PROSTATE CANCER

Honing in on the true value of PSA-based screening

Re-examination of data collected during the European Randomised Study of Screening for Prostate Cancer (ERSPC) has confirmed and strengthened the primary conclusion of the original analysis.

The ERSPC is one of two long-awaited studies of PSA-based screening. When data collected during the first decade were published earlier this year, discrepancies between the conclusions drawn from the ERSPC and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial became evident. The US-based PLCO team detected no significant reduction in disease-specific mortality in their screened cohort. By contrast, the ERSPC investigators determined that screening reduced the rate of prostate-cancer-related death by 20%.

Various explanations for the divergence were proffered, including 'contamination' of the control groups. Monique Roobol and colleagues have now adjusted ERSPC data to account for PSA testing in the control arm. Additional adjustment for nonattendance by men randomized to the screening group was performed. Rather than diluting the initial estimate of benefit, these re-analyses strengthened the original conclusion—screening reduced the risk of dying due to prostate cancer by up to 31%.

Incorporating information derived from population-based studies such as the ERSPC into a management plan for individual patients is problematic. Lead author Roobol explains that "this analysis was mainly done … to provide a risk reduction estimate for screened individuals." To further this goal of individualization, Roobol has headed up a further two studies.

The first of these aimed to identify factors that are associated with an increased risk of developing prostate cancer. Determining which men are more likely to develop the disease would facilitate more-prudent use of screening. Following a comprehensive literature scan, Roobol *et al.* established a framework for risk estimation that includes commonly measured clinical variables. PSA had the greatest predictive power of any single parameter. Useful additional information was provided by prostate volume, ethnicity, and biopsy and family history.

More-selective application on the basis of risk estimation should go some way to overcoming the problems of overdiagnosis and subsequent overtreatment that currently plague PSA-based screening. During the ERSPC, 1,410 men had to be screened and 48 treated to prevent the disease-induced death of 1 man. For many, this is an unacceptable cost–benefit ratio.

The third study published recently by Roobol and colleagues aimed to develop a strategy for reducing the number of unnecessary biopsies without compromising detection of clinically important cancer. The Risk Indicator logistic regression model (www.prostate-riskcalculator.com) was used to estimate the probabilities of screened men in the Rotterdam section of the ERSPC having a positive biopsy or an indolent cancer.

Restricting biopsy to those men with a PSA value and positive-core probability exceeding 3 ng/ml and 12.5%, respectively, would reduce the number of biopsies performed by a third. Up to 15% of malignancies would be missed if this initial screening strategy were employed; however, 70% of these were categorized as potentially indolent—and curable if detected at a later date. All cases of lethal prostate cancer would be diagnosed.

"Efforts should be made [to inform] the general public—as well as treating physicians—of the benefits and risks of PSA testing, and such information should be given to a man before the actual PSA testing takes place." So says Mattias Johansson from the International Agency for Research on Cancer. Johansson and colleagues have concluded that PSA is not sufficiently accurate for use in population-based screening of asymptomatic men.

Likelihood ratios—which are not affected by disease prevalence—are powerful tools for determining a biomarker's value. A positive likelihood ratio of at least 10, and a negative ratio of 0.1 or less, indicates suitability for use in large-scale screening programs. According to Johansson and colleagues' publication in the *British Medical Journal*, PSA cutoffs of 3, 4 and 5 ng/ml failed to satisfy these criteria. The authors recommend that implementation of population-based screening for prostate cancer is delayed until more-suitable biomarkers and diagnostic tools are validated.

Suzanne J. Farley

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Original articles Roobol, M. J. *et al.* Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur. Urol.* doi:10.1016/j.eururo.2009.07.018
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