Editorial

Is a single screening round sufficient to detect all high-risk prostate cancers?—lessons learned from the European Randomized Study of Screening for Prostate Cancer Study

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The widespread availability of PSA testing in the late 80s to early 90s subsequently led to questions being asked regarding its suitability in mass screening for the early detection of prostate cancer (PC). The low specificity of PSA for PC in the lower PSA ranges has resulted in over-investigation, and over-diagnosis of indolent cancers, leading to a scenario where the burden of cure frequently exceeded the burden of the disease if left untreated.

The European Randomised Study of Screening for Adenocarcinoma of the Prostate (ERSPC) was started in 1994 to answer whether screening using PSA resulted in a reduction of PC related death and an overall improved quality of life (1). The concurrent Prostate Lung Colorectal and Ovarian (PLCO) trial on PC mortality mirrored this study in the United States (2).

Eight European countries participated in the study, with a total of 162,388 men aged 55–70 years old invited to participate. They were randomly allocated to the Screening arm or the Control arm. Finland was exceptional in recruiting a fixed 32,000 men to the Screening arm meaning that the ratio of Screened:Control was 1:1.5.

Men in the Control arm had no investigations. Men in the Screening arm were invited for a PSA test. If PSA was <3 ug/L then no further investigations were performed. Where PSA was ≥3 ug/L, men had a digital rectal examination (DRE) and a standard set of random sextant transrectal ultrasound-guided prostate (TRUS) biopsies with separate biopsies of any hypoechoic lesions. Where the biopsy was positive, men were referred to the regional centre for consideration of radical prostatectomy or radical radiotherapy. Where biopsy was negative, but a strong suspicion of cancer remained (either due to abnormal DRE or significantly elevated PSA), men were offered a repeat biopsy at 3 months.

All men in the Screening arm were re-screened every 4 yrs with a repeat PSA, leading to a period of further observation or repeat biopsy. The results of the ERSPC study were published in 2009 (for 9 yrs follow-up), in 2012 (for 11 yrs follow-up), and most recently in 2014 (for 13 yrs follow-up) (1,3,4)

Broadly the results demonstrated that to prevent one PC death:

- 1,410, 1,055 and 781 men would need to be screened (at 9, 11 and 13 yrs follow-up);
- 48, 37 and 27 men would need to be treated for PC.

Absolute risk reduction (ARR) of death from PC was 0.71 (after 9 and 11 yrs follow-up) and 0.73 (after 13 yrs follow-up). The relative risk reduction (RRR) of death from PC between the screened and the control arms was 21%.

Screening resulted in diagnosis rates of 40–50% of indolent cancers, often leading to overtreatment of this group of patients.

There was statistically significant reduction in PC mortality in the screened population compared to the control group, but there was no difference in the all-cause mortality.

In comparison, the PLCO trial recruited 76,685 men aged 55–74 years old (2). They were again randomised to Screening and Control arms. The Screened men received annual PSA tests for 6 yrs and annual DRE for 4 yrs with abnormal results prompting biopsy. The Control patients received no formal screening but continued to get opportunistic PSA tests and DRE, leading to significant cross-contamination. 92% of study participants were followed up to 10 yrs and 57% to 13 yrs. At 13 yrs follow-up, there were 3.7 *vs*. 3.4 prostate-cancer deaths per 10,000 person-years with no statistically significant reduction in mortality by screening.

These results were analysed by the US Preventive Services Taskforce in 2012, which concluded that there was no or very little reduction in PC mortality by screening and there was evidence of significant harm in terms of morbidity of overtreatment, and significant psychological harm in terms of anxiety and distress (5). The Taskforce therefore concluded that the benefits of screening outweighed the benefits and recommend against a US screening program.

The Finnish arms of the ERSPC are to be commended for their role in the largest recruitment, rigorous randomisation and longest follow-up. The present study looks at the rate of detection of PC in men after completion of screening cycles as opposed to those detected during the screening process (6).

The participants in the Screening arm were divided into three groups according to whether they were not screened, screened once (at year 0), or twice (at years 0 and 4), or thrice (at years 0, 4 and 8). These subgroups were matched to age-matched equivalent subgroups selected from the Control arm.

PC data was collected from the Finnish National registry, which is 98% complete. Those men who had a PC diagnosis within 1 year of screening were excluded as screening-detected. The remainder were therefore patients whose cancer was detected out with the screening program. This incidence was compared with the age-matched controls.

PC incidence among men who never participated with screening was 6.3 cases per 1,000 person-year *vs*. 7.1 in the matched non-screened. Unsurprisingly, there was no statistically significant difference between the groups. In the group who were screened once, the PC incidence was 11.2 *vs*. 8.1 in their control group. For men screened twice the incidence in the screened group was 8.9 *vs*. 9.1 in their controls. Men who had been screened thrice had a PC incidence of 4.5 *vs*. 7.9 for their controls.

Further analysis suggests that the increased incidence of cancer among men screened once compared to their controls was comparable at age groups 55–59 years and 63–67 years. In those screened twice, there was a reduction in cancer incidence for the older group, 63–67 years, but increased incidence in the 55–59 age group. Only in those screened thrice was there a significant reduction in PC incidence in the screened population with respect to their controls at both 55–59 and 63–67 years age groups.

A reduction in the incidence of high-grade PC was seen only after two or three screening visits.

Overall, these results imply that:

- A single screening round does not detect enough cancers so that the incidence after screening is less than that of those who were never screened;
- Even after two rounds of screening, only higher-grade cancer incidence was reduced not overall cancer rates;
- There is likelihood that a significant proportion of PCs arise *de novo* after one round of screening and that to detect them requires re-screening, and this is more likely to include higher-grade cancers;
- Three rounds of screening are necessary to achieve any substantial benefit in terms of reduction of PC incidence.

Screening for PC remains very controversial, especially after the findings of the US Preventive Services Taskforce. These results imply that for screening to be of any utility, participants must be screened at least thrice. This is likely to increase potential morbidity and patient anxiety and distress.

These results will probably make screening even more unpalatable for policymakers in national governments debating on whether or not mass screening should be introduced, making screening even less likely to be put into practice.

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Footnote

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