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# Screening for Prostate Cancer With PSA Testing: Current Status and Future Directions

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**Abstract:** The ultimate utility of the serum prostate specific antigen (PSA) assay as a screening test for reducing prostate cancer mortality has been an area of intense controversy since its introduction. PSA testing was not initially envisioned as a screening tool, but as a way to evaluate treatment responses in men with prostate cancer. Far in advance of evidence from randomized trials, the rapid and widespread uptake of PSA screening into US practice was initially driven by the intuitively logical assumption that the earlier one detects a malignancy, the more likely treatment is to be curative while minimizing associated harms. However, a growing body of observational evidence began to point to a substantial burden of associated overdiagnosis and overtreatment triggered by PSA testing. The interim results of several randomized clinical trials specifically designed to evaluate the impact of PSA testing on prostate cancer mortality have recently become available, but their incongruent results seem to have added fuel to the debate. This article presents a review of the literature on screening for prostate cancer with PSA testing; we include a detailed discussion of potential explanations for the contradictory results of the two largest randomized trials as well as reflections on the future of prostate cancer screening.

## Introduction

Prostate cancer is the most common non-skin cancer diagnosed in the United States (an estimated 217,730 cases in 2010); it is also the second leading cause of cancer death in men, accounting for approximately 32,000 deaths in 2010.[1] Screening has been advocated as a means of improving these statistics, since early-stage prostate cancer is more easily amenable to curative interventions. Early detection methods have included the digital rectal examination, serum prostate-specific antigen (PSA) concentrations, and, less commonly, transrectal ultrasound (TRUS). The digital rectal exam had for many years been the modality traditionally employed for prostate cancer screening, although rigorous evaluation of the test was largely lacking. Since the introduction of PSA screening assays into clinical practice in the late 1980s, the digital rectal exam is no longer commonly used alone. The PSA assay has been demonstrated to have a superior sensitivity, specificity, and positive predictive value compared to digital rectal exam.[2] However, serum PSA testing has important limitations, and it remains unclear whether any benefits of screening outweigh its harms.[3]

First, increased PSA levels are not specific to prostate cancer but can also be caused by prostatic infection and inflammation, as well as by benign prostatic hyperplasia (BPH). More importantly, there is no clear cutpoint value at which a man can be assured that he does not harbor prostate cancer: a continuum of risk exists at all PSA values. The Prostate Cancer Prevention Trial (which primarily examined whether [finasteride](#) (Drug information on finasteride) was effective for the prevention of prostate cancer) was unique in that a subset of participants in the control group with negative PSA test results—all less than 4.0 ng/mL—and normal digital rectal exams (2,950 out of 9,459 men) underwent prostatic biopsy at the end of the trial. Study investigators demonstrated wide variance in the sensitivity and specificity depending on the value utilized: PSA cutoff points of 1.1, 2.1, 3.1, and 4.1 ng/mL yielded sensitivities and specificities of 83%/39%, 53%/73%, 32%/87%, and 21%/94%, respectively.[4] There was no PSA value at which the prevalence of prostate cancer dropped to zero, even at the lowest ranges; it was 7% with a PSA value 0.5 ng/mL, 10% with values between 0.6 and 1.0 ng/mL, and 17% with values between 1.1 and 2.0 ng/mL.[5]

PSA testing was not initially envisioned as a screening strategy; rather, its first use was for the evaluation of treatment responses in men with prostate cancer. It is now one of the most common cancer screening activities in the United States. According to 2008 Behavioral Risk Factor Surveillance System (BRFSS) data, the estimated prevalence of men in the United States aged 40 years or older who had a PSA test during the preceding 2 years ranged from 38.9% to 70.1%, depending on locale (median: 56.2%).[6] Despite its widespread use, the ultimate utility of the PSA assay as a screening test has been questioned since its first introduction into practice. A large body of observational evidence has been amassed in regard to the question; interim results of several randomized, clinical trials specifically designed to evaluate the impact of PSA testing on prostate cancer mortality have also recently become available. This article will present a detailed review of this body of evidence, with reflections on the resulting future of prostate cancer screening.

### **Observational Evidence of the Efficacy of PSA Screening for Prostate Cancer**

Ecologic and case-control studies have addressed the association between screening and prostate cancer mortality, although they are weak study designs for the determination of screening efficacy. Farkas et al examined the US Surveillance, Epidemiology, and End Results (SEER) database for the years 1973 to 1994 and noted a marked increase in the overall proportion of clinically localized, moderate- to well-differentiated tumors diagnosed in the population after the widespread introduction of PSA testing; this suggested that the test was effective at detecting earlier-stage disease.[7] Several other ecologic studies demonstrated greater decreases in prostate cancer mortality in areas where screening was commonly performed, compared with those regions where it was not. For example, Collin et al compared age-specific and age-adjusted prostate cancer mortality rates in the United States (where PSA screening had become widespread) and in the United Kingdom (where routine PSA screening remained less common) between 1975 and 2004. After 1994, they found a four-fold difference in the rate of decline of prostate cancer mortality between the United States (4.17% annual decrease [95% confidence interval {CI}, 3.99-4.34]) and the UK (1.14% annual decrease [95% CI, 0.84-1.44]); rates were most divergent for men aged 75 years and older. The stage shift toward predominately localized disease in the United States, as noted by Farkas, was also observed by Collin et al; this phenomenon was not paralleled in the United Kingdom.[8] A retrospective analysis of age-adjusted community prostate cancer-specific mortality rates in Olmsted County, Minnesota before and after the introduction of PSA screening showed a decline from a baseline rate of 25.8 per 100,000 men between 1980 and 1984 to 19.4 per 100,000 men between 1993 and 1997.[9] Finally, an ecologic study compared prostate cancer mortality rates in the Austrian state of Tyrol, where routine screening was introduced in 1993, to rates in the rest of the country, where screening was not freely available; the study found that while mortality rates decreased throughout Austria, the rate of decline was statistically significantly greater for Tyrol between

1993 and 1999 than for other regions.[10] In these studies, however, concomitant changes in treatment strategies may be important confounding factors that make interpretation of changes in mortality rates difficult.

In addition, not all observational evidence has supported the efficacy of PSA screening in reducing prostate cancer mortality rates. A case-control study of New Jersey men between 1989 and 2000, which compared prostate cancer mortality rates in those who ever received screening with rates in those who did not, found no difference between the two groups.[11] A comparison of men in the Seattle–Puget Sound area between 1987 and 2001—where screening uptake was rapid with the introduction of PSA testing—and Connecticut—where uptake was slower—revealed, despite higher resulting rates of radical prostatectomy and radiotherapy in Seattle, that the adjusted rate ratio of prostate cancer mortality between the two regions was 1.02 (95% CI, 0.96-1.09).[12] Perron et al examined 15 birth cohorts of men aged 50 years and older in Quebec, Canada to determine the relationship of changes in prostate cancer incidence between 1989 and 1993 to subsequent prostate cancer mortality between 1995 and 1999 (after the introduction of PSA screening). The study found that although most birth cohorts did show both an increase in prostate cancer incidence and a decrease in prostate cancer deaths, there was no statistically significant correlation between the two variables (Pearson’s  $r = 0.33$ ,  $P = 0.89$ ). The authors repeated the analysis, dividing the men into 15 regional populations, and again found no association between the size of the increase in prostate cancer incidence due to screening and the size of reductions in mortality (Pearson’s  $r = 0.13$ ,  $P = 0.68$ ).[13] Some of the “positive” observational studies have also demonstrated important limitations to PSA testing: for example, in the Collin study, although the comparative annual rate of decline in prostate cancer mortality in the US population (screened) vs the UK population (unscreened) appears large, the *absolute* difference in death rates for all ages combined between the two countries is about 5 men per 100,000 person-years or less, depending on year.[8]

Perhaps most critically, a growing body of observational evidence points to the existence of overdiagnosis and overtreatment of prostate cancer triggered by PSA testing. Cancer is a heterogeneous disease, resulting from a lengthy process of cellular and molecular events that do not always follow a predictable course. PSA testing, by detecting asymptomatic disease, identifies lesions whose biological behavior may not be the same as that of clinically detected tumors. Overdiagnosis occurs when a screening test detects a tumor so indolent it would not impact the life span of the person harboring it, either because it would progress so slowly that the person would die of another cause first, or because it is essentially benign despite its histological appearance. Autopsy studies of men who have died of unrelated causes have shown that there is a large reservoir of histologically detectable but clinically silent prostate cancer in the population.[14-16] For example, in an autopsy study of men aged 40 to 59 years, occult prostate cancer was identified in approximately one-third of subjects.[17] A recent review—based on a series of previously published autopsy studies—estimated the reservoir of potentially screen-detectable prostate cancer in men over the age of 60 years to be in the range of 30% to 70%.[18]



FIGURE  
Ecologic Evidence of Overdiagnosis in Prostate Cancer

Ecologic evidence supports the presence of overdiagnosis with PSA screening. An effective early detection strategy should “pull” advanced cancers out of the future and permit treatment at an earlier stage, thus preventing late-stage tumor development. With such a strategy, one should observe a clear association between an increase in early-stage cancers and a decrease in late-stage disease for a given screened population over time, ideally at a 1:1 ratio. A signal that overdiagnosis is occurring is the appearance of a large increase in the incidence of early-stage tumors with the introduction of the new screening test (as is necessary—but not sufficient—for a successful early detection program), but without a decline of similar magnitude in the incidence of late-stage disease. The US SEER database demonstrates this exact scenario in prostate cancer (Figure). For US men aged 40 years and older, the incidence of localized prostate cancers increased from 184 cases per 100,000 men in 1983, to a peak of 416 cases per 100,000 men in 1992 (shortly after the widespread introduction of PSA testing); in 2006, the incidence was 352 cases per 100,000 men. Although one can observe a decline in the incidence of distant prostate cancer diagnoses, the absolute rate of the reduction represents a tiny fraction of the persistent associated increase in early-stage disease. The net increase in early-stage disease for the period 1983 to 2006 is 168 cases per 100,000 men, whereas the net decrease in late-stage disease is only 33 cases per 100,000 men: this represents an excess of more than 100 early-stage diagnoses per 100,000 men during this time. [19] A recent study using the SEER database has estimated that since the widespread introduction of PSA screening in the late 1980s, 1,305,600 additional men have been diagnosed with prostate cancer and 1,004,800 additional men have received definitive therapy, compared with what would have been expected in the absence of screening. However, the decline in the prostate cancer mortality rate during this time period does not approach the magnitude of change just described.[20] In addition, the decline in mortality occurred concomitantly with increasing use of therapies known to improve mortality outcomes, such as hormonal therapy.

In summary, observational studies are largely concordant that the introduction of PSA screening leads to an increased incidence of prostate cancer diagnoses, as well as to an overall trend towards more localized disease at time of diagnosis in the population. However, the impact of screening on prostate cancer mortality, and on the overall risk-benefit ratio, is much less clear.

### **Randomized, Controlled Trials of PSA Screening for Prostate Cancer**

Unfortunately, it is impossible to tease out from observational evidence the relative effects on prostate cancer mortality of new treatments, early detection with PSA screening, chance, and misclassification bias. Thus, randomized controlled trials are critical to evaluation of the efficacy of PSA screening. Since the introduction of the PSA assay as a screening test in the 1980s, five unique randomized controlled trials of screening for prostate cancer have been reported in the literature.

#### ***Three early trials***

One of the earliest of these trials, by Labrie et al, identified men aged 45 to 80 years from the electoral rolls of the Quebec City metropolitan area and randomly assigned 31,133 to PSA and digital rectal examination screening and 15,353 to observation. Of the men in the intervention arm, 7,348 (24%) actually underwent screening; 23,785 (76%) did not. Of the men in the observation arm, 1,122 (7%) also underwent screening during the study. Because of the high cross-over rate, the authors decided to analyze the data according to whether the participant actually received screening or not, deviating from the standard “as-randomized” analysis. When viewed this way, the relative risk for death from prostate cancer in those screened compared with the risk in those not screened was 0.39 (95% CI, 0.21-0.71) (11 prostate cancer deaths among screened men vs 217 deaths among unscreened men). A key limitation to this approach is that it breaks randomization; thus, these results essentially represent an observational study. Importantly, the authors did not report information on the baseline demographic characteristics of screened vs unscreened participants, making it impossible to gauge the comparability of these populations—nor did they adjust for potential confounders with their analysis. If the data are analyzed

using an intention-to-screen approach, no difference in prostate cancer mortality is observed between the two arms (relative risk [RR], 1.09; 95% CI, 0.82 to 1.43) (153 deaths among men randomly assigned to screening vs 75 deaths among those randomly assigned to observation).[21]

In 1987, investigators in Sweden used the national population register to assign every sixth man living in Norrköping aged 50 to 69 years ( $n = 1,494$ ) to screening with digital rectal exam—and later, with PSA in addition to DRE—every three years; the remaining 7,532 men, who were not contacted about their participation in the trial, were treated as controls. This quasi-randomized pilot trial was not powered to detect a statistically significant difference in prostate cancer mortality. There were 43 screening-detected cases of prostate cancer in the intervention arm (3%), along with 42 interval cancers, and there were 292 prostate cancer diagnoses (4%) in the control group. The authors found that more tumors in the screened arm were of a lower grade at the time of diagnosis compared with those in the control arm; however—unsurprisingly, given the limitations of the study design—no differences in prostate cancer-specific or overall mortality were seen.[22]

A study of one-time prostate cancer screening using a combination of PSA, digital rectal exam, and transrectal ultrasonography was initiated in Stockholm, Sweden in 1988. Investigators invited for screening 2,400 randomly chosen men who were 55 to 70 years of age and living in the catchment area of Stockholm South Hospital; 1,796 (74%) participated, and 24,804 men from the remaining source population, who were not contacted about their participation in the trial, served as controls. Follow-up was 15 years (median, 12.9 years). The authors found no statistically significant difference in the risk of prostate cancer mortality between the screen-invited arm and control arm (incidence rate ratio, 1.10; 95% CI, 0.83–1.46; 53 prostate cancer deaths in the screen-invited group [26% of diagnosed] vs 506 deaths in the control group [28% of diagnosed]). There are several important limitations to this trial. The PSA threshold for biopsy was  $>10$  ng/ml, and the screening approach was a simultaneous employment of PSA, digital rectal exam, and ultrasound, making applicability to current practice challenging. The authors also note that the treatments employed in this trial likely do not represent current standard of practice. Finally, although causes of death were assigned by a review committee and verified against a national Cause of Death Register, it is unclear whether the reviewers were blinded to study arm allocation, raising the possibility of misattribution bias.[23]

Although each of the above trials provide useful context regarding prostate cancer screening methods and programs, all have sufficient methodological limitations that the ultimate efficacy of PSA testing for reducing prostate cancer mortality cannot be definitely demonstrated or refuted by them.

### *The PLCO trial*

In 2009, interim results from two very large randomized controlled trials were reported.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial randomly assigned 76,693 men aged 55 to 74 years at 10 US study centers to annual screening with PSA testing for 6 years and with digital rectal examination for 4 years or to usual care (which could potentially include screening); the period covered by the study was 1993 to 2001. Men were excluded from participating if they had received more than one PSA test in the three years prior to randomization. A PSA level  $> 4$  ng/ml was considered positive. Subjects' personal health care providers received results and determined diagnostic follow-up and treatment for positive findings. Overall rates of compliance with screening in the intervention group were 85% for PSA testing and 86% for digital rectal exam. In the control arm, PSA testing rates increased from a baseline of 40% to 52% at year six; digital rectal exam rates were 41% to 46%.

After seven years of follow-up (98% of men with known vital status), there was a higher incidence of prostate cancer in the screened arm than in the control arm (incidence rate ratio, 1.22, 95% CI,

1.16-1.29). However, there was no statistically significant difference in the prostate cancer mortality rates between the screened and control arms, with a trend towards an increased number of deaths in the screened arm (50 deaths in the screening group vs 44 in the control group; mortality rate ratio, 1.13; 95% CI, 0.75-1.70). At 10 years of follow-up (complete for 67% of men), the findings remained essentially the same: the excess in prostate cancer cases persisted in the screened arm (incidence rate ratio, 1.17; 95% CI, 1.11-1.22), but mortality was roughly equivalent (92 deaths in the screened arm vs 82 in the control arm; rate ratio, 1.11; 95% CI, 0.83-1.50). The number of subjects with advanced tumors (stage III/IV) was also similar in the two groups (122 in the screened arm vs 135 in the control arm). Subgroup analyses stratified by history of PSA testing prior to study entry did not reveal differential effects on prostate cancer mortality rates. Overall mortality rates were also the same in the two study arms.[24]

### ***The ERSPC trial***

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a multi-national trial of eight European countries (previously nine—Portugal dropped out in 2000 without contributing data) begun in the 1990s; 182,160 men between the ages of 50 and 74 years were randomly assigned to either a group offered PSA testing or a control group not offered screening. The study included a predefined “core” group of 162,387 men aged 55 to 69 years. Randomization occurred prior to consent in three countries and after consent in four. Of note, data from France was not included in this interim analysis because that country first began participating in 2001, limiting length of follow-up. Most countries utilized PSA testing alone, although cut-off values varied by country: most considered 3 ng/ml as positive, but Finland used a cutoff of 4 ng/ml with ancillary testing (digital rectal exam or free:total PSA ratio, depending on year) for values between 3.0 and 3.9 ng/ml, Italy had men with a PSA value between 2.5 and 3.9 ng/ml undergo digital rectal examination and transrectal ultrasonography, and until 1995, Belgium used a PSA cutoff of 10 ng/ml. Belgian and Dutch centers used a combination of digital rectal exam, ultrasound, and PSA testing as the primary screening approach until 1997. There were also variations in the number of core biopsies performed for a positive screening test, as well as differences in the frequency of screening: most of the participating countries tested every 4 years, but Sweden screened every 2 years and Belgium had one 7-year interval. Compliance rates varied across countries, but overall, 82.2% of men in the screening group received at least one test. Although the study was designed to have sufficient power to account for a 20% contamination rate, no specific information was provided about actual rates of screening in the control arm for all but one study center.

After an average of 8.8 years of follow up (median, 9 years), no statistically significant reduction in prostate cancer mortality was observed in the *overall* study population (rate ratio, 0.85; 95% CI, 0.73-1.00). However, analysis of the prespecified “core” group (men aged 55 to 69 years) revealed a statistically significant 20% relative reduction in prostate cancer mortality (214 deaths in the screened group vs 326 deaths in the controls; rate ratio, 0.80; 95% CI, 0.65-0.98)—or an absolute reduction of 0.71 prostate cancer deaths per 1,000 men, with differences between the screened and control groups first beginning to emerge after about eight years. Additionally, an exploratory analysis of mortality according to age group revealed a statistically significant reduction in men aged 65 to 69 years (rate ratio, 0.74; 95% CI, 0.56-0.99) but a possible trend towards increased prostate cancer-specific deaths for those aged 50 to 54 years and 70 to 74 years (rate ratios, 1.47 [95% CI, 0.41-5.19] and 1.26 [95% CI, 0.80-1.99], respectively). An increased incidence of prostate cancer was observed in the screened arm compared with controls: 5,990 cases vs 4,307 cases, or a net increase in cumulative incidence of 34 cases per 1,000 men. These findings translate into 1,410 men aged 55 to 69 years needing to be screened and 48 additional prostate cancers treated to prevent or delay one prostate cancer death.[25]

In 2010, Hugosson et al separately reported findings from Göteborg in Sweden, one of the participating countries in the ERSPC trial (data from participants born between 1930 and 1939 were included in the pooled ERSPC data). A total of 20,000 men aged 50 to 64 years were randomized to PSA screening or a

control group not offered screening; screening was every 2 years, and the PSA biopsy threshold was 3.0 ng/ml between 1995 and 1998 and 2.5 ng/dL thereafter. Median follow-up was 14 years (complete for 78% of men). As with the larger ERSPC trial, more prostate cancers were diagnosed in the screening arm than in the control arm (11.4% of those screened vs 7.2% of controls). The authors report a statistically significant relative reduction in prostate cancer deaths (rate ratio, 0.56; 95% CI, 0.39-0.82). Overall, there were 44 prostate cancer deaths in the screened group (0.44%) vs 78 deaths in the control group (0.78%)—an absolute risk reduction of 0.34%. Thus, to avert one prostate cancer death, the corresponding number that would need to be invited to be screened would be 293, and the number who would need to be diagnosed and potentially treated (some men chose active surveillance) would be 12. No difference in overall mortality rates between the screened and control arms was found.[26]

### ***Making sense of the differences between the ERSPC and PLCO results***

Of the available randomized trials, the ERSPC and PLCO studies represent the current best evidence regarding the efficacy of PSA screening for prostate cancer—although both have limitations. The divergent findings of the two trials have, however, contributed further to the long-standing debate surrounding the widespread population use of PSA screening (a “controversy that refuses to die,” as the editorial accompanying the publication of these two landmark studies termed it[27]). There are several potential explanations for the differences in the findings that are important to consider.

First, the observed disparity between the results of the two trials may eventually resolve. The confidence intervals for the mortality estimates (0.75-1.70 in the PLCO trial and 0.73-1.00 in the ERSPC trial) make the results of both studies potentially consistent with either a modest mortality benefit or no effect. The Göteborg subtrial reported a lower relative risk, and therefore a lower confidence interval (0.39-0.82); the bulk of the results are embedded in the overall ERSPC study. A recent meta-analysis of all five randomized controlled trials reveals a confidence interval of the magnitude of the effect of PSA screening on prostate cancer mortality rates that is similar to those of the two largest trials (risk ratio, 0.88; 95% CI, 0.71-1.09).[3]

Length of follow-up is an important factor. The PLCO trial had essentially complete follow-up for 7 years and data for nearly three-quarters of the men at 10 years, and it demonstrated no statistically significant effect on mortality to date. However, given that the lead time for PSA screening and prostate cancer has been estimated as being as long as 15 years,[28] it is possible that a small benefit might emerge with continued follow-up. The level of screening in the control arm of the PLCO trial is also a consideration. However, the usual statistical methods that are used to adjust for this contamination in the control arm would increase the estimate of harm, since the relative risk was >1.0, and statistical adjustments for the dilution of effect size attributable to contamination move the effect size estimate away from 1.0. Similarly, pre-enrollment PSA screening may also have had an impact on the observable mortality rates. Approximately 44% of men in the PLCO trial had a PSA test before entering the study. This likely reduced the number of prevalent tumors remaining to be detected, lowering the trial’s power to detect a modest mortality difference.

Conversely, the ERSPC trial did show a mortality reduction for its “core” subgroup emerging at about seven to eight years. However, it is important to consider that its mean follow-up period is only slightly longer than the point at which the mortality benefit begins to emerge, and that several of the participating centers have not yet provided data for the period at which the major effect seems to occur. As such, the mortality estimate may change with further analyses, either qualitatively or quantitatively. Contamination rates in the control arm of the ERSPC trial were only captured for the Rotterdam site, but were extrapolated to be about 20% for the overall trial. The trial investigators performed a separate statistical analysis in an attempt to adjust for noncompliance and contamination, and they reported an adjusted relative prostate cancer mortality reduction of about 30%.[29]

The trend towards increased mortality with screening that was seen in the PLCO trial remains an important difference between the two studies. Two factors that might have played a role in this finding include a higher frequency of testing and more interventional management of diagnosed disease in the US trial than in the European trial. In the ERSPC trial, men were most often screened at 4-year intervals, whereas in the PLCO trial, men were screened annually. More frequent screening may increase the probability of overdiagnosis. For example, ERSPC investigators compared the 10-year cumulative incidence of all diagnosed prostate cancers vs interval cancers of two countries that employed different frequencies of screening (the Dutch Rotterdam center, with screening every 4 years, and the Swedish Göteborg center, with screening every 2 years). If more frequent screening successfully increases the proportion of late-stage cancers “pulled out of the future” and prevented from progressing, an associated drop in the number of interval cancers (as symptomatic, later-stage lesions) should be observed. In comparing the data from the two ERSPC screening centers, investigators found that although a greater total number of prostate cancers were diagnosed in the more frequently screened population (1,118 cancers at the Swedish Göteborg center [8.41%] vs 552 cancers at the Dutch Rotterdam center [13.14%];  $P < .001$ ), the incidence of aggressive interval cancers was essentially equivalent in the two groups (15 cancers [0.11%] vs 5 cancers [0.12%];  $P = .72$ ).<sup>[30]</sup> In the screening arms, a lower percentage of men employed watchful waiting as their treatment strategy in the PLCO trial than in the ERSPC trial (11% vs 18.6%), whereas a higher percentage of men in the PLCO trial underwent radical prostatectomy. Taken together, these differences may have resulted in a relative increase in the number of indolent prostate cancers diagnosed in the PLCO trial, along with a greater mortality risk from more invasive treatments, resulting in a net harm.

There is one additional difference in design that could have led to the observed difference in the outcomes of the two studies. In several ERSPC centers, control subjects were unaware that they were participating in a trial, and when diagnosed, they received treatment at their usual place of care. However, the participants in the screening arm, who were diagnosed at the major screening centers, tended to receive treatment from high-volume tertiary referral centers. This led to differences in treatment approaches, delivered by urologists of potentially different expertise.<sup>[31,32]</sup> By contrast, in the PLCO trial, all men knew they were participating in a trial, and analyses confirmed the same stage-specific therapy for diagnosed prostate cancer in each study arm.<sup>[24]</sup>

### **Harms of PSA Screening**

The foregoing discussion highlights the important possibility that the harms inherent in PSA screening for prostate cancer may ultimately outweigh the benefits. Although the blood draw itself has nominal effects, false-positive results are of some concern. Analyses of the PLCO trial and the Finnish portion of the ERSPC trial have found that 10.4% and 12.5% of the participants, respectively, received at least one false-positive test result after four or three screening rounds.<sup>[33,34]</sup> Several studies have demonstrated that false-positive results can have an important psychological impact on men, including a higher probability of worry about prostate cancer, an inaccurately elevated perceived risk for the disease, and an increase in sexual dysfunction issues compared to men with negative screening results. Fowler et al found that these effects persisted for at least 1 year after receipt of a normal biopsy; they also found that men who received a false-positive test result were more likely to have additional PSA tests, biopsies, and urologist visits for the first year after the test than those with a negative screening result.<sup>[35,36]</sup> Prostatic biopsies may result in modest harms, including pain, fever, and urinary tract infections. There is a 0.4% post-procedure sepsis rate.<sup>[37]</sup>

Potential harms associated with treatment must also be factored into the overall risk-benefit profile for PSA screening, because the exam can confer no benefit without associated therapy. Sanda et al examined quality of life among localized prostate cancer survivors one year after treatment with radical prostatectomy, brachytherapy, or external-beam radiotherapy. They reported that 54% to 75% could not maintain erections sufficient for sex, 6% to 16% had urinary incontinence at least once a day, and 3% to



14% experienced bowel urgency that was “a moderate or big problem.”[38] These complications are frequently long-term issues: in the Prostate Cancer Outcomes Study (PCOS), 4% to 15% of men experienced frequent urinary leakage, 15% to 18% had rectal wetness, and 64% to 79% reported impotence severe enough to prohibit intercourse at five years after radical prostatectomy or radiation therapy.[39] Depending on the analysis, 30-day post-operative mortality rates after radical prostatectomy range between 0.5% and 4.5% (rates increase with age), and 30-day complication rates of up to 29% have been documented.[40-42]

Overdiagnosis and overtreatment of prostate cancer are of great concern. As previously discussed, autopsy studies have shown that a considerable proportion of men—even men in their forties and fifties—harbor histologically evident but clinically silent prostate cancer. SEER data suggest that more than 1 million additional men in the United States have been diagnosed and treated for prostate cancer since the introduction of PSA screening, and that even with the most optimistic estimation of the magnitude of benefit, the majority of these men were not helped by early detection.[20] The PLCO trial’s trend toward a higher mortality rate in the screened arm reinforces this concept, and the ERSPC trial suggests that up to 48 men would be at risk for potentially life-altering harms for each man who benefited from the PSA test.

### The Future of Prostate Cancer Screening

The best quality evidence currently available suggests that PSA screening for prostate cancer is either ineffective at reducing deaths due to prostate cancer, or confers a modest mortality advantage, but at the cost of an important degree of overdiagnosis and overtreatment in the population. Responses to this revelation by professional medical societies, advocacy organizations, clinicians, and researchers have varied significantly. Some have stressed the importance of developing better risk stratification methods in order to mitigate the potential for net harm that PSA screening incurs.[43,44] Methods such as determining PSA velocity; free PSA; complexed PSA; or combining the standard PSA test with PSA derivatives or other markers, such as hK2, proPSA, and nicked PSA, are under active investigation,[45] but their ultimate utility is unproven.

TABLE  
Summary of Screening Recommendations for Prostate Cancer

The US Preventive Services Task Force, the American College of Preventive Medicine, and the American Academy of Family Physicians have not updated their recommendation statements since the release of the interim results of the PLCO and ERSPC trials (Table). In the wake of the publication of these results, the American Cancer Society chose to emphasize the necessity of informed decision-making as a prerequisite to prostate cancer screening (ie, testing should not be automatic).[46] In contrast, the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN) revised their guidelines to recommend beginning screening earlier in life (at age 40 rather than age 50), although neither the PLCO trial nor the ERSPC trial included men between the ages of 40 and 50 in their study populations.[47,48] The NCCN explains their decision to recommend expanding the pool of men exposed to PSA testing by describing the findings of the Baltimore Longitudinal Study on Aging. This 2001 observational study found an increased risk of men aged 40 to

49.9 years being diagnosed with prostate cancer within 10 to 25 years (median age at diagnosis, 67.5 years) if their PSA level was greater than the median for that age group (RR, 3.75; 95% CI, 1.6-8.6).[49] No information on health outcomes was provided in the study. Autopsy studies documenting a 25% histological prostate cancer prevalence rate for men in their 40s (discussed above in the context of overdiagnosis) were also emphasized as a reason to initiate screening earlier.[47] The AUA also references the Baltimore Longitudinal Study; other considerations behind the AUA recommendation were the improved specificity of PSA testing in this population (due to a lower incidence of BPH) and the rates of curable cancers identified in several older observational studies in younger age groups.[48]

In light of the above, an important question to consider is what manner of evidence, if any, once mass screening has been introduced into the general population and embraced by clinicians and the public alike, will be sufficient to change practice patterns? The concept of cancer screening as a system without negative feedback has been eloquently set forth by David Ransohoff et al, who note that strong positive feedback is generated at each step along the screening, diagnosis, and treatment pathway, when viewed from the individual experiential level of the practitioner and the patient; this holds true even though the test could incur net harm. For patients, a negative screening test provides emotional reassurance and relief, whereas a positive test results in gratitude to the practitioner for catching the tumor early. For providers, counseling against a commonly advertised practice takes time that is not compensated and that can limit the provision of other services; in addition, a medical malpractice allegation could follow if cancer were to be diagnosed later on. Once cancer is diagnosed, the adverse effects of aggressive treatment may simply be accepted as the price of survival, and the patient feels fortunate to have bested the disease (and grateful once again to the practitioner).[50] The positive feedback loop may be further reinforced in the individual practitioner by the spike in incidence within his or her own practice that will likely accompany the introduction of a new screening test, falsely inflating the relative impact of the disease compared with other illnesses. Furthermore, because it is likely that screening will generate a greater proportion of diagnoses of milder forms of the disease, screened patients will also appear to do better than those who present symptomatically.[51] All of the above make it nearly impossible for a patient or clinician to get direct experience that early detection and aggressive treatment did not work.

It is hoped that the final results from the PLCO and ERSPC trials will clarify the ultimate net impact of PSA screening. However, interim findings from these landmark studies have already demonstrated that much of the original health messaging surrounding the promise of PSA testing was overstated. It is of interest to note that the scientist who first discovered the marker—Dr. Richard Albin—recently wrote that he has come to believe that the widespread deployment of screening for men over age 50 constitutes “a public health disaster.”[52] As we move ahead, it is critical that we admit our past enthusiasm was too strong, and that clinicians have clear and careful discussions with men about the continued uncertainty of the overall value of PSA screening, including information about the documented potential for harm, particularly in terms of overdiagnosis and overtreatment.

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