Does PSA screening reduce prostate cancer mortality?

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In this issue (page 586),[1] Linda Perron and colleagues question whether the recent decline in age-standardized prostate cancer mortality rates in Quebec could be attributed to screening with the serum prostate-specific antigen (PSA) test. By comparing the change in the incidence rate of prostate cancer between 1989 and 1993 with the change in the prostate cancer mortality rate between 1995 and 1999 in 15 birth cohorts, and in 15 regions of Quebec, the authors have elegantly shown that increased screening efforts with the PSA test were not correlated with the subsequent declining mortality rate.

PSA-based screening for prostate cancer remains a controversial issue. The availability of presumably valid screening tests and the potential success of curative treatment options such as radical prostatectomy have prompted some health authorities in the United States to advocate prostate cancer screening in men who ask about the PSA test.[2,3] On the other hand, the Canadian Urological Association and most health authorities in the European Union still discourage the practice of prostate cancer screening.[4,5]

In the United States, following several decades of gradually increasing death rates that reached their peak in 1993, the prostate cancer mortality rate began to decline steadily in the late 1990s. Since 1993, the prostate cancer mortality rate has decreased by 17.6%, at an annual mean rate of 4.4% between 1994 and 1997.[3,6] In Canada, the age-standardized prostate cancer mortality rate declined by 9.6% between 1991 and 1996.[7] Some have already suggested that this trend provides evidence for the effectiveness of screening with the PSA test,[8] however, the significance of the data concerning the decline in prostate cancer mortality is subject to differing interpretations.[9–11]

Many physicians consider that the application of the PSA test may not be the main reason for the decline in prostate cancer mortality. The reported decline may be the result of increased use of curative treatment options in cancers diagnosed by digital rectal examination (DRE) before the advent of PSA screening and the availability of improved treatment options for advanced prostate cancer, such as the early application of luteinizing hormone-releasing hormone (LHRH) agonists. Changes in diet and lifestyle[12,13] and improvements in environmental conditions[14] may also have been responsible for improved outcomes in recent cohorts. The observation that mortality rates for prostate cancer have also declined in England and Wales, countries in which prostate cancer screening was only infrequently applied in that same period, seem to support these assumptions.[15] Last, misclassification of deaths, that is "attribution bias" or the incorrect labelling of deaths from other causes as being death from prostate cancer, may account for some of the reported changes as well.[16]

Indirect evidence for a possible beneficial effect of prostate cancer screening came from the urology department of the University of Innsbruck, Austria, where, in contrast to other parts of Austria, the PSA test had been made freely available to the population in 1993 and acceptance of testing was high.[17] The investigators reported 33% fewer prostate cancer deaths than expected in the Innsbruck area between 1996 and 1999 in men aged 40–79 years. The authors concluded that the policy of making the PSA assay universally available to the population (and at no cost) might have reduced the prostate cancer mortality rate in that population.[17]

In the Innsbruck study, however, ascribing observed changes in mortality to widespread PSA testing done only 3–6 years earlier is dubious. By comparison, in breast cancer screening an interval of at least 9 years was expected before any impact of an effective breast cancer screening program with mammography could be seen in the population.[18] As shown by Perron and colleagues,[1] the observed changes in the prostate cancer mortality rates so soon after the onset of widespread PSA testing are unlikely to be the result of increased screening efforts given the long natural course of most prostate cancers. If a beneficial effect of screening for prostate cancer with the PSA blood test is present at a population level, it will only begin to appear when the mean lead time of prostate cancer (the time by which diagnosis is advanced by screening) and the mean time from the clinical diagnosis to prostate cancer death have passed, that is, at least a decade after the initiation of screening efforts.[11,19]

The definitive answer to the question of whether PSA-based screening for prostate cancer leads to a decline in disease-specific mortality lies in the careful performance and completion of randomized controlled trials (RCTs). In such trials, following randomization, the screened group and the control group would be similar with respect to baseline characteristics, biases and confounders would be prevented, and changes in cause-specific mortality could be attributed to the application of the screening tests and early treatment. To date, only one RCT has reported an important primary end point of prostate cancer screening, namely, the prostate cancer death rate.[20] This trial in Quebec showed that PSA-

based screening for prostate cancer resulted in a reduction in prostate cancer mortality of up to 70% in those subjected to screening compared with those who were not.[20]

This study has been criticized, because the reseachers randomly allocated men to study groups before they agreed to take part in the RCT. In fact, only 23% of the trial population were willing to participate. The resulting decrease in statistical power could not be resolved, as the authors attempted, by transferring men from the control group who spontaneously sought a PSA test to the treatment arm of the trial or by the reverse manoeuvre for men in the treatment group who refused screening. Both ploys further compromised and invalidated the randomization.[21] The study has also been faulted for the long lag time between randomization and screening — on average, 3 years. Given that only men without a diagnosis of prostate cancer could participate in the trial, those who were not screened at the time of analysis were at risk of prostate cancer mortality for a substantially longer period than those men in the screened group.[22]

Large-scale RCTs with the prostate cancer death rate as the primary end point were also begun in Europe and the United States in the early 1990s, namely, the European Randomized study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, Ovarian cancer (PLCO) screening trial respectively. Therefore, a final answer to the question of whether screening for prostate cancer is truly beneficial at a population level can only be answered when these trials have been completed and properly analyzed, that is, not until the middle of the present decade.

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Competing interests: None declared.

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