

## Various Statistical Analyses Indicate a Marked Reduction of Prostate Cancer Death in the Quebec Trial

To the Editor:

The title of the Letter-to-the-Editor suggested by Boer and Schröder is at best misleading and certainly wrong.

First, our study was not an observational study but, as clearly described, a prospective and randomized trial, the first to be started and therefore analyzed and possibly the only one having a true control group with minimal contamination by screening (estimated at 6.4%). Contrary to what Boer and Schröder said, the data were first and most importantly analyzed according to the design of the trial. The difference between the invited screened and the not-invited, not-screened men was, as mentioned above, 67% in favor of screening ( $P = 0.02$ ). In fact, this is already conclusive evidence and no pooling of data is necessary, although this was done in order to examine in detail all possibilities and maximize the use of the data.

In fact, the three potential biases suggested by Boer and Schröder are not valid, and we are pleased to explain why:

1. Contrary to their suggestion, the exposure of men in the unscreened group occurred at a younger age, i.e., 3 years, thus with a lower risk of prostate cancer death. Moreover, the longer duration of exposure in this group was taken into account by expressing the data per 100,000 man-years, as discussed above. In addition to this oversight of Boer and Schroder, the example provided is wrong for at least two reasons:
  - a. With the hypothetical situation proposed, namely a linear model with 10% of deaths per year among the men diagnosed with prostate cancer, men will start dying for the second time at the eleventh year (certainly not realistic). This model leads to more deaths from prostate cancer than the number of men diagnosed with prostate cancer! It is clear that the death rate should go on a plateau much earlier, as explained above.
  - b. The calculations regarding the number of deaths obtained by multiplying by an average time corresponding to half the duration of screening

does not properly express the hypothesis proposed. In the nonscreened group, the number of deaths should thus be 560 instead of 490 for an incidence of 80 per 100,000 men over 7 years. The more important error is in the screened group, where the incidence of death should be 60/100,000 instead of the 40/100,000 reported by Boer and Schröder. The calculations presented by Boer and Schroder rely on a linear progression of deaths, while their assumption requires an arithmetic increase in the number of deaths. Every year, deaths occurred in the groups of men diagnosed each year, up to the current year. Moreover, as shown above (see fourth paragraph of the answer to Alexander and Prescott), adjustment for the number of years of follow-up in the screened group leads in fact to a reduction of deaths from prostate cancer in the screened group, of 65%.

The model proposed is thus clearly inappropriate and, in addition, errors were made in the calculations.

2. The same errors of calculations are found in this paragraph. Instead of  $490 - 160 = 330$  deaths, one should read  $560 - 240 = 320$  deaths. This would lead to 125 deaths per 100,000 man-years and thus to a ratio of death rates of 60/125 or 0.48 in favor of screening, instead of the 0.34 indicated.

In fact, the real data obtained show a non-significant difference between the invited, not-screened group (53.0 deaths/100,000 man years) and the noninvited, not-screened group (41.6 deaths/100,000 man-years). The actual ratio that we reported (1) was 0.78 and not 0.48. The true data thus show a major difference that provides another argument for invalidating the model suggested by Boer and Schroder. When a model does not fit the experimental data, the problem is with the model.

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TABLE I.

	Not invited			Invited		
	No. of men	No. of man-years	No. of prostate cancer deaths	No. of men	No. of man-years	No. of prostate cancer deaths
Men not screened						
A) Not exposed for 7.4 years	14,419	106,701	69	24,067	178,096	116
Men screened						
B) Not exposed for 3.4 years	1,013	3,444	2	7,233	24,592	16
C) Exposed for 4.0 years		4,052	1		28,932	6
Total	15,432	114,197	72	31,300	231,620	138
Death rate (per 100,000 man-years)			63.05			59.58

3. The possibility of the men screened being more health-conscious is taken into account by the intent-to-treat analysis. This analysis, despite the 76.9% noncompliance, shows a 6% benefit of screening. Contrary to what was mentioned by Boer and Schröder, the intent-to-treat analysis takes care of this potential bias.

The lack of bias towards less prostate cancer death risk in the men who accepted the invitation is further demonstrated by the  $2 \times 2$  table statistics (1). In fact, one would think that the opposite would be true and that the men who accepted screening are those who have symptoms or signs compatible with prostate cancer or who have a family history.

Boer and Schröder suggested other methods of analysis for observational studies, but these do not apply to our study since it was a randomized and not an observational study.

In the second analysis performed according to the randomization arm, we performed the analysis on a most rigorous intent-to-treat basis, without elimination of any man, which led to a relative risk of 0.94 in favor of screening as presented in our paper. One cannot eliminate any subject and still comply with the intent-to-treat principle.

## GENERAL

Since the authors of both Letters-to-the-Editor are closely involved in the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, it is tempting to mention that their trial included only two visits performed at a 4-year interval [J Med Screening 3:97–104, 1996], thus carrying the risk of a very loose association with screening since there will be a large opportunity for cancer to appear and develop to a

relatively advanced stage between the two widely separated visits. Such a trial is in a weak position, because of its own design, to assess the effect of screening on prostate cancer mortality.

It seems appropriate, however, to present our data in a different manner in order to offer new perspectives and facilitate interpretation of the results.

If one takes a population of men at any given time and divides them into two groups (invited and not invited to participate to screening, with no exclusion of any man), men in both groups have thus an equivalent initial risk of dying from prostate cancer. This is exactly what we did at randomization, also making sure that the sociodemographic factors and the age distribution were equal in both groups. The average annual death rate from prostate cancer is approximately 65/100,000 men in the studied population (age 45–80 years), while the average overall follow-up period per man was 7.4 years. Since enrollment in screening was gradual, the average time period during which screened men were actually exposed to the intervention was 4.0 years. This left the screened men with an average period of 3.4 years unexposed to screening, and thus at the same risk to die from prostate cancer as men in the control group.

If, as concluded from our first analysis of this trial, screening leads to a 69% reduction of death from prostate cancer, Table I illustrates the estimated numbers which, in fact, correspond very closely to what we found when performing the intent-to-treat analysis at randomization.

For those who were not screened (line A of Table I), whether invited or not, the number of deaths would be equal to the number of men  $\times$  number of years  $\times$  the death rate, i.e., 69 and 116 in the not-invited and invited groups, respectively. The screened men were, on average, not exposed to screening for 3.4 years (line B

of Table I) before actually being exposed to the intervention for 4 years (line C of Table I). This latter subgroup was the only one that could have benefited from the reduction of mortality due to screening. This would have led to 1 death among the 1,013 contaminants and 6 deaths in the 7,233 men following their positive response to the invitation to be screened. These results are simply based on the subdivisions of the invited and not-invited groups into screened and not-screened men (identical to the suggestion of Alexander and Boer) and the use of a single cause-specific death rate that could only be modified for those exposed to screening.

The calculated relative risk is thus 0.94 in favor of screening, which is exactly what we found (1), accord-

ing to the intent-to-screen analysis, thus confirming our initial estimate of a 69% decrease of prostate cancer deaths in screened men. As the above demonstration and discussion show, all possible statistical methods end up with the same conclusions: screening and early treatment decrease prostate cancer death by about two thirds (as demonstrated by the Quebec Prospective Randomized Controlled Trial).

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