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**Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP
randomized clinical trial**

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Key Points

Question: What is the effect of an invitation to a single PSA-screen for prostate cancer on prostate cancer detection and median 10-year prostate cancer mortality?

Findings: In this randomized clinical trial comparing 189,386 men aged 50-69 receiving a single PSA-screen and 219,439 controls undergoing standard (unscreened) practice, the proportion of men diagnosed with prostate cancer was higher in the intervention (4.3%) group than control (3.6%) group, but there was no significant difference in prostate cancer mortality (intervention, 0.29% vs. control, 0.29%) after a median follow-up of 10-years.

Meaning: The CAP single PSA-screen intervention detected more prostate cancer cases, but after a median of 10-years' follow-up has, thus far, had no significant effect on prostate cancer mortality.

Abstract

Importance: Prostate-cancer screening remains controversial because of concerns that potential mortality or quality of life benefits are outweighed by harms from over-detection and subsequent over-treatment.

Objective: To evaluate the effect of a low-intensity, single PSA screening intervention and standardized diagnostic pathway on prostate cancer specific mortality.

Design, Setting, Participants: Cluster-randomized clinical trial conducted in 573 general practices (the clusters) across the UK and including 419,582 men aged 50-69 who were randomized between 2001 and 2009. Follow-up was completed March 31, 2016.

Intervention: An invitation to a single PSA-test versus standard (unscreened) practice.

Main outcome and measures: Primary outcome: prostate cancer mortality at a median of 10-years' follow-up, analyzed by intention-to-screen. Pre-specified secondary outcomes: diagnostic stage and grade of prostate cancers identified, all-cause mortality and instrumental variable analysis estimating the causal effect of attending PSA screening.

Results: Among 415,357 eligible men who were randomized (mean age, 59.0 years), 189,386 men in the intervention-group and 219,439 controls were included in the analysis (n=408,825, 98%). In the intervention-group, 75,707 (40%) attended PSA-testing and 6,857 (4%) had a PSA ≥ 3 -<20ng/ml, of whom 5,850 (85%) had a prostate biopsy. After a median follow-up of 10-years, 549 (0.30 per 1000-person years) men had died from prostate cancer in the intervention group compared with 647 (0.31 per 1000-person years) in the control-group (rate difference -0.013 per 1000-person years, 95%CI -0.047, 0.02; rate-ratio [RR] 0.96, 95%CI 0.85,1.08; p=0.50). The number of prostate cancers diagnosed was higher in the intervention-group (n=8,054; 4.3%) than control-group (n=7,853; 3.6%) (RR 1.19, 95%CI 1.14,1.25; p<0.001). More Gleason grade ≤ 6 tumors were identified in the intervention than control groups (n=3,263/189,386 [1.7%] vs. n=2,440/219,439 [1.1%]; difference per 1000 = 6.11, 95% CI 5.38, 6.84; p<0.001). In the analysis of all-cause mortality, there were 25,459 deaths in the intervention group, and 28,306 deaths in the control group (RR 0.99, 95%CI 0.94,1.03; p=0.49). In instrumental variable analysis, the adherence-adjusted causal RR for prostate cancer mortality was 0.93 (95%CI 0.67,1.29; p=0.66).

Conclusion and relevance: Among practices randomized to a low-intensity PSA screening intervention compared with standard practice, there was no significant difference in prostate cancer mortality after a

median 10-years follow up, but the detection of low-risk prostate cancers increased. Although longer-term follow-up is in progress, the current findings do not support single PSA-testing for population-based screening.

Current Controlled Trials number: ISRCTN92187251.

Introduction

Evidence from randomized clinical trials (RCTs) in Europe (ERSPC, n=162,243)¹ and the USA (PLCO, n=76,693)² has not resolved the controversies surrounding prostate-specific antigen (PSA)-based prostate cancer screening, resulting in different recommendations worldwide.^{3,4} The prognosis for low- and intermediate-risk localized prostate cancer is excellent,⁵ and although there is fair-quality evidence that screening by PSA testing reduces prostate cancer deaths,⁶ debate continues about the trade-off between the mortality benefit and risks of harm from over-detection and over-treatment.²⁻⁴

Current UK policy does not advocate screening.⁷ The proposed 2017 update from the US Preventive Services Task Force recommends individualized decision-making for men between the ages of 55 and 69 after a discussion of risks and harms with their physician.⁶ This latest guidance comes amidst concerns about the quality of previous evidence,⁴ favorable modelling projections,⁸ new secondary analyses,⁸ greater absolute risk (but not rate) benefits with long-term follow-up,⁹ the use of active surveillance to avoid radical treatment unless cancer is progressing,¹⁰ and long-term data on the effects of different treatment options for localized prostate cancer.^{5,10} The PLCO and ERSPC trials undertook repeated PSA testing at intervals of 1, 2 or 4 years.^{1,2} Less intensive strategies, such as longer screening intervals or one-off screens have been predicted to reduce over-detection, over-treatment and costs relative to more frequent screening.^{11,12} However, opportunistic screening may increase over-detection without reducing prostate cancer mortality.¹³

The Cluster randomized trial of PSA testing for Prostate cancer (CAP) was designed to determine the effects of a low-intensity, single invitation PSA test and standardized diagnostic pathway on prostate cancer-specific and all-cause mortality while minimizing over-detection and over-treatment. This article reports the median 10-years' follow-up of this trial.

Methods

Ethical and regulatory approvals

Derby National Research Ethics Service Committee East Midlands (formerly Trent Multi-Centre Research Ethics Committee) provided approval for flagging for mortality and cancer incidence [MREC/03/4/093] and review of medical records of men with prostate cancer [05/MRE04/78]. Approval for flagging of men in the control group and non-responders in the intervention-group without individual consent was obtained under Section 251 of the NHS Act 2006 [PIAG 4-09 (k)/2003] from the UK Patient Information Advisory Group (PIAG) (now Confidentiality Advisory Group, CAG). PIAG/CAG approval allowed review of medical records of men who died of a cause potentially related to prostate cancer before consent could be gained (provided the man did not record an objection to medical records being used for research whilst alive) [PIAG 1-05(f)/2006]. Men who attended for PSA testing in the intervention group gave individual informed consent (Trent MREC/01/4/025). All clinical centers had local research governance approval. The University of Bristol acted as sponsor (the institution taking overall responsibility). The trial is registered at Current Controlled Trials (ISRCTN92187251).

Randomization

This trial is a primary-care based cluster-randomized trial of a single PSA test,¹⁴ within which the ProtecT trial of treatments for localized prostate cancer was embedded¹⁵ (**Supplementary Figure S1**). Between 2001 and 2009, 785 eligible general practices around 8 hospital centers in England and Wales were randomized before recruitment ('Zelen' design) to intervention- or control-groups and approached for consent to participate. Randomization was blocked and stratified within geographical groups of 10-12 neighboring practices, using a computerized random number generator. Because allocation preceded practices being invited to take part in the study, and because the invitation was tailored to the group the practice had been allocated to, it was not possible to conceal allocation whilst practices decided whether to participate. We therefore compared characteristics of practices that agreed to participate in the intervention and control groups. In total, 573 (73%) practices agreed to participate (**Figure 1**).

Participants

The inclusion criterion was all men aged 50-69 years in each of the randomized general practices. The exclusion criteria were a history of prostate cancer on or before the randomization date and registration with the practice on a temporary or emergency basis.

Intervention

In the intervention group, men aged 50-69 received a single invitation to a nurse-led clinic appointment (the intervention) where they were provided with information about PSA testing and the treatment trial. Screened men with a PSA ≥ 3.0 ng/ml were offered a standardized 10-core transrectal ultrasound-guided biopsy. Those diagnosed with clinically localized prostate cancer were offered recruitment to the ProtecT treatment trial comparing radical prostatectomy, radical conformal radiotherapy with neoadjuvant androgen deprivation therapy and active monitoring.⁵ Control practices provided standard NHS management, with information about PSA testing provided only to men who requested it.¹⁶ Prostate cancers detected amongst men in the intervention-group who did not attend the nurse-led PSA clinic appointment, and in the control-group, were managed by the same clinicians as PSA clinic attendees in the intervention group. All men were linked to NHS Digital and the Office for National Statistics (ONS) for deaths and cancer registrations, with only 639 (0.15%) untraced or unregistered. Prostate cancer stage and grade at diagnosis were obtained from Public Health England and Wales, supplemented with routine hospital data from the study centers. We were unable to abstract good quality data on metastases from routine records.

Primary and secondary outcome measures

Outcome measures and the statistical analysis were pre-specified prior to data release in a published statistical analysis plan.¹⁷ The final version of the pre-specified analysis plan was uploaded on 26/07/2016 at the following URL: <http://hdl.handle.net/1983/e49f5d0f-5139-4fef-912b-525e0b6ed616>. The primary outcome was definite, probable or intervention-related prostate cancer mortality at a median of 10-years' follow-up, assigned by the Cause of Death Evaluation (CoDE) committee blinded to the trial groups.¹⁸ Secondary outcomes analysed for this report were all-cause mortality, and prostate cancer stage and grade at diagnosis. Prostate cancer and all-cause mortality at 15 years, health-related quality of life and cost-

effectiveness were also pre-specified secondary endpoints and are not reported in this article (see the Protocol provided as **Supplementary material**).

Statistical analysis

The primary analysis was based on intention-to-screen, comparing outcomes in men in the participating practices according to the randomized allocation (see the Statistical Analysis Plan provided as **Supplementary material**).¹⁷ Cumulative incidence of primary and secondary outcomes was displayed using Kaplan-Meier plots. Incidence rate ratios (IRRs) were estimated, comparing prostate cancer incidence and mortality in intervention- vs control-practices using mixed-effects Poisson regression, allowing for clustering of men within GP practices, and of neighboring GP practices within randomization strata. As the incidence of prostate cancer varies greatly by age, each man's follow-up was divided into periods of time defined by their age using a lexis-diagram approach¹⁹: ≤59, 60-64, 65-69, 70-74 and ≥75 years (the youngest age-stratum was larger to compensate for fewer events). With a separate mean baseline rate for each age group, the assumption of a constant baseline rate applies to each group separately.

A pre-specified secondary analysis was estimation, using random allocation as an instrumental variable, of the effect of the trial intervention in those accepting the invitation and attending the PSA-testing clinic, employing a generalized method of moments estimator.^{17,20,21} Pre-specified subgroup analyses investigated the effects of PSA testing on prostate cancer-specific mortality by baseline age-group and socioeconomic status using a likelihood ratio test for interaction. Pre-specified sensitivity analyses were: adjustment of the primary analysis for baseline measures observed to differ between intervention and comparison groups (not required, as baseline measures did not differ between groups); and estimation of the intervention effect on the primary outcome if all patients treated within ProtecT had received the treatment shown to be superior (not required, as no treatment was shown to be superior). In exploratory analyses, differences in rates of prostate cancer detection during the initial 18-month screening period, post screening period and overall, were estimated. In a further exploratory analysis, we examined the evidence that the prostate cancer mortality rate ratio changed over time, by testing for non-proportional hazards using scaled Schoenfeld residuals derived from Cox models.

Since there were few missing data, and in accordance with our statistical analysis plan, we did not conduct multiple imputation analyses. All presented p-values are two-sided. In interpreting our results we focused on estimated effects of intervention compared with control, and associated 95% confidence intervals.²² However, in accordance with *JAMA* editorial guidance we described some results as “significant” or “not significant” according to whether the *P* value was <0.05 or ≥ 0.05 . All analyses were conducted using Stata, version 14.2 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Power

Original power calculations were based on the estimated 10-year incidence of prostate cancer mortality using 1994 England and Wales data, assuming a plausible between-practice coefficient of variation of 0.2 (see the Protocol provided as **Supplementary material**). Calculations predicted that 209,000 men in each group would yield 1,720 incident prostate cancer deaths over a median of 10-years, and allow a prostate cancer mortality IRR of 0.87 to be detected with 80% power at 5% significance: assuming uptake of PSA testing of between 35% and 50%, this corresponds to IRRs among men actually undergoing PSA testing of between 0.62 and 0.73. These IRRs are similar to those assumed in the power calculations for ERSPC.²³ Estimates of the effect on power of ever having a PSA test during follow-up in the control-group suggested that the effect would be minimal unless reaching 20%.

Results

Study population

In total, 911 GP practices were randomised in 99 geographical areas. Of these, 126 were subsequently excluded as ineligible (**Figure 1** and¹⁴). Consent rates amongst the remaining eligible intervention (n=398) and control (n=387) group GP practices were 68% (n=271) and 78% (n=302), respectively: 195,912 and 219,445 men registered with these practices were eligible for the intervention and control groups. After exclusions, the main analysis was based on 189,386 men in the intervention-group and 219,439 men in the control-group (**Figure 1**). There are some differences between numbers of participants in the intervention-group of this trial¹⁴ and the published ProtecT study population⁵ (**Supplementary Table S1**). There were no important

differences comparing measured characteristics of practices that did vs did not agree to participate.¹⁴ There were also no important differences in measured baseline characteristics between intervention-group vs control-group practices or men (**Table 1**), indicating that post-randomization exclusions did not introduce detectable selection biases.

Adherence

Among 189,386 intervention-group men, 75,707 (40%) attended the PSA-testing clinic, 67,313 (36%) had a blood sample taken and 64,436 had a valid test result. Of these 64,436 men, 6,857 (11%) had a PSA between 3 and 20ng/ml (eligible for ProtecT) of whom 5,850 (85%) had a prostate biopsy. Intervention-group men who attended PSA-testing clinics were socio-demographically similar to non-attenders.²⁴ Cumulative contamination (PSA testing in the control group) was indirectly estimated at ≈10-15% over 10-years, based on previously reported diagnostic referral rates and ≈20% of follow up being subsequent to a PSA test undertaken for screening.²⁵⁻²⁷

Primary analysis

After a median of 10-years' follow-up, 549 (0.30 per 1000-person years) men had died from prostate cancer (including intervention-related deaths) in the intervention group, compared with 647 (0.31 per 1000-person years) in the control-group (**Figure 2B**) (rate difference -0.013; 95%CI -0.047, 0.022; IRR 0.96; 95% CI 0.85, 1.08; p=0.50) (**Table 2**), (exploratory analysis, p=0.38, for non-proportional hazards).

Secondary analyses

After a median 10-years' follow up, 8,054 (4.3%) prostate cancers were identified in the 189,386 intervention-group men and 7,853 (3.6%) in the 219,439 control-group men (**Table 3**), corresponding to incidence rates of 4.45 (95% CI 4.36, 4.55) and 3.80 (95% CI 3.72, 3.89) per 1000 person-years, respectively (**Figure 2A**). The between-group rate difference was 0.65 per 1000 person-years (95% CI 0.52, 0.78; p<0.001).

Compared to the control group, intervention group men were 1.34 years younger at prostate cancer diagnosis (95% CI -1.59, -1.10; p<0.001). The proportion of men in the intervention group vs control group with low-

grade prostate cancer was 1.7% vs 1.1% (difference = 6.11 per 1000, 95% CI 5.38, 6.84; $p<0.001$); with localized prostate cancer was 2.6% vs 1.9% (difference = 6.97 per 1000, 95% CI 6.05, 7.89; $p<0.001$); with high-grade prostate cancer was 0.7% vs 0.7% (difference = -0.58 per 1000, 95% CI -1.09, -0.06; $p=0.030$); and with advanced-stage cancer was 0.5% vs 0.6% (difference = -0.91 per 1000, 95% CI -1.36, -0.46; $p<0.001$) (**Table 3, Supplementary Figures S3 and S4**). Thus, as a proportion of detected cancers, the tumors in the intervention-group were less likely to be high-grade (odds ratio 0.68; 95%CI 0.64, 0.73; $p<0.001$, comparing ≤ 6 vs. 7 vs. ≥ 8) or advanced-stage (odds ratio 0.68; 95%CI 0.62, 0.75; $p<0.001$, comparing T1/T2 vs. T3 vs. T4/N1/M1). The clinical characteristics of prostate cancers amongst intervention-group non-attendees were not significantly different from those in control-group men (**Table 3, Supplementary Figures S5 and S6**).

Using instrumental variable analysis, the estimated prostate cancer mortality rate ratio for the effect of screening amongst men attending PSA-testing clinics was 0.93 (95% CI 0.67, 1.29; $p=0.66$) (**Table 2**). This represents an increase of the effect-estimate compared to the intention-to-screen analysis (from a 4% to 7% relative reduction), but remains a small and imprecisely estimated effect. There were 25,459 deaths in the intervention group, and 28,306 deaths in the control group. There was no significant difference in rates of all-cause mortality between these groups (rate ratio 0.99: 95% CI 0.94, 1.03; $p=0.49$) (**Table 2, Supplementary Figure S7**). Prostate cancer specific mortality effect estimates were consistent when based on alternative definitions of prostate cancer mortality (**Supplementary Table S2**).

Pre-specified subgroup analyses

There were no significant differences in the effect of the intervention on prostate cancer mortality according to age or socioeconomic status (**Table 4**). There were 8 deaths in the intervention-group and 7 in the control-group related to a diagnostic biopsy or prostate cancer treatment (**Supplementary Table S5**).

Exploratory analysis

After a median of 10-years' follow up, 4,687 of 75,707 (6.2%) intervention group men were diagnosed with prostate cancer following attendance for PSA testing, compared with 3,367 of 113,679 (3.0%) who did not attend (**Table 3**). Among the 4,687 men with incident prostate cancers amongst PSA attenders, 4,160 cancers

were following a valid PSA test result, of which 1,172 (28%) were in men with a baseline PSA <3ng/ml (**Supplementary Table S1**). These 1,172 initially test-negative cancers were diagnosed a mean 7.9 years after randomization. Prostate cancer detection was lower amongst non-attenders compared with controls (difference -6.17 per 1000, 95% CI -7.42, -4.91; $p < 0.001$, **Supplementary Figure S2A**).

During the first 18 months following recruitment (the screening phase), the rate of prostate cancer detection was 10.42 (95% CI 10.04, 10.80) compared with 2.15 (95% CI 2.00, 2.31) per 1000 person-years amongst controls (rate difference: 8.27; 95% CI 7.86, 8.68; $p < 0.001$) (**Supplementary Table S4**). By contrast, the rate of prostate cancer after the screening phase was 3.36 per 1000 person-years (95% CI 3.27, 3.45) in the intervention group vs 4.11 per 1000 person-years (95% CI 4.02, 4.21) in the control group (rate difference -0.75 per 1000 person years, 95% CI -0.61, -0.88; $p < 0.001$), and when restricted to intervention-attenders was 3.41 (95% CI 3.27, 3.56) vs. controls (rate difference -0.70 per 1000 person years, 95% CI -0.87, -0.53; $p < 0.001$) (**Supplementary Figure S2, Panel B**).

The higher proportion of low-grade and early-stage prostate cancer in the intervention-group was related to large between-group differences during the screening phase (**Supplementary Figures S3 and S4 and Supplementary Table S4**). In contrast, the proportions of all categories of Gleason grade and TNM stage prostate cancers diagnosed more than 18-months after randomization were lower in the intervention- than control-group (**Supplementary Table S4**).

Among the 549 intervention-group men who died from prostate cancer, 188 (34%) had attended a screening appointment, and 59 deaths were in men eligible for the Protect trial. However, lethal cancer had not been identified by the single PSA test screening in the majority ($n=129/188$; 69%): 42 had not received a PSA test at all, and 15 eligible men had not received a prostate biopsy; 68 had a PSA level of <3.0 ng/ml at screening (and therefore were below the threshold for recommending biopsy); and 4 had a benign prostate biopsy result (**Supplementary Table S1**). Other causes of death were similarly distributed between trial groups (**Supplementary Table S3**).

Discussion

In this randomized clinical trial among men aged 50-69, the low intensity intervention consisting of a single invitation to PSA screening, compared with standard (unscreened) practice, had no significant effect on prostate cancer-specific mortality after a median follow-up of 10-years, but did significantly increase the detection of early-stage, low-grade prostate cancers.

This trial provides new evidence that complements previously published trials such as ERSPC and PLCO^{1,2} (**Supplementary Table S6**). First, recruitment was based on general practice clusters, minimizing volunteer bias and lessening PSA-testing contamination amongst controls,²⁵ compared to trials with individually randomized men. The lower proportion of prostate cancers detected, and the greater proportion of higher stage and Gleason grade amongst prostate cancers detected in the controls (compared with ERSPC and PLCO), suggest low background PSA-testing rates over the duration of follow-up, consistent with current UK policy.¹⁶ Second, diagnostic pathways were standardized, and intervention-group men with localized prostate cancer were randomized into the ProtecT trial to determine the effectiveness of treatment following screening.^{5,10} As there was little evidence of a difference in mortality between the ProtecT trial groups after a median of 10 years follow-up,⁵ it is unlikely that the randomization to ProtecT within the intervention-arm had any effect on the CAP primary mortality results. Third, screening was less intensive than in ERSPC or PLCO, aiming to reduce over-detection. The higher age, Gleason grade and stage at diagnosis in this trial's intervention-group compared with ERSPC and PLCO reflect adherence to the low-intensity strategy. Fourth, this trial recruited in a more recent PSA-testing era between 2001-2009, compared to 1993-2003 and 1993-2001 in ERSPC and PLCO, and all participants had access to similar advances for all stages of prostate cancer treatments, providing estimates of PSA screening effectiveness in the context of contemporary management. Fifth, all clinical centers followed the same screening and diagnosis protocol, with high rates of biopsy in those with a raised PSA, and 10-core rather than sextant biopsy to improve prostate cancer detection. Sixth, compared with ERSPC and PLCO, this trial included a much greater number of participants, all following a single randomization and recruitment process, allowing for more precise estimates of the effect of the intervention. Additionally, this trial's design enabled the follow-up of all men in the source population for key outcomes.²⁸

It has been hypothesized that screening men in their early 50s may be more effective than at a later age²⁹ but we did not find statistical evidence to support this (**Table 4**). Recent reports suggest that evidence from trials about screening effectiveness should consider the intensity of testing.^{13,30} A between-centre analysis of ERSPC suggested that more intensive screening reduces mortality relative to no screening,⁸ but also that intensive screening strategies detect high numbers of low-risk cases - with a strong positive correlation between the extent of benefits gained and harms caused.³⁰ The results of this trial show that even a low-intensity strategy aiming to reduce over-detection leads to an increased detection of low-risk cancers, without benefit in reducing mortality from the disease (**Tables 3 and S4**).

Determining the rate of over-detection in screening is critical but challenging because it is influenced by the target population, screening protocol, clinical and demographic factors and prostate cancer's long lead-time.³¹ There is little consensus about methods for determining over-detection, and estimates range between 2% and 67%.³² This trial provides a low-intensity benchmark against which other screening strategies can be compared in lifetime models of over-detection, over-treatment and screening cost-effectiveness.

This trial also identified the under-detection of lethal cancers in initial screening and amongst non-responders (**Table S4**). While this may be in-part related to the low-intensity intervention, it raises the question of whether under-detection of clinically important cancers also occurs with more intensive screening strategies in other trials, but has not been evident in those lacking comprehensive follow-up and flagging of the target population. The diagnostic pathway for prostate cancer detection is changing, with advances in imaging, such as multiparametric MRI, now being introduced with prostate biopsy to improve the identification and targeting of clinically important cancers,³³ and blood-based biomarkers to enhance the specificity of the serum PSA test, including genetic testing.³⁴ It is becoming clear that a PSA test alone with transrectal ultrasound (TRUS)-guided biopsies is no longer the standard of care in the early detection of prostate cancer. Furthermore, offering multiparametric MRI or novel biomarkers to men based on PSA thresholds will still miss potentially lethal cancers.

Limitations

This study has several limitations. First, its single screen may fail to reflect the long-term effect of multiple PSA-testing rounds seen in ERSPC and PLCO. Nevertheless, we observed both a grade- and stage-shift, and a reduction in long-term prostate cancer incidence following a single screening round. In PLCO³⁵ and ERSPC centers,^{36,37} cancers identified in second and subsequent screening rounds were more likely to be localized, small volume, and with favorable histological grading compared to first round cancers, supporting model based estimates that suggest over-detection increases with repeat screening.³⁷ Second, an important number of incident and lethal prostate cancers were not identified through the initial screening intervention (e.g. amongst men with an initial PSA < 3ng/ml or among screening non-attenders (**Supplementary Table S1**)), suggesting the inadequacy of conventional PSA testing followed by TRUS guided biopsies. These cancers were clinically comparable to those in the control-group, suggesting similar routes to diagnosis. The single PSA-testing protocol followed by 10-core trans-rectal ultrasound (TRUS)-guided biopsies in this trial may have led to the under-detection of some lethal cases. Pre-biopsy multiparametric magnetic resonance imaging (MRI) may improve this pathway in the future.³³ However, initial screening also did not identify many higher Gleason grade or advanced stage cases, even in this population with little background testing (**Table 3**), as also noted in the Swedish center of ERSPC.³⁸

Third, in this trial there was 40% adherence with the intervention. This compares with 59-69% in ERSPC centers employing post-randomization consent, although adherence was higher in ERSPC centers with pre-randomization consent.³⁹ The instrumental variable analysis, estimating the causal effect of screening attendance on mortality outcomes, found similar results to the primary analysis. Intervention-group attendees were socio-demographically similar to non-attendees,²⁴ although the measures were somewhat crude, and non-attendees had lower rates of incident prostate cancer than controls - men not entering the trial might be less likely to seek a PSA-test subsequently. The similarity of non-prostate cancer deaths between intervention- and control-groups indicates the success of randomization (**Supplementary Table S3**).

Fourth, a median follow-up of 10-years may be too short a time to identify the effect of screening. Over half the prostate-cancer deaths in the intervention-group occurred in the first 7 years after randomization, a time-period during which it is unlikely that PSA screening would have an effect (**Figure 2B**). Although the cumulative incidence of prostate cancer mortality in the intervention and control groups appeared to diverge after 12 years of follow up, only 71/1196 of the prostate cancer deaths occurred after 12 years and an exploratory analysis found no significant change in the rate ratio over time. In the embedded ProtecT trial, prostate cancer-specific mortality was approximately 1% after a median 10-years, with no evidence of a difference between randomized groups.⁵ However, surgery and radiotherapy reduced the rate of metastatic disease compared with active monitoring (2.4, 3.0 and 6.3 per 1000 person-years, respectively). Given the very low disease-specific mortality at 10-years and the long prostate cancer lead-time (≈ 12 years in the UK³¹), extended follow-up of this trial is crucial to ascertain whether the evidence of increased detection from the screening intervention coupled with treatment-related effects on the occurrence of metastases translate into longer-term survival benefits. After a median 12.7-years' follow-up, the Prostate Intervention versus Observation trial (PIVOT) reported little evidence of a difference in disease-specific or all-cause mortality, but that intermediate-risk disease may benefit from early intervention.⁴⁰ Nevertheless, there was no significant effect of the intervention on the pre-specified primary outcome of prostate cancer mortality at a median of 10-years' follow-up.

Fourth, while post-randomization exclusions have the potential to lead to bias (see **Figure 1**), there were no differences between excluded practices in the intervention and control groups for key variables such as general practice list size, material deprivation index, or urban/rural location.¹⁴ Further, the cumulative incidence of all-cause mortality was near-identical in the intervention and control groups. Therefore it seems unlikely that the post randomisation exclusions biased our results.

Conclusions

Among practices randomized to a low-intensity PSA screening intervention compared with standard practice, there was no significant difference in prostate cancer mortality after a median 10-years follow up, but the

detection of low-risk prostate cancers increased. Although longer-term follow-up is in progress, the current findings do not support single PSA-testing for population-based screening.

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Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; RMM,ELT, JAL, JLD, FCH, DEN and CM have received grants from Cancer Research UK in the previous three years for this research; no other relationships or activities exist that could appear to have influenced the submitted work.

Author Contributions

R Martin drafted the manuscript, to which all authors made amendments and approved the final version. The CAP trial was led by R Martin, J Donovan, F Hamdy, D Neal, E Turner, A Lane. C Metcalfe and G Young performed the data analysis. Professors Martin and Metcalfe had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. E Walsh, M Tazewell and L Down managed the CAP trial database. S Noble, SE Oliver, S Evans, JAC Sterne, Y Ben-Shlomo, and P Brindle provided study oversight. NJ Williams, EM Hill, S-Y Ng, J Toole, LJ Hughes, CF Davies, J Thorn and P Holding were responsible for data acquisition. All authors read and critically commented on the manuscript.

References

1. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360:1320-1328.

2. Andriole GL, Crawford ED, Grubb RL, III, et al. Mortality Results from a Randomized Prostate-Cancer Screening Trial. *The New England Journal of Medicine*. 2009;360(13):1310-1319.
3. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157(2):120-134.
4. Pinsky PF, Prorok PC, Kramer BS. Prostate Cancer Screening — A Perspective on the Current State of the Evidence. *New England Journal of Medicine*. 2017;376(13):1285-1289.
5. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *New England Journal of Medicine*. 2016;375:1415-1424.
6. Bibbins-Domingo K, Grossman DC, Curry SJ. The US Preventive Services Task Force 2017 draft recommendation statement on screening for prostate cancer: An invitation to review and comment. *JAMA*. 2017;317(19):1949-1950.
7. UK National Screening Committee (NSC). The UK NSC recommendation on Prostate cancer screening/PSA testing in men over the age of 50 (currently under review). 2014; <http://legacy.screening.nhs.uk/prostatecancer>. Accessed 03/10/2015).
8. Tsodikov A, Gulati R, Heijnsdijk EAM, et al. Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials. *Ann Intern Med*. 2017.
9. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014;384(9959):2027-2035.
10. Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *New England Journal of Medicine*. 2016;375:1425-1437.
11. Heijnsdijk EAM, Wever EM, Auvinen A, et al. Quality-of-Life Effects of Prostate-Specific Antigen Screening. *New England Journal of Medicine*. 2012;367(7):595-605.
12. Pataky R, Gulati R, Etzioni R, et al. Is prostate cancer screening cost-effective? A microsimulation model of prostate-specific antigen-based screening for British Columbia, Canada. *International Journal of Cancer*. 2014;135(4):939-947.
13. Arnsrud Godtman R, Holmberg E, Lilja H, Stranne J, Hugosson J. Opportunistic Testing Versus Organized Prostate-specific Antigen Screening: Outcome After 18 Years in the Göteborg Randomized Population-based Prostate Cancer Screening Trial. *European Urology*. 2015;68(3):354-360.
14. Turner EL, Metcalfe C, Donovan JL, et al. Design and preliminary recruitment results of the Cluster randomised trial of PSA testing for Prostate cancer (CAP). *Br J Cancer*. 2014;110(12):2829-2836.
15. Lane JA, Donovan JL, Davis M, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. *Lancet Oncology*. 2014;15(10):1109-1118.
16. Burford D, Kirby M, Austoker J. *Prostate Cancer Risk Management Programme. Information for primary care; PSA testing in asymptomatic men. Evidence Document*. NHS Cancer Screening Programmes: Available at <http://www.cancerscreening.nhs.uk/prostate/pcrmp02.pdf>; 2010.
17. Metcalfe C, Sterne J, Turner E, Martin R. CAP: Cluster randomised trial of PSA testing for Prostate cancer Statistical Analysis Plan: version 1.5 26/07/. 2016. [http://research-information.bristol.ac.uk/en/publications/cap-cluster-randomised-trial-of-psa-testing-for-prostate-cancer-statistical-analysis-plan\(e49f5d0f-5139-4fef-912b-525e0b6ed616\)/export.html](http://research-information.bristol.ac.uk/en/publications/cap-cluster-randomised-trial-of-psa-testing-for-prostate-cancer-statistical-analysis-plan(e49f5d0f-5139-4fef-912b-525e0b6ed616)/export.html). Accessed 12/10/2016.
18. Turner EL, Metcalfe C, Donovan JL, et al. Contemporary accuracy of death certificates for coding prostate cancer as a cause of death: Is reliance on death certification good enough? A comparison with blinded review by an independent cause of death evaluation committee. *Br J Cancer*. 2016;115(1):90-94.
19. Keiding N. Lexis Diagram. In: *Encyclopedia of Biostatistics*. John Wiley & Sons, Ltd; 2005.
20. Baum CF, Schaffer ME, Stillman S. Instrumental variables and GMM: Estimation and testing. *Stata Journal*. 2003;3:1-31.
21. Bokhorst LP, Bangma CH, van Leenders GJLH, et al. Prostate-specific Antigen-Based Prostate Cancer Screening: Reduction of Prostate Cancer Mortality After Correction for Nonattendance and Contamination in the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer. *European Urology*. 2014;65(2):329-336.
22. Sterne JAC, Smith GD. Sifting the evidence—what's wrong with significance tests? *BMJ*. 2001;322(7280):226-231.

23. De Koning HJ, Liem MK, Baan CA, et al. Prostate cancer mortality reduction by screening: power and time frame with complete enrollment in the European Randomised Screening for Prostate Cancer (ERSPC) trial. *International Journal of Cancer*. 2002;98(2):268-273.
24. Walsh E, Turner E, Lane J, et al. Characteristics of men responding to an invitation to undergo testing for prostate cancer as part of a randomised trial. *Trials*. 2016;17(1):497.
25. Williams N, Hughes LJ, Turner EL, et al. Prostate-specific antigen testing rates remain low in UK general practice: a cross-sectional study in six English cities. *BJU International*. 2011;108(9):1402-1408.
26. Young GJ, Harrison S, Turner EL, et al. Prostate-specific antigen (PSA) testing of men in UK general practice: a 10-year longitudinal cohort study. *BMJ Open*. 2017;7(10).
27. Moss S, Melia J, Sutton J, Mathews C, Kirby M. Prostate-specific antigen testing rates and referral patterns from general practice data in England. *Int J Clin Pract*. 2016;70(4):312-318.
28. Donovan JL, Young GJ, Walsh EI, et al. A prospective cohort and extended comprehensive-cohort design provided insights about the generalizability of a pragmatic trial: the ProtecT prostate cancer trial. *J Clin Epidemiol*. 2017;10.1016/j.jclinepi.2017.12.019.
29. Carlsson S, Assel M, Ulmert D, et al. Screening for Prostate Cancer Starting at Age 50–54 Years. A Population-based Cohort Study. *European Urology*. 2017;71(1):46-52.
30. Auvinen A, Moss SM, Tammela TLJ, et al. Absolute Effect of Prostate Cancer Screening: Balance of Benefits and Harms by Center within the European Randomized Study of Prostate Cancer Screening. *Clinical Cancer Research*. 2016;22(1):243-249.
31. Pashayan N, Duffy SW, Pharoah P, et al. Mean sojourn time, overdiagnosis, and reduction in advanced stage prostate cancer due to screening with PSA: implications of sojourn time on screening. *British Journal of Cancer*. 2009;100(7):1198-1204.
32. Loeb S, Bjurlin MA, Nicholson J, et al. Overdiagnosis and Overtreatment of Prostate Cancer. *European Urology*. 2014;65(6):1046-1055.
33. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*. 2017;389(10071):815-822.
34. Cucchiara V, Cooperberg MR, Dall'Era M, et al. Genomic Markers in Prostate Cancer Decision Making. *Eur Urol*. 2017.
35. Grubb RL, Pinsky PF, Greenlee RT, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. *BJU International*. 2008;102(11):1524-1530.
36. Draisma G, Boer R, Otto SJ, et al. Lead Times and Overdetection Due to Prostate-Specific Antigen Screening: Estimates From the European Randomized Study of Screening for Prostate Cancer. *JNCI Cancer Spectrum*. 2003;95(12):868-878.
37. Postma R, Schroder FH, van Leenders GJLH, et al. Cancer Detection and Cancer Characteristics in the European Randomized Study of Screening for Prostate Cancer (ERSPC) Section Rotterdam: A Comparison of Two Rounds of Screening. *European Urology*. 2007;52(1):89-97.
38. Hugosson J, Aus G, Lilja H, Lodding P, Pihl CG. Results of a randomized, population-based study of biennial screening using serum prostate-specific antigen measurement to detect prostate carcinoma. *Cancer*. 2004;100(7):1397-1405.
39. De Koning HJ, Auvinen A, Berenguer SA, et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial. *International Journal of Cancer*. 2002;97(2):237-244.
40. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. *New England Journal of Medicine*. 2017;377(2):132-142.
41. Altman DG MD, Bryant TN, & Gardner MJ. *Statistics with confidence*. 2nd ed. London: BMJ Books; 2000.

Figure Legends

Figure 1: Recruitment and retention of practices and patients in CAP, England and Wales (updated to June 2017 from Turner et al¹⁴)

Footnotes: Shaded boxes: Flow of GP practices through trial recruitment; unshaded boxes: flow of men through trial recruitment.

IQR: Interquartile range.

^aDefinition of terms used in Exclusion's boxes:

Practice level exclusions:

Consented but out of time: Practices consented too late to take part in the intervention; Unable to produce list: This indicates that the primary care practice could not provide a list of men registered at the practice aged 50 -69, usually as a result of the practice specializing in a subset of the UK population, for example the homeless or a care home for the elderly; Randomized in error: these practices took part in the feasibility study for the intervention and therefore were not eligible for inclusion in the main trial.

Individual level exclusions: As of June 2017 and are subject to small changes over time because of continued updates from NHS digital.

Failed to trace at NHS Digital: NHS Digital was not able to identify the individual in their dataset using personal identifiable characteristics extracted from the primary care practice; No record of registration with NHS Digital: These were individuals not registered with NHS Digital, for example due to emigration out of the UK; NHS Digital type-2 opt outs: Where individuals requested that their personal confidential information is not to be shared by NHS Digital for purposes other than their own direct care - these records were removed before data were provided to us; No consent for flagging: Individuals who when providing informed consent into the trial did not wish researchers to trace them with NHS Digital; Event date on randomisation date: the individual died or had a diagnosis of prostate cancer on the randomisation date. The time window for exclusions of men "pre-randomisation" was any time prior to randomization - no new men were added to the study after randomization.

^bExplicit refusal = Refused to participate (lack of interest, time or space³⁸); ^cImplicit refusal = no definitive response to invitation to participate; ^dList size: The total number of individuals registered at the GP practices (primary care practices); ^eList size: The total number of men registered at practices aged 50-69 eligible or included in the analysis; ^fPseudo-anonymised follow-up: Aggregate data provided by NHS Digital to allow rates of prostate cancer diagnoses and mortality to be compared to those in individuals included in the study.

Figure 2. Effect of the CAP trial intervention on the cumulative incidence of prostate cancer detection (A) and prostate cancer-specific mortality^a (B)

| Number at risk at the start of each year (events within that year) | | | | | | | | | | | | | | | | |
|---|---------------------------|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|----------------|----------------|----------------|--------------|
| Time (years) | Median (IQR) follow up | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| A: Prostate cancer diagnosis, crude rate difference 0.65 per 1000 (95% CI 0.52, 0.78) | | | | | | | | | | | | | | | | |
| Intervention | 9.85 (8.61, 11.43) | 189,386 (2459) | 184,549 (674) | 181,301 (371) | 178,385 (421) | 175,057 (477) | 171,650 (499) | 168,234 (535) | 164,467 (668) | 159,939 (593) | 125,146 (513) | 91,419 (378) | 59931 (266) | 36222 (154) | 16387 (43) | 1589 (3) |
| Control | 9.82 (8.67, 10.92) | 219,439 (455) | 216,057 (555) | 212,739 (597) | 209,018 (663) | 205,021 (749) | 200,496 (758) | 196,022 (858) | 191,503 (929) | 185,601 (881) | 148,182 (669) | 103,578 (406) | 48701 (206) | 22905 (90) | 12894 (37) | 1747 (0) |
| B: Prostate cancer mortality ^a , crude rate difference -0.01 per 1000 (95% CI -0.05, 0.02) | | | | | | | | | | | | | | | | |
| Intervention | 10.03 (8.80, 11.50) | 189,386 (4) | 186,989 (19) | 184,370 (21) | 181,778 (39) | 178,777 (40) | 175,750 (58) | 172,702 (55) | 169,353 (63) | 165,313 (69) | 129,718 (67) | 95,089 (52) | 62,558 (29) | 38,003 (27) | 17,273 (6) | 1,649 (0) |
| Control | 9.92 (8.74, 10.93) | 219,439 (4) | 216,504 (23) | 213,705 (27) | 210,530 (41) | 207,112 (53) | 203,235 (82) | 199,382 (69) | 195,578 (65) | 190,408 (86) | 152,725 (84) | 107,186 (49) | 50,531 (26) | 23,811 (26) | 13,468 (12) | 1,816 (0) |

Footnotes:

CI: confidence interval, IQR: Interquartile range, ^aDefinite, probable or intervention related prostate cancer mortality as determined by the independent cause of death committee.

Table 1: Individual and practice level characteristics at baseline amongst consented GP practices and men included in the analysis (adapted from Turner et al¹⁴)

| | Intervention arm | Control arm |
|--|------------------------|------------------------|
| Individual Characteristics | n= 189,386 men | n= 219,439 men |
| Median age (IQR) | 58.5 (54.3, 63.5) | 58.6 (54.3, 63.5) |
| Median IMD score, England (IQR) | 17.5 (10.1, 33.2) | 16.9 (9.8, 32.4) |
| Median IMD score, Wales (IQR) | 17.6 (9.2, 29.5) | 13.7 (7.1, 29) |
| Urban area (%) ^a | 163,751 (86%) | 189,707 (86%) |
| Practice Characteristics | n= 271 practices | n= 302 practices |
| Median practice list size (IQR) ^b | 6,300 (4,150 , 9,107) | 6,300 (3,793 , 9,000) |
| Number of urban practices (%) | 244 (90%) | 267 (88%) |
| Number of multiple partner GP practices (%) ^c | 242 (89%) | 267 (88%) |
| Median QOF points achieved (%) ^d (IQR); n | 98.9 (97.4, 99.6); 224 | 99 (97.4, 99.7); 266 |
| Median IMD score, England (IQR); n | 21.8 (12.7, 44.1); 231 | 23.6 (13.3, 46.7); 271 |
| Median IMD score, Wales (IQR); n | 18.8 (11.9, 22.9); 40 | 20.1 (7.6, 34.5); 31 |
| <i>Mean prevalence from QOF^e</i> | | |
| All cancers (s.d.) | 0.57% (0.25%) | 0.53 (0.22%) |
| Diabetes (s.d.) | 3.6% (0.96%) | 3.7% (0.99%) |
| Obesity (s.d.) | 8.0% (2.83%) | 7.8% (2.83%) |
| Coronary heart disease (s.d.) | 4.1% (1.36%) | 3.9% (1.26%) |

IMD= Index of Multiple Deprivation, a measure of relative deprivation for small areas: a higher score indicates more deprivation and the range is [0-100]. English and Welsh IMD scores are not directly comparable and are, therefore, reported separately; QOF = Quality and Outcomes Framework, a system for the performance management and payment of GPs based on the quality of their care: data are % of total QOF points achieved; IQR = interquartile range (25th percentile, 75th percentile); s.d. = standard deviation; ^aRural/urban classification 2004, ^bthe total number of individuals registered at the GP practices (primary care practices). ^cMultiple partner GP practices are primary care practices with more than one General Practitioner registered and practicing from there. ^dBased on 2007/2008 data, England only. ^eCalculated as follows: the average across all practices of (the number of individuals registered with a health condition at each practice divided by the total number of individuals registered at each practice size)x100.

Table 2. Effect of the CAP trial intervention on prostate cancer specific and all-cause mortality by random allocation and by instrumental variable analysis

| | Intervention group (<i>n</i> =189,386) Person years=1,853,167 | | Control group (<i>n</i> =219,439) Person years=2,095,405 | | Instrumental variable estimate ^c | | | | |
|---|--|---|---|---|---|-------------------------------------|-------------------------|-------------------------------------|----------------------|
| | Deaths (%) | Rate per 1000 person-years (95% CI) | Deaths (%) | Rate per 1000 person-years (95% CI) | Crude rate difference per 1000 men (95% CI) | Rate ratio (95% CI) ^b | P value ^b | Rate ratio (95% CI) ^c | P value ^c |
| Primary outcome: prostate cancer mortality ^a | | | | | | | | | |
| Intention-to-screen | 549 (0.29%) | 0.30 (0.27, 0.32) | 647 (0.29%) | 0.31 (0.29, 0.33) | -0.013 (-0.047, 0.022) | 0.96 (0.85, 1.08) | 0.50 | 0.93 (0.67, 1.29) | 0.66 |
| Secondary outcome: all-cause mortality | | | | | | | | | |
| Intention-to-screen | 25,459 (13%) | 13.74 (13.57, 13.91) | 28,306 (13%) | 13.51 (13.35, 13.67) | 0.229 (-0.001, 0.460) | 0.99 (0.94, 1.03) | 0.49 | 1.07 (0.93, 1.23) | 0.35 |

CI: confidence interval;

^aDefined as definite or probable prostate cancer death or intervention related death by an independent cause of death committee

^bLikelihood ratio test of the null hypothesis “no difference in prostate cancer mortality between the groups”, adjusted for randomization cluster and age stratum.

^cAnalysis to obtain the causal effect of screening amongst those attending the PSA testing clinic using a generalized method of moments (gmm) estimator with random allocation as an instrumental variable.

Table 3. Effect of the CAP trial intervention on characteristics of prostate cancer cases at diagnosis

| | | Intervention group (<i>n</i> =189,386) | | | Control group (<i>n</i> =219,439) | Crude absolute difference between the intervention and control groups (95% CI) |
|---|----------------|--|---|-----------------------------|---------------------------------------|---|
| | | Attended PSA clinic (<i>n</i> =75,707) 4,687 (6.2%) | Did not attend PSA clinic (<i>n</i> =113,679) 3,367 (3.0%) | All invited 8,054 (4.3%) | 7,853 (3.6%) | |
| Number of prostate cancers (%): | | | | | | |
| Clinical characteristics at diagnosis | | | | | | |
| Person-years of follow up | | 750,573 | 1,057,458 | 1,808,031 | 2,063,912 | |
| Rate per 1000-person years | | 6.24 (6.07, 6.43) | 3.18 (3.08, 3.29) | 4.45 (4.36, 4.55) | 3.80 (3.72, 3.89) | 0.65 (0.52, 0.78) ^a |
| Median age (IQR) | | 65.3 (61.2, 69.0) | 67.9 (63.7, 71.5) | 66.3 (62.1, 70.0) | 67.7 (63.6, 71.6) | -1.37 (-1.56, -1.19) ^b |
| Median years between randomization and diagnosis (IQR) | | 1.2 (0.5, 7.0) | 6.2 (3.4, 8.7) | 4.3 (0.8, 7.9) | 6.2 (3.6, 8.4) | -1.49 (-1.61, -1.37) ^b |
| Grade (% ^c) | | | | | | |
| | Grade recorded | 4,388 (94%) | 2,888 (86%) | 7,276 (90%) | 6,899 (88%) | |
| | ≤6 | 2,297 (3.0%) | 966 (0.8%) | 3,263 (1.7%) | 2,440 (1.1%) | 6.11 (5.38, 6.84) ^d |
| | 7 | 1,526 (2.0%) | 1,184 (1.0%) | 2,710 (1.4%) | 2,823 (1.3%) | 1.44 (0.73, 2.16) ^d |
| | ≥8 | 565 (0.7%) | 738 (0.6%) | 1,303 (0.7%) | 1,636 (0.7%) | -0.58 (-1.09, -0.06) ^d |
| Stage (% ^c) | | | | | | |
| | Stage recorded | 4,299 (92%) | 2,898 (86%) | 7,197 (89%) | 7,009 (89%) | |
| | T1/T2 | 3,308 (4.4%) | 1,630 (1.4%) | 4,938 (2.6%) | 4,192 (1.9%) | 6.97 (6.05, 7.89) ^d |
| | T3 | 690 (0.9%) | 639 (0.6%) | 1,329 (0.7%) | 1,540 (0.7%) | -0.00 (-0.51, 0.51) ^d |
| | T4/N1/M1 | 301 (0.4%) | 629 (0.6%) | 930 (0.5%) | 1,277 (0.6%) | -0.91 (-1.36, -0.46) ^d |

IQR = interquartile range (25th percentile, 75th percentile), ^aRate difference, ^bDifference in medians with confidence intervals for generalized Hodges-Lehmann median differences,⁴¹ ^cPercentage within that arm (or subset of the intervention arm), ^dDifference per 1000.

Table 4: Prostate cancer mortality rate ratios comparing intervention vs control groups, according to age and deprivation scores

| | Intervention group (<i>n</i> =189,386) Person years=1,853,167 | | Control group (<i>n</i> =219,439) Person years=2,095,405 | | Crude rate difference (95% CI) | Rate Ratio (95% CI) ^a | P-value for interaction ^a |
|--|--|---|---|---|--------------------------------------|-------------------------------------|---|
| | Deaths/ Person years | Rate per 1000 person-years (95% CI) | Deaths/ Person years | Rate per 1000 person-years (95% CI) | | | |
| Age at baseline | | | | | | | 0.14 |
| 50-54 | 46/563,086 | 0.08 (0.06, 0.11) | 64/628,611 | 0.10 (0.08, 0.13) | -0.02 (-0.05, 0.01) | 0.79 (0.49, 1.10) | |
| 55-59 | 110/547,996 | 0.20 (0.17, 0.24) | 125/613,997 | 0.20 (0.17, 0.24) | -0.00 (-0.06, 0.05) | 0.98 (0.72, 1.23) | |
| 60-64 | 166/421,111 | 0.39 (0.34, 0.46) | 222/481,235 | 0.46 (0.40, 0.53) | -0.07 (-0.15, 0.02) | 0.85 (0.68, 1.03) | |
| 65-69+ | 227/320, 974 | 0.71 (0.62, 0.81) | 236/371, 563 | 0.64 (0.56, 0.72) | 0.07 (-0.05, 0.20) | 1.11 (0.90, 1.32) | |
| IMD area deprivation England (tertile ranges)^b | | | | | | | 0.22 |
| Tertile 1 (1.08 to 12.17) | 132/525, 973 | 0.25 (0.21, 0.30%) | 196/651,184 | 0.30 (0.26, 0.35) | -0.05 (-0.11, 0.01) | 0.84 (0.64, 1.03) | |
| Tertile 2 (12.18 to 25.95) | 174/529,621 | 0.33 (0.28, 0.38) | 189/628,337 | 0.30 (0.26, 0.35) | 0.03 (-0.04, 0.09) | 1.10 (0.86, 1.33) | |
| Tertile 3 (25.97 to 79.98) | 176/540,949 | 0.33 (0.28, 0.38) | 208/593,187 | 0.35 (0.31, 0.40%) | -0.03 (-0.09, 0.04) | 0.93 (0.73, 1.12) | |
| IMD area deprivation Wales (tertile ranges)^b | | | | | | | 0.79 |
| Tertile 1 (1.40 to 10.30) | 20/80,425 | 0.25 (0.16, 0.39) | 21/91,112 | 0.23 (0.15, 0.35) | 0.02 (-0.13, 0.17) | 1.02 (0.38, 1.66) | |
| Tertile 2 (10.40 to 23.30) | 21/92,373 | 0.23 (0.15, 0.35) | 16/63,855 | 0.25 (0.15, 0.41) | -0.02 (-0.18, 0.13) | 0.88 (0.30, 1.47) | |
| Tertile 3 (23.40 to 78.90) | 26/83,826 | 0.31 (0.21, 0.46) | 17/67,729 | 0.25 (0.16, 0.40) | 0.06 (-0.11, 0.23) | 1.22 (0.45, 1.98) | |

^aAdjustment for age stratum and practice cluster effects apart from age which was not adjusted for age stratum

^bScores range from 0 to 100 with higher scores indicating higher levels of deprivation (England and Wales do not share the same scale).