

CORRESPONDENCE



Prostate-Cancer Screening

TO THE EDITOR: The results of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (ClinicalTrials.gov number, NCT00002540) by Andriole et al.¹ were released prematurely, at the same time that Schröder et al.² were reporting, on the basis of the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Current Controlled Trials number, ISRCTN49127736), that screening with prostate-specific antigen (PSA) saves lives (March 26 issue). The PLCO trial is being portrayed as the underpinning for proposed changes in the mind-set of physicians and patients that prostate-cancer screening and treatment do more harm than good. However, the PLCO trial used an outdated PSA cutoff and permitted the enrollment of a large proportion of men (>40%) who had undergone prostate-cancer screening in the previous 3 years. Furthermore, more than 50% of the control subjects underwent screening during the study. Most men with abnormal results in the screening group did not undergo prostate biopsy for 1 year or more. In the ERSPC trial, mortality curves did not begin to diverge until 7 to

8 years. The PLCO investigators reported their results after a median follow-up of 5 to 6 years for patients with cancer — 2 years before expected metastases and 6 years before expected death from prostate cancer.³ The PLCO trial was flawed at the starting gate, is a mere snapshot taken half-way around the track, and will never be informative regarding the effect of screening on prostate-cancer mortality among healthy men who undergo intelligent screening and prompt biopsy and who receive effective treatment.

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TO THE EDITOR: It is important to recognize that the two randomized trials of PSA screening reported by Andriole et al. and Schröder et al. do not relate directly to the question of whether we should be doing PSA screening. They relate to whether screening should be expanded beyond the levels that are typical of the populations in which the trials were conducted — levels that are reflected in the control groups and in pretrial conditions.

The U.S. National Health Interview Survey in 2005 showed that 62.7% of men between the ages

of 50 and 79 years who did not have prostate cancer had undergone a PSA test and that 48.4% had been tested within the previous 2 years.¹ These frequencies are much greater than those in 14 economically developed countries for which similar data have been compiled. This difference may be related to the fact that the decline in prostate-cancer mortality has been significantly faster in the United States than elsewhere.² A cautious interpretation of the results to date is that the United States would gain no mortality benefit by expanding PSA screening beyond its already high levels, whereas European countries would benefit from such an expansion.

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TO THE EDITOR: The estimation by Andriole et al. that the PLCO trial had a crossover contamination rate of 52% in the control group is almost certainly an underestimate. Subjects were allowed to have one screening within 3 years before enrollment and an unlimited number of earlier screenings. Moreover, the estimation of contamination was made by surveys of patients, but men may have been screened without their knowledge during routine physical examinations.¹ The strong effect of this contamination is reflected in the fact that the likelihood of diagnosis was only 22% higher in the screening group than in the control group and that 94.3% of the tumors that were diagnosed in the control group were at clinical stage I or II — tumors that are diagnosed nearly exclusively by screening. Thus, the study was not a fair comparison between screening and no screening; instead, it was a comparison between annual and ad hoc screening.

We agree entirely that overtreatment of patients with low-risk prostate cancer is a major public health problem.² However, high-risk prostate cancer remains a leading cause of death from cancer, and men should not be denied the opportu-

nity for early diagnosis and selective treatment on the basis of data from the PLCO trial.

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TO THE EDITOR: The findings of the PLCO trial could be explained by attribution bias, a misclassification that occurs when death certificates are used to determine the cause of death in a screened population.¹ Improved prostate-cancer detection was attributed to screening on the basis of a 22% higher incidence of prostate cancer after 7 years in the screening group than in the control group. The cause of death in cases detected by screening is often mislabeled on death certificates as prostate cancer, despite the greater probability of death from other causes among men with prostate cancer.¹ In contrast, prostate cancer would not have been labeled as the cause of death among the undiagnosed cases in the control group, even if it had been the underlying cause (i.e., unrecognized incidence-based mortality²). Therefore, misclassification of the cause of death because of overreporting in the screening group and underreporting in the control group could explain the observed lack of reduced mortality after screening with PSA testing and digital rectal examination.

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TO THE EDITOR: I was not able to discern whether the primary end-point statistic had crossed the efficacy boundary in the ERSPC results. In his editorial, Barry¹ conjectures that the design-adjusted statistical significance was based on a potentially data-driven cash-out on the remaining alpha at the third of four planned interim analyses. However, since Schröder et al. report that PSA-based screening reduced the rate of death from prostate cancer by 20%, the boundary must have been crossed. If so, I think it is very important to point out that the reason for early reporting was the crossing of an efficacy boundary. After all, any attachment of meaning to the qualification “statistically significant” within the context of a sequentially monitored trial requires a crossing of the efficacy boundary. Furthermore, any future discussion of the primary end point of this trial should refer to the numbers therein, even after further follow-up, since follow-up reports can be considered only secondarily to the primary analysis.²⁻⁴

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TO THE EDITOR: The studies by Schröder et al. and Andriole et al. have insufficient discriminatory power to detect an effect of prostate-cancer screening on mortality.¹ Such a conclusion appears to be generally impossible for statistical and practical reasons and clearly marks a limitation of evidence-based medicine. Results of underpowered trials are prone to chance, which also explains why the outcomes of the ERSPC and PLCO trials are ambiguous.

Furthermore, the ERSPC findings depend on a small number of cases. If there had been 11 more deaths from prostate cancer in the screening group, the statistical significance would have van-

ished. With an additional 51 deaths, any benefit of screening would have been lost. Given these numbers, it should be noted that all results from Portugal (involving 17,000 subjects) were excluded after the study was concluded because investigators “were unable to provide the necessary data.” Furthermore, results from only a predefined “core age group” were analyzed. However, this age group differs from the age group specified a priori in the Current Controlled Trials register. This leads to an estimated additional exclusion of 10,000 subjects.

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DR. ANDRIOLE AND COLLEAGUES REPLY: Catalonia states that the results of the PLCO trial were released prematurely and that they provide “a mere snapshot taken halfway around the track.” The published results were complete for 7 years. These results will not change and are important for elderly men and other men with a limited life expectancy. Indeed, in the PLCO trial, more men had been followed for 7 to 10 years than in the ERSPC trial. However, we agree that additional follow-up is needed, and it is ongoing. Also, the PLCO trial was conducted according to standard U.S. practice, with physicians and subjects in the two groups likely to use similar PSA levels to trigger the decision for and the timing of biopsy, and treatments were similar in the two groups.

We agree with Preston that one interpretation of the PLCO trial is that additional annual screening with PSA and digital rectal examination does not further lower prostate-cancer mortality, as compared with the screening and treatment that are already occurring in the United States. However, we are not convinced by Preston that other countries should follow the example of the United States in advocating PSA screening, because the U.S. trends in death from prostate cancer may be due to other factors, including improved treatment, rather than screening.¹ In addition, differences in treatment in the ERSPC trial (as outlined in Section 7 in the Supplementary Appendix accompanying the online version of the article, avail-

able at NEJM.org) may explain the reported differentials in screening-related mortality.

Cooperberg and Carroll seem willing to discount the lack of mortality benefit we demonstrated between the organized screening in the intervention group and the “ad hoc” screening in the control group. If, as they infer, deaths from prostate cancer were largely due to high-risk cancers, it seems very probable that more such prostate cancers would have been detected in the intervention group than in the control group. Moreover, for the majority of men with lower-risk prostate cancer for whom the date of diagnosis was advanced by screening (many men in the screening group and some in the control group), there can only be a detriment associated with side effects of treatment. Also, even with high levels of screening in both groups in our study, at 10 years, with 67% follow-up, 174 men still died of prostate cancer.

With respect to the comments of Ojha et al.: we took great care in the death-review process to avoid the attribution bias they describe. Our unpublished comparison between the results of the blind reviews conducted by the end-point verification team and the death-certificate data showed that such bias did not occur.

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DR. SCHRÖDER AND COLLEAGUES REPLY: We agreed with Preston that the results of the ERSPC and PLCO trials can be interpreted as answers to the question of whether PSA screening should be expanded beyond the ongoing levels of screening in the respective populations. In this sense, unlike the situation in the United States, in Europe the formal introduction of PSA screening might yield an additional effect on prostate-cancer mortal-

ity. In addition, adjustment for noncompliance indicates that among men who actually undergo screening for prostate cancer, a decrease of 27% in the rate of death from this cancer can be expected. Since uncertainty about the adverse effects of screening remains high at this time, this knowledge will be of crucial importance for the decision-making process for patients and their physicians. We doubt that the decrease in mortality from prostate cancer in the United States since 1993 can be attributed to screening alone. Screening has a lead time of 10 years or longer, whereas the extensive use of PSA testing started after 1991.¹ In addition, two treatment regimens, which were used in practice long before 1993, have been shown to reduce prostate-cancer mortality.^{2,3} Furthermore, the frequent use of statins in the United States is likely to have contributed to the decrease in prostate-cancer mortality.⁴ Clearly, the reasons for the decrease in prostate-cancer mortality in the United States are multifactorial.

Izmirlan raises a question about whether the efficacy boundary was crossed in the ERSPC trial. We found the described effect of screening by applying a predefined significance limit of $P < 0.05$, which was adjusted for sequential testing, as described in reference 4 of our article. We believe that Izmirlan is addressing two different terminologies describing the same procedure, since a predefined significance limit is identical to an efficacy-boundary crossing. In addition, at the time of the reported interim analysis of the ERSPC data (including data up to December 31, 2006), the data collection up to December 31, 2008, was already far advanced. The limitations indicated by Izmirlan mainly apply to later follow-up reports, when screening in the control group may have become common.

Dubben questions whether the ERSPC and PLCO trials had sufficient statistical power. Our data satisfy the power calculation that is presented in reference 4 of our article, with sensitivity analysis taking into account both noncompliance and contamination. Statistical significance was observed on the basis of predefined levels. We believe that a reduction of at least 20 to 30% in prostate-cancer mortality will be of great importance for public health and for individual patients worldwide. Agreement on the core age group was reached in 1994 and fixed by contracts in 1996.

Data in the Current Controlled Trials register (ISRCTN) refer to inclusion only and do not specify plans for monitoring and evaluation. Unfortunately, there were no data available from Portugal that would have justified the inclusion of those findings.

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Esomeprazole for Asthma

TO THE EDITOR: In their article on the use of esomeprazole in patients with poorly controlled asthma (April 9 issue),¹ Mastronarde et al. conclude that treatment with proton-pump inhibitors does not improve asthma control in such patients. They also state that despite a high prevalence of asymptomatic gastroesophageal reflux in these patients, the condition is not a likely cause of poorly controlled asthma. In clinical practice, esophageal reflux is usually confirmed by ambulatory pH monitoring with the use of an instrument that assesses reflux episodes in patients with acid reflux but not in those with nonacid reflux.^{2,3} In addition, acid-reflux events that are identified by pH monitoring probably represent a subgroup of reflux events, and pH monitoring during treatment has been considered to be a low-yield measurement.⁴ The data reported by Mastronarde et al. show only that acid reflux is not a likely cause of poorly controlled asthma. In the subgroup analyses, no significant interaction was found between gastroesophageal reflux and factors that are known to be associated with risk, including body-mass index, older age, sex, and former smoking status.⁵ Thus, other possibilities should be explored to explain the high prevalence of asymptomatic gastroesophageal reflux in these patients.

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TO THE EDITOR: Mastronarde et al. conclude that asymptomatic gastroesophageal reflux may not be a frequent cause of poor asthma control. We disagree, because although the use of proton-pump inhibitors diminishes the acidity of the refluxate, it does not reduce either the number or proximal extent of reflux events.¹ Microaspiration and esophageal reflexes may still contribute to airway inflammation in patients with asthma who are receiving a high-dose proton-pump inhibitor. Only trials that include a study group undergoing effective reflux control could possibly support the conclusion cited above. As the authors point out, asymptomatic reflux may be responsible for adverse health effects that are unrelated to asthma. Endoscopy with bi-