

Author Response: The Quebec Screening Study Shows a 62% Decrease in Prostate Cancer Death

To the Editor: Mark Elwood advises readers to pay attention when reading. Although this goes without saying, we can only agree with his advice. However, as indicated by his letter, all the key elements of our analysis and interpretation are sufficiently clear and fully described in our paper [1] although he suggests that other readers might not interpret correctly the proper information. M. Elwood essentially refers readers to previously published criticisms [2,3] for details on how our conclusions might have been based on “faulty” analyses.

Although answers have already been provided in 1999 [4], this 2004 update of our data provides an excellent opportunity to confront the critics with the predictions they made at that time in 1999. It was then suggested that the screening effect was a mere effect of the differences in the duration of follow-up between the screened and the unscreened men. The recent 2004 publication presents 3 more years of follow-up in both groups, so that the difference in follow-up duration has decreased significantly. According to the reasoning presented then, the so-called “apparent” effect should have dropped by 50% as a consequence of assessing 3 more years of follow-up in both groups. However, this is not verified by our latest data that show that the effect of screening remains very similar: 64% versus 69% specific mortality reduction. Moreover, since the risk was calculated according to the years of exposure, this possibility of bias never existed.

The second argument of the previous criticisms published in 1999 is also expressed in the present letter from Paul Pinsky. In his theoretical example, P. Pinsky adds ten cases of prostate cancer deaths from the invited-screened men to the uninvited-unscreened group to obtain what is qualified again as an “apparent” reduction of 39%. When comparing the invited-screened with the uninvited-unscreened men with his simplified theoretical model, the predicted 39% reduction should drop by almost 2/3; but this is not what is found in our study. In fact, the data show, on the contrary, that the cases in the invited-unscreened group have no impact on the outcome (62% vs. 64% mortality reduction, see Figs. 1 and 4 in Ref. 1). If Paul Pinsky’s theoretical suggestion was valid, it should come to a similar conclusion. Clearly, his model does not hold!

Moreover, since the critical comparison made according to the original randomization is between invited-screened and uninvited-unscreened men (see Fig. 1 in Ref. 1), the possibility of cases of prostate cancer being transferred from invited and screened men to the group of non invited non screened men does not exist.

Moreover, it is not correct to state, as Paul Pinsky does, that the unscreened men in the invited group had to be added to the uninvited-unscreened group to conclude to a two third reduction in prostate cancer deaths. Our paper, in fact, has been careful to make the calculations (see Fig. 1 in Ref. 1) that are limited to the men originally randomized to be screened versus those randomized not to be screened. When the analysis is made between these two groups, the relative risk of death is reduced by 62% ($P < 0.002$) in the screened men. Figure 4 in Reference 1 is simply added as complementary information and there is no need to pool the groups, as indicated in the paper.

Concerning the possibility, as suggested by Paul Pinsky, that there could be a large protective effect of choosing to be screened, this possibility has been clearly seen by us at the beginning and the answer has been clearly stated in our 1999 paper [4]. Moreover, one should refer to our 2004 paper where we can read, on page 312, left column: “We do not believe that the low 24% rate of acceptance of screening introduced a bias. In fact, no shift was seen of men at greater risk of dying from prostate cancer from the screened group towards the group of men who did not accept the invitation to be screened. Accordingly, if men at greater risk would have declined the invitation for screening, the death rate would have been higher among the group of 23,785 men who did not accept the invitation for screening. Accordingly, as will be described later, the incidence of prostate cancer death was the same in the group of 23,785 men who did not accept the invitation to be screened and in the true control group of 14,231 men who were not invited to be screened and

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were not screened at our clinic." The difference between 62 and 52 is not statistically significant and it is therefore not acceptable to build arguments based on data showing no difference. Again, no statistical difference should simply be viewed as no statistical difference. If data showing no statistical difference are interpreted as statistically significant differences, what is the use of statistics, and randomized studies?

Third, it is speculated that there might be a theoretical 50% lower underlying risk of dying from prostate cancer among men invited for screening and who accepted screening. The existence of a lower risk population is not supported by any data and does not fit with what is observed. Reduction in the risk of dying from prostate cancer could, if true, come from two sources. Either there is a lower incidence of the disease in the screened men or the cases diagnosed in those screened men is not (or much less often) clinically significant. The detection rate in our screened population is very comparable to that of other prostate cancer trials [5–9], if not frequently higher. The distribution of the stages and grades (two of the most important prognostic factors) of the detected cases has also shown that the screen-detected cancers were significant and required treatment. Therefore, the facts do not support this purely theoretical assumption either.

Last, it is very unfortunate to read the suggestion from M. Elwood to cite studies supposedly concluding to no relationship between decreases in prostate cancer mortality and screening. This is driven by the very well known cognitive error that misinterprets "lack of proof" as corresponding to "proof of lack of effect." This concept is statistically expressed by the notion of the power of a study design. However, none of the studies cited by M. Elwood has provided an estimate of the statistical power of their studies, thus leading to the conclusion that they cannot and should not conclude rather than conclude negatively. Implying that the lack of proof is a proof of lack of effect is in fact very misleading but rather commonly and unfortunately used in the field of prostate cancer screening.

We can only hope, as time goes by, that the debate on the potential impact of prostate cancer screening, a disease expected to kill 29,900 men in 2004 in the US alone, becomes more objective and positive and that criticisms will be based on arguments thoroughly derived from actual data obtained in high quality and randomized clinical studies. This has been an excellent opportunity to do so. We would like to add that our study has the additional advantage of having been

performed at a time when screening was relatively unknown to the study population, thus limiting contamination of the unscreened group by men who are being screened. Moreover, it should be mentioned that the statistical power of a study is largely dependent upon the amplitude of the difference between groups, thus resulting in a 62% ($P < 0.002$) reduction of deaths from prostate cancer in the 7348 screened men followed for a median of 7.9 years, compared to 14,231 men who were randomly chosen not to be screened. Clearly, the size of our study provides all the statistical significance needed ($P < 0.002$). Moreover, it should not be surprising to realize that statistically significant results are available earlier, since the Laval University Prostate Cancer Screening Trial started 6 and 7 years before the European and US studies, respectively. We can simply hope that these later studies have adopted trial designs and screening algorithms that will allow to show similar effects.

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REFERENCES

1. Labrie F, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. *Prostate* 2004;59(3):311–318.
2. Alexander FE, Prescott RJ, Reply to Labrie, et al. Results of the mortality analysis of the Quebec randomized/controlled trial (RCT). *Prostate* 1999;40(2):135–137.
3. Boer R, Schroder FH. Quebec randomized controlled trial on prostate cancer screening shows no evidence for mortality reduction. *Prostate* 1999;40(2):130–134.
4. Labrie F, Candas B. Various statistical analyses indicate a marked reduction of prostate cancer death in the Quebec trial. *The Prostate* 1999;40:132–134.
5. Labrie F, et al. Screening decreases prostate cancer death: First analysis of the 1988 Quebec prospective randomized controlled trial. *The Prostate* 1999;38:83–91.
6. Candas B, et al. Evaluation of prostatic specific antigen and digital rectal examination as screening tests for prostate cancer. *Prostate* 2000;45(1):19–35.
7. Hoedemaeker RF, et al. Pathologic features of prostate cancer found at population-based screening with a four-year interval. *J Natl Cancer Inst* 2001;93(15):1153–1158.
8. Makinen T, et al. Tumor characteristics in a population-based prostate cancer screening trial with prostate-specific antigen. *Clin Cancer Res* 2003;9(7):2435–2439.
9. Hugosson J, et al. Prostate specific antigen based biennial screening is sufficient to detect almost all prostate cancers while still curable. *J Urol* 2003;169(5):1720–1723.