

Contribution of the Cluster randomised triAl of PSA testing for Prostate cancer (CAP) to the ongoing debate on the value of prostate cancer screening

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There is currently no population screening programme for prostate cancer in the UK, a position that is reflected internationally (e.g. the USA Preventative Services Taskforce recommends shared decision-making¹). This is because the effect of prostate specific antigen (PSA)-based screening on prostate cancer-specific mortality and quality of life compared with no organised screening remains unclear and may result in overdiagnosis, biopsy-related complications and overtreatment.

Alternative screening and treatment strategies may improve the benefit-harm trade-offs, but the value of these strategies - such as polygenic risk-tailored approaches,² magnetic resonance imaging (MRI) (either added to PSA screening or alone)³ or the Stockholm-3 (STHLM3) model,⁴ plus greater use of conservative management for low-risk prostate cancer - is uncertain.

Paschen et al. have undertaken an excellent review of the evidence on PSA-based screening for prostate cancer, that adds to this debate. They analysed 11 randomised controlled trials (RCTs), including treating the 8 national trials conducted under the umbrella of the European Randomized study of Screening for Prostate Cancer (ERSPC) as individual studies. This was done to exploit the clinical heterogeneity in the ways each of these 8 separate trials were conducted to identify factors that may be associated with an increase in screening effectiveness. The combined total of men in these 11 RCTs was 416,000. The authors excluded the UK based Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP), which involved nearly as many men as the 11 included RCTs in total: 415,357 men aged 50-69 from 573 general practitioner (GP) practices across in 8 centres in England and Wales.⁵

The authors excluded the CAP RCT because *“after allocation approximately 30% of randomized primary care practices in both groups chose not to participate.”* A specific rationale for a 30% cut-off for post-randomization exclusions was not offered. It is not clear if other studies, potentially eligible for inclusion in the review, would have been affected by a higher or lower cut-off. While it is crucial to consider selection bias in the face of post-randomization exclusions, it should be noted that there were no differences in measured characteristics between intervention vs. control practices as randomised in CAP,⁵ showing the success of the randomisation, or by consent status, indicating that post-randomisation exclusions did not introduce selection bias. All men were linked to the Health and Social Care Information Centre (HSCIC) for deaths and cancer registrations, with only 0.03% untraced. Among the 415,357 randomized men, 189,386 in the intervention group and 219,439 in the control group were included in the primary analysis (n = 408,825; 98%).⁵

CAP also provides at least three other pieces of important evidence in the ongoing debate about the balance of benefits and harms of prostate cancer screening.

First, the CAP intervention was low intensity PSA screening, in an attempt to reduce overdiagnosis while maintaining mortality benefits. Importantly, the single PSA screening intervention significantly increased the early detection of prostate cancer: during the first 18 months following recruitment (the screening phase) there was a 5-fold increase in rate of prostate cancer detection: 10.42 per 1000 person-years in the intervention group vs 2.18 per 1000 person-years in the control group ($P < 0.001$). Such a difference would be expected to lead to mortality benefits over long-term follow-up, but at a median 10-years follow-up there was little evidence of any subsequent mortality reduction from earlier detection: 549 (0.30 per 1000 person-years) died of prostate cancer in the intervention group vs 647 (0.31 per 1000 person-years) in the control group (rate ratio: 0.96; 95%CI: 0.85 to 1.08; $p=0.5$).

Second, the CAP trial observed that PSA-screening misses lethal cancers: 36% (68/188) of men who died from prostate cancer attended the screening clinic, highlighting that clinically significant prostate cancer is not uncommon among men with low PSA levels. A major problem with PSA-based screening is that it leads to both under-, as well as over-, diagnosis, as found in the CAP RCT.⁵

Third, CAP makes a unique contribution to the evidence-base because of important differences from ERSPC and the USA PLCO trial. In particular, diagnostic processes were standardised, and intervention-arm men detected with localised prostate cancer were randomised into ProtecT to determine the optimum treatment following screening.⁶ The inclusion of active monitoring in ProtecT assesses whether delayed or avoided radical intervention improves the benefit-to-harm trade-off, and informs on the long-term natural history of prostate cancer. As follow-up of CAP continues beyond a median 15 years now, prostate cancer deaths will rise, increasing the statistical precision of the intervention effect and capturing later effects.

Research now focuses on identifying novel ways to promote PCa-mortality and quality of life benefits while minimising harms by investigating new screening and diagnostic strategies. Polygenic risk scores (PRS) are increasingly being explored for disease prediction in asymptomatic people,² demonstrated by the newly created NHS Genomic Medicine service to support genetic sequencing in routine NHS care, but their clinical utility is uncertain. Evidence from other cancers suggests that polygenic risk may modulate risks associated with penetrant monogenic mutations to the point of modifying treatment decisions.⁷ The UK National Prostate Cancer Audit (NPCA) estimates substantial reductions in overdiagnosis with the introduction of multi-parametric MRI (mpMRI) prior to biopsy. The STHLM3 test, combining PSA, genetics, clinical variables and protein biomarkers, may safely reduce unnecessary biopsies.⁴

However, there is little understanding of the costs associated with taking samples to generate the relevant PRS or STHLM3 test data on all eligible men, remuneration for their integration into routine NHS care, or the downstream economic sequelae in primary and secondary care of detecting prostate cancer via these novel routes. Informing current policy necessitates well calibrated and validated decision analytic models, where several data sources, including RCTs, are synthesised. Sustained follow-up of RCTs like CAP offers a unique opportunity to inform health economic models to answer the outstanding clinical- and policy-related questions.

The outstanding clinical and policy questions are whether recent novel developments in screening and detection will improve the balance of benefits and harms of prostate cancer screening. Synthesis of the evidence, such as that conducted by Paschen et al in this edition of the journal, and the exploitation of long-term natural history data from population-based RCTs like CAP to inform health economic models, will help answer these important questions that would take decades for newly established RCTs to answer.

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