Screening for prostate cancer: time to put all the data on the table

Ian Haines and colleagues call for access to all the publicly funded clinical trial data from two major trials to settle the controversies around screening for prostate cancer with prostate specific antigen

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Screening for prostate cancer with the prostate specific antigen (PSA) test remains controversial, and guidance varies around the world. One urology association in Australia and New Zealand recommends offering PSA testing to men aged 55-69, while the US Preventive Services Task Force recommends against its use, giving it a D recommendation—that is, “moderate or high certainty that the service has no net benefit or that the harms outweigh the benefit.” How are patients and physicians to reconcile these divergent views?

On the one hand, 2-3% of men die from painful metastatic prostate cancer at a median age of 80, and invariably men want to take all reasonable steps to avoid this. On the other hand, the incidence of disease is 20-25% in a random population within the generally accepted normal range of PSA of 0-4 ng/ml; overdiagnosis and overtreatment are common; the benefits of radical treatments are small; and the common toxicities of radical treatments, such as impotence and urinary incontinence, are a concern for many men. With these considerations in mind, physicians depend largely on the evidence from three high profile randomised clinical trials to advise men whether to be screened, and perhaps treated, for early stage prostate cancer. Although two of these trials—the European Randomised Study of Screening for Prostate Cancer (ERSPC) and the Gothenburg trial—reported a benefit for PSA screening, the large US Prostate, Lung, Colorectal and Ovarian (PLCO) trial found no benefit. As the debate about PSA screening for prostate cancer continues, we believe that there are questions that can be answered only by de-identified patient data from all three trials. However, only the data from the US trial have been made available for independent scrutiny. We call for de-identified data from the two European trials also to be made available.

Incidence and treatment of prostate cancer in era of PSA screening

Before the availability of PSA for screening, the age standardised incidence of prostate cancer in Australia in 1982 was 79 per 100 000 men. Incidence of prostate cancer has since risen by 144% to 194 per 100 000 men by 2009. A fifth of Australian men aged 65-74 had a PSA screening test in 2012. The death rate from prostate cancer death decreased slightly from 34/100 000 men to 31/100 000 over these 30 years, which could be due to improvements in treatment as much or more than to early detection by screening. By 2009, an extra 115 men out of every 10 000 were having prostate cancer diagnosed to possibly save up to three lives. This indicates a high rate of overdiagnosis.

Testing has also led to a high rate of overtreatment. For every 1000 men having a PSA test, 87 will have a false positive result that will lead to a biopsy and 28 will experience a side effect from the biopsy that they consider to be a moderate or major problem. Twenty eight of every 1000 tested will have prostate cancer diagnosed, and 25 will choose radical treatment (surgery or radiation) because of uncertainty about progression, many of whom would have remained asymptomatic for life. Seven of these 25 will develop persistent impotence or urinary incontinence and some will develop chronic bowel symptoms. Current evidence suggests two of the 1000 men will avoid death from prostate cancer and two more will avoid metastatic disease before 85 years of age.

What are the results from the three trials?

The table summarises the three major publicly funded trials. The most widely publicised study to claim benefits for PSA screening was the ERSPC trial (published in 2009 and updated in 2014). There were 355 deaths from prostate cancer.
in the core age (55-69) screened group of 72,891 men (0.49%) and 545 in the core age control group of 89,352 men (0.61%). The authors claimed a significant 2% reduction (95% confidence interval 0.69 to 0.91, P=0.001) in relative risk of death from prostate cancer specific from PSA screening in men aged 55-69. However, when the complete dataset of men between 50 and 74 years of age is used, rather than just those aged 55-69, the difference falls to 15%, which is not significant.9 Without examining individual patient data it is not possible to confirm any benefit.

Overview of publicly funded clinical trials of PSA based prostate cancer screening

Why we need de-identified patient data

These data matter because the two positive European studies are influencing many men worldwide to have regular PSA screening. However, it has still not been established that the improved outcomes for the screened groups was due to screening rather than the apparent large imbalance in treatments used between equivalent risk patients in the study and control groups. The detailed mortality data for both studies remains unreported and unavailable for independent review.

Independent evaluation of the European studies have drawn attention to their apparent shortcomings and possible unintended biases, but the study authors have dismissed these evaluations without directly answering the core questions.1-14 For ERSPC, these include:

- The extent of contamination by previous PSA screening in each of the seven European countries
- Whether the much greater use of androgen deprivation monotherapy in control patients was associated with increased mortality. If so, this unintended bias would affect any conclusion that PSA screening reduced deaths
- Whether data pooling between the seven countries was valid when five of the seven studies, including the largest study from Finland (which contributed nearly half the patients overall), found no benefit2
- Whether the claim of a significant 20% relative risk reduction in disease specific mortality in men aged 55-69 years is valid, and why the reduction is not significant in the wider age group
- Whether the policy in some countries of not informing the controls they were in a study created awareness bias towards the screened group
- The extent of harms of screening, investigating, and treating men for early stage prostate cancer.

Why haven’t the data been made available?

Validation by independent outside investigators is the bedrock on which the integrity of all scientific research rests. More than seven and five years, respectively, after their initial publication, much of the data from ERSPC and Gothenburg remain embargoed despite requests for their release.

For the ERSPC trial, Schroder and coauthors recently stated that: “Further analyses are continuing within ERSPC, and unpublished data will not be released until these analyses have been completed.”15

For the Gothenburg screening trial, Carlsson and coauthors have stated that: “Data from the Gothenburg randomized trial are not available to outside investigators.”16

If physicians are to be able to provide the most up-to-date advice to patients, the above statements are no longer acceptable. Given that the first ERSPC publication was in 2009, it seems reasonable that the authors provide a more specific timetable for the release of de-identified raw data than the current open ended position, which can go on for years.

In stark contrast, the US National Cancer Institute provided access to de-identified participant level data for the PLCO trial less than four years after initial publication. The data, which are available through the Cancer Data Access System web portal,17 include PSA screening results, compliance, control arm screening contamination, diagnostic work-up, complications, screen detected v. interval diagnosis, histopathological type, grade, stage, initial treatment, and cause of death from death review.

The institute has shown that data from publicly funded clinical trials can be released within a short time frame. As has been pointed out previously, the process of de-identifying patient data is not particularly time consuming, and failure to share raw data “will only strengthen the public perception that we do clinical trials to benefit ourselves, not our patients.”18

Researchers should therefore be legally required to publish the raw data from human trials within five years after first publication of results.19

Access to publicly funded trial data

Since the ERSPC and Gothenburg trialists and their institutions are funded by taxpayers and philanthropic sources, the policy of restricting publicly funded data from external inspection is not consistent within the expectations of their funders. It is also at odds with widespread investigator and international policy statements,19-20 as well as editorial statements from many high impact medical journals. The European Medical Agency (EMA) has a policy that “data recipients should be granted complete freedom to engage in exploratory reanalyses of the evidence,”21 and its policy on enhanced access to clinical trial data provides a legal basis for the release of data produced in the European Union.22

Krumholz and Peterson have summarised the detailed arguments for data sharing.23 Lehman and Loder’s perspective, although dealing predominantly with missing data, is also applicable to PSA trials: “Retrospective disclosure of full individual participant data would be an important first step towards understanding of the benefits and harms of many kinds of treatment.”24

Countless people worldwide have provided funds to cancer organisations with the expectation that their contributions will help to accelerate progress towards cancer “cures.” The data from these trials therefore ultimately belong to the public. In addition, the WHO has outlined the compelling reasons, including the Declaration of Helsinki, why prompt public disclosure of clinical trial data is an ethical imperative.25

What is the solution?

Researchers who provide timely access to clinical trial data are meeting their duty to trial participants and funders as well as helping to ensure that physicians and patients do not have to make decisions based on partial evidence. In the future, we propose that access to de-identified patient data within a specified timeframe should be a precondition for receiving

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public funding, and breach of the agreement should lead to cessation of funding until data are shared. Journal editors should also insist on data release as a condition for publication of these studies. If questions about trial findings persist and clinically important data about screening for prostate cancer remain inaccessible to outside investigators, the two European trials should be deemed inconclusive. Clinicians giving advice to men on PSA screening should reflect the uncertainty about the balance of benefits and harms.

Contributors and sources: IH has been a full time medical oncologist for over 30 years. He helped to analyse the clinical trial data and added the clinical expertise and experience of treating and advising many men with either early or advanced prostate cancer. RA is an immunologist who discovered PSA in 1970, which led to the development of the PSA test. He has expertise in biomarkers, and in the development and metastasis of cancer, particularly of the prostate. He has written numerous articles and books about PSA screening. GM analysed clinical trial data and liaised with trial authors and funders on aspects of data release. His expertise is in molecular and clinical genomics, biomarker analyses, and invited commercial-in-confidence advice to private institutions, investors, and companies on technologies in translational medicine. All authors contributed to writing and revising the article. IH is guarantor.

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**Key messages**

Prostate specific antigen testing of asymptomatic men has created a public health problem of overdiagnosis and overtreatment.

Data from two of the three major publicly funded clinical trials have not been made publicly available.

Publicly funded trial data, particularly for areas like PSA testing, largely belong to the patients and to the public.

Funders and journals should consider imposing conditions requiring release of data for future trials.

Physicians should make clear to all asymptomatic men considering screening that the evidence on the benefits remains unresolved.

### Table

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison</th>
<th>Population</th>
<th>Effect on disease specific mortality</th>
<th>Why de-identified patient data are needed</th>
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</thead>
<tbody>
<tr>
<td>ERSPC* (pooled data from 7 independent trials)</td>
<td>4 yearly PSA screening versus control*</td>
<td>182,000 men aged 50-74 but reported results emphasised men aged 55-69 in a core group</td>
<td>Reduction at 13 years' follow-up (355/72,891 v 545/89,352; 95% CI 0.69 to 0.91, P=0.001)</td>
<td>Clarify whether mortality benefit is significant in both the core age group and the complete dataset</td>
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<tr>
<td>Gothenburg16</td>
<td>2 yearly PSA screening versus control</td>
<td>20,000 men aged 50-64 in Gothenburg, Sweden (60% of these patients were also included in ERSPC)</td>
<td>Reduction at 14 years' follow-up (44/1138 v 78/718 relative risk=0.56, 95% CI 0.39 to 0.82, P=0.002)</td>
<td>Resolution of claimed mortality benefit versus claimed non-significant mortality due to screening</td>
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<tr>
<td>PLCO8</td>
<td>Annual PSA screening for 6 years versus control</td>
<td>76,685 men aged 55-74 in US</td>
<td>No difference at 13 years' follow-up (158/38,340 v 145/38,345)</td>
<td>Independent analyses of between-patient heterogeneity</td>
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*Two centres also used digital rectal examination and transrectal ultrasound until 1997.