EDITORIAL

What now on screening for prostate cancer?

J Med Screen 2009;**16**:109–111
DOI: 10.1258/jms.2009.009067

Earlier this year the results of two randomized trials of screening for prostate cancer by prostate-specific antigen (PSA) testing, one European and the other American, were reported.[1,2] The European trial, the larger of the two, with four-yearly screening, reported a statistically significant reduction in overall prostate cancer mortality of 20% ($P = 0.01$).[1] The American trial, with annual screening for six years, reported no reduction – indeed there was a non-significant increase of 11%[2] (see Figure 1). The reason for the difference was not immediately clear.

So is there an inconsistency? The accompanying editorial suggested that the difference may be due to chance.[3] If it were, it would be reasonable to combine the two results, in which case the summary relative risk estimate is not statistically significant ($P = 0.61$) and provides no indication of a worthwhile reduction in mortality (Figure 1). But in fact the difference between the two results is of borderline statistical significance ($P = 0.06$) and may be real. Chance may not be the explanation.

Delay in benefit may be the reason for the difference: the prostate cancer death rate in the screened group in the European trial diverged from that in the control group only seven years after screening was initiated (see Figure 2). The benefit increased with duration of follow-up, and after 10 years the mortality reduction was about 50%. The American trial on the other hand reported mortality results only up to 10 years,[2] and between 7 and 10 years its results are statistically consistent (95% CI) with a 30% reduction or a 69% increase in prostate cancer mortality in screened men. Hence the two trials agree on an absence of a reduction in prostate cancer mortality up to about seven years after the start of screening, and the European trial shows an increasing effect thereafter. Perhaps a better summary of the European trial result is not the 20% overall reduction in prostate cancer mortality, but the combination of no reduction in the first seven or so years and a reduction of about 50% after 10 years.

The fact that the American trial did not detect a mortality reduction between 7 and 10 years may have been due to two serious problems in the trial. First, 15% of men allocated PSA testing declined, while the proportion of control group participants who had PSA testing during the trial was as high as 52% (it was only 20% in the European trial). This will have substantially reduced the statistical power of the American trial; if the effect of screening and treatment was to reduce prostate cancer mortality by, say, 30%, the expected result in the American trial on an intention-to-treat analysis would have been a reduction of only 10%. The second problem is that nearly half (44%) of the participants in the American trial had had PSA testing at least once over the three years before entering the trial. This means that the trial will have selectively included men with prostate cancers not detected by PSA screening, which will have biased the trial against showing an effect of screening. The extent of PSA testing before recruitment in the European trial was not reported, but one suspects that it was lower because PSA testing was not widely promoted in European countries. It may therefore be reasonable to consider the American trial uninformative because of short follow-up and 'contamination', and to accept the European result. A problem with the interpretation of the European trial result is that there was no prior specification that a mortality reduction, if observed at all, would occur at a particular time after the start of screening, and adjustment for sequential testing rendered the statistical significance of the observed mortality reduction marginal ($P = 0.04$).

In summary, screening probably reduces prostate cancer mortality after about seven years or so, but this is not certain. More data are needed and as the accompanying editorial pointed out,[3] despite the seemingly long follow-up in these trials the results were published prematurely.

There is a long recognized serious problem associated with PSA testing for prostate cancer, the high level of overdiagnosis (that is, the detection of indolent prostate cancers that would never come to clinical attention in the absence of screening). A multinational collaborative study of autopsy findings in men who died of causes other than prostate disease showed that the prevalence of cancers in prostates was 20% at age 60, rising to 40% by the age of 80,[4] while only about 4% of men die of prostate cancer. In the European trial, as summarized in Figure 3, 1410 men needed to be screened to prevent one prostate cancer death, at a cost of identifying 48 additional prostate cancers that proved to be indolent but could not at the time of diagnosis be distinguished from the one that would have caused death. The men with these cancers had major treatment: 40% had surgery, 31% radiotherapy and 8% hormonal treatment; only 21% had 'watchful waiting'.[1] In the American trial, in which similarly large numbers of indolent cancers were detected, treatment was even more aggressive, 18% had both surgery and radiotherapy and only 11% had 'watchful waiting'.[2] The rates of serious complications of treatment in the two trials have not yet been published, but we know from other studies that surgery and radiotherapy for prostate cancer frequently cause serious complications including urinary incontinence and impotence.[5,6] These treatments were nonetheless considered warranted in the trials because the cancers were mostly of higher histological grade and had relatively advanced clinical staging.[1,2]

The 24% prevalence of prostate cancer in men with high PSA in the European trial (Figure 3) is similar to the proportion expected from the autopsy study described above. The 16% screen-positive rate, which is high for cancer screening, reflects the low PSA cut-off value (a level of

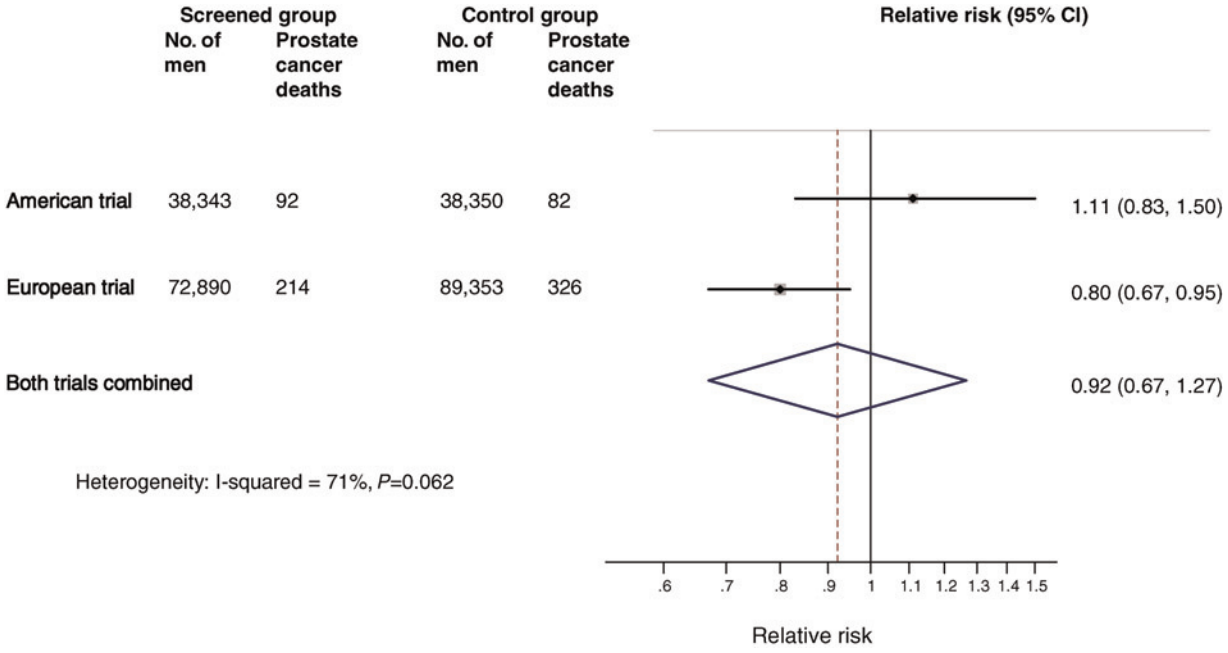

Figure 1 Risk of death from prostate cancer in two randomized controlled trials of PSA testing,[1,2] and the summary result for both trials combined

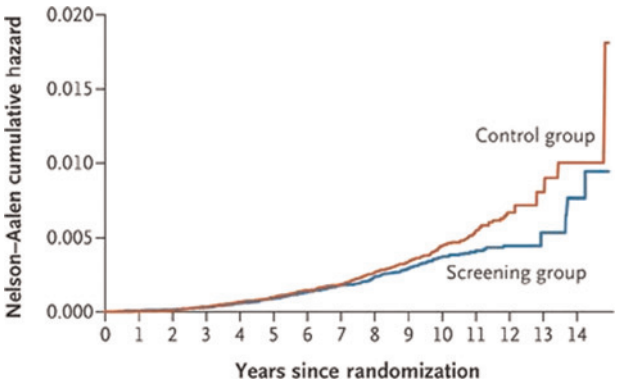

Figure 2 Cumulative risk of death from prostate cancer according to time since randomization in the European Randomized Study of Screening for Prostate Cancer (reproduced from Schröder *et al.*[1] with permission. Copyright ©2009 Massachusetts Medical Society. All rights reserved)

3.0 ng/mL was used in most of the centres). Whether so low a cut-off, and the consequent high false-positive rate, was necessary to prevent the prostate cancer deaths is uncertain. It is a great pity that blood from the men in the control group was not collected and stored for PSA measurement at the end of the trial: this would have allowed a stratified analysis according to serum PSA on entry that may have indicated whether the mortality reduction was limited to men with PSA in a particular range. Given the need to predict prostate cancer deaths many years into the future however, the high false-positive rate may be unavoidable, as suggested by data from a collaboration of four cohort (prospective observational) studies (the BUPA study [London], North Karelia and Social Insurance Institution studies [both Finland] and Washington County [CLUE] study [USA]), together recording 100 prostate cancer deaths in 49,000 men.[7] Among men who died of prostate cancer between 6 and 20 years after recruitment, only 55% (95% CI 44–66) were even in the top 16% of the PSA distribution at baseline while as few as 31% (21–41%) were in the top 5% of the distribution. This indicates that the 16% screen-positive rate was necessary to detect even half the men who would die of prostate cancer and therefore to secure the observed reduction in prostate cancer mortality. A false-positive rate of 5%, while beneficial in subjecting only a third as many men to unnecessary treatment, may have prevented only around half as many deaths.

It is instructive to see if the data from this PSA cohort study collaboration[7] are consistent with the results of the European trial. In the cohort studies 55% of the deaths

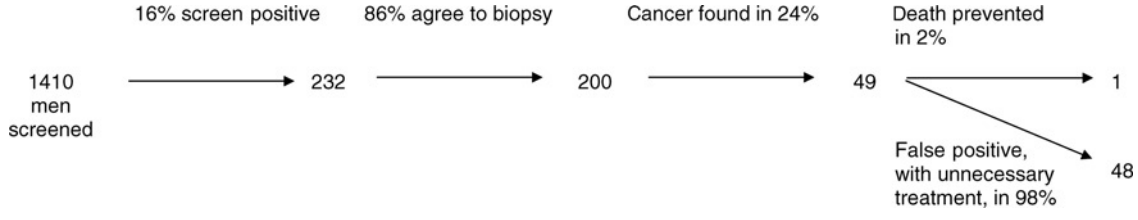

Figure 3 Outcomes in the 1410 men who needed to be screened to prevent one death from prostate cancer in the European Randomized Study of Screening for Prostate Cancer[1] (additional prostate cancers presented in men who declined screening, were screen negative, and were screen positive but declined biopsy)

from prostate cancer after 6 to 20 years follow-up were in men in the top 16% of the PSA distribution. In the trial, therefore, in the absence of treatment, one would expect 55% of these deaths to have occurred in screen-positive men, assuming full compliance, or 39% of these deaths after allowing for the fact that 82% of men invited for screening accepted and 86% of screen-positive men had a prostate biopsy ($55\% \times 82\% \times 86\% = 39\%$). The prostate cancer mortality reduction in the trial was approximately 25% from 7 to 10 years and 50% beyond 10 years (see Figure 2), which broadly fits with the 39% expected reduction, on the assumption that most of these deaths were prevented by early treatment.

What have we learnt from these two trials? Both show no mortality reduction within the first seven years after the start of screening. A reduction in prostate cancer mortality of about 50% after 10 years or so is possible, but not proven. Both trials confirm the problem of overdiagnosis: PSA testing detects large numbers of indolent cancers that are best not detected. In both trials indolent cancers could not be distinguished at the time of diagnosis from those that caused death, so that unnecessary hazardous treatment was given to many men (about a quarter of screen-positive men, or 4% of all men). The human cost of screening is therefore high.

So what is the verdict? For the present, a screening programme that requires 16% of screened men to have a prostate biopsy and a quarter of these (4%) to have surgery or radiotherapy to the prostate, with their serious complications, but cannot guarantee any reduction in mortality, is unacceptable. To do so much harm, we would need a guarantee of sizable benefit. But there is hope for the future, if the prostate cancer mortality reduction were confirmed and if a method of distinguishing the lethal from the indolent cancers on biopsy specimens were identified (work on this is ongoing). Screening might then be justified, though about 16% of screened men would still have to have prostate biopsies yielding a reduction in prostate cancer mortality that may be as high as 50% from 10 years after the start of screening.

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ACKNOWLEDGEMENT

I thank Jon Bestwick for statistical assistance.

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