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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Prostate cancer screening: and yet it moves!

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The debate of prostate cancer (PCa) screening has been shaped over decades. There is a plethora of articles in the literature supporting as well as declining prostate-specific antigen (PSA) screening. Does screening decrease PCa mortality? With the long-term results of the European Randomized Study of Screening for Prostate (ERSPC) the answer is clearly YES. It moves! However, in medicine there are no benefits without any harm and thus, screening has to be performed in targeted and smart way-or in other words-in a risk-adapted fashion when compared with the way it was done in the past. Here, we discuss the main findings of the ERSPC trials and provide insights on how the future screening strategies should be implemented.

RESULTS OF THE EUROPEAN RANDOMIZED STUDY OF SCREENING FOR PROSTATE CANCER AT 13 YEARS OF FOLLOW-UP

The ERSPC research trial has been started by 7 European countries between 1994 and 1998. In the "core age group" between 55 and 69 years, 72 891 and 89 352, respectively men were subsequently randomized into intervention (PSA testing and prostate biopsy at the PSA threshold of 3.0 ng ml^{-1}) and control group. The recent report of the ERSPC showed a decreased PCa-specific mortality of 21% with data truncated at 13 years of follow-up.[1] The rate ratio was 0.79 with 95% confidence interval (95% CI) of 0.69–0.91, which was highly significant (P = 0.001). Moreover, for all randomized men aged between 50 and 74 years (82 816 *vs* 99 183 men), the rate ratio is now 0.83 (95% CI: 0.73–0.94, P = 0.004). This is for the first time that the significant reduction of PCa mortality could be demonstrated not only for the predefined "core-age" group but also for the whole cohort in the "intention-to-treat" analysis. The relative difference in mortality between the intervention group and control group remained similar at 21%, but with 4 years of added follow-up the level of significance increased from P = 0.04[2] to P = 0.001.[1] Importantly, the number needed to invite (NNI) decreased by almost half from 1410 to 781 as did the number needed to detect from 48 to 27. This shows that the net benefit of screening intervention is increasing over time, the message of particular importance for younger men with longer life expectancy. In addition to the net benefit, quality of life aspects are of crucial importance when weighing harms versus benefits. In our modeling study, a gain of 73 life years or 56 quality-adjusted-life-years per 1000 men[3] could be demonstrated in the base model. Thus, in conclusion PSA-based screening can reduce disease-specific mortality while maintaining quality of life issues. Notwithstanding this conclusion, the harms of screening are considered to be substantial with as many as up to 50% of PCa overdiagnosis.[4,5] In the ERSPC, men were screened regardless of their life expectancy and irrespective of existing risk for PCa. This underlines the emerging need for a risk-based PCa screening in order to perform a smarter and more targeted PSA-screening of men at risk.

RISK-ADAPTED PROSTATE CANCER SCREENING IN THE FUTURE

The ERSPC is a population-based trial meaning that the results are generalizable for men of each participating country. Among screening attendees, there are healthy men as well as men with various comorbidities. Of 181 999 men randomized, 24.8% men died from all causes during follow-up while only 0.52% in the intervention and 0.62% in the control group died from PCa. This clearly underlines the importance of risk-adapted screening, for both younger ages – as they might suffer longer from treatment-associated side effects and older ages-as they benefit less due to their usually more limited life expectancy.

To further improve the screening efficacy, adoption of retest intervals according to the powerful predictive properties of baseline PSA[6] is recommendable. For instance, the majority of men in screening trials have a baseline PSA below the biopsy threshold (<3 ng ml^{-1}). These men can be offered a risk-adapted screening according to the individual baseline PSA.[7] Moreover, further improvement can be achieved by using risk calculators. Because PCa has a two-faced disease, that can either present with an indolent appearance or an aggressive clinical course, the accurate risk prediction is absolutely mandatory. The fear of missing aggressive PCa had led to early retesting strategies in primary care leading to an increased detection of indolent disease due to the high underlying prevalence of PCa. The rationale for this comes from the misinterpretation of the Prostate Cancer Prevention Trial (PCPT) showing that there is no PSA cut-off at which PCa cannot be detected.[8] However, this study rather showed the prevalence of PCa detectable by prostate biopsy than the true biological dynamics of clinically relevant PCa. This is important, because not every PCa has the same tumor biology. Importantly, roughly 50% of men in the PCPT trial had an age ≥ 70 years, which inevitably leads to a higher detection rate because of a higher prevalence than in men in their 50s or 60s.

There are several online risk-predictors available. The Canadian Sunnybrook risk calculator and the San Antonio PCPT risk calculator are among the known ones.

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However, data from both calculators were collected in very selected cohorts. For instance, the frequency of family history in the Sunnybrook calculator is as high as 50%, and the mean PSA of men without cancer was 8.1 ng ml^{-1}. This does not reflect the normal population characteristics and therefore presumably overestimates the PCa risk.[9] The aim for risk prediction must be to lower the number needed to biopsy ideally without reducing the detection rate for aggressive PCa. The area under the curve for finding aggressive PCa is moderate in both calculators with 0.72 (Sunnybrook) and 0.67 (PCPT).[9] The ERSPC Rottderdam risk calculator instead is more accurate with an AUC of 0.86.[10] When validating calculators for the Chinese cohort Zhu *et al*. could show the clear outperformance of the ERSPC calculator over PCPT, due to previously mentioned flaws. Still even the ERSPC calculator overestimated PCa due to lower underlying disease incidence in the Chinese men. The further improvement appears to be the ProstateCheck App (available from January 2015) with a diagnostic AUC of even 0.89, incorporating prospectively the free-to-total PSA-ratio as one of the first risk calculators worldwide. Moreover, along with proper risk-management by calculators, the use of magnetic resonance imaging (MRI) seems to be a promising tool in daily routine practice. Multiparametric MRI appears to be capable of detecting intermediate and high-grade disease, with negative and positive predictive values above 90%. These improvements along with many to come will help to further optimize PCa screening and reduce the burdensome morbidity and mortality caused by PCa. Further updates and studies emerging from ERSPC will be gold-mine to understand both screening intervention and the natural history of the disease and the extent to which screening is apt for improving patient healthcare.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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