EUROPEAN JOURNAL OF CANCER 46 (2010) 3037–3039

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# Foreword: Meeting the challenge of prostate cancer

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ARTICLE INFO

*Article history:*
Received 23 September 2010
Accepted 27 September 2010

*Keywords:*
Prostate neoplasms
Early detection of cancer
Screening
Prognosis
Therapeutics

ABSTRACT

Prostate cancer is a key medical and public health challenge. Though it is currently the most common cancer among men in Europe, its natural history, prognosis and treatment are poorly understood in comparison to breast cancer. Prostate cancers diagnosed are very small and prediction of their progression at the individual level is difficult and hence need for aggressive management is unclear. The number of randomised treatment trials remains shamefully small and hence the relative effectiveness of the new treatment modalities introduced is unclear.



The first evidence of prostate cancer mortality reduction by screening was shown by the ERSPC trial in 2009,[1] but no population-based screening programs have been started, as the balance between benefits and harms is still not well established. A major uncertainty is due to overdiagnosis or detection of cancers that would not have surfaced clinically during a man's lifetime. Even if the pathologists largely agree about histological criteria for prostate malignancy, they lack the means to distinguish potentially progressive from non-progressive tumours.

In this special issue, authors involved in the European trials address important aspects of PSA screening. Prostate-specific antigen is one of the most accurate cancer biomarkers, though its characteristics are not ideal. Bangma and Co-workers review the development of the PSA test and several new prostate cancer biomarkers that have been developed to improve specificity and sensitivity of screening.[2] New approaches have also been tested within the ERSPC trial. So far, no consensus has been reached concerning the optimal screening test.

Prostate cancer incidence increased in the 1990s at a pace rarely seen for any cancer type. This is likely to reflect the use of prostate specific antigen testing, though no large comprehensive databases of laboratory tests seem to exist allowing systematic evaluation of the frequency of PSA testing and its contribution to the epidemic of prostate cancer. Bray and co-workers show striking differences across Europe in the most recent temporal trends in prostate cancer incidence and mortality.[3] Highest incidence rates were found in the Nordic countries and lowest in eastern Europe. Even if all 24 countries in the analysis show increases in incidence at some point during the past two decades, some exhibit already a decrease. Mortality has decreased in several western and northern European countries, while an increase was shown for some east European populations. No consistent pattern was found between prior increase in incidence (indicating an effect of screening) and subsequent mortality decline, suggesting that it cannot be attributed solely to screening, but also to improved treatment (surgical, radiotherapy and hormonal approaches as well as combined modality treatment). But the different time trends in PSA testing and treatment throughout the different countries make these ecological analyses difficult to interpret.

Striking differences in prostate cancer occurrence are also reflected between screening programmes. Otto and col-

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0959-8049/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2010.09.037

leagues found no straight forward relation between median serum PSA concentration and detection rate between the ERSPC centers.[4] The median PSA was relatively constant by age and did not reflect the risk of prostate cancer. Yet, populations with higher underlying incidence rates also tended to show higher detection rates. Low risk populations exhibit PSA levels similar to those with higher prostate cancer incidence, which then unfortunately results in lower specificity of screening.

The primary end-point of the ERSPC trial is prostate cancer mortality. Unequivocal determination of causes of death requires extensive and accurate documentation, which is not always available. Cases on hormonal therapy, with comorbidities and particularly multiple cancers often constitute a challenge for cause of death adjudication. Misclassification of causes of death could dilute the effect of screening, if similar in both arms. Comparison of the official statistics with assessment of the cause of death committee in Rotterdam by Otto et al. showed a reasonably high agreement (kappa approximately 0.9), with both sensitivity and specificity of Statistics Netherlands close to 90% (with the expert committee assignments as the reference standard).[5] There was some indication of differences between age groups and over time, which may merit further assessment. However, the analysis also shows differences per arm, possibly due to what is called 'sticky diagnosis'. All in all they feel that reviewing of causes of death using detailed anonymous data has been crucial.

Lead-time is the advancement in time of diagnosis through screening. On the one hand it offers a window of opportunity for cure, but it is also an indicator of overdiagnosis (most obvious when the lead-time exceeds life expectancy). PSA-based screening in the ERSPC has yielded detection rates varying 1.5–5% per screen, which is relatively high given life-time risks of around 10% or lower. Finne and others obtained a rough estimate of lead-time by relating the risk of screen-detected cancer to the cumulative incidence in the control arm by ERSPC center.[6] The estimated lead-times were generally close to 7 years and reflected the underlying incidence rates in the populations. The results suggest similar performance of screening in various centres and indicate that the lead-time exceeded the screening interval but was shorter than the life expectancy, as is desirable.

The long inter-screening interval following the first round (on average 6 years) in Belgium (due to logistic problems) resulted in a substantially higher risk of interval cancers than in other ERSPC centers. Nelen and others estimated that the cumulative incidence was 3%, clearly increasing after 4 years, with no aggressive cases occurring before the 4-year limit.[7] This unfortunate natural experiment suggests that extending the screening interval beyond 4 years may decrease the effectiveness of screening.

A range of neoplastic lesions are detectable in prostate tissue including prostatic intraepithelial neoplasia (PIN) and atypical lesions suspect for prostate cancer (LSPC). The terminology and classification have evolved during the past decade as has understanding of their relation to malignancy. Laurila and co-workers describe the frequency of PIN and LSPC during the entire history of ERSPC covering more than 15 years and more than 50,000 screened men.[8] A strong increase in PIN occurred over the screening rounds, while the prevalence of LSPC remained practically unchanged. The wide variation in frequency of these lesions indicates differences in classification between centres. Both diagnoses were associated with a cancer in the subsequent biopsy, LSPC with probability high enough to constitute an indication for rebiopsy.

Similar to the differences between populations, the temporal trends are reflected in screening. According to Boevee and others, the proportion of T1 tumours among screen-detected cases increased by screening round.[9] The proportion of tumours with favourable prognostic characteristics increased over time also in the control arm. This development was reflected in increasing proportions of patients offered expectant management, while the proportions undergoing surgery or radiotherapy as primary treatment decreased. In organ-confined disease, surgery and expectant management were slightly more common in the screening than in the control arm and correspondingly hormonal therapy in the control arm. These differences may reflect the effect of minor differences in stage, grade or age distribution between the arms.

In a situation where no population-based screening programs have been launched, decision-making requires balancing the pros and cons of screening case by case, by discussions between men somehow being at risk and their physicians, be it general practitioners or urologists with a different spectrum of disease in their mind. This is particularly relevant for men at increased risk for prostate cancer, for instance those with suspected familial prostate cancer. Korfage and others show that recently developed Internet resources provided mainly by non-profit organizations do at their best offer correct, balanced and up-to-date information pertinent for decision-making that enhances autonomous choices.[10] A clear course of action should be defined prior to testing regarding also biopsy decisions and extending to potential treatment for eventual prostate cancer.

The UK ProtecT trial is one of the few randomised trials evaluating the effectiveness of active monitoring relative to radical prostatectomy and external beam radiotherapy.[11] As case finding, PSA testing has been offered to men aged 50–69 years and close to 100,000 (half of the invited) have consented (this part comprising the CaP trial evaluating effect of screening). Approximately 3000 cancers have been detected (detection rate 2%). The study is also collecting biological samples and risk factor information for aetiological research and numerous articles have already been published on psychosocial, genetic and other aspects of prostate cancer.

The papers in this special issue highlight different aspects of the rapidly evolving era of prostate cancer screening and treatment and an emerging knowledge base with a central contribution from the ERSPC trial. The pioneering work has been led for nearly two decades by Professor Fritz Schröder from Rotterdam. He was joined first by Professor Louis Denis and subsequently by teams of pathologists, urologists, epidemiologists, chemists and other scientists from eight countries and their collaborative efforts have showed the way in this crucial issue through a well coordinated effort with a trial involving more than 200,000 men.

## Conflict of interest statement

We declare that we have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within that could inappropriately influence this work.

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