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Words of Wisdom

Re: Mortality Results from a Randomized Prostate-Cancer Screening Trial

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N Engl J Med 2009;360:1310–19

Expert's summary:

The prostate component of the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial in the United States was designed to determine the effect of annual prostate-specific antigen (PSA) testing and digital rectal examination (DRE) on mortality from prostate cancer [1]. From 1993–2001, men aged 55–74 yr were enrolled at 10 study centers across the United States. Individual randomisation was performed within blocks stratified according to center and age. The primary exclusion criteria at study entry were a history of prostate cancer and, importantly, starting in 1995, having had more than one PSA blood test in the previous 3 yr. A total of 76 693 men were randomised. Men who were assigned to the screening group (n = 38 343) were offered annual PSA testing for 6 yr and annual DRE for 4 yr. All men who underwent screening and their health-care providers were notified of the PSA value and the results of the DRE. Men with positive test results (ie, a PSA >4.0 ng/ml and/or an abnormal DRE) were advised to seek diagnostic evaluation.

After 7 yr of follow-up after randomisation, vital status was known for 98% of the men. There were 50 deaths attributed to prostate cancer in the screening group and 44 in the control group (rate ratio: 1.13; 95% CI, 0.75–1.70). The authors conclude that screening was associated with no reduction in prostate cancer mortality during the first 7 yr of the trial. However, the confidence intervals around the estimate are wide and are consistent with a reduction in mortality of up to 25% or an increase in mortality of up to 70%. Follow-up in the PLCO trial is planned to continue until all men reach at least 13 yr of follow-up.

Expert's comments:

Is this result surprising, and is it wise to continue this study? In other words, is it reasonable to assume that the results so far will change with more follow-up?

To answer these questions, a closer look at the organisation and reported results of the prostate component of the PLCO study is needed.

A randomised trial, which is designed to explore the effect of an intervention on disease outcome, should fulfill certain requirements.

The first basic requirement is that randomisation is carried out in a blinded fashion. However, next to this, if one wants to be able to measure an effect of the intervention under study, it is of utmost importance that this intervention has not already been applied to the potential participants. Men randomised in the PLCO trial were prescreened. Approximately 44% of the men in each study arm had undergone one or more PSA tests at baseline. Undoubtedly, this will have eliminated prostate cancers detectable with screening from the randomised population. This is confirmed by the fact that the cumulative death rate from prostate cancer at 10 yr in the two arms combined was 25% lower in those who had undergone previous testing at baseline than in those men who had not been tested, an observation that will not change with longer follow-up.

Secondly, to be able to assess the effect of the intervention on disease outcome, the intervention should preferably be applied solely to men randomised to the screening arm. This will ensure a correct assessment of the true effect of the intervention on outcome. However, looking at the rate of testing

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within the two arms of the PLCO trial, we see that this requirement is not met.

The authors report a compliance with the screening protocol of 85% for PSA testing and 86% for DRE, acceptable percentages and similar to the design estimates. However, as noted above, men with abnormal test results were advised to seek diagnostic evaluation to confirm the possibility of having prostate cancer. Results from another report of the same trial show that compliance with this second part of the screening procedure was extremely low [2]. At first screening, the percentages of men with an elevated PSA level (ie, >4.0 ng/ml) or abnormal DRE were 7.9% and 7.2%, respectively. First of all, this is low as compared to men in a similar age range randomised to the Dutch part of the European Randomised Study of Screening for Prostate Cancer (ERSPC), where 13% of men initially presented with PSA levels ≥4.0 ng/ml [3], which, again, points toward prescreening activities before randomisation.

In addition to this low proportion of positive tests, only 40.2% were actually biopsied at first screening. During subsequent screenings in year 2, 3, and 4, this percentage dropped even further, to 32.8%, 31.2%, and 30.1%, respectively. This means that compliance with the complete screening procedure at initial screening was not in the order of 85% but much lower.

In the control arm, PSA testing was also prevalent. According to the data published in the present paper, the rate of PSA testing was 40% in the first year and increased to 52% in the sixth year. The rate of screening by DRE ranged from 41–46%. These data show very clearly that the comparison within the PLCO study is not one between a screening and a control arm but between a screening and a somewhat less-intensive screening arm. It is, therefore, no surprise that no difference is seen with respect to disease outcome, prostate cancer mortality.

Furthermore, the mentioned weaknesses of the PLCO trial will not disappear with more follow-up, since the effect of screening before randomisation and screening in the control arm is irreversible. Therefore, the costs and efforts needed to continue this trial can be better spent. The ERSPC will, however, be able to provide even more convincing estimates than the recently reported 20% prostate cancer mortality reduction in favour of screening because this trial is not plagued with weaknesses in design, low compliance, and high contamination rates [4].

Conflicts of interest: The author has nothing to disclose.

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DOI: 10.1016/j.eururo.2009.03.085

Re: Efficacy of Everolimus in Advanced Renal Cell Carcinoma: A Double-Blind, Randomised, Placebo-Controlled Phase III Trial

Motzer RJ, Escudier B, Oudard S, et al

Lancet 2008;372:449–56

Experts' summary:

The oral agent everolimus (RAD001) is a derivative of rapamycin and is a specific inhibitor of the mammalian target of rapamycin (mTOR) serine/threonine kinase. In a prospective randomized double-blind phase 3 study, Motzer et al have evaluated the efficacy of everolimus (10 mg by mouth daily) in the treatment of patients with metastatic renal cell carcinoma (mRCC) that have failed prior first-line targeted agents for mRCC. Patients included had mRCC with a component of clear cell histology and had progressed on or had stopped previous tyrosine kinase inhibitor (TKI) treatments (sunitinib [(Sutent] or sorafenib [Nexavar]) within 6 mo of their inclusion in the study.