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Prostate Cancer:

Estimating the benefits of PSA screening

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Abstract

Two groundbreaking trials have this year reported conflicting results as to the benefit of screening for prostate cancer. Careful interpretation in the light of contemporary data might, however, reveal the true value of this intervention.

Interim results have recently emerged from two large-scale prostate cancer screening trials initiated in the 1990s—the PLCO Cancer Screening Trial in the USA[1] and the ERSPC in Europe.[2] The PLCO found no difference in prostate cancer mortality between men who were offered annual PSA testing and those who received usual care, whereas the ERSPC reported that PSA screening did reduce prostate cancer mortality—by about 20% at 9 years. It is important, however, that we interpret the results of these studies correctly. Here we argue that new data on prostate cancer prediction and the outcomes of curative therapy should inform our estimates of the benefits of PSA screening.

On consideration, it is difficult to have anything but admiration for the investigators of these two trials. They are audacious is scope—the ERPSC includes more than 180,000 men aged 50–74 years from eight countries—and of high methodologic rigor. Perhaps above all, one must respect the investigators' willingness to grasp the nettle of testing what has become a widespread technology, despite a lack of clear evidence as to benefit.

The PLCO trial has been criticized on the grounds that over 40% of the participants had undergone a PSA test before the trial and about half of those in the control arm did so after randomization. Our view is that the trial is perfectly sound as long as it is interpreted correctly: it tells us that it is probably not worth telling American men to get a PSA test because they are likely to have already had one, and will continue to do so regardless of our recommendation. In the ERSPC, the benefit of screening came at high cost in terms of the number of men needing to be screened, biopsied and treated to prevent each death. Nonetheless this, like any study, needs to be evaluated in the light of contemporary data.

We recently started to report results from what we believe is the largest and most rigorous study ever conducted on the long-term prediction of prostate cancer. In brief, over 21,000 Swedish men aged 33–50 years who participated in the Malmö Preventive Project (MPP), a cardiovascular study, gave blood samples during 1974–1986. We have followed up these men using the Swedish Cancer Registry to determine prostate cancer outcomes, and then retrieve archived blood samples to measure PSA. As the rate of PSA screening in Sweden has been very low, our study constitutes a ‘natural experiment’ to examine the relationship between PSA levels before the age of 50 years and the risk of subsequent prostate cancer.

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In our first report, we demonstrated that a single PSA test before the age of 50 years could predict clinically diagnosed prostate cancer occurring up to 25 years later, with an area-under-the-curve of 0.76.[3] Perhaps our key finding concerned prediction of cancers that were advanced at diagnosis, defined as clinically T3, T4 or metastatic. While for many men prostate cancer is an indolent disease, a T3 or T4 tumor, or a prostate cancer metastasis, is very likely to affect quality of life and survival. We found that 50% of men diagnosed with advanced prostate cancer had PSA levels in the top 10% at age 44–50 years (corresponding to about 1.5 ng/ml or higher); 67% of cancers were in the top 20% of PSA (corresponding to about 1.1 ng/ml or higher); and 80% of men diagnosed with advanced prostate cancer had PSA above the median at age 44–50 years (corresponding to about 0.6 ng/ml or higher).[4] Our findings are supported by several previous reports suggesting that PSA predicts long-term risk of prostate cancer in unscreened men, although none had the very large number of cases (1,408 to date, 385 with advanced cancer) and long-term follow-up of the MPP study cohort.

These findings have two implications for interpretation of the PSA screening trials. First, the current trials do not start screening at an early enough age. In ERSPC-Göteborg, for example, the median age at the first PSA screen was 58 years, with nearly 10% of men aged 65 years or older. In ERSPC-Rotterdam, the median age of men biopsied in the first round was 66 years, with 25% aged over 70 years. The only way that cancer screening can reduce mortality is by detecting cancers before they become incurable. Yet, as might be expected by the age of study participants, many of the cancers detected in the screening arm of the ERSPC were already advanced at the time of diagnosis: in ERSPC-Rotterdam, nearly 20% of cancers were clinical stage T3 or T4 in the first round.[5] The MPP cohort demonstrates that we can identify men at increased risk for advanced cancer at early middle age and up to 25 years before clinical diagnosis. These data suggest that most advanced cancers can be detected with sufficient lead-time to allow curative therapy. Indeed, ERSPC-Göteborg and ERSPC-Rotterdam show that the rate of detection of advanced cancers was dramatically reduced during subsequent rounds of screening in comparison with the initial round.[5,6]

Second, current screening trials include all men at risk, rather than focusing on the subgroup at highest risk. The greater the proportion of men at low risk included in a screening trial, the greater the capacity for harm. The Prostate Cancer Prevention Trial,[7] in which participants were biopsied irrespective of PSA level, indicates that a very large number of men will have prostate cancer detectable on biopsy at age 62–91 years. The MPP findings suggest that it is feasible to predict at early middle age which men are at increased risk for advanced prostate cancer, and that most men are at very low risk. Such men are at substantial risk of harm from screening: increased PSA values associated with benign prostate disease will lead to unnecessary biopsy, and biopsy might discover cancers unlikely to affect a man's survival or quality of life, but which lead to anxiety and treatment-associated morbidity.

Importantly, cancer screening can only extend lives if early curative treatment is effective. Since the randomized screening trials were designed, data have emerged to suggest that the efficacy of both radiation therapy and surgery can vary greatly.

The key determinant of cure for radiation therapy is dose. Several randomized trials have demonstrated that increasing the dose of radiation to the prostate from 70 Gy to 79 Gy, something only possible through the use of conformal therapy, decreases 5-year recurrence rates from 21% to 9%.[8] The key determinant of cure from surgery is surgeon experience. We have reported that the probability of being free of cancer 5 years after surgery increases from 82.1% for a patient treated by an inexperienced surgeon (10 prior cases) to 89.1% for a patient treated by a more experienced surgeon (250 prior cases).[9] In organ confined disease,

the most common presentation among screened men, the differences are more dramatic, with recurrence rates of 14.2% for inexperienced surgeons decreasing to 1% or less for surgeons with 1,000 prior cases.[10] In the mid-1990s, typical radiation therapy doses in Europe were often less than 70Gy, and radical prostatectomy was relatively rare, entailing that many surgeons had only limited experience of the procedure. Thus, many of the patients identified with early stage prostate cancer in the randomized screening studies are likely to have received suboptimal treatment.

The current trials are not trials of PSA screening *per se*, but of particular implementations of screening. The ERSPC, for example, tests a strategy of starting PSA screening between the ages of 50 and 75 years (with a core age group of 55–69 years) and performing biopsy in men who have PSA ≥3ng/ml. This strategy might do more harm than good if many men had advanced cancers when they entered the trial, or if many unnecessary procedures were conducted on men at low risk. The MPP data suggest an alternative screening strategy: offer a single PSA test at age 45–50 years to all men and then risk-stratify subsequent screening; for example, recommend frequent (yearly) screening for men with PSA in the top quartile, offer a 5-yearly PSA retest for men with PSA higher than the median but lower than the upper quartile, and offer a single retest at age 60 years for men with PSA below the median. Men with elevated PSA might be selected for biopsy on the basis of additional markers, such as free PSA, and possibly also other investigational measurements in blood, such as a panel of kallikrein markers, or in urinary sediments, such as *PCA3*.

The problem is that evaluating such as program in a randomized trial would be of doubtful feasibility, simply because of the length of trial required. The prostate cancer death rate only starts to accelerate after the age of 65 years, so any trial screening men in their late 40s would take at least 25–30 years to complete. Moreover, it is hard to imagine that funding bodies would be ready to initiate additional large trials, considering their ongoing commitment to the ERSPC and PLCO.

Accordingly, we believe that the only way to evaluate the likely impact of any particular population strategy for PSA screening would be by statistical modeling. In the ERSPC, the prostate cancer death rate was 29 per 10,000 in the screening arm and 36 per 10,000 among controls. A straightforward interpretation of this result would be that regular PSA screening starting at age 55–65 years reduces prostate cancer death rates by 7 per 10,000 at 9 years. However, imagine that we examined the data in greater detail and found that 14 of the 29 prostate cancer deaths occurred in men aged over 60 years who were diagnosed with advanced prostate cancer in the first screening round. We might then look at the stage distribution and death rates in subsequent rounds and estimate that, for example, 5 of these 14 deaths could have been prevented had these men had an earlier PSA test. This hypothetical result would indicate that regular PSA screening starting at age 45–50 years would reduce prostate cancer death rates by 12 (7+5) per 10,000. Naturally, more-sophisticated statistical approaches could factor in the effects of changes in treatment patterns or risk stratification, and sensitivity analysis could examine how the model assumptions—such as the number of deaths that could be prevented by earlier screening—affect results.

Note that we are not advocating the mentally lazy position of ‘medicine changes; therefore, old trials are irrelevant’. Rather, we are advocating a careful, systematic, quantitative evaluation of how changes in a trial intervention might modify its effectiveness.

In conclusion, the published trials[1,2] are not trials of prostate cancer screening *per se*, but of particular approaches to screening in the context of available treatments. Data published since these trials were designed suggest that both the screening approaches and the

treatments used in the trials were not as effective as they might be. Estimation of the likely effects of prostate cancer screening in a population is better achieved by statistical modeling than by naïve application of the effect sizes reported as the principal findings of randomized screening trials.

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