Prostate Cancer: Current Evidence Weighs Against Population Screening

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Prostate–specific antigen (PSA) measurement, obtained from a simple blood sample, has been widely proposed as a screening tool for prostate cancer, which is currently the leading cancer diagnosis in men in several developing countries.\(^1\) In many parts of the world, the PSA test is now widely used, and is frequently used indiscriminately. For example, in a cohort of greater than half a million men aged ≥70 years assembled from 104 US Veterans Administration hospitals during 2002 and 2003, 56% of elderly men had a PSA test (64% of men ages 70–74 years and 36% of men aged ≥85 years).\(^2\)

PSA screening has remained a controversial topic, and findings from 2 large randomized trials have been eagerly awaited.

The PSA test was first approved by the US Food and Drug Administration in 1986 for monitoring progression in patients with prostate cancer. It was later approved for the detection of disease in symptomatic men and has not been approved for screening asymptomatic men.\(^3\)

In 1991, Catalona et al\(^4\) published results from a large series of men in whom PSA was measured and concluded that the screening program was able to identify patients at a high risk for prostate cancer. For the purposes of evaluating PSA as a screening tool, the absence of a parallel control group was a major handicap; the study simply involved testing levels of PSA in a large series of consecutive male patients. It demonstrated that PSA could be used to help diagnose early stage prostate cancer. It did not address the question of whether PSA screening reduces the prostate cancer mortality rate or saves lives.

Findings from prospective randomized clinical studies were/are desperately needed. To our knowledge, to date 4 randomized trials have investigated the efficacy of prostate cancer screening, mainly using the PSA test. The Quebec study\(^5,6\) was proclaimed as the first randomized trial to demonstrate the efficacy of screening for prostate cancer. Labrie et al\(^5\) presented the data in the plenary session at the annual meeting of the American Society of Clinical Oncology in Los Angeles, California, in 1998. They reported death rates of 48.7 per 100,000 in unscreened men and 15 per 100,000 in screened men, with a claimed odds ratio of 3.25 in favor of screening. This analysis was widely criticized as flawed. It excluded men assigned to the screening group who were invited to screening and did not participate. Reanalysis with a more appropriate intention–to–screen method found a 16% excess of deaths in the group invited to screening compared with those in the control group. The reanalysis strongly suggested that the original findings were significantly affected by selection bias.\(^7\) In other words, men who were invited to screening may have opted to accept the invitation because they were more healthy than men who refused the invitation. To exclude this latter group biases the data and the findings.\(^8\)

The second randomized trial to be published came from Sandblom et al in Sweden\(^9\) and reported a 47% higher rate of diagnosis in screened men than in controls. The intention–to–screen analysis of the data calculated the relative risk of death from prostate cancer to be 1.04 (ie, a [statistically nonsignificant] 4% increase in the risk of death from prostate cancer.

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in the group that was offered screening). A Cochrane collaboration review concluded that both of these randomized trials had significant limitations in their methods, and a pooled analysis produced an increased relative risk of death in the screened group with a nonsignificant confidence interval.\(^7\)

The results of 2 large randomized trials have been awaited for several years to provide some additional light on this controversial topic, and interim analyses of both have recently been published. The Prostate, Lung, Colorectal and Ovarian (PLCO)\(^11\) Cancer Screening Trial in the United States was initiated in 1993. It recruited \(\geq 38,000\) men ages 55 to 74 years into a screening group and a similar number into a parallel control group. The European Randomized Study of Screening for Prostate Cancer (ERSPC)\(^12\) was initiated in 1991 and recruited \(\geq 162,000\) men ages 55 to 69 years. These trials had been ongoing for 14 years and 17 years, respectively, without publishing results on the efficacy of screening until the recent publications of the interim analyses.

The PLCO concluded that, after 7 to 10 years of median follow–up, the rate of death from prostate cancer was very low and did not differ significantly between the 2 study groups.\(^11\) The ERSPC concluded that PSA–based screening reduced the rate of death from prostate cancer by 20% with a median of 9 years of follow–up, but was associated with a high risk of overdiagnosis (diagnosis of cancers that would not have caused morbidity or death).\(^12\)

**Hindrances to the Interpretation of the Trial Findings**

Like all large–scale trials, these recent trials had strengths and weaknesses. The nature of the 2 trials\(^11,12\) is such that the findings are not truly inconsistent or at odds, as has been reported in the lay media. The PLCO study was tightly run, with a common protocol followed at all sites. The ERSPC was effectively a collection of 7 trials with substantial differences in their protocols. These 7 trials had different designs with different screening test(s) used, different screening intervals, and different ages of entry and choice of controls.

The PLCO trial was really a trial comparing a more thoroughly screened group of men with a less thoroughly screened group of men. Approximately 40% to 50% of men in the PLCO control group received some screening. The ERSPC compared 7 highly screened groups with 7 groups that had significantly less contamination than the PLCO study.

Indeed, a key methodologic feature of these trials has been the issue of “contamination” in the group not assigned to the intervention (screening). This is not usually a significant issue in randomized treatment trials. The sample size for a clinical trial is calculated to provide the number of events required to achieve an appropriate level of statistical power. The study by Zelen\(^13\) demonstrated that the effective sample size, and consequently the power of the study, rapidly falls off with an increasing proportion of the control group who received the treatment (contamination rate) and, similarly, with the proportion of the treatment group who did not participate in the study. The likely consequence of the high rate of PSA testing in the population is that contamination rates in the trials would be approximately 20% to 50%, and this appears to be having a major impact on the effective sample size, and the statistical power, of the studies. Consequently, because recruitment has long since closed, considerable delays have been encountered in acquiring enough events (deaths from prostate cancer) to make statistically meaningful comparisons between the screened and unscreened groups. It also will remain unclear why some men (in the control groups of these studies) sought the PSA test and others did not and whether this induced a bias into the findings. The widespread contamination of the control group due to members seeking PSA testing presents obstacles to a simple interpretation of the findings.

The consequences on the statistical power of these trials are considerable, and the trials could very well be compromised. There are additional difficulties in interpreting the results from the ERSPC, which can be viewed as not a single study with a common protocol but rather a series of studies with differences in many aspects of the methodology. It might be more appropriate to analyze the core data as a meta–analysis rather than a pooled analysis and it would be invaluable to view the findings from each of the component studies before they are combined.

Both studies have not fully matured, and it is essential to continue the follow–up in each group in each of the studies. Unfortunately, the authors of the ERSPC have already performed 3 interim analyses. The criteria for statistical significance in subsequent analyses have become much more rigorous as the
number of interim analyses has increased. The ER-SPC has “eroded its α,” meaning it may have difficulty conducting future statistically valid analyses. It may be impossible for future analyses of the ERSPC to have a statistically significant finding that screening is beneficial. It is important to have information from this study regarding the statistical power associated with the quoted significance level.

Consequences of Overdiagnosis and Overtreatment

The PSA test is a simple blood test that, by itself, involves minimal risk of harm; the risk increases only when a patient is treated after receiving a diagnosis of prostate cancer. The availability of such a simple and inexpensive test has some very interesting and important consequences.

Overdiagnosis and the resultant overtreatment and significant adverse events have been clearly established as a result of screening. Notably, in the ERSPC, screening the 73,000 men in the screened group resulted in >17,500 biopsies being performed to find a total of >5,900 prostate cancers. These figures are considerably higher than those in the unscreened group. Men in the screened group were 2.77 times more likely than those in the control group to undergo a radical prostatectomy and were twice as likely to receive radiation therapy.

Therapy for localized prostate cancer is not without its adverse effects, and undoubtedly many men suffered impotence, incontinence, and other complications as a result of this overtreatment. It is essential to have more information concerning the occurrence of such adverse events in these trials. The ERSPC concluded that it was necessary to screen 1,410 men and to have an additional 48 cancers diagnosed to prevent 1 prostate cancer death with a median follow-up of 9 years.

Given the known side effects of all forms of therapy for localized prostate cancer, the question of whether to recommend screening depends on whether any moderate reduction in mortality is offset by a decreased quality of life for the men treated. Treatment needs to be in place for all men in the community. It could lead to a situation in which a huge loss in quality of life more than offsets a moderate reduction in mortality through screening. Even the strategy of watchful waiting is associated with side effects. It is known that a large number of men with a history of prostate cancer suffer from depression and mental anguish leading to an increased risk of suicide, and these men are at risk of losing health insurance.

In addition, it is concerning that in the PLCO study, the risk of death from all causes combined appeared to be higher in the screened group than in the control group. This is a weak observation, but it has been observed in 2 previous randomized trials. It raises the possibility that it could be due to a small increased risk of non-prostate cancer death from prostate cancer treatment. It has been reported that hormonal therapies in men with locoregional prostate cancer with gonadotropin-releasing hormone analogs increase the risk of diabetes, cardiovascular disease, and stroke. In the absence of details concerning treatment in these trials, it is not known how many of these men were treated with these drugs, but it needs to be ruled out that treatment may be harmful. This is an unknown that must be the focus of further investigation.

Quantifying the Risks and Possible Benefits of Screening

At this point, only the findings of the ERSPC can possibly justify screening to any extent and then only within the physician–patient relationship. This is a weak justification, given the $P$ value of .04 and a 95% confidence interval with an upper bound of 0.98. It is important to remember that the history of randomized clinical trials is littered with findings that were weakly statistically significant and with additional follow-up were found to lose their statistical significance. Longer follow-up of both these trials is desirable, although the ERSPC, due to its 3 interim analyses, may be unable to provide statistically significant findings.

If one is to accept the ERSPC finding that screening decreases the risk of prostate cancer death by 20%, one must also accept the other findings of this trial. Forty-eight additional men were diagnosed in the screening group to save 1 life. This means an average man who gets screened is 48 times more likely to be harmed by screening than he is to be saved by screening at 9 years after diagnosis. The harms include that he may be diagnosed, undergo needless treatment, and suffer the side effects of prostate cancer treatment, which can include impotence, incontinence, mental anguish, and even death.
The real impact and tragedy of prostate cancer screening is the doubling of the lifetime risk of a diagnosis of prostate cancer with little if any decrease in the risk of dying from this disease. In 1985, before PSA screening was available, an American man had an 8.7% lifetime risk of being diagnosed with prostate cancer and a 2.5% lifetime risk of dying from the disease.\textsuperscript{18} Twenty years later, in 2005, an American man had a 17% lifetime risk of being diagnosed with prostate cancer and a 3% risk of dying from prostate cancer.\textsuperscript{19}

In the best case scenario, applying the ERSPC findings, a 20% reduction in the risk of death means the average man who chooses screening decreases his risk of prostate cancer death from a lifetime risk of 3% to a lifetime risk of 2.4%. In exchange, he increases his risk of diagnosis from between 6% and 9% to at least 17%. In a heavily screened population, the risk of diagnosis is likely more than doubled to \textgreater 20%.

Is more than doubling one’s risk of diagnosis worth the absolute decrease in prostate cancer death risk from 3% to 2.4%, if indeed there is this 20% decrease in risk? Men should discuss the now quantifiable risks and benefits of having a PSA test with their physician and then share in making an informed decision.

Interpreting the Results of Screening Trials

Trial results for and against testing have always been contentious among supporters and opponents of screening. In the case of breast cancer, even with data available from 9 randomized trials with reasonable methods, claims have been made that there is no evidence to support mammographic screening, especially among women ages 40 to 49 years. It should be noted that such claims are contrary to mainstream interpretation of available evidence. With fewer trials available for evaluating prostate cancer screening, and with contamination rates in the control group likely to be very high, questions will undoubtedly be posed regarding the reliability of the findings. However, there is currently weak to no evidence available from these trials indicating that PSA testing reduces the risk of death from prostate cancer.

In the United States, widespread prostate cancer testing is commonly practiced. For nearly 2 decades, testing has been based on blind faith in early detection as opposed to being based on evidence of a decrease in mortality as observed in well–designed clinical trials. Prostate cancer screening and the treatment of early stage disease is also a profitable industry. Despite discouraging findings from now 4 randomized trials of prostate cancer screening, much of the controversy surrounding the use of PSA as a population screening test remains unresolved. The high prevalence of PSA testing will be difficult to reverse. If we are to stem the spiraling costs of health care, we must move toward the use of evidence–based rather than the faith–based or profit–based practice of medicine.

The collective data clearly cannot justify mass screening and indeed appear to justify support for a recommendation against mass screening. Given all the information available, the best that can be deduced is that guidelines such as those of the American Cancer Society appear to remain valid.\textsuperscript{20} Shared decisions to use or not use PSA testing for the early detection of prostate cancer should remain within the physician–patient relationship, and should include discussion of the quantified risks and benefits. The patient and physician should make a shared decision about screening, taking into account the patient’s concerns regarding prostate cancer and its treatment. Shared decision making, compared with simple “informed consent,” should become standard. We use the term “shared decision making” to stress that the weight of the decision should not be thrown into the patient’s lap.

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