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COMMENTARY

Prostate-specific antigen testing in Tyrol, Austria: prostate cancer mortality reduction was supported by an update with mortality data up to 2008

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Oberaigner et al. 2011 present an update of the Tyrol cohort study of screening for prostate cancer utilizing an observational design with five additional years of follow-up. The study was initiated in 1993 by offering a free PSA-test to all men in the age group 45–74. It is estimated that about 75% of the men had undergone at least one time PSA testing. The study shows for the observation period of 2004–2008 in men above the age of 50, a 30% significant reduction of prostate cancer mortality with respect to the reference period of 1993–1998. This effect increases sequentially during the 5-year observation period chosen by the authors. Also, different risk reductions were seen for different age cohorts. The effect of screening on prostate cancer mortality seen in this study is in line with observations obtained in the European Randomized study of Screening for Prostate Cancer were mortality reduction in men who were in fact screened amounts to 27% after 9 years and 44% after 14 years of follow-up (Schröder et al. 2009, Hugosson et al. 2010).

The authors are correct when they claim that the presented data 'permit to investigate the effect of PSA screening in a real life situation'. Also, the set-up allows a comparison between Tyrol and the rest of Austria. However, inherent to the study are also all the potential disadvantages of a cohort study with poor definition of a number of parameters that could influence the endpoint of prostate cancer mortality. As a consequence, the study remains uninformative with respect to the true value of screening, to future policy making in terms of screening procedures, as well as on potential benefits and harms.

The authors did not clarify the trend in mortality from PCA which occurred before the start of the program. In fact, in the Tyrol area an increase was observed up to 1990 when a decrease started. In the rest of Austria, a rather flat trend was observed up to 2000 when a slight decrease began. The reason of the different trends before the beginning of the PSA testing is not explained. Have factors not related to PSA played a role? This could partially explain the slope of the decrease afterward.

The methodology used is based on prostate cancer mortality estimates in the region of Tyrol and the region of Austria without Tyrol. Three different cohorts based on age and the time of evaluation are formed and provide the basis for this evaluation.

The authors carried out an age-period cohort analysis in order to disentangle the net effect of time periods. The results are interesting, showing no reduction in PCA mortality in the Tyrol study in the first period (1994–1998) as compared to the reference period (1983–1993) (estimator = 0.97, 95% CI 0.84–1.12). A reduction in mortality occurred, although not statistically significant, in the second period (1999–2003) (estimator = 0.86, 95% CI 0.72–1.04) and finally the decrease reached the statistical significance in the third period (2004–2008) (estimator = 0.70, 95% CI 0.57–0.87). This pattern supports the hypothesis that the reduction in mortality is really the consequence of the introduction of PSA testing. In fact, either from a theoretical point of view or as observed in the ERSPC study (Schröder et al. 2009), the effect of early diagnosis on mortality can not be expected in the first

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5 years after the start of the programs. It is worth nothing that this analysis gives a different and more realistic interpretation from what was reported in 2001 (Bartsch et al. 2001). In that paper, a reduction in mortality in the Tyrol area was reported since 1995 (i.e. 2 years after the start of the program) and was interpreted as a consequence of PSA testing.

Some of the limitations of the protocol and present report are described in the paper. These include the inability to evaluate the confounders in relation to the endpoint such as the use of a historical control group, the absence of a validation of the causes of death assigned in the cancer registry and the lack of detailed knowledge about the volume and timing of PSA testing, as well as the limited knowledge that can be accumulated on the harms of screening. These limitations and several others mentioned in this commentary are essential for the understanding of the screening process and for the potential introduction of screening as a healthcare policy.

- The number of participants remains unknown and this prohibits the calculation of detection rates per PSA ranges and per age groups. It would be very interesting to learn about the effect of the application of age-specific reference range and specifically about the effect of cutting these in half after October 19, 1996. This comes down to extremely low cut-off values for biopsy indications for PSA per age group between 1.25 and 3.25. The effect in terms of diagnosis of aggressive lesions and over diagnosis remains unfortunately unknown.
- The absence of data on the frequency of testing, participation rates and biopsy compliance make it impossible to put the data into the context of the controlled trials. During a period where screening for prostate cancer is scrutinized and criticized worldwide, the knowledge provided in this paper is non-contributory in too many important aspects.
- The authors state by citing the paper of Pelzer et al. (2008) that overdiagnosis may have been in an acceptable range of 8–17% based on radical prostatectomy findings. This is very unlikely if one considers that the incidence of prostate cancer given in Fig. 3 increased by a factor of 4 from the baseline figure of about 30/100,000 in 1983 to about 120/100,000 in 2003. Unfortunately, the complete absence of data on the frequency and the results of biopsies in relation to different levels of PSA make a proper appreciation impossible.
- As mentioned, the effect on prostate cancer mortality is evaluated by age groups and time periods of follow-up. The study shows an increasing effect with increasing age at the time of death. Unfortunately, this can not be related to the time of diagnosis or inclusion. It is probable that the increase of the effect obtained when people older than 74 are excluded from the analysis is the consequence of the fact that part of the men older than 74 did not have the opportunity to be screened because they fell out of the target population at the time of the program started. Again, this data support the role of PSA in reducing the specific mortality.
- In measuring the effect on prostate cancer mortality, the added 5-year time period 2004–2008 is utilized. This again creates an artifact which is well demonstrated in the evaluation of the results of the ERSPC study (Schröder et al. 2009) by Hanley (2010). Considering only the last time period of 5 years instead of studying a cumulative effect over the whole time period must show a more favorable mortality reduction because the early periods where no effect is seen are excluded**.** On the other hand, the increasing effect over time is an important observation. In this setting, it gives a rough indication of the time period needed to evaluate screening for prostate cancer. The presented data suggest that even 16 years after the initiation of the study the mortality reduction seen does not level-off. The latter would be an indication of the ultimate follow-up period needed to evaluate prostate cancer screening studies.

This observational cohort study provides additional evidence for an effect of PSA-driven screening on prostate cancer mortality. A number of important confounders mentioned and the potential effectiveness of treatment regimens applied to cancer patients remain unknown. On the other hand, the continuous increase of the prostate cancer mortality reduction over time lends credibility to an effect of PSA-driven screening, even without knowledge of essential details on the procedures followed in this study.

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