Evaluation'.)

Other methods have been developed to try to differentiate between higher-risk cancers and low-risk, indolent cancers. However, the clinical utility of these strategies is uncertain, there is no consensus on using any of these tests, and additional studies for clinical effectiveness are needed. The American Urological Association (AUA) guideline noted the lack of evidence for using any tests other than PSA to determine the need for a referral for biopsy [49]. (See "Measurement of prostate-specific antigen", section on 'Advances in PSA testing' and "The role of magnetic resonance imaging in prostate cancer", section on 'Clinical applications'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Screening for prostate cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Prostate cancer screening (PSA tests) (The Basics)")
- Beyond the Basics topics (see "Patient education: Prostate cancer screening (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Benefits and harms of screening** – The best available evidence from randomized trials found that screening has at most a small benefit in reducing prostate cancer mortality and the risk of developing metastatic disease.

  The potential benefits of screening must be balanced against the potential harms to quality of life, including the risks of false-positive tests, prostate biopsy, anxiety, overdiagnosis, and treatment complications. (See 'Benefits and harms of screening' above.)

- **Shared decision-making for most patients** – For average-risk men, many clinicians do not specifically advise in favor of or against screening. Men who are candidates for screening should be engaged in shared decision-making about whether they choose to be screened. Individual patient preferences for specific health outcomes are a deciding factor in determining whether to screen for prostate cancer. Decision aids may help patients receive consistent, complete, objective information. (See 'Shared decision-making' above.)

- **Age to begin screening** – The age to initiate discussion about prostate cancer screening depends on the patient's risk for prostate cancer. We use race, age, and family history to identify whether a man is at higher or average risk for prostate cancer. (See 'Age to begin discussing screening' above.)

  - In average-risk men, we initiate discussion of screening at age 50 years. (See 'Age to begin discussing screening' above.)

  - Men known or likely to carry *BRCA1* or *BRCA2* genetic mutations or Lynch syndrome genetic mutations are at increased risk. Initiating screening discussions for prostate cancer may begin as early as age 40 years, depending in part on the specific mutation, although data on the effectiveness of early screening are limited. Recommendations vary and are discussed separately. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Management of male BRCA1/2 carriers without cancer' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

  - For other men at higher risk for prostate cancer, including Black men and men with a family history of prostate cancer, we suggest initiating discussion of screening at age 40 to 45 years. (See 'Age to begin discussing screening' above.)

- **Screening with prostate-specific antigen -** If a decision is made to screen for prostate cancer, prostate-specific antigen (PSA) testing alone is the most appropriate test for screening. We suggest a screening interval of one to two years. For most patients, we offer screening up to age 70 years, stopping earlier if comorbidities limit life expectancy to less than 10 years. (See 'Discontinuing screening' above.)

- **Interpretation and follow-up of abnormal findings -** A patient with an abnormal PSA value should be referred to urology for further evaluation. (See 'Referral to urology' above.)

  - Men with a PSA level above 7 ng/mL should be referred, without further testing, to a urologist for evaluation.

  - For men with a PSA level between 4 and 7 ng/mL (inclusive of both values), we repeat the PSA testing in six to eight weeks. Factors known to transiently increase PSA should be addressed prior to repeating the PSA test (see 'Reasons to temporarily defer PSA testing' above). Men with a repeat PSA level ≥4 ng/mL should be referred to a urologist for evaluation.

  - For a man being screened for prostate cancer who is taking a 5-alpha reductase inhibitor (ARI) for benign prostatic hyperplasia (BPH), the PSA result needs to be corrected prior to interpretation (see 'Correction for 5-alpha reductase inhibitor' above). Additionally, a man taking finasteride or dutasteride for BPH with a confirmed PSA level rise >0.5 ng/mL (over any time frame) should be considered for urology referral. (See 'Referral to urology' above.)

  - We do not perform digital rectal examination (DRE) as part of screening (see 'Digital rectal examination' above). However, if a DRE is performed, men with a nodule, induration, or asymmetry on prostate examination should be referred to a urologist, regardless of the PSA result. (See 'Referral to urology' above.)

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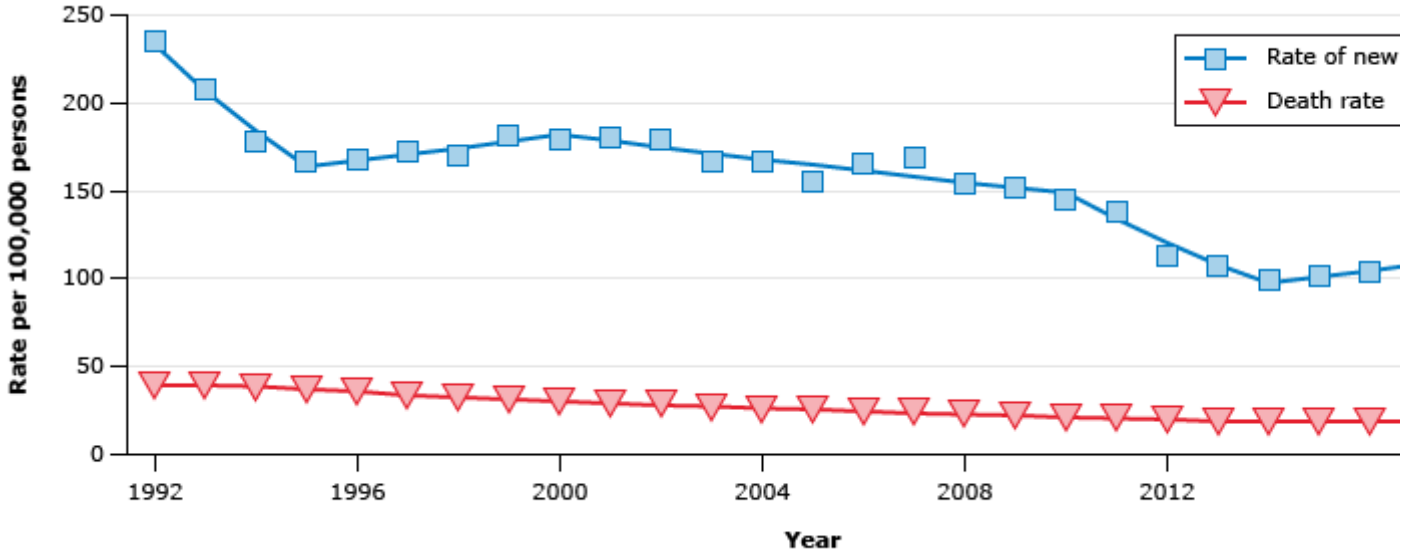
Topic 7567 Version 99.0

GRAPHICS

Prostate cancer: Changes over time in average annual age-adjusted incidence a mortality rates in the United States, 1992 to 2018



Incidence of prostate cancer in the United States (US) during the widespread use of screening with prostate-specific antigen (PSA). New cases come from SEER 9 Incidence. Deaths come from US mortality, 1992 to 201 races, males. Rates are age-adjusted. Modeled trend lines were calculated from the underlying rates using t Joinpoint Trend Analysis Software.

Reproduced from: Cancer Stat Facts: Prostate Cancer. Surveillance Epidemiology and End Results (SEER) Program. National Cancer Ins Available at: https://seer.cancer.gov/statfacts/html/prost.html (Accessed on March 22, 2021).

Graphic 75684 Version 12.0

Benign causes for an elevated PSA

Benign prostatic hyperplasia
Acute prostatitis
Subclinical inflammation
Prostate biopsy
Cystoscopy
TURP
Urinary retention
Ejaculation
Perineal trauma
Prostatic infarction

PSA: prostate-specific antigen; TURP: transurethral resection of the prostate.

Graphic 79754 Version 3.0

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Conflict of interest policy