

Screening decreases prostate cancer death: first analysis of the 1988 Quebec Prospective Randomized Controlled Trial

Trial: Labrie F, Candas B, Dupont A et al. Screening decreases prostate cancer death: first analysis of the 1988 Quebec Prospective Randomized Controlled Trial. Prostate 1999; 38: 83-91.

Question

Does early detection (by prostate-specific antigen [PSA] testing and digital rectal examination) and treatment of prostate cancer reduce the risk of death from prostate cancer among men aged 45–80 years invited to screening?

Trial details

Design: Randomised controlled trial.

Setting: Population-based study in Quebec City, Canada.

Participants: 46 193 men aged 45–80 years registered on the electoral roll of Quebec City and metropolitan area.

Interventions: Invitation to attend annual PSA testing and digital rectal examination to screen for prostate cancer from November 1988 to December 1996.

Main outcome measure: Deaths from prostate cancer.

Main results: Death rates from prostate cancer over 8 years were 48.7 per 100 000 man-years for unscreened men and 15 per 100 000 man-years for screened men; the death rate was 69% lower in screened men.

Conclusions: The authors concluded that "... this approach demonstrates, for the first time, that early diagnosis and treatment permits a dramatic decrease in deaths from prostate cancer."

Commentary

Rationale for the trial

Screening for prostate cancer could be done by means of PSA testing, but whether this would reduce mortality from the disease was not known. No randomised trials on the question had been undertaken when the study began in 1988.

Trial methods

Benefit from cancer screening can only be validly assessed by randomised trials which compare mortality rates over the same time period among people randomly allocated to early detection and treatment or to usual care. This is necessary because studies of cancer screening can show an apparent benefit even if screening is completely ineffective, because:

- Survival may appear better among screen-detected cases simply because the diagnosis was made earlier ("lead-time bias") — if the time of death is not altered, cases detected by screening may be getting more "disease time" rather than more life time;
- Screening preferentially detects slower, less aggressive cancers which have a longer preclinical (but screen-detectable) phase — fast-growing cancers are more likely to be missed by screening because they are more likely to develop and progress in the

interval between screenings, giving the appearance of better outcomes among screened people ("length-time bias"); and

- People who attend for screening are generally healthier and more health conscious, so their risk of death from any cause is lower.¹

The major strength of this study is that it was designed as a randomised trial and therefore could potentially validly answer the question. Important methodological features of good randomised trials are:

- high-quality randomisation with allocation concealment;
- blinded assessment of outcomes;
- high follow-up rates; and
- analysis by intention to treat.²

The major (and fatal) weakness of this study is that the primary analysis was not as a randomised trial (ie, by intention to screen). The authors compared the prostate cancer mortality rate among men who were screened (15 deaths/100 000 man-years) with that among men who were not screened (48.7 deaths/100 000 man-years). However, they included in the screened group men who had not been allocated to screening, but who sought screening anyway. They also included in the non-screened group men who were allocated to screening but did not attend. They thus destroyed their randomisation, reducing the study to an observational one. Their analysis yields a statistically significant, and apparently impressive, 69% relative reduction in prostate cancer mortality. However, this analysis is almost certainly biased (by one or more of the biases listed above).

The authors also report what they originally set out to do — an intention-to-screen analysis which preserves the randomisation — as a secondary analysis. They report a 6% relative reduction in prostate cancer mortality (relative risk, 0.94) but provide no significance test or confidence interval. We have estimated these from the article's data and found the result to be non-significant, with a 95% confidence interval of about 0.71–1.25. This means the true effect could be anywhere between about a 30% reduction to a 25% increase in prostate cancer mortality. The null result may be attributed to the poor participation in screening in the study. In the group invited to screening, only 23.1% actually attended for screening. In the control group, 6.5% of uninvited men attended for screening. While these "drop-out" and "drop-in" rates do not invalidate the study if it is analysed correctly, they inevitably cause a substantial attenuation of the intervention if it is effective. It is possible to adjust for this attenuation (due to poor participation) by methods previously described.^{3,4} However, in the case of this trial, adjustment will not be useful, as the adjusted estimate will also be non-significant, with a wide confidence interval.

New information

None — this trial contributes no new valid information.



Implications for clinical practice

None — we still have no evidence from good-quality, randomised trials about whether screening for prostate cancer reduces prostate cancer mortality. Two large trials are in progress, but are not expected to report results for some years yet.

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Competing interests

None identified.

References

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