Prostate Cancer Screening (PDQ®)
Health Professional Version

PDQ Screening and Prevention Editorial Board.
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This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about prostate cancer screening. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

This summary is reviewed regularly and updated as necessary by the PDQ Screening and Prevention Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Overview

Note: Separate PDQ summaries on Prostate Cancer Prevention, Prostate Cancer Treatment, and Levels of Evidence for Cancer Screening and Prevention Studies are also available.

Inadequate Evidence of Benefit Associated With Screening for Prostate Cancer Using Prostate-Specific Antigen (PSA) or Digital Rectal Exam (DRE)

The evidence is insufficient to determine whether screening for prostate cancer with prostate-specific antigen (PSA) or digital rectal exam (DRE) reduces mortality from prostate cancer. Screening tests are able to detect prostate cancer at an early stage, but it is not clear whether this earlier detection and consequent earlier treatment leads to any change in the natural history and outcome of the disease. Observational evidence shows a trend toward lower mortality for prostate cancer in some countries, but the relationship between these trends and intensity of screening is not clear, and associations with screening patterns are inconsistent. The observed trends may be due to screening, or to other factors such as improved treatment.[1] Results from two randomized trials showed no effect on mortality through 7 years but are inconsistent beyond 7 to 10 years.

Magnitude of Effect: Uncertain.

- **Study Design:** Evidence obtained from observational and descriptive studies (e.g., international patterns studies, time series).
- **Internal Validity:** Fair.
- **Consistency:** Poor.
- **External Validity:** Poor.

Harms

Based on solid evidence, screening with PSA and/or DRE results in overdiagnosis of prostate cancers, and detection of some prostate cancers that would never have caused significant clinical problems. Thus, screening leads to some degree of overtreatment. Based on solid evidence, current prostate cancer treatments, including radical prostatectomy and radiation therapy, result in permanent side effects in many men. The most common of these side effects are erectile dysfunction and urinary incontinence.[1-4] Screening also leads to false-positive findings, with sequelae involving unnecessary diagnostic procedures. In addition, the screening process itself can lead to adverse psychological effects in men who have a prostate biopsy but do not have identified prostate cancer.[5] Prostatic biopsies are associated with complications, including fever, pain, hematospermia/hematuria, positive urine cultures, and rarely sepsis.[6]
Magnitude of Effect: 20% to 70% of men who had no problems before radical prostatectomy or external-beam radiation therapy will have reduced sexual function and/or urinary problems.\[1\]

**Study Design:** Evidence obtained from cohort or case-control studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

References


Description of the Evidence

**Background**

**Incidence and mortality**

Prostate cancer is the most common cancer diagnosed in North American men, excluding skin cancers. It is estimated that in 2017, approximately 161,360 new cases and 26,730 prostate cancer–related deaths will occur in the United States. Prostate cancer is now the third leading cause of cancer death in men, exceeded by lung cancer and colorectal cancer. It accounts for 19% of all male cancers and 8% of male cancer-related deaths.\[1\] Age-adjusted incidence rates increased steadily from 1975 through 1992, with particularly dramatic increases associated with the inception of widespread use of prostate-specific antigen (PSA) screening in the late 1980s and early 1990s, followed by a fall in incidence. A decline in early-stage prostate cancer incidence rates from 2011 to 2012 (19%) in men aged 50 years and older persisted through 2013 (6%) in Surveillance, Epidemiology, and End Results (SEER) registries following the U.S. Preventive Services Task Force recommendations against routine PSA testing of all men, which were published in 2012. Whether this pattern will lead to an increase in diagnosis of distant-stage disease and prostate cancer mortality is not yet known and will require long-term follow-up.\[2\] Between 2007 and 2011, mortality rates decreased by 3.5% per year.\[3\] It has been suggested that declines in mortality rates in certain jurisdictions reflect the benefit of PSA screening,\[4\] but others have noted that these observations may be explained by independent phenomena such as improved treatments.\[5\] The estimated lifetime risk of a prostate cancer diagnosis is about 14.0%,\[3\] and the lifetime risk of dying from this disease is 2.6%.\[6\]

Cancer statistics from the American Cancer Society and the National Cancer Institute (NCI) indicated that between 2005 and 2011, the proportion of disease diagnosed at a locoregional stage was 93% for whites and 92% for African Americans; the proportion of disease diagnosed at a late stage was 4% for whites and 5% for African Americans.\[6\] Stage distribution of prostate cancer is affected substantially by the intensity of early detection efforts.

**Biology and natural history of prostate cancer**

The biology and natural history of prostate cancer is not completely understood. Rigorous evaluation of any prostate
cancer screening modality is desirable because the natural history of the disease is variable, and appropriate treatment is not clearly defined. Although the prevalence of prostate cancer and preneoplastic lesions found at autopsy steadily increases for each decade of age, most of these lesions remain clinically undetected.[7] An autopsy study of white and Asian men also found an increase in occult prostate cancer with age, reaching nearly 60% in men older than 80 years. More than 50% of cancers in Asian men and 25% of cancers in white men had a Gleason score of 7 or greater, suggesting that Gleason score may be an imprecise indicator of clinically insignificant prostate cancer.[8,9]

There is an association between primary tumor volume and local extent of disease, progression, and survival.[10] A review of a large number of prostate cancers in radical prostatectomy, cystectomy, and autopsy specimens showed that capsular penetration, seminal vesicle invasion, and lymph node metastases were usually found only with tumors larger than 1.4 mL.[11] Furthermore, the semiquantitative histopathologic grading scheme proposed by Gleason is reasonably reproducible among pathologists and correlates with the incidence of nodal metastases and with patient survival in a number of reported studies.[12]

Pathologic stage does not always reflect clinical stage and upstaging (owing to extracapsular extension, positive margins, seminal vesicle invasion, or lymph node involvement) occurs frequently. Of the prostate cancers detected by digital rectal exam (DRE) in the pre–PSA screening era, 67% to 88% were at a clinically localized stage (T1–2, NX, M0 [T = tumor size, N = lymph node involvement, and M = metastasis]).[13,14] However, in one series of 2,002 patients undergoing annual screening DRE, only one-third of men proved to have pathologically organ-confined disease.[14]

### Risk Factors

Prostate cancer is uncommonly seen in men younger than 50 years; the incidence rises rapidly each decade thereafter. The incidence rate is higher in African American men than in white men. From 2008 to 2012, the overall age-adjusted incidence rate was 214.5 per 100,000 for African American men and 130.4 per 100,000 for white men.[6] African American males have a higher mortality from prostate cancer, even after attempts to adjust for access-to-care factors.[15] Men with a family history of prostate cancer are at an increased risk of the disease compared with men without this history.[16,17] Other potential risk factors besides age, race, and family history of prostate cancer include alcohol consumption, vitamin or mineral interactions, and other dietary habits.[18-22] A significant body of evidence suggests that a diet high in fat, especially saturated fats and fats of animal origin, is associated with a higher risk of prostate cancer.[23,24] Other possible dietary influences include selenium, vitamin E, vitamin D, lycopene, and isoflavones. (Refer to the PDQ summary on Prostate Cancer Prevention for more information.) Evidence from a nested case-control study within the Physicians’ Health Study,[25] in addition to a case-control study[26] and a retrospective review of screened prostate cancer patients,[27] suggests that higher plasma insulin-like growth factor-I levels may be associated with a higher prostate cancer risk.[28] Not all studies, however, have confirmed this association.[29]

### Screening by Serum PSA

The PSA test has been examined in several observational settings for initial diagnosis of disease, as a tool in monitoring for recurrence after initial therapy, and for prognosis of outcomes after therapy. Numerous studies have also assessed its value as a screening intervention for the early detection of prostate cancer. Potential value of the test appears to be its simplicity, objectivity, reproducibility, relative lack of invasiveness, and relatively low cost. PSA testing has increased the detection rate of early-stage cancers, some of which may be curable by local-modality therapies, and others that do not require treatment.[30-33] The possibility of identifying an excessive number of false-positives in the form of benign prostatic lesions requires that the test be evaluated carefully. Furthermore, there is a risk of overdiagnosis and overtreatment (i.e., the detection of a histological malignancy that if left untreated would have had a benign or indolent natural history and would have been of no clinical significance). Randomized trials have therefore been conducted.

### Randomized trials of PSA screening

**The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial**

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial is a multicenter, randomized, two-armed trial designed to evaluate the effect of screening for prostate, lung, colorectal, and ovarian cancers on disease-specific...
mortality. From 1993 through 2001, 76,693 men at ten U.S. study centers were randomly assigned to receive annual screening (38,343 subjects) or usual care (38,350 control subjects). Men in the screening group were offered annual PSA testing for 6 years and DRE for 4 years. The subjects and health care providers received the results and decided on the type of follow-up evaluation. Usual care sometimes included screening, as some organizations have recommended.

In the screening group, rates of compliance were 85% for PSA testing and 86% for DRE. Self-reported rates of screening in the control group increased from 40% in the first year to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE.\[34\]

After 7 years of follow-up, with vital status known for 98% of men, the incidence of prostate cancer per 10,000 person-years was 116 (2,820 cancers) in the screening group and 95 (2,322 cancers) in the control group (rate ratio, 1.22; 95% confidence interval [CI], 1.16–1.29). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (ratio rate, 1.13; 95% CI, 0.75–1.70). The data at 10 years were 67% complete and consistent with these overall findings (incidence ratio rate, 1.17; 95% CI, 1.11–1.22 and mortality ratio rate, 1.11; 95% CI, 0.83–1.50). Thus, after 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups.\[34\]

Prostate cancer mortality data after 13 years of follow-up continued to show no reduction in mortality resulting from prostate cancer screening with PSA and DRE.\[35\] Organized screening in the intervention group of the trial did not produce a mortality reduction compared with opportunistic screening in the usual care group. There were 4,250 men diagnosed with prostate cancer in the intervention group and 3,815 men in the usual care group. Cumulative incidence rates were 108.4 per 10,000 person-years in the intervention group and 97.1 per 10,000 person-years in the usual care group (relative risk [RR], 1.12; 95% CI, 1.07–1.17). The cumulative prostate cancer mortality rates were 3.7 (158 deaths) per 10,000 person-years in the intervention group and 3.4 (145 deaths) per 10,000 person-years in the usual care group (RR, 1.09; 95% CI, 0.87–1.36).

There were no apparent associations with age, baseline comorbidity, or PSA testing before the trial as hypothesized in an intervening analysis by a subgroup analysis. These results are consistent with the previous report at 7 to 10 years of follow-up described above.\[34\] The update accounts for 76,685 men, aged 55 to 74 years, enrolled at 10 screening centers between November 1993 and July 2001 who were randomly assigned to either annual PSA screening for 6 years and DRE for 4 years (38,340 men) or usual care (38,345 men), which sometimes included opportunistic screening in local communities. All prostate cancer incidents and deaths through 13 years of follow-up or through December 31, 2009 were ascertained.\[35\]

The 13-year follow-up analysis reported 45% of men in the PLCO trial had at least one PSA test in the 3 years before randomization. PSA screening in the usual care arm was estimated to be as high as 52% by the end of the screening period. The intensity of PSA screening in the usual care group was estimated to be one-half of that in the intervention group. Stage-specific treatment between the two arms was similar.\[35\]

The following are several possible explanations for the lack of a reduction in mortality in this trial:\[34,36\]

- Annual screening with the PSA test using the standard U.S. threshold of 4 ng per mL and DRE to trigger diagnostic evaluation may not be effective.
- The substantial level of screening in the control group could have diluted any modest effect of annual screening in the intervention group.
- Approximately 44% of the men in each study group had undergone one or more PSA tests at baseline, which would have eliminated some cancers detectable on screening from the randomly assigned population; thus, the cumulative death rate from prostate cancer at 10 years in the two groups combined was 25% lower in those who had undergone two or more PSA tests at baseline than in those who had not been tested.
- Improvement in therapy for prostate cancer during the course of the trial may have resulted in fewer prostate-cancer deaths in the two study groups, which blunted any potential benefits of screening.
- After a PSA finding greater than 4.0 ng/mL, within 1 year only 41% of men underwent prostate biopsy; within 3 years of this finding, only 64% of men underwent prostate biopsy. Such lower biopsy rates, associated with lower prostate cancer detection rates, may have blunted the impact of screening on mortality.
The European Randomized Study of Screening for Prostate Cancer (ERSPC)

The ERSPC was initiated in the early 1990s to evaluate the effect of screening with PSA testing on death rates from prostate cancer. Through registries in seven European countries, investigators identified 182,000 men between the ages of 50 and 74 years for inclusion in the study. The men were randomly assigned to either a group that offered PSA screening at an average of once every 4 years or to a control group that did not receive screening. The predefined core age group for this study included 162,243 men between the ages of 55 years and 69 years. The primary outcome was the rate of death from prostate cancer. Mortality follow-up was identical for the two study groups and has been reported through 2010.[37]

Recruitment and randomization procedures differed among countries and were developed in accordance with national regulations. In Finland, Sweden, and Italy, the men in the trial were identified from population registries and were randomly assigned to the trials before written informed consent was provided. In the Netherlands, Belgium, Switzerland, and Spain, the target population was also identified from population lists, but when the men were invited to participate in the trial, only those who provided consent were randomly assigned.

In the screening group, 82% of men accepted at least one offer of screening. At a median follow-up of 9 years, there were 5,990 prostate cancers diagnosed in the screening group (a cumulative incidence of 8.2%) and 4,307 prostate cancers in the control group (a cumulative incidence of 4.8%). There were 214 prostate-cancer deaths in the screening group and 326 prostate cancer deaths in the control group in the core age group (RR, 0.80; 95% CI, 0.67–0.95). The rates of death in the two study groups began to diverge after 7 to 8 years and continued to diverge further over time.[38] With follow-up through 13 years, there were 7,408 prostate cancers in the intervention group during 775,527 person-years of follow-up and 6,107 cancers in the control group with 980,474 person-years of follow-up (RR, 1.57; 95% CI, 1.51–1.62). There were also 355 prostate cancer deaths over 825,018 person-years of follow-up in the intervention group and 545 deaths over 1,011,192 person-years of follow-up in the control group (RR, 0.79; 95% CI, 0.69–0.91). Consequently, 781 men needed to be invited for screening to avert one prostate cancer death.

Thus, PSA-based screening was reported to reduce the rate of death from prostate cancer by about 20% but was associated with a high risk of overdiagnosis.[37]

Important information that was not reported includes the contamination rate in the entire control group, and the treatment administered to the prostate cancer cases by stage and by randomly assigned group. Incompleteness of data is also a concern because it appears that several of the participating countries have not yet provided data beyond the 10-year point at which the major effect appears to occur. Longer follow-up will be needed to determine the final results of this trial.

The Finnish Randomized Screening Trial

The Finnish Randomized Screening Trial is the largest component of the multicenter ERSPC consortium. From the Finnish Population Registry, 80,144 men born between 1929 and 1944 were identified. Men with a previous prostate cancer diagnosis were excluded. Among these men, 31,866 were randomly assigned to the screening arm (SA) and the remaining 48,278 men were randomly assigned to the control arm (CA). Randomization occurred annually from 1996 to 1999 (at ages 55, 59, 63, or 67 years at entry, which led to a similar age distribution in both arms). Men randomly assigned to the CA were not contacted. Men randomly assigned to the SA were invited to an initial screen, and if living in the study area and not already diagnosed with prostate cancer, were invited to second and third screenings at 4 and 8 years after randomization. Men with a PSA of 4.0 ng/mL or higher were referred to a local urological clinic for diagnosis. Men with a PSA of 3.0 to 3.99 ng/mL were referred for further testing. Median follow-up in both arms was 10.8 years. The SA had a nonstatistically significant reduction in prostate cancer mortality, based on an analysis of those who were invited to be screened. The hazard ratio between trial arms was 0.85 (95% CI, 0.69–1.04; P = .10). No screening effect was seen in all-cause mortality. Treatment differed between the two arms within each risk category. In all risk categories, radical prostatectomy was more common in the SA (statistically significant at P < .05 for moderate- and high-risk cancers) and radiation and endocrine treatment were more common in the CA (statistically significant at P < .05 for radiation in the moderate-risk category and for both radiation and endocrine treatment in the high-risk category). It was unknown whether this affected mortality. Contamination in the CA was not measured.[39]

Possible harms included overdiagnosis, which was estimated at 30% on the basis of excess cases in the SA if the cumulative risk of prostate cancer had been the same as the CA.[39]
The Goteborg (Sweden) trial

The Goteborg trial is a prospective randomized trial of approximately 20,000 men born between 1930 and 1944. Data from participants born between 1930 and 1939 is used in the pooled ERSPC data. With up to 14 years of follow-up, 12.7% of participants were diagnosed with prostate cancer in the screening group versus 8.2% in the control group. The absolute risk of prostate death was 0.9% in the control group and 0.5% in the screening group (95% CI, 0.17–0.64). This is a 44% RR reduction in prostate-cancer mortality (95% CI, 0.28–0.68; \( P = .0002 \)). Of note, the number of deaths from all causes was equal in the intervention group and the control group.[40] With follow-up extended to 18 years, there were 1,396 men in the screening group (16% cumulative incidence) and 962 men in the control group (11% cumulative incidence). In the screening group, 79 men died of prostate cancer (0.98% cumulative mortality) compared with 122 prostate cancer deaths in the control group (1.5% cumulative mortality), a 35% relative reduction. The authors reported that 139 men needed to be invited for screening to avert one prostate cancer death.[41]

Unlike the other ERSPC centers, not all the participants in the Goteborg trial were included in the ERSPC study. Further, Sweden and the Netherlands are the only centers to report a screening benefit. Some have argued that the ERSPC trial should be treated as a meta-analysis.[42]

The Norrkoping (Sweden) study

The Norrkoping study is a population-based nonrandomized trial of prostate cancer screening. All men aged 50 to 69 years living in Norrkoping, Sweden in 1987 were allocated to either an invited group (every sixth man allocated to invited group) or a not-invited group. The 1,494 men in the invited group were offered screening every 3 years from 1987 to 1996. The first two rounds were by DRE; the last two rounds were by both DRE and PSA. About 85% of men in the invited group attended at least one screening; contamination by screening in the not-invited group (n = 7,532) was thought to be low. After 20 years of follow-up, the invited group had a 46% relative increase in prostate cancer diagnosis. Over the period of the study, 30 men (2%) in the invited group died of prostate cancer, compared with 130 (1.7%) men in the not-invited group. The RR of prostate cancer mortality was 1.16 (95% CI, 0.78–1.73). This nonstatistically significant finding provides no evidence that screening leads to a reduction in prostate cancer mortality, even after 20 years of follow-up.[43]

The Quebec (Canada) trial

In the randomized, prospective Quebec study, 46,486 men identified from the electoral rolls of Quebec City and its metropolitan area were randomly assigned to be either approached or not approached for PSA and DRE screening. A total of 31,133 men were randomly assigned to screening, while a total of 15,353 were randomly assigned to observation. (It appears that these men were unaware that they had been enrolled in a randomized clinical trial.) A notable difference from other screening studies was that a PSA of 3.0 ng/mL was used to determine whether further evaluation was warranted. In this study (in which the patient numbers have been variously reported by the authors), of the 31,133 men who were randomly assigned to screening, 7,348 actually underwent screening while 23,785 did not. Of the 15,353 who were randomly assigned to observation, 1,122 actually underwent screening while 14,231 did not. Among the 38,016 men who did not undergo screening, 217 deaths were noted, compared with only 11 deaths among the 8,470 men who underwent screening. Using an intention-to-treat analysis based on the study arm to which an individual was originally assigned, no difference in mortality was seen; there were 75 deaths among the 15,353 men who were randomly assigned to observation compared with 153 deaths among the 31,133 men randomly assigned to screening (RR, 1.085). Because of noncompliance, this study does not answer the question of whether early detection with PSA and DRE will reduce prostate cancer mortality.[44]

Treatment of Prostate Cancer

Because the efficacy of screening depends on the effectiveness of management of screen-detected lesions, studies of treatment efficacy in early-stage disease are relevant to the issue of screening. Treatment options for early-stage disease include radical prostatectomy, definitive radiation therapy, and watchful waiting (no immediate treatment until indications of progression are present, but treatment is not designed with curative intent). Multiple series from various years and institutions have been reported on the outcomes of patients with localized prostate cancer who received no treatment but were followed with surveillance alone. Outcomes have also been reported for active treatments, but valid comparisons of efficacy between surgery, radiation, and watchful waiting are seldom possible because of differences...
in reporting and selection factors in the various reported series.

A randomized trial in Scandinavian men published in 2002 explored the benefit of radical prostatectomy over watchful waiting in men with newly diagnosed, well-differentiated, or moderately well-differentiated prostate cancers of clinical stages T1b, T1c, or T2.[45] In this trial, 698 men younger than 75 years, most with clinically detected cancers (unlike most newly diagnosed patients in North America) were randomly assigned to the two-arm trial. After 5 years of follow-up, the difference in prostate cancer-specific mortality between radical prostatectomy and watchful waiting groups was 2%; after 10 years of follow-up, the difference was 5.3% (RR, 0.56; 95% CI, 0.36–0.88). There was also a difference of about 5% in all-cause mortality that was apparent only after 10 years of follow-up (RR, 0.74; 95% CI, 0.56–0.99). Thus, to extend one life, 20 men with palpable, clinically localized prostate cancer would need to undergo radical prostatectomy rather than watchful waiting. Because most prostate cancers that are detected today with PSA screening are not palpable, this study may not be directly generalizable to the average newly diagnosed patient in the United States.[46]

A Swedish retrospective study of a nationwide cohort of patients with localized prostate cancer aged 70 years or younger reported that 10-year prostate cancer-specific mortality was 2.4% among men diagnosed with clinically local stage T1a, T1b, or T1c, with a serum PSA of less than 10 ng/mL, and with a Gleason score of 2 to 6, referred to as low-risk cases, of which there were 2,686.[47] This subgroup analysis was derived from a cohort study of 6,849 men diagnosed between January 1, 1997 and December 31, 2002, aged 70 years or younger, who had local stage T1 to T2 with no signs of lymph node metastases or bone metastases, and a PSA serum level of less than 20 ng/mL, as was abstracted from the Swedish Cancer Registry, which captured 98% of solid tumors among men aged 75 years or younger. Cohort treatment options were surveillance (n = 2,021) or curative intent by radical prostatectomy (n = 3,399) or radiation therapy (n = 1,429), which were to be determined at the discretion of treating physicians. Surveillance or expectancy treatment was either active surveillance with curative treatment if progression occurred or watchful waiting—a strategy for administering hormonal treatment upon symptomatic progression. Using all-cause mortality as the benchmark, the study calculated cumulative incidence mortality for the three treatment groups of the entire cohort and the low-risk subgroup. Surveillance was more common among men with high comorbidity and among men with low-risk tumors. The 10-year cumulative risk of death from prostate cancer for the entire 6,849 person cohort was 3.6% in the surveillance group and 2.7% in the curative-intent group compared with the low-risk surveillance group (2.4%) and the low-risk curative-intent group (0.7%). Biases inherent in treatment assignment could not be accounted for adequately in the analysis, which prevented conclusions about the relative effectiveness of alternative treatments. However, a 10-year prostate cancer-specific mortality of 2.4% among patients with low-risk prostate cancer in the surveillance group suggested that surveillance may be a suitable treatment for many patients with low-risk disease compared with the 19.2% 10-year risk of death from competing causes observed in the surveillance group and 10.2% in the curative-intent group of the total 6,849 person cohort.[47]

The Prostate Intervention Versus Observation Trial (PIVOT) was the first trial conducted in the PSA screening era that directly compared radical prostatectomy with watchful waiting.[48] From November 1994 through January 2002, 731 men aged 75 years or younger with localized prostate cancer were randomly assigned to one of the two management strategies. About 50% of the men had nonpalpable, screen-detected disease. After a median follow-up of 10 years (maximum up to about 15 years), there was no statistically significant difference in overall or prostate-specific mortality. (Refer to the Treatment Option Overview section in the PDQ summary on Prostate Cancer Treatment for a more detailed description of the study and results.)

A second trial done in the PSA screening era, the Prostate Testing for Cancer and Treatment (ProtecT) study,[49] randomly assigned 1,643 men with localized prostate cancer equally to active monitoring, surgery, or radiation therapy. The primary endpoint was death from prostate cancer, and secondary outcomes were clinical (local) progression, metastases, and death from all causes. Active monitoring in this study, unlike the PIVOT and Scandinavian Prostate Cancer Group Trial 4 (SPCG-4) trials, used PSA levels to determine when more aggressive treatment would be administered. Within 9 months of randomization, compliance rates for the three groups were 88% for the monitoring group, 71% for the surgery group, and 74% for the radiation therapy group. By 10 years, 55% of men in the active monitoring group had undergone radical prostatectomy. Seventeen deaths occurred during the median 10 years of follow-up, and no significant differences were seen between the groups in prostate cancer-specific or all-cause mortality. More metastases ($P = .004$) and more disease progression ($P < .001$) were seen in the monitoring group. There were 62 cases of metastases and 204 cases of disease progression.
The results suggest that radical treatment has no effect on mortality, although the power to see cause-specific mortality effects was low. Avoidance of metastases or progression could be a rationale for more aggressive treatment, although another study [50] showed that active monitoring eliminated much of the pain and suffering caused by aggressive treatments.

In a substudy of ProtecT that examined patient-reported outcomes, the response rate was over 85% for most of the questionnaires used to examine quality of life. The study addressed urinary, bowel, and sexual function, and specific effects of treatment on quality of life, anxiety and depression, and general health. No methods were employed to deal with nonresponse or missing responses. In a quality-of-life study, nonresponse tends to be informative, so this is unusual.[50]

Results showed that men who had undergone prostatectomy reported more impotence and incontinence; men who received radiation therapy reported more bowel dysfunction; and men who received active monitoring reported the lowest levels of these adverse effects. In general, differences decreased over the 6 years that data were collected. Overall, mental and physical health did not differ by treatment.[50]

**Methods to Improve the Performance of Serum PSA Measurement for the Early Detection of Prostate Cancer**

Various methods to improve PSA testing in early cancer detection have been developed (see below). The proportion of men who have abnormal PSA test results that revert to normal after 1 year is high (65%–83%, depending on the method).[51] This is likely because of a substantial biological or other variability in PSA levels in individual men. Several variables can affect PSA levels. Besides normal biological fluctuations that appear to occur,[51,52] pharmaceuticals such as finasteride (which reduces PSA by approximately 50%) and over-the-counter agents such as PC-SPES (an herbal agent that appears to have estrogenic effects) can affect PSA levels.[53,54] Some authors have suggested that ejaculation and DRE can also affect PSA levels, but subsequent examination of these variables have found that they do not have a clinically important effect on PSA.[55] Given this high variability, an elevated PSA should be confirmed by repeat testing before more invasive diagnostic tests are performed.

**Complexed PSA and percent-free PSA**

Serum PSA exists in both free form and complexed to a number of protease inhibitors, especially alpha-1-antichymotrypsin. Assays for total PSA measure both free and complexed forms. Assays for free PSA are available. Complexed PSA can be found by subtracting free PSA from the total PSA. Several studies have addressed whether complexed PSA or percent-free PSA (ratio of free to total) are more sensitive and specific than total PSA. One retrospective study evaluated total PSA, free/total, and complexed PSA in a group of 300 men, 75 of whom had prostate cancer. Large values of total, small values of free/total, and large values of complexed PSA were associated with the presence of cancer; the authors chose the cutoff of each measure to yield 95% sensitivity and found estimated specificities of 21.8% in total PSA, 15.6% in free/total PSA, and 26.7% in complexed PSA.[56] The preponderance of evidence concerning the utility of complexed and percent-free PSA is not clear; however, total PSA remains the standard.

A number of authors have considered whether complexed PSA or percent-free PSA in conjunction with total PSA can improve total PSA sensitivity. Of special interest is the gray zone of total PSA, the range from 2.5 ng/mL to 4.0 ng/mL. A meta-analysis of 18 studies addressed the added diagnostic benefit of percent-free PSA. There was no uniformity of cutoff among these studies. For cutoffs ranging from 8% to 25% (free/total), results ranged from about 45% sensitivity/95% specificity to 95% sensitivity/15% specificity.[57]

Percent-free PSA may be related to biologic activity of the tumor. One study compared the percent-free PSA with the pathologic features of prostate cancer among 108 men with clinically localized disease who ultimately underwent radical prostatectomy. Lower percent-free PSA values were associated with higher risk of extracapsular disease and greater capsular volume.[58] Similar findings were reported in another large series.[59]

**Third-generation PSA**

The third-generation (ultrasensitive) PSA test is an enzyme immunometric assay intended strictly (or solely) as an aid in the management of prostate cancer patients. The clinical usefulness of this assay as a diagnostic or screening test is
unproven.\[60,61\]

**PSA density**

Because larger prostates caused by increased amounts of transition-zone hyperplasia are known to be associated with higher serum PSA levels, reports have suggested indexing PSA to gland volume, using a measure known as PSA density. PSA density is defined as serum PSA divided by gland volume. Generally, ultrasound is used to measure gland volume. While early studies suggested that this measure may discriminate between patients with cancer and those with benign disease,\[62\] subsequent evaluations have failed to confirm any clinically useful association.\[63,64\]

**PSA density of the transition zone**

PSA density of the transition zone (serum PSA divided by the volume of the transition zone) has been suggested to better adjust for benign sources of PSA. One study prospectively evaluated 559 men with PSA levels between 4 ng/mL and 10 ng/mL. A total of 217 of these men were ultimately found to have prostate cancer; of all PSA variants analyzed, percent-free PSA and PSA density of the transition zone were found to have the best predictive values (area under the receiver operator curve value for percent-free PSA, 0.78; for PSA density, 0.83).\[65\] Another study also found that PSA density of the transition zone had superior performance characteristics. In this study of 308 volunteers undergoing first-time screening, it was reported that the combination of percent-free PSA (<20%) and PSA density of the transition zone resulted in elimination of 54.2% of biopsies that ultimately proved to be benign.\[66\]

**Age-adjusted PSA**

Many series have noted that PSA levels increase with age, such that men without prostate cancer will have higher PSA values as they grow older. One study examined the impact of the use of age-adjusted PSA values during screening and estimated that it would reduce the false-positive screenings by 27% and overdiagnosis by more than 33% while retaining 95% of any survival advantage gained by early diagnosis.\[67\] While age adjustment tends to improve sensitivity for younger men and specificity for older men, the trade-off in terms of more biopsies in younger men and potentially missed cancers in older men has prevented uniform acceptance of this approach.

**PSA velocity**

A study using frozen serum from 18 patients concluded that an annual rise of PSA level of 0.8% ng/mL warranted a prostate biopsy.\[68\] In a follow-up study that used serum collected serially from men without known prostate cancer (two groups with benign prostatic hyperplasia, one diagnosed by histology and the other clinically, both with PSA levels no higher than 10 ng/mL, and a third group with no more than one PSA exceeding 10 ng/mL), it was reported that averaging three PSA changes measured at 2-year intervals could be useful for cancer discrimination, while changes measured at 3-month or 6-month intervals were volatile and nonspecific, perhaps because of a biologic fluctuation of PSA that may be as high as 30%.\[52,69\] One study followed 1,249 men screened by PSA and concluded that patients with a 20% annual increase in their PSA level should undergo further evaluation.\[70\]

A study specifically tested whether total PSA velocity (tPSAv) improves the accuracy of total PSA level (tPSA) to predict long-term risk of prostate cancer. In the 1974 to 1986 Swedish Malmo Preventive Medicine cardiovascular risk study, 5,722 men younger than 51 years gave two blood samples about 6 years apart. Of the archived plasma samples, 4,907 were analyzed for tPSA. Prostate cancer was subsequently diagnosed in 443 (9%) of the men via the Swedish National Cancer Registry through December 31, 2003. Cox proportional hazards regression was used to evaluate tPSA and tPSAv as predictors of prostate cancer. Predictive accuracy was assessed by the concordance index (similar to the area under the receiver operating characteristic).\[71\]

The median time from the second blood draw to cancer diagnosis was 16 years. Median follow-up for men not diagnosed with prostate cancer was 21 years. PSA assays were done in plasma stored under conditions that preserved the integrity of PSA. tPSA and tPSAv were highly correlated. Both tPSA and tPSAv were associated with prostate cancer in univariate models ($p < .001$). Men subsequently diagnosed with prostate cancer had increased tPSA and increased tPSAv up to 20 years before diagnosis. Overall predictive accuracy of tPSA plus tPSAv was equivalent to tPSA alone (concordance index, 0.771 tPSA alone; 0.712 tPSAv alone; 0.771 tPSA added to tPSA). tPSAv did not aid long-term prediction of cancer in early middle-aged men.\[71\]

In the Prostate Cancer Prevention Trial (PCPT), full ascertainment was attempted, regardless of PSA value; PSA
velocity added no independent value to the prediction of prostate cancer after adjustment for family history, age, race/ethnicity, PSA, and history of prostate biopsy. For this reason, in the PCPT risk calculator, PSA velocity is not an included variable.[72]

**Alteration of PSA cutoff level**

A number of authors have explored the possibility of using PSA levels lower than 4.0 ng/mL as the upper limit of normal for screening examinations. One study screened 14,209 white and 1,004 African American men for prostate cancer using an upper limit of normal of 2.5 ng/mL for PSA. A major confounding factor of this study was that only 40% of those men in whom a prostate biopsy was recommended actually underwent biopsy. Nevertheless, 27% of all men undergoing biopsy were found to have prostate cancer.[73] Several collaborating European jurisdictions, including Rotterdam (the Netherlands) and Finland, are conducting prostate cancer screening trials. In Rotterdam, data for 7,943 screened men between the ages of 55 and 74 years have been reported. Of the 534 men who had PSA levels between 3.0 ng/mL and 3.9 ng/mL, 446 (83.5%) had biopsies and 96 (18%) of these had prostate cancer. In all, 4.7% of the screened population had prostate cancer.[74] In Finland, 15,685 men were screened and 14% of screened men had PSA levels of at least 3.0 ng/mL. All men with PSAs higher than 4.0 ng/mL were recommended for diagnostic follow-up by DRE, ultrasound, and biopsy; 92% complied, and 2.6% of the 15,685 men screened were diagnosed with prostate cancer. Of the 801 men with screening PSAs between 3.0 ng/mL and 3.9 ng/mL (all biopsied), 22 (3%) had cancer. Of the 1,116 men with screening PSAs between 4.0 ng/mL and 9.9 ng/mL, 247 (22%) had cancer; of the 226 men with screening PSAs of at least 10 ng/mL, 139 (62%) had cancer.[75] Several factors could have contributed to these differences, including background prostate cancer prevalence, background screening levels, and details regarding diagnostic follow-up practices; the necessary comparative data are not available.

Another study adopted a change in the PSA cutoff to a level of 3.0 ng/mL to study the impact of this change in 243 men with PSA levels between 3.0 ng/mL and 4.0 ng/mL. Thirty-two of the men (13.2%) were ultimately found to have prostate cancer. An analysis of radical prostatectomy specimens from this series found a mean tumor volume of 1.8 mL (range, 0.6–4.4). The extent of disease was significant in a number of cases, with positive margins in five cases and pathologic pT3 disease in six cases.[76]

**Population Observations of Early Detection, Incidence, and Prostate Cancer Mortality**

While DRE has been a staple of medical practice for many decades, PSA did not come into common use until the late 1980s for the early diagnosis of prostate cancer. Following widespread dissemination of PSA testing, incidence rates rose abruptly. In a study of Medicare beneficiaries, a first-time PSA test was associated with a 4.7% likelihood of a prostate cancer diagnosis within 3 months. Subsequent tests were associated with statistically significant lower rates of prostate cancer diagnosis.[77]

In an examination of trends of prostate cancer detection and diagnosis among 140,936 white and 15,662 African American men diagnosed with prostate cancer between 1973 and 1994 in the NCi's SEER database, substantial changes were found beginning in the late 1980s as use of PSA diffused through the United States; age at diagnosis fell, stage of disease at diagnosis decreased, and most tumors were noted to be moderately differentiated. For African American men, however, a larger proportion of tumors were poorly differentiated.[78]

Since the outset of PSA screening beginning around 1988, incidence rates initially rose dramatically and fell, presumably as the fraction of the population undergoing their first PSA screening initially rose and subsequently fell. There has also been an observed decrease in mortality rates. In Olmsted County, Minnesota, age-adjusted prostate cancer mortality rates increased from 25.8 per 100,000 men from 1980 to 1984 to a peak of 34 per 100,000 from 1989 to 1992; rates subsequently decreased to 19.4 per 100,000 from 1993 to 1997.[79] Similar observations have been made elsewhere in the world,[4,80] leading some to hypothesize that the mortality decline is related to PSA testing. In Quebec, Canada, however, examinations of the association between the size of the rise in incidence rates (1989–1993) and the size of the decrease in mortality rates (1995–1999), by birth cohort and residential grouping, showed no correlation between these two variables.[80] This study suggests that, at least during this time frame, the decline in mortality is not related to widespread PSA testing.

Cause-of-death misclassification has also been studied as a possible explanation for changes in prostate cancer mortality. A relatively fixed rate was found at which individuals who have been diagnosed with prostate cancer are mislabeled as dying from prostate cancer. As such, the substantial increase in prostate cancer diagnoses in the late
1980s and early 1990s would then explain the increased rate of prostate cancer death during those years. As the rate of prostate cancer diagnosis fell in the early 1990s, this reduced rate of mislabeling death due to prostate cancer would fall, as would the overall rate of prostate cancer death.[81] Since the evidence in this respect is inconsistent, it remains unclear whether the causes of these mortality trends are chance, misclassification, early detection, improved treatments, or a combination of effects.

The incidence of distant-stage prostate carcinoma was relatively flat until 1991 and then started declining rapidly. This decline probably was caused by the shift to earlier stage disease associated with the rapid dissemination of PSA screening. This stage shift can have a fairly sizable and rapid impact on population mortality, but it is possible that other factors such as hormonal therapy are responsible for much of the decline in mortality. Ongoing randomized clinical trials in the United States and Europe are designed to determine whether a mortality benefit is associated with PSA screening.[82]

The Gleason score is an important prognostic measure relying on the pathologic assessment of the architectural growth patterns of prostate biopsy. The Gleason grading system assigns a grade to each of the two largest areas of prostate cancer in the tissue samples. A sampling of eight or more biopsy cores improves the pathological grading accuracy.[83] Grades range from 1 to 5, with 1 being the most differentiated and 5 the least differentiated. Grade 3 tumors seldom have associated metastases, but metastases are common with grade 4 or grade 5 tumors. The two grades are added together to produce a Gleason score. A score of 2 to 4 is rarely given, 5 to 6 is low grade, 7 is intermediate grade, and 8 to 10 is high grade. The overall rate of concordance between original interpretations and review of the needle biopsy specimens has been reported to be 60%, with accuracy improving with increased tumor grade and percentage of tumor involvement in the biopsy specimen.[84]

As of 2005, approximately 90% of prostate cancers detected are clinically localized and have more favorable tumor characteristics or grades than the pre-PSA screening era.[85] A retrospective population-cohort study using the Connecticut Tumor registry reviewed the mortality probability from prostate cancer given the patient’s age at diagnosis and tumor grade.[86] Patients were treated with either observation or immediate or delayed androgen withdrawal therapy, with a median observation of 24 years. This study was initiated before the PSA screening era. Transurethral resection or open surgery for benign prostatic hyperplasia identified 71% of the tumors incidentally. The prostate cancer mortality rate was 33 per 1,000 person-years during the first 15 years of follow-up (95% CI, 28–38) and 18 per 1,000 person-years after 15 years of follow-up (95% CI, 10–29). Men with low-grade prostate cancers had a minimal risk of dying from prostate cancer during 20 years of follow-up (Gleason score of 2 to 4; six deaths per 1,000 person-years; 95% CI, 2–11). Men with high-grade prostate cancers had an increased probability of dying from prostate cancer within 10 years of diagnosis (Gleason score of 8 to 10, 121 deaths per 1,000 person-years; 95% CI, 90–156). Men with tumors that had a Gleason score of 5 or 6 had an intermediate risk of prostate cancer death. The annual mortality rate from prostate cancer appears to remain stable after 15 years from diagnosis.[86]

**Digital Rectal Exam**

Although DRE has been used for many years, careful evaluation of this modality has yet to take place. The examination is inexpensive, relatively noninvasive, and nonmorbid and can be taught to nonprofessional health workers; however, its effectiveness depends on the skill and experience of the examiner. The possible contribution of routine annual screening by rectal examination in reducing prostate cancer mortality remains to be determined.

Several observational studies have examined process measures such as sensitivity and case-survival data, but without appropriate controls and with no adjustment for lead-time and length biases.[87,88]

In 1984, one study reported on 811 unselected patients aged 50 to 80 years who underwent rectal examination and follow-up.[89] Of 43 patients with a palpable abnormality in the prostate, 38 agreed to undergo biopsy. The positive predictive value (PPV) of a palpable nodule, i.e., prostate cancer on biopsy, was 29% (11 of 38). Further evaluation revealed that 45% of the cases were stage B, 36% were stage C, and 18% were stage D. More results from the same investigators revealed a 25% PPV, with 68% of the detected tumors clinically localized but only approximately 30% pathologically localized after radical prostatectomy.[13] Some investigators reported a high proportion of clinically localized disease when prostate cancer is detected by routine rectal examination,[90] while others reported that even with annual rectal examination, only 20% of cases are localized at diagnosis.[91] It has been reported that 25% of men presenting with metastatic disease had a normal prostate examination.[92] Another case-control study examining
screening with both DRE and PSA found a reduction in prostate cancer mortality that was not statistically significant (odds ratio, 0.7; 95% CI, 0.46–1.1). Most men in this study were screened with DRE rather than PSA.[93] All four of these case-control studies are consistent with a reduction of 20% to 30% in prostate cancer mortality. Potential biases inherent in this study design, however, limit the ability to draw conclusions on the basis of this evidence alone.

Since PSA assays became widely available in the late 1980s, DRE alone is rarely discussed as a screening modality. A number of studies have found that DRE has a poor predictive value for prostate cancer if PSA is at very low levels. In the European Study on Screening for Prostate Cancer, it was found that if DRE is used only for a PSA higher than 1.5 ng/mL (thus, no DRE is performed with PSA < 1.5 ng/mL), 29% of all biopsies would be eliminated while maintaining a 95% prostate cancer detection sensitivity. By applying DRE only for patients with a PSA higher than 2.0 ng/mL, the biopsy rate would decrease by 36% while sensitivity would drop to only 92%.[94] A previous report from this same institution found DRE to have poor performance characteristics. Among 10,523 men randomly assigned to screening, it was reported that the overall prostate cancer detection rate using PSA, DRE, and transrectal ultrasound (TRUS) was 4.5% compared with only 2.5% if DRE alone had been used. Among men with a PSA lower than 3.0 ng/mL, the PPV of DRE was only 4% to 11%.[95] Despite the poor performance of DRE, a retrospective case-control study of men in Olmsted County, Minnesota, who died of prostate cancer found that case patients were less likely to have undergone DRE during the 10 years before diagnosis of prostate cancer (OR, 0.51; 95% CI, 0.31–0.84). These data suggested that screening DREs may prevent 50% to 70% of deaths from prostate cancer.[96] Contrary to these findings, results from a case-control study of 150 men who ultimately died of prostate cancer were compared with 299 controls without disease. In this different population, a similar number of cases and controls had undergone DRE during the 10-year interval before prostate cancer diagnosis.[97] One case-control study reported no statistically significant association between routine screening with DRE and occurrence of metastatic prostate cancer.[98] The PCPT requested that all men undergo prostate biopsy at study end to address ascertainment bias; the sensitivity of DRE for prostate cancer was 16.7%. The sensitivity increased to 21.3% in men receiving finasteride.[99]

Transrectal Ultrasound (TRUS) and Other Imaging Tests

Imaging procedures have been suggested as possible screening modalities for prostate cancer. Prostatic imaging is possible by ultrasound, computed tomography, and magnetic resonance imaging. Each modality has relative merits and disadvantages for distinguishing different features of prostate cancer. Ultrasound has been examined by several investigators in observational settings and has received the most attention.[100] Ultrasound sensitivity for prostatic carcinoma ranged from 71% to 92%, and for subclinical disease, it ranged from 60% to 85%. Specificity values ranged from 49% to 79%, and PPV in the 30% range have been reported. The sensitivity and PPV of ultrasound as a single test may be better than those for rectal examination. The rate of cancer is extremely low among ultrasound-positive patients in whom rectal and PSA examinations are normal.[101] TRUS is generally relegated to a role in the diagnostic work-up of an abnormal screening test rather than in the screening algorithm. The cost and poor performance of other imaging modalities have led to their elimination from all early detection algorithms.

Contemporary prostate biopsy relies on spring-loaded biopsy devices that are either digitally guided or guided via ultrasound. TRUS guidance is the most frequently used method of directing prostate needle biopsy because there is some suggestion that the yield of biopsy is improved with this method.[102] With the virtually simultaneous clinical acceptance of TRUS, spring-loaded biopsy devices, and the proliferation of PSA screening in the late 1980s, the number of prostate cores obtained from patients with an abnormal DRE or an abnormal PSA was most commonly six, using a sextant method of sampling the prostate.[103] There is evidence that the predictable increase in cancer detection rates that would be expected by increasing the number of biopsy cores beyond six does occur; e.g., biopsies with 12 or 15 cores would increase by 30% to 35% the proportion of biopsied men having cancer detected.[104,105] The extent to which such increased detection will reduce morbidity and mortality from the disease or increase the fraction of men treated unnecessarily is unknown.

Prostate Cancer Gene 3 (PCA3)

The PCA3 gene assay was approved by the U.S. Food and Drug Administration in early 2012, with the intended use to improve the selection of men with a previous negative biopsy for an elevated PSA and who a repeat biopsy is being considered for a persistently elevated PSA. This test is performed on a urine sample collected after an attentive DRE (several strokes applied firmly to the prostate to the right and left prostatic lobes). Using a threshold value of 60, this test enhances the detection of prostate cancer while reducing the number of biopsies in men who are expected to
ultimately have a negative biopsy.\[106]\]

**Frequency of Screening**

The optimal frequency and age range for PSA (and DRE) testing are unknown.\[67,107,108\] Cancer detection rates have been reported to be similar for intervals of 1 to 4 years.\[109\] With serial annual screening in the PLCO cancer screening trial, 8% of men with baseline PSA lower than 1 ng/mL had a prostate cancer diagnosis within 2 years.\[110\] In the same trial, 2-year intervals in screening produced average delays of 5.4 to 6.5 months, while 4-year screening intervals produced average delays of 13.6 months (baseline PSA <1 ng/mL) to 20.9 months (baseline PSA 3–4 ng/mL).\[110\] While the authors caution that an optimal prostate screening frequency cannot be determined from these data, they conclude that among men who choose to be screened, these data may provide a context for determining a PSA screening schedule.

A report from the ERSPC trial demonstrated that while more frequent screenings lead to more diagnosed cancers, the detection rates for aggressive interval cancers was very similar to the different screening intervals in place in the two countries reporting (0.11 with a 4-year interval in Rotterdam and 0.12 with a 2-year interval in Gothenburg). The report suggests that mortality outcomes from the ERSPC (2- and 4-year intervals) and PLCO (1-year interval relative to opportunistic screening) trials should facilitate a more reliable assessment of the benefits and costs of different screening intervals.\[111\]

**Types of Tumors Detected by Prostate Cancer Screening**

Of serious concern with regard to prostate cancer screening is the high prevalence of histological cancer. It has been demonstrated that a considerable fraction (approximately one-third) of men in their fourth and fifth decades have histologically evident prostate cancer.\[7\] Most of these tumors are well-differentiated and microscopic in size. Conversely, evidence suggests that tumors of potential clinical importance are larger and of higher grade.\[112\] Since the inception of PSA screening, several events have occurred: (1) a contemporaneous but unrelated decrease in detections of transition-zone tumors caused by a fall in the number of transurethral resections of the prostate due to the advent of effective treatment for benign prostatic hyperplasia (including alpha blockers and finasteride); and (2) an increase in detection of peripheral-zone tumors due to the incorporation of TRUS-guided prostate biopsies. Because transition-zone tumors are predominantly low volume and low grade and because peripheral-zone tumors have a preponderance of moderate-grade and high-grade disease, the proportion of higher grade tumors detected by current screening practices has increased substantially. A Detroit study found that between 1989 and 1996, poorly differentiated tumors remained stable and well-differentiated tumors fell in frequency while moderately differentiated disease increased in frequency. The largest rise in incidence was in clinically localized disease.\[113\] It is now known that systematic changes to the histological interpretation of biopsy specimens by anatomical pathologists has occurred during the PSA screening era (i.e., since about 1985) in the United States.\[114\] This phenomenon, sometimes called “grade inflation,” is the apparent increase in the distribution of high-grade tumors in the population over time but in the absence of a true biological or clinical change. It is possibly the result of an increasing tendency for pathologists to read tumor grade as more aggressive.\[115\]

Prostate biopsies in a small percentage of men will demonstrate prostatic intraepithelial neoplasia (PIN). High-grade PIN is not cancer but may predict an increased risk of prostate cancer. PSA does not appear to be elevated with PIN.\[116,117\]

**Physician Behaviors Related to Screening**

A variety of variables affect the likelihood of a recommendation for prostate cancer screening from a physician. In Washington State, 1,369 primary care physicians were surveyed to determine patterns of PSA screening recommendations. Of the 714 respondents, 68% routinely recommended PSA screening. The survey results suggest that gender (male), age (medical school graduation before 1974), and mode of reimbursement (fee for service) all increase the likelihood of PSA screening recommendations among this population.\[118\]

**Simulation Models**

A number of computer simulation models have been developed to analyze trends in prostate cancer detection. The models were also developed to compare these trends with the reported decrease in prostate cancer deaths observed in
the United States since the early 1990s, to investigate the cost-effectiveness of various screening strategies, and to attempt to estimate overdiagnosis resulting from screening.

One of the first models looked at trends in prostate cancer detection compared with prostate cancer deaths between 1992 and 1994. Changes in prostate cancer mortality could not be explained entirely by PSA screening alone.[119] Simulation modeling from the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) program suggested that the combination of changes in prostate cancer treatment, improvements in disease management after primary therapy, and screening contributed to the drop in prostate cancer mortality.[120] CISNET models calibrated to SEER incidence data were also used to estimate overdiagnosis caused by PSA screening in the United States, suggesting 23% to 42% of all screen-detected prostate cancers were overdiagnosed.[121] An analysis using the Microsimulation Screening Analysis (MISCAN) model and data from the ERSPC trial predicted the numbers of prostate cancers diagnosed, the prostate cancer deaths averted, the quality-adjusted life years (QALYs) gained, and the cost-effectiveness of 68 screening strategies.[122]

An example of the underlying assumptions and concerns about models is provided by a microsimulation modeling effort that examined the comparative effectiveness of 35 screening strategies, which varied by start and stop ages, screening intervals, and thresholds for biopsy referral.[123] The CISNET model assumes prostate cancer progression from onset to metastasis to clinical diagnosis in the absence of screening, with risks of events indicated by PSA levels. Event rates through the progression states are identified by matching model incidence to observed incidence, although it is not clear that the rates so identified are unique. Survival depends on stage at diagnosis, and screening is assumed to identify some cancers at an earlier stage than without screening, leading to a reduction in mortality. This stage-shift model is virtually guaranteed to produce a benefit of screening.

Providing Information to the Public, to Patients, and to Their Families

While awaiting results of current studies, physicians and men (and their partners) are faced with the dilemma of whether to recommend or request a screening test. A qualitative study undertaken on focus groups of men, physician experts, and couples with screened and unscreened men has explored types of information that may help inform a man undertaking a decision regarding PSA screening.[124] At a minimum, men should be informed about the possibility that false-positive or false-negative test results can occur, that it is not known whether regular screening will reduce the number of deaths from prostate cancer, and that among experts, the recommendation to screen is controversial. The PLCO-1 (NCT00002540) trial, which is now closed to accrual, is monitoring participants to test the effect of early detection by DRE and PSA on reducing mortality. A trial of screening is also being performed in Europe.[125,126]

References


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Harms of Screening

Any potential benefits derived from screening asymptomatic men need to be weighed against the harms of screening and diagnostic procedures and treatments for prostate cancer. These harms are particularly burdensome to individuals with false-positive screening results and those who are unnecessarily treated because of overdiagnosis.

Three cohort studies in Sweden and the United States linked databases to examine the association between a new diagnosis of prostate cancer and cardiovascular events/death or suicide. One Swedish study found that in the first year after a diagnosis of prostate cancer, the risk of death from cardiovascular disease (CVD) was increased in men diagnosed with prostate cancer compared with men who were not diagnosed with prostate cancer (relative risk [RR], 1.9; 95% confidence interval [CI], 1.9–2.0; adjusted for age, calendar time period, and time since diagnosis). The risk of death from CVD was highest in the first week after diagnosis (RR, 11.2; 95% CI, 10.4–12.1) and was also higher in younger men (age <54 years). These risks were less in men diagnosed in the most recent time periods. Also in the first year after diagnosis, the risk of committing suicide was higher for men who had been diagnosed with prostate cancer (RR, 2.6; 95% CI, 2.1–3.0; adjusted for age, calendar time period, marital status, educational level, and history of psychiatric hospitalization). Again, this was highest in the first week after diagnosis (RR, 8.4; 95% CI, 1.9–22.7). A second Swedish study largely confirmed these findings.[2]

A U.S. cohort study explored the association between prostate cancer diagnosis and CVD mortality or suicide in men diagnosed with prostate cancer compared with population-level expected rates during three different time periods (preprostate-specific antigen [pre–PSA], peri–PSA, and post–PSA). For CVD mortality, the standardized mortality ratio (SMR) was elevated for men diagnosed with prostate cancer in the first month after diagnosis in all time periods (overall SMR, 2.05; 95% CI, 1.89–2.22), but decreased in later months during the first year (decreasing to <1.0 in the PSA time period). This association was not changed significantly by age, race, or tumor grade. SMRs were higher for nonmarried men, for men who lived in lower educational status or higher poverty counties, and for men with metastatic disease at diagnosis. Also, in the first 3 months after diagnosis, the SMR for suicide was higher in men with prostate cancer (SMR, 1.9; 95% CI, 1.4–2.6). In months 4 to 12, the SMR was lower but still greater than 1.0. The SMR for suicide, however, was greater than 1.0 only in the pre–PSA and peri–PSA time periods, but not in the post–PSA time period. SMR was higher for nonmarried men but did not vary by education or poverty.[3]

These data lend credence to the concern that overdiagnosis of prostate cancer due to screening could lead to an increased risk of CVD mortality or suicide.

Although there is no literature suggesting serious complications of digital rectal examination (DRE) or transrectal sonography, and the harms associated with venipuncture for PSA testing can be regarded as trivial, prostatic biopsies are associated with important complications. Transient fever, pain, hematospermia, and hematuria are all common, as are positive urine cultures.[4-6] Sepsis occurs in approximately 0.4% of men.[5,7]

Long-term complications of radical prostatectomy include urinary incontinence, urethral stricture, erectile dysfunction, and the morbidity associated with general anesthesia and a major surgical procedure. Fecal incontinence can also occur. The associated mortality rate is reported to be 0.1% to 1%, depending on age. In the population-based Prostate...
Cancer Outcomes Study. 8.4% of 1,291 men were incontinent and 59.9% were impotent at 18 or 24 months following radical prostatectomy. More than 40% of men reported that their sexual performance was a moderate-to-large problem. Both sexual and urinary function varied by age, with younger men relatively less affected.\[7,8\]

Definitive external-beam radiation therapy can result in acute cystitis, proctitis, and sometimes enteritis. These are generally reversible but may be chronic. In the short-term, potency is preserved with irradiation in most cases but may diminish over time. A systematic review of evidence of complications of radiation therapy shows that 20% to 40% of men who had no erectile dysfunction before treatment developed dysfunction 12 to 24 months afterwards. Furthermore, 2% to 16% of men who had no urinary incontinence before treatment developed dysfunction 12 to 24 months afterward, and about 18% of men had some bowel dysfunction 1 year after treatment. The magnitude of effects of brachytherapy has not been determined, but the spectrum of complications are similar.\[9\] Radiation to the prostate has been reported to increase the risk of secondary malignancies, most notably of the rectum and bladder. While the relative risk in a large Surveillance, Epidemiology and End Results (SEER)-based study was 1.26 (95% CI, 1.21–1.30), the absolute increase in risk is low. The same review of evidence found hormone therapy with luteinizing hormone-releasing hormone (LHRH) agonists reduces sexual function by 40% to 70%, and is associated with breast swelling in 5% to 25% of men. Hot flashes occur in 50% to 60% of men taking LHRH agonists.\[7\] (Refer to the PDQ summary on Prostate Cancer Treatment for more information.)

The question of whether prostate cancer treatment contributes to symptoms among screened prostate cancer survivors was addressed in an analysis from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. The randomized controlled PLCO analysis compared 529 prostate cancer survivors, 5 to 10 years postdiagnosis, with 514 noncancer controls, regarding prostate cancer-specific symptomatology. There was poorer sexual and urinary function among prostate cancer survivors compared with noncancer controls, suggesting that these symptoms are related to prostate cancer treatment and not aging or comorbidities.\[10\]

Screening has increased the incidence of prostate cancer. In the current medical climate, most early-stage prostate cancers are treated by radical surgery or irradiation with intent to eradicate the pathology. There is evidence that not all patients diagnosed with prostate cancer as a consequence of screening are in immediate need of curative treatment. Death from other causes often occurs before screen detected, localized, and well-differentiated malignancies affect the survival of these patients. To avoid overtreatment and consequent morbidity events, active surveillance (AS) is an emerging strategy applicable in these kinds of cases wherein curative treatment is delayed pending objective medical evidence of disease progression.

The effectiveness of AS was investigated retrospectively in the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial. Data from 577 men diagnosed with prostate cancer as a consequence of periodic screening between 1994 and 2007 at a mean age of 66.3 years in four participating clinical centers in the Netherlands, Sweden, and Finland were evaluated. Selection criteria for inclusion in the analysis were:

- PSA less than or equal to 10 ng/mL.
- PSA density less than 0.2 ng/mL.
- Stage T1C/T2.
- Gleason score less than or equal to 3 + 3 = 6.
- No more than two positive biopsy cores.

Men with positive lymph nodes or distant metastases at the time of diagnosis were excluded from the analysis. These are the same thresholds being applied in the (as yet unreported) prospective Prostate Cancer Research International: Active Surveillance study on AS originating from ERSPC and in the (also unreported) protocol-based prospective study of AS in Canada.

The mean follow-up time for the 577 men in the retrospective assessment was 4.35 years (0–11.63 years). The calculated 10-year prostate cancer-specific survival rate was 100%. The overall 10-year survival rate was 77%. The calculated 10-year deferred treatment-free survival rate was 43%.

After 7.75 years, 50% of men had received treatment. The median treatment-free survival was 2.5 years. Men treated during follow-up were slightly younger at diagnosis than men remaining untreated (64.7 years vs. 67.0 years; P <
Of the 110 men shifting to active treatment despite favorable PSA levels and PSA doubling times, DRE was known in 53 of the men and played a role in nine of them, whereas rebiopsies were known in 27 of the men and played a role in none of them. On the basis of PSA characteristics, 1.9% of patients who remained untreated may have been better candidates for active treatment, while 55.8% of men who received active treatment were not obvious candidates for radical treatment and neither DRE nor rebiopsy explained the discrepancy. Factors like anxiety and urologic complaints may have been more explanatory, but the data were not available.

The authors conclude that their data confirm previous studies' findings, that many screen-detected prostate cancers may be actively followed (e.g., AS), and curative treatment delayed, thereby delaying or avoiding the morbid consequences of radical therapy without diminishing survival. The authors also note that a considerable fraction of men do not comply with the AS regimen, apparently for psychological reasons, and AS often results in delay, not avoidance, of radical therapy.

In the Prostate Testing for Cancer and Treatment (ProtecT) study, 1,643 men with localized prostate cancer were randomly assigned equally to active monitoring, surgery, or radiation therapy. The primary endpoint was death from prostate cancer, and secondary outcomes were clinical (local) progression, metastases, and death from all causes. In a substudy of ProtecT that examined patient-reported outcomes, the response rate was over 85% for most of the questionnaires used to examine quality of life. The study addressed urinary, bowel, and sexual function, and specific effects on quality of life, anxiety and depression, and general health. No methods were employed to deal with nonresponse or missing responses. In a quality-of-life study, nonresponse tends to be informative, so this is unusual.

Results showed that men who had undergone prostatectomy reported more impotence and incontinence; men who received radiation reported more bowel dysfunction; and men who received active monitoring reported the lowest levels of these adverse effects. In general, differences decreased over the 6 years that data were collected. Overall, mental and physical health did not differ by treatment.

Whatever the screening modality, the screening process itself can lead to psychological effects in men who have a prostate biopsy but do not have prostate cancer. One study of these men at 12 months after their negative biopsy who reported worrying that they may develop cancer (P < .001), showed large increases in prostate-cancer worry compared with men with a normal PSA (26% vs. 6%). In the same study, biopsied men were more likely than those in the normal PSA group to have had at least one follow-up PSA test in the first year (73% vs. 42%; P < .001), more likely to have had another biopsy (15% vs. 1%; P < .001), and more likely to have visited a urologist (71% vs. 13%; P < .001).

References


**Changes to This Summary (02/15/2017)**

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

**Description of the Evidence**

Updated statistics with estimated new cases and deaths for 2017 (cited American Cancer Society as reference 1).

Revised text to state that the Prostate Intervention Versus Observation Trial (PIVOT) was the first study conducted in the prostate-specific antigen (PSA) screening era that directly compared radical prostatectomy with watchful waiting.

Added text about a second trial done in the PSA screening era, the Prostate Testing for Cancer and Treatment (ProtecT) study that randomly assigned 1,643 men with localized prostate cancer equally to active monitoring, surgery, or radiation therapy; the primary endpoint was death from prostate cancer, and secondary outcomes were clinical progression, metastases, and death from all causes; only 17 deaths occurred during the median 10 years of follow-up, and no significant differences were seen between the groups in prostate cancer-specific or all-cause mortality (cited Hamdy et al. as reference 49).

Added text to state that the results suggest that radical treatment has no effect on mortality, although the power to see cause-specific mortality effects was low; avoidance of metastases or progression could be a rationale for more aggressive treatment, although another study showed that active monitoring eliminated much of the pain and suffering caused by aggressive treatments (cited Donovan et al. as reference 50).

Added text to state that in a substudy of ProtecT that examined patient-reported outcomes, the response rate was over 85% for most of the questionnaires used to look at quality of life.

Added text to state that results showed that men who had undergone prostatectomy reported more impotence and incontinence; men who received radiation reported more bowel dysfunction; and men who received active monitoring reported the lowest levels of these adverse effects.

**Harms of Screening**

Added text to state that in the ProtecT study, 1,643 men with localized prostate cancer were randomly assigned equally to active monitoring, surgery, and radiation therapy; the primary endpoint was death from prostate cancer, and secondary outcomes were clinical progression, metastases, death from all causes (cited Hamdy et al as reference 11).

Added text to state that in a substudy of ProtecT that examined patient-reported outcomes, the response rate was over 85% for most of the questionnaires used to examine quality of life.

Added text to state that results showed that men who had undergone prostatectomy reported more impotence and incontinence; men who received radiation reported more bowel dysfunction; and men who received active monitoring reported the lowest levels of these adverse effects (cited Donovan et al. as reference 12).
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About This PDQ Summary

Purpose of This Summary

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- be cited with text, or
- replace or update an existing article that is already cited.

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