Chapter 18
Prostate Cancer Screening

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18.1 Introduction

Two tests have been advocated for screening for prostate cancer, the digital rectal examination (DRE) and the determination of the amount of prostate-specific antigen (PSA) in the blood. Although there has been a tendency to use both tests together, experience has shown the DRE is unreliable and fails to detect many early prostate cancers detected by PSA. Further, the evidence available on the efficacy of prostate screening relates largely to PSA. Therefore, in this chapter, I shall concentrate on the evidence relating to the effectiveness of screening with PSA.

Since the introduction of the PSA test, with wide adoption for screening in the United States, a number of jurisdictions in other countries with publicly funded or insurance-based health systems have agreed that PSA testing would be funded, though in many parts of Canada, the funding is for tests ordered for diagnosis and not screening by a physician. However, such types of funding are difficult to monitor, and it seems probable that the majority of the tests now performed in Canada and other countries are for screening. This is because the public and many of their physicians believe that the early detection and proper treatment of prostate cancer must be beneficial. A significant proportion of the male population, as well as many advocacy groups, have agreed testing for elevated PSA levels is good. For example, over 25 % of men over the age of 40 reported they had had a PSA screening test in a 2003 Canadian survey (Canadian Cancer Society 2006).

However, the release of mortality results on prostate cancer from two large screening trials, the prostate component of the Prostate, Lung, Colon and Ovary (PLCO) trial in the United States (Andriole et al. 2009) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Schröder et al. 2009), and their

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recent update (Andriole et al. 2012; Schröder et al. 2012) has served to fuel the debate. In this chapter, I shall try and clarify the present situation and address the issue as to whether, and if so at what ages, PSA testing should be offered.

18.2 The Potential Benefits of PSA as a Screening Test

Prostate cancer is the most common cause of death from cancer in men in most technically advanced countries. It is by far the most prevalent cancer with 30–40 % of men over 60 found to have prostate cancer at autopsy (Miller 2007). The lifetime risk of a man developing microscopic prostate cancer has been estimated to be 42 % (Frankel et al. 2003). The sensitivity of the PSA tests depends on the cutoff level selected. If the cutoff for an abnormal PSA test is 4 ng/ml, then the sensitivity of a PSA test is about 75 %, rising to over 80 % if the cutoff is lowered to 3 ng/ml. However, there is a reciprocal relationship between sensitivity and specificity. The specificity if the cutoff is 3 ng/ml is approximately 80 %, i.e., 20 % of those screened would have a false-positive result, resulting in substantial numbers of men placed under supervision and many unnecessary biopsies. At the cutoff level of 4 ng/ml, the specificity rises to about 90 %, making it a more reasonable test as a false-positive PSA test leads only to temporary anxiety while awaiting a negative biopsy, and the unnecessary biopsies can be accepted if there is benefit from the test. Physicians console themselves that patients are always grateful for early detection of disease especially with a good outcome which they believe is more likely than not with early detection of cancer. These arguments have made the PSA test attractive to many patients and their physicians.

18.3 The Risks of PSA as a Screening Test

Although the PSA screening test can detect most men with prostate cancer with some accuracy, over 80 % of them will die with the disease but from another cause, and only a small proportion of men with prostate cancer will die from the disease. The treatment of prostate cancer has modestly lowered the mortality rate, but as screening rates have risen, prostate cancer detection has increased quite dramatically, but with little improvement in mortality. Recent declines in prostate cancer mortality in many countries are probably attributable to prolongation of life from hormone therapy of more advanced cases, with most of them dying from other causes. Frankel et al. (2003) estimated if 1 million men over 50 were screened with a PSA test cutoff at 4 ng/ml, 110,000 would have elevated PSA on the first test, 90,000 would have a biopsy, and 20,000 will be found to have cancer. Of this group, 10,000 will have a prostatectomy, of whom 300 will be left with chronic incontinence, 4,000 will be impotent, and 10 will die from the surgery. In Finland, component of the ESPC trial 12.5 % of the screened men had at least one

false-positive PSA test during the three rounds of 4-yearly screening (Kilpeläinen et al. 2010). Thus, evidence of benefit is necessary to justify all this morbidity and mortality.

18.4 The ERSPC and PLCO Randomized Screening Trials

Both trials commenced in the early 1990s. The ERSPC trial enrolled more than 260,000 men from 8 countries (Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, Switzerland) (Schröder 2008). In all countries, men ages 55–69 were included; in Sweden, men ages 50–54 were also included, and in four countries, men up to age 74. The PLCO trial enrolled nearly 77,000 men ages 55–74 from 10 centers across the United States. In both trials, many have been followed for more than 13 or more years. There have been reports on screening from both trials (Crawford et al. 2006; Grubb et al. 2008; Schröder 2008; Schröder and Roobol 2009). The mortality results in PLCO were related to all subjects randomized (Andriole et al. 2009, 2012), in ERSPC to a subgroup of 182,160 men (Schröder et al. 2009, 2012). The difference between this number and the total randomized as previously reported (Schröder 2008) is unexplained, apart from the absence of those recruited in France, where randomization did not begin until 2001.

The PLCO trial was conducted on a background of persistent, long-term advocacy of PSA screening for prostate cancer in the United States (American Urological Association 2000; American Cancer Society 2008), though not all organizations shared the view that screening should be offered (US Preventive Task Force 2008). In contrast, in the ERSPC trial, PSA screening in the population was infrequent in most countries when the trial was initiated, though that situation probably changed during the course of the trial. The two trials differ in some other important respects. In PLCO, annual PSA screening to a total of 6 screens and 4 annual DRE were offered to the intervention group; in the ERSPC trial, in most countries, two or more PSA screens at 4-year intervals were offered, though the interval was two yearly in Sweden. The cutoff for a positive PSA was 4 ng/ml in PLCO, and in general 3 ng/ml in ERSPC, though the use of ancillary tests such as DRE and transrectal ultrasound (TRUS) varied between countries, sometimes being applied to those with a PSA <3 ng/ml. PLCO was an individually randomized trial following informed consent, as was the case in Belgium, the Netherlands, Spain, and Switzerland in ERSPC, but in the other four countries (France, Finland, Italy, Sweden), randomization on the basis of population registers was performed prior to consent, which was only obtained in those who accepted the offer of screening. In PLCO, the results of screening were reported to the participant and their physicians, and they decided on subsequent management. This resulted in many being placed on regular PSA surveillance, rather than immediate biopsy, though by 4 years, over 80 % of those with positive tests had achieved resolution (biopsy or PSA falling to lower levels) (Grubb et al. 2008). In ERSPC, immediate biopsy of those with an abnormal test result was encouraged, treatment of those found to have cancer often

being conducted under the supervision of the trial investigators. In the control groups, care of prostate cancers that were diagnosed occurred in the community.

In both trials, there was no reduction in prostate cancer mortality in the first 7 years after randomization in the screened groups compared to the control (Andriole et al. 2009; Schröder et al. 2009). After that, there was a difference between the trials. In PLCO, with 92 % of those enrolled followed to 10 years and 57 % to 13 years, there was if anything higher mortality from prostate cancer in the intervention arm (the screened group) than in the usual care control group, though the difference was nonsignificant (rate ratio 1.09, 95 % confidence intervals 0.87–1.36) (Andriole et al. 2012). Mortality from all causes other than prostate, lung, and colorectal cancer was identical in both arms. In ERSPC with a median follow-up of 11 years, the reverse occurred, with lower prostate cancer mortality observed in the screened group than the control group (RR 0.79, 95 % CI 0.69–0.91) (Schröder et al. 2012). As the confidence intervals surrounding the point estimates of the reported mortality rate ratios in the two trials overlap, chance cannot be excluded as an explanation for the differences between them.

However, there are other major differences between the US and European trials that need to be considered. The first relates to the degree of background screening that occurred in the control groups. In PLCO, 45 % of those randomized had had at least one PSA test in the 3 years preceding randomization, and screening in the usual care group (opportunistic screening in the community) reached an estimated 52 % by the time screening came to an end in the intervention group. Nevertheless, the level of screening in the intervention arm was substantially higher than that in the usual care arm in the early study years, and throughout, screening levels remained distinctly higher. In ERSPC, the degree of contamination was certainly less, though details are not provided in the reports. The second is the different PSA cutoff level applied in the trials. This seems to have resulted in a higher detection rate of prostate cancer following screening in ERSPC than PLCO and substantially more overdiagnosis. It seems unlikely that this resulted in a mortality differential in ERSPC being missed in PLCO, however, as the lethality of prostate cancer increases with increasing PSA levels (as well as the converse), while it has been shown in ERSPC that cancers detected by screening with a PSA of <4 ng/ml have a favorable prognosis (Schröder 2008). The third possible reason for the difference in the results is differences in the application of treatment for prostate cancer. Given the way the ERSPC trial was conducted, with treatment of screen-detected cancers directly controlled by trial investigators, but carried out in the community for those diagnosed in the control group, the potential for treatment differences existed (Barry 2009), and in a publication by some of the ERSPC investigators, it was reported that men diagnosed with prostate cancer were more likely to be treated at an academic center in the screening arm than men diagnosed in the control arm (Wolters et al. 2010). To the extent that outcomes after major surgery may be better in major referral centers than in community hospitals, this difference in place of treatment may have favored the screening arm. Further, trial arm was associated with treatment choice, especially in men with high-risk prostate cancer. Thus, a control subject with high-risk prostate

cancer was more likely than a screen subject to receive radiotherapy (OR 1.43, 95 % CI 1.01–2.05), expectant management (OR 2.92, 95 % CI 1.33–6.42), or hormonal treatment (OR 1.77, 95 % CI 1.07–2.94) instead of radical prostatectomy. In contrast, the policy in the PLCO trial not to mandate specific therapies after screen detection resulted in substantial similarity in treatment by stage between the two arms (Andriole et al. 2009, 2012).

A report of follow-up through to 14 years of the Goteborg component of ERSPC has been published, combined with findings from some subjects who were not part of the ERSPC analysis (Hugosson et al. 2010). Comparing the earlier ERSPC report (Schröder et al. 2009) with this manuscript, it seems reasonable to conclude that 60 % of the Goteborg cohort was included in the core age group (55–69) of ERSPC. Of the 122 deaths from prostate cancer reported in the Goteborg trial, 109 (89 %) occurred in those 55–64 at entry. Schröder et al. (2012) only reported deaths by country in an appendix figure, while Hugosson et al. (2010) did not report how many of the Goteborg deaths were included in the core age-group analysis of ERSPC, so the extent of the overlap in deaths between the two analyses is unclear; it seems reasonable, though, to assume that most or all of these 109 were included in the core group analyses of Schröder et al. (2009, 2012). Thus, the Goteborg study's finding concerning a prostate cancer mortality reduction seems largely derived from previously reported ERSPC data and cannot be regarded as independent validation of the findings of Schröder et al. (2009, 2012). Further, as the control group in the Goteborg trial were followed passively through national registers, probably did not know they were part of a trial and were treated in community centers, it seems likely that differences in treatment had a major impact upon the reported results.

Crawford et al. (2011) utilizing PLCO prostate mortality data through to 10 years reported a statistically significant interaction of trial arm by comorbidity status. However, a similar analysis using a modified Charlson score of comorbidity through to 13 years did not confirm this (Andriole et al. 2012), casting substantial doubt on the claim by Crawford et al. (2011) that those with no comorbidity at baseline derive a benefit from PSA screening.

In the USA, men are often advised to have annual PSA tests, yet if the ERSPC result is accepted, annual testing is unnecessarily frequent. But before accepting these results to guide policy, we need further clarification on what actually happened in the trial, especially with regard to treatment, and confirmation that the compared arms were balanced (Miller 2012a).

Reconciling the ERSPC results with the results of PLCO is difficult. What PLCO seems to show is that adding organized screening to opportunistic screening will result in no benefit and many adverse effects. Those effects include false-positive screening tests, unnecessary biopsies, overdiagnosis, and impaired quality of life. The latter will be the subject of a later report from ERPSC as it will from PLCO. In ERSPC, 13 % of the screening tests were false positives compared to 7 % in PLCO, 76 % of biopsies did not result in the diagnosis of prostate cancer in ERSPC compared with 62 % in PLCO, and overdiagnosis approximated to 50 % and 17–30 %, respectively (Miller 2012a).

Although the natural history of prostate cancer is believed to be long, leading many to suggest that the follow-up in PLCO has been too short to show a benefit, the likelihood of a change in its negative findings if follow-up was extended has been reduced by the negative finding from a 20-year follow-up of a community based trial from Sweden (Sandblom et al. 2011). The participants were all men aged 50–69 in the city of Norrköping, identified in 1987 in the National Population Register ($n = 9026$). From the study population, 1494 men were randomly allocated to be screened by including every sixth man from a list of birth dates who were invited to be screened every third year from 1987 to 1996; the remainder served as controls. DRE was used for the first two tests, and PSA was added for the next two. There were 85 cases (5.7 %) of prostate cancer diagnosed in the screened group and 292 (3.9 %) in the control group. The risk ratio for death from prostate cancer in the screened group was 1.16 (95 % confidence interval 0.78–1.73).

18.5 Discussion

In PLCO, the screening that occurred in the usual care arm was not enough to eliminate the expected impacts of the annual screening in the intervention arm such as earlier diagnosis and a persistent excess of cases. Therefore, what the trial was evaluating was the effect of adding an organized component of annual screening to the opportunistic screening already in place, and even with the extension of the follow-up to 13 years, there is no evidence of a benefit; indeed there are major harms, in part, associated with the false-positive screening tests but also with the overdiagnosis inseparable from PSA screening, especially in older men. What the trial does seem to confirm, however, would be the futility of making any attempt to set up organized screening programs in addition to what is currently ongoing in any country. This seems to be a generally accepted conclusion. Even when authors conclude that PSA screening reduces prostate cancer mortality, they also conclude that screening cannot be justified yet in the context of public health policy (van Leeuwen et al. 2010; Chou and LeFevre 2011).

Nevertheless, the question that has to be addressed is whether the European trial results support the continuation of the opportunistic screening that is ongoing in North America and some other countries. The uncertainty that surrounds the validity of the results of ERSPC makes that difficult to answer with certainty. The delay in seeing a possible benefit is certainly compatible with what is known about the long natural history of prostate cancer. Although the separation of the mortality curves in ERSPC beyond 10 years has been confirmed with more data (Schröder et al. 2012), it is still necessary to be certain that other factors, especially treatment differences between the randomized groups, are not responsible for the benefit seen. However, it is important to note that both trials support the recommendation of the US Preventive Services Task Force (2008) against screening men older than 69.

The harms from prostate screening are considerable. In addition to the complications associated with false-positive diagnoses, and the risk of postoperative

mortality in elderly men subjected to prostatectomy, there is evidence of substantial overdiagnosis, estimated in ERSPC to be 27 % from a single screening test at age 55 to 56 % for a single screening test at age 75 (Draisma et al. 2003). These harms have to be set against a low probability of benefit. Even if the ERSPC findings of benefit represent the truth, the investigators estimated that to prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be invited for screening and 37 cancers would need to be detected (Schröder et al. 2012). Thus, the large majority of men who believe that their lives have been saved by PSA testing have been deceived. Raffle and Gray (2007) have coined the term "the popularity paradox" for this situation: "The greater the harm from overdiagnosis and overtreatment from screening, the more people there are who believe they owe their health, or even their life, to the programme."

I conclude that from our present knowledge of risks and benefits attributable to prostate cancer screening and treatment, we cannot justify advocating screening programs for prostate cancer. Each physician has an ethical responsibility to inform their patients of potential risks and benefits of any procedure. There is a great need for alignment of all organizations with currently available evidence. Mass PSA screening cannot be justified, and most PSA screening should be stopped to prevent more unjustified death and morbidity. So the answer to the question men often ask their physician as to whether they should have a PSA test is "Do not Screen for Prostate cancer with PSA" (Rosser W, personal communication 2010).

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