The dilemmas of prostate cancer screening

TO THE EDITOR: Recent articles in the Journal reflect the continuing polarisation of the debate on prostate-specific antigen-based screening and the extent to which major clinical trials reveal whether lives are saved by intervention and/or watchful waiting.1,2 All clinical trials have limitations, and the ERSPC (European Randomized Study of Screening for Prostate Cancer)3 and the United States PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) are no exception.3,4 The calls by two senior authors of the ERSPC trial to evaluate only high-quality studies and to avoid pooling heterogeneous data are commendable.1 However, to then argue that only their trial satisfies these criteria is scientifically questionable, since this multi-country trial is compromised precisely by this action.

In the ERSPC, prostate cancer mortality data from Finland, Italy, Switzerland, Belgium and Spain showed minimal mortality differences between the screening and control arms, and were congruent with the PLCO data, in which no lives were saved by intervention. The data from Sweden and the Netherlands, however, were clearly divergent from other European countries and yet were inexplicably pooled with them. Further, no consideration was given to the equal plausible alternative of an increase in prostate cancer mortality in some control cohorts owing to their differential treatment. This would also yield fewer deaths in the screening arm, but not because of lives saved by intervention. It is therefore still premature to so boldly claim that significant numbers of lives are saved by screening. In terms of avoiding harm and maximising hope, is it not prudent to more closely and carefully scrutinise such crucial aspects of clinical trial data?

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Competing interests: No relevant disclosures.
doi: 10.5694/mja13.10851


TO THE EDITOR: We are concerned by conclusions drawn by Del Mar and colleagues,1 in stating that because some autopsy studies have claimed more than 50% prevalence of latent prostate cancer in men aged over 60 years, this could be considered normal, and that these latent cancers result in a high level of overdiagnosis of prostate cancer. The study cited was conducted at Wayne State University, Detroit, in the early 1990s and indeed showed that as many as 70% of African American men in that age group showed latent prostate cancer.2 However, other articles relating to these data show that the lesions were very small, on average less than 2.3 mm, and were of a very low grade, mainly with a Gleason score of 2-5.3,4

In 2013, pathologists would regard carcinoma with a Gleason score of less than 6 as a rarity, and question the existence of neoplasia with a Gleason score of 1+ 1 = 2. This is reinforced by a study that reviewed 150 cases of low-grade carcinoma diagnosed at the Mayo Clinic between 1960 and 1970 and showed 21% of these to be misdiagnosed benign lesions.5 Reliance on studies such as that cited by Del Mar et al can greatly overestimate the risk of overdiagnosis of prostate cancer. Contemporary studies have shown a rate of about half this prevalence.6 Further, the clinical relevance of such small lesions has to be questioned as they would be unlikely to cause a detectable PSA rise or to be sampled by undirected core biopsies using current methods.

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McKenzie et al

TO THE EDITOR: Recent articles in the Journal evaluating the evidence on screening for early-stage prostate cancer1,2 failed to mention one of the most important pieces of evidence ever published on the treatment of prostate cancer.3 This randomised controlled trial (RCT) showed that, compared with observation, radical prostatectomy did not significantly reduce all-cause or prostate cancer mortality over at least 12 years among men with clinically localised prostate cancer diagnosed in the era of prostate-specific antigen (PSA) testing.3

The underlying premise of performing screening trials to detect cancers at an earlier stage is that the treatment given to the increased number of patients diagnosed with early-stage disease will cure or benefit more patients than no treatment at all. While this is true for surgery for bowel cancer, it has not been proven for radical treatment, particularly prostatectomy, for early-stage prostate cancer. In spite of this fact, there has recently been a stage migration towards earlier diagnosis in Victoria, and a large increase in the use of radical...
prostatectomy among men with clinically localised disease.4

Hugosson and Carlsson conclude by stating, very reasonably, that men facing a decision about PSA screening should be given written information about the best evidence available today.2 Surely this evidence should include that, in the PSA-testing era, the only RCT of the surgical treatment recommended to many of these men has shown that this treatment is no better than no treatment, and that it also causes significant morbidity?

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Competing Interests: No relevant disclosures.
doi: 10.5694/mja13.10833


TO THE EDITOR: We read with interest Del Mar and colleagues’ “re-examination” of the evidence for prostate cancer screening.1 Rather than presenting a balanced view, they have pursued a lopsided and flawed review of the data.

First, they have given equal weighting to the results of the screening trials from Europe (ERSPC [European Randomized Study of Screening for Prostate Cancer]) and North America (PLCO [Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial]), when clearly the contamination of the “non-screened” arm of the PLCO (about 50% of men in the non-screening arm were actually screened) is, by any statistical analysis, a failure of study design. The authors’ comment that “those on either side of the debate read the same information but interpret it differently, declaring that it supports their unchanged positions”,1 is disingenuous. What they should point out is that opposers of screening point to a flawed study (PLCO), and supporters of selective screening use a superior trial (ERSPC). As Hugosson and Carlsson’s article highlights, they also fail to include the latest update from the ERSPC.2

Second, Del Mar et al misrepresent the positive effect that prostate-specific antigen testing has had on prostate cancer mortality. Between 1991 and 2010, the age-standardised mortality rate for prostate cancer fell from 44/100,000 to 31/100,000, a 30% reduction.3

Australia has embraced surveillance,4 further minimising the impact of overdiagnosis, the very problem that even the ERSPC trial raises. But over time, the number of men needed to treat will continue to fall, resulting in harm reduction, and appropriately selected men will have radical treatment, saving lives. This perspective is missed by Del Mar et al.

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Competing interests: No relevant disclosures.
doi: 10.5694/mja13.10779


IN REPLY: We wish to make some comments in response to Haines’s point that the PIVOT (Prostate Cancer Intervention Versus Observation Trial) failed to show any benefit from radical prostatectomy (RP) over surveillance.

First, in the PIVOT, a benefit of RP in terms of reduced all-cause mortality was suggested in men with a prostate-specific antigen (PSA) level > 10 ng/mL and in men with intermediate- and high-risk prostate cancer (PC).1

Second, the PIVOT is not the only randomised controlled trial of RP versus observation. The large, well conducted, SPCG-4 (Scandinavian Prostate Cancer Group Trial Number 4) showed a clear benefit from RP over watchful waiting

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Lawrentschuk et al

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Haines

Del Mar et al
It is a common misunderstanding to believe that screening trials could show any effect on all-cause mortality; this is not possible because of the low statistical power at early follow-up.\(^4\) Miklos’s statement about differential treatment is another false apprehension of our trial. In the ERSPC, as well as in the Göteborg trial, the proportion that had curative treatment (RP or radiotherapy) was similar among men with low- and moderate-risk tumours in the screening groups compared with those in the control groups.\(^5,6\)

Finally, we agree that the focus of PSA screening should be on maximising benefits and minimising harms, especially minimising long-term side effects from treatment that substantially affect quality of life.\(^6\) Future screening calls for a risk-stratified approach that focuses on the benefit for the individual.

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Competing Interests: No relevant disclosures.
doi: 10.5694/mja13.10905


\(^5\) Wolters T, Roobol MJ, Stenling M, \emph{et al.} The effect of study arm on prostate cancer treatment in the large screening trial ERSPC. \emph{Int J Cancer} 2010; 126: 2387-2393.


IN REPLY: We thank Lawrentschuk and colleagues for the critical response. We would like to respond to several wrong assertions:

1. We did not give equal weighting to the results of the ERSPC (European Randomized Study of Screening for Prostate Cancer) and the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial). Standard meta-analysis practice is to weight studies by the inverse variances of their effect estimates.\(^1\) Accordingly, the results of the ERSPC were weighted about double those of the PLCO.

2. We adjusted the Cochrane review for contamination of the non-screened arm of studies (see Del Mar et al., Box\(^6\)).

3. We included the updated data of the ERSPC (published between our original submission and its accepted revision).

4. We do not misrepresent the positive effects of prostate-specific antigen (PSA) testing: the observed 30% reduction in prostate cancer mortality is based on selected data, and can be credibly explained by many possible confounders (including improved treatment), reinforcing the need for randomised controlled trials (RCTs) to evaluate screening.

So, we do not agree that our perspective is unbalanced. Rather, we believe that the proposal by Lawrentschuk et al, that surveillance be used as an alternative to full screening — without mentioning the potential harms of surveillance itself\(^6\) — suggests imbalance. Surveillance is a management option after screening, and is in urgent need of critical evaluation.

We also thank Miklos for pointing out the difficulties associated with heterogeneity of studies. We agree that careful assessment of trials is important.

We thank Haines for pointing out an RCT that showed radical prostatectomy to be ineffective compared with watchful waiting for early prostate cancer\(^4\) (now supported by a cost-effectiveness analysis).\(^6\) However, this study was possibly underpowered, and many men were not referred from PSA screening (so more men may have had microscopic metastases than in a screening trial).

We thank McKenzie and colleagues for drawing attention to different prevalence estimates of latent prostate cancer.\(^6,7\) There have been many similar studies. One summary of these suggests that rates vary by as much as 31%-83% in those aged older than 80 years and by 5%-46% in those aged 51-60 years\(^6\) (with some of this variation no doubt originating from different diagnostic thresholds, but also different sampling rates: by race, higher in African Americans than in Caucasian Americans; and by geography, higher in developed economies such as Australia than in developing economies such as in Africa). These latent prostate cancers in developed economies\(^8\) are so much more prevalent than the incidence identified by PSA testing that they must be contributing to overdiagnosis.

The observation by McKenzie et al, that pathologists now rarely report prostate carcinoma with a Gleason score less than 6, begs an explanation. One possibility is diagnostic drift, in which what was once low-grade is now reported as higher to be on the safe side.

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Competing Interests: No relevant disclosures.
doi: 10.5694/mja13.10923


\(^3\) Bergman I, Litwin MS. Quality of life in men undergoing active surveillance for localized prostate cancer. \emph{J Natl Cancer Inst Monogr} 2012; 2012: 242-249.


\(^7\) Sakai WA, Haas GP, Cassin BF, \emph{et al.} The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. \emph{J Urol} 1993; 150: 379-385.