A Different Method of Evaluation of the ERSPC Trial Confirms That Prostate-specific Antigen Testing Has a Significant Impact on Prostate Cancer Mortality

Marco Zappa a,*, Donella Pulitita, Jonas Hugosson b, Fritz H. Schröder c, Pim J. van Leeuwen c, Ries Kranse c,d, Anssi Auvinen e, Sigrid Carlsson b,f, Maciej Kwiatkowski g,h, Vera Nelen i, Alvaro Paez Borda i, Monique J. Roobol c, Arnauld Villers k

* Clinical and Descriptive Epidemiology Unit, ISPO–Cancer Research and Prevention Institute, Florence, Italy; b Department of Urology, Sahlgrenska University Hospital, Göteborg, Sweden; c Department of Urology, Erasmus MC, Rotterdam, The Netherlands; d Comprehensive Cancer Centre The Netherlands, Utrecht, The Netherlands; e School of Health Sciences, University of Tampere, Tampere, Finland; f Department of Surgery (Urology Service), Memorial Sloan-Kettering Cancer Center, New York, NY, USA; g Department of Urology, Kantonsspital Aarau, Aarau, Switzerland; h Department of Urology, Academic Hospital Braunschweig, Braunschweig, Germany; i Provinciaal Instituut voor Hygiène, Antwerp, Belgium; j Department of Urology, Hospital Universitario de Fuenlabrada, Madrid, Spain; k Department of Urology, CHU Lille, University Lille Nord de France, Lille, France

In early 2012, the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial published its findings on the efficacy of prostate-specific antigen (PSA) testing in reducing prostate cancer (PCA) mortality after an 11-yr follow-up period [1], an update of an earlier report [2]. The impact of intervention on PCA (ie, disease-specific) mortality is evaluated by comparing PCA deaths in the screening and control arms. In addition to disease mortality, the trial may be evaluated by a between-arm comparison of the excess all-cause mortality rates in PCA patients [3]. These rates are calculated by dividing, for each arm, the excess number of deaths in cancer patients by the total number of person-years in all participants for the respective arms. The excess number of deaths is defined as the difference between the actually recorded number of deaths and the expected number of deaths in PCA patients (Fig. 1).

What are the advantages and disadvantages of these methods? Disease-specific mortality is considered the best
end point for evaluating the effect of PCa screening in a trial. However, in some PCa patients, the primary cause of death is uncertain; relatively more men with PCa are diagnosed in the intervention arm, so the disease-specific mortality could be seriously biased. An excess mortality rate analysis is unaffected by cause-of-death misclassification but requires an accurate estimation of the expected mortality to avoid biased results.

1. Inaccurate estimation of the expected mortality

In the excess mortality analysis, a valid estimation of the expected mortality is the key assumption. The expected mortality in PCa patients and in PCa-free individuals are assumed to be equal, meaning no increased risk of death other than from PCa.

Two important issues should be carefully taken into account in the estimation of the expected mortality. First, it is well known that people accepting an invitation to screening are generally healthier and may have a lower baseline risk for mortality compared with nonattendees (healthy screenee bias). This concept was also shown in the ERSPC study [4,5]. Second, since PSA screening causes a strong increase in PCa incidence (because of early diagnosis and overdiagnosis), the proportion of attendees among PCa patients is expected to be much higher than that observed in the entire arm. For illustration, in the screening arm of ERSPC, 78% of men were screened at least once, as compared with 90% of PCa patients [6]. The PCa patients in the screening arm represent a selective sample consisting of healthier people with a lower baseline mortality rate [4,5]. It follows that the comparison of the excess mortality rates of PCa patients in the screening and control arms tends to favor the screening arm.

A valid comparison of the excess mortality rates between the two study arms hinges on a correct estimation of the expected mortality (accounting for attendance status) [7].

2. Misclassification of the cause of death

The disease-specific mortality analysis requires an accurate cause-of-death classification. A nondifferential misclassification of the cause of death may cause a loss of statistical power and weakens the strength of association between determinant and event [8]. A bias (systematic error), which would tend to classify the cause of death in relation (positive or negative) to the arm of randomization of the dead subject, is a more worrying possibility. These biases have been called slippery-linkage bias and sticky-diagnosis bias [9]. In the former bias, because of early diagnosis of PCa, deaths for the disease “slip” to deaths for other causes, favoring the screening arm. In the latter bias, because the target of screening is PCa, the disease “sticks” when there are other-cause deaths in the screening arm, favoring the control arm.

To avoid these biases, a standardized causes-of-death revision process carried out blinded for the screening arm by an independent expert committee has been implemented [10]. Nevertheless, blinding can fail, which may induce a bias (eg, cancers with low PSA and small tumor volume are more likely screen-detected).

3. Disease-specific mortality compared with excess mortality: what is expected

Consider a hypothetical situation in which none of the previously mentioned biases affects our mortality estimates, that is, for neither the disease-specific nor the excess mortality analysis. Are the results of these two methods expected to be equal in the absence of biases? Not necessarily.

A death caused by diagnostic/therapeutic interventions is defined as a PCa death if it occurs quite close to the diagnosis/treatment and the relationship is deterministic; if the death occurs some time after the procedure with a probabilistic relationship (eg, a second lethal tumor caused by radiotherapy), it is not counted despite being a consequence of the screening program. This problem could be relevant, since advanced cancer therapies differ from early cancer therapies (more frequent in the screening arm). Overdiagnosis has to be taken into account. In fact, in prostate screening, PCa is detected more frequently in the screening arm than in the control arm. Thus, many more men in the screening arm receive treatment for PCa.

4. All-cause mortality analysis

Theoretically, all-cause mortality analysis is the best approach. This approach overcomes the shortcomings previously mentioned, since it is based on all causes of death (misclassification is no issue) and accounts for indirect mortality. However, PCa accounts for <3% of all...
deaths in the control arm [1]. Therefore, an intervention that decreases disease-specific mortality by 21% would decrease the total mortality by approximately 0.06%. A trial would require >2 million men to have the statistical power to detect such a small reduction in all-cause mortality. Therefore, a decrease in all-cause mortality is not chosen as an end point in trials.

5. Comparison of results

5.1. Disease-specific mortality analysis

PCA-specific mortality results were published in 2009 with an average follow-up of 9 yr [2] and in 2012 with a follow-up of 11 yr [1]. Initially, a 20% reduction (relative risk [RR]: 0.80; 95% confidence interval [CI], 0.65–0.98) in the RR for PCA death was reported, which increased to 21% (RR: 0.79; 95% CI, 0.68–0.91) with the two extra years of follow-up [1]. A statistically nonsignificant 1% reduction in all-cause mortality was reported in both papers (odds ratio: 0.99; 95% CI, 0.97–1.01).

5.2. Excess mortality analysis

Two papers describing an excess mortality analysis within the ERSPC have been published [6,11]. Contrary to the analysis described by van Leeuwen et al. [11], the analysis in the most recent paper [6] properly accounts for the expected mortality estimation issues. In that paper by van Leeuwen et al. [6], the excess mortality rates were 0.29 and 0.37 per 1000 person-years in the screening and control arms, respectively. The RR for excess mortality was 0.77 (95% CI, 0.55–1.08). The result, although not statistically significant, is close to the PCA mortality reduction observed by Schröder et al. [2]: 0.80 (95% CI, 0.62–0.98). In van Leeuwen et al. [6], only four centers were included (Netherlands, Finland, Sweden, and Italy; follow-up to the end of 2006); however, these centers contributed approximately 87% of the entire population enrolled.

6. Conclusions

Taking into account all the previously mentioned caveats, the fact that the analysis by excess mortality reproduces the result obtained in the traditional analysis in terms of reduction of mortality seems to indicate the absence of biases in the coding of PCA mortality in both arms of the ERSPC trial. The same analysis showed that mortality from other causes related to diagnosis and treatment (for the considered period) was no major issue. In conclusion, the excess mortality analysis confirms the robustness of the trial results: PSA screening does reduce PCA mortality.

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**Analysis and interpretation of data:** Zappa, Puliti.

**Drafting of the manuscript:** Zappa, Auvinen, Puliti, van Leeuwen, Kranse.

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