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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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IMPORTANCE Prostate cancer screening remains controversial because potential mortality or quality-of-life benefits may be outweighed by harms from overdetection and overtreatment.

OBJECTIVE To evaluate the effect of a single prostate-specific antigen (PSA) screening intervention and standardized diagnostic pathway on prostate cancer–specific mortality.

DESIGN, SETTING, AND PARTICIPANTS The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) included 419 582 men aged 50 to 69 years and was conducted at 573 primary care practices across the United Kingdom. Randomization and recruitment of the practices occurred between 2001 and 2009; patient follow-up ended on March 31, 2016.

INTERVENTION An invitation to attend a PSA testing clinic and receive a single PSA test vs standard (unscreened) practice.

MAIN OUTCOMES AND MEASURES Primary outcome: prostate cancer–specific mortality at a median follow-up of 10 years. Prespecified secondary outcomes: diagnostic cancer stage and Gleason grade (range, 2-10; higher scores indicate a poorer prognosis) of prostate cancers identified, all-cause mortality, and an instrumental variable analysis estimating the causal effect of attending the PSA screening clinic.

RESULTS Among 415 357 randomized men (mean [SD] age, 59.0 [5.6] years), 189 386 in the intervention group and 219 439 in the control group were included in the analysis (n = 408 825; 98%). In the intervention group, 75 707 (40%) attended the PSA testing clinic and 67 313 (36%) underwent PSA testing. Of 64 436 with a valid PSA test result, 6857 (11%) had a PSA level between 3 ng/mL and 19.9 ng/mL, of whom 5850 (85%) had a prostate biopsy. After a median follow-up of 10 years, 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 difference, −0.013 per 1000 person-years [95% CI, −0.047 to 0.022]; rate ratio [RR], 0.96 [95% CI, 0.85 to 1.08]; $P = .50$). The number diagnosed with prostate cancer was higher in the intervention group (n = 8054; 4.3%) than in the control group (n = 7853; 3.6%) (RR, 1.19 [95% CI, 1.14 to 1.25]; $P < .001$). More prostate cancer tumors with a Gleason grade of 6 or lower were identified in the intervention group (n = 3263/189 386 [1.7%]) than in the control group (n = 2440/219 439 [1.1%]) (difference per 1000 men, 6.11 [95% CI, 5.38 to 6.84]; $P < .001$). In the analysis of all-cause mortality, there were 25 459 deaths in the intervention group vs 28 306 deaths in the control group (RR, 0.99 [95% CI, 0.94 to 1.03]; $P = .49$). In the instrumental variable analysis for prostate cancer mortality, the adherence-adjusted causal RR was 0.93 (95% CI, 0.67 to 1.29; $P = .66$).

CONCLUSIONS AND RELEVANCE Among practices randomized to a single PSA screening intervention vs standard practice without screening, there was no significant difference in prostate cancer mortality after a median follow-up of 10 years but the detection of low-risk prostate cancer cases increased. Although longer-term follow-up is under way, the findings do not support single PSA testing for population-based screening.

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Evidence from randomized clinical trials conducted in Europe (the European Randomized Study of Screening for Prostate Cancer [ERSPC], N = 162 243)[1] and in the United States (the Prostate, Lung, Colorectal, and Ovarian Cancer Screening [PLCO] trial, 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 overdetection and overtreatment.[2-4]

Current UK policy does not advocate screening.[7] The 2017 draft recommendations from the US Preventive Services Task Force advocate individualized decision making for men between the ages of 55 and 69 years 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 modeling 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 screenings, have been predicted to reduce overdetection, overtreatment, and costs relative to more frequent screening.[11,12] However, "opportunistic testing" may increase overdetection 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 overdetection and overtreatment. The results from the median follow-up of 10 years are reported in this article.

Key Points

Question What is the effect of an invitation to a single prostate-specific antigen (PSA) screening on prostate cancer detection and median 10-year prostate cancer mortality?

Findings In this randomized clinical trial comparing men aged 50 to 69 years undergoing a single PSA screening (n = 189 386) vs controls not undergoing a PSA screening (n = 219 439), the proportion of men diagnosed with prostate cancer was higher in the intervention group (4.3%) than in the control group (3.6%); however, there was no significant difference in prostate cancer mortality (0.30 per 1000 person-years for the intervention group vs 0.31 for the control group) after a median follow-up of 10 years.

Meaning The single PSA screening intervention detected more prostate cancer cases but had no significant effect on prostate cancer mortality after a median follow-up of 10 years.

Methods

The Derby National Research Ethics Service Committee East Midlands (formerly the Trent Multi-Centre Research Ethics Committee) provided approval for identifying mortality and cancer incidence and review of patient medical records for prostate cancer. Approval for the identification of men in the control and intervention groups without individual consent was obtained from the UK Patient Information Advisory Group (now the Confidentiality Advisory Group) under §251 of the National Health Service Act 2006.

Approval from the UK Patient Information Advisory Group allowed review of the medical records for men who died of a cause potentially related to prostate cancer before consent could be obtained (provided the man did not record an objection to his medical records being used for research). Men who underwent PSA testing in the intervention group gave individual informed consent. All clinical centers had local research governance approval. The University of Bristol acted as the study sponsor (the institution taking overall responsibility). The trial protocol appears in Supplement 1.

Randomization

This was a primary care–based cluster randomized trial of an invitation to a single PSA test followed by standardized prostate biopsy in men with PSA levels of 3 ng/mL or greater.[14] The Prostate Testing for Cancer and Treatment (ProtecT) trial of treatments for localized prostate cancer was embedded[15] within the CAP trial (eFigure 1 in Supplement 2). Between 2001 and 2009, 911 primary care practices geographically located near 8 hospital centers in England and Wales were randomized to the intervention and control groups prior to practice recruitment and obtaining consent. Randomization was stratified within geographical groups and block sizes of 10 to 12 neighboring practices using a computerized random-number generator. Because randomization preceded practices being invited to take part in the study and because the invitation was tailored to the group (intervention or control) to which the practice had been randomized, it was not possible to conceal randomization while practices decided whether to participate. Therefore, we compared the characteristics of the practices that agreed to participate (**Table 1**).

Participants

The inclusion criterion was all men aged 50 to 69 years in each of the randomized primary care practices. The exclusion criteria were a history of prostate cancer on or before the randomization date and patient registration with the practice on a temporary or emergency basis. Follow-up was completed on March 31, 2016.

Intervention

In the intervention group, men aged 50 to 69 years received a single invitation to a nurse-led clinic appointment. At the

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Table 1. Baseline Individual and Primary Care Practice Level Characteristics[a]

Characteristics	Intervention Group	Control Group
Individual		
No. of men	189 386	219 439
Age, median (IQR), y	58.5 (54.3-63.5)	58.6 (54.3-63.5)
Index of Multiple Deprivation, median (IQR)[b]		
England	17.5 (10.1-33.2)	16.9 (9.8-32.4)
Wales	17.6 (9.2-29.5)	13.7 (7.1-29.0)
Live in urban area, No. (%)	163 751 (86)	189 707 (86)
Primary Care Practice		
No. of practices	271	302
No. of individuals per practice, median (IQR)	6300 (4150-9107)	6300 (3793-9000)
Located in urban area, No. (%)	244 (90)	267 (88)
Multiple partners within practice, No. (%)	242 (89)	267 (88)
Quality and Outcomes Framework[c]		
No. of practices in England	224	266
Percentage of total points achieved, median (IQR)[d]	98.9 (97.4-99.6)	99.0 (97.4-99.7)
Index of Multiple Deprivation[b]		
No. of practices in England	231	271
Median (IQR)	21.8 (12.7-44.1)	23.6 (13.3-46.7)
No. of practices in Wales	40	31
Median (IQR)	18.8 (11.9-22.9)	20.1 (7.6-34.5)
Prevalence across practices, mean (SD), %[e]		
All types of cancer	0.6 (0.3)	0.5 (0.2)
Diabetes	3.6 (1.0)	3.7 (1.0)
Obesity	8.0 (2.8)	7.8 (2.8)
Coronary heart disease	4.1 (1.4)	3.9 (1.3)

Abbreviation: IQR, interquartile range (25th to 75th percentile).

[a] Adapted from Turner et al.[14]

[b] A measure of relative deprivation for small areas; a higher score indicates more deprivation (range, 0-100). English and Welsh scores are not directly comparable; therefore, they are reported separately.

[c] A system for the performance management and payment of primary care clinicians based on the quality of their care.

[d] Based on data from 2007 and 2008.

[e] Calculated as (No. of individuals registered with a health condition at each practice/total No. of individuals registered at each practice) × 100.

appointment, men were provided with information about PSA testing. After giving consent, men were offered the PSA test. Men with PSA levels of 3.0 ng/mL or greater were offered a standardized 10-core transrectal ultrasound-guided biopsy. Those diagnosed with clinically localized prostate cancer and who met the eligibility criteria were recruited to participate in the ProtecT trial to receive treatment. The ProtecT trial compared radical prostatectomy, radical conformal radiotherapy with neoadjuvant androgen deprivation therapy, and active monitoring.[5] In contrast, the control practices provided standard National Health Service management, and information about PSA testing was provided only to men who requested it.[16]

Management of Cases and Data Collection

Cases of prostate cancer that were detected among men in the intervention group who did not attend the nurse-led PSA clinic appointment and among men in the control group were managed by the same clinicians as those who attended the PSA clinic in the intervention group. Men were linked to the National Health Service Digital Organization and the Office for National Statistics for deaths and cancer registrations. There were only 639 men (0.15%) unable to be linked or who were not registered. Prostate cancer stage and Gleason grade at diagnosis were obtained from Public Health England and Public Health Wales, and supplemented with routine hospital data from the study centers. We were unable to abstract good quality data on metastases from routine records. Study data were collected using the REDCap (Research Electronic Data Capture) electronic data capture tool (a secure, web-based application designed to support data capture for research studies) hosted at the University of Bristol.

Primary and Secondary Outcome Measures

The outcome measures and methods for statistical analysis were prespecified prior to data release in a published statistical analysis plan[17] (also appears in Supplement 1), which was updated and finalized on July 26, 2016. The primary outcome was definite, probable, or intervention-related prostate cancer mortality at a median follow-up of 10 years and was determined by an independent cause of death evaluation committee that was blinded to trial group assignment.[18]

The secondary outcomes were all-cause mortality, prostate cancer stage, and Gleason grade at prostate cancer diagnosis. Prostate cancer and all-cause mortality at 15 years, health-related quality of life, and cost-effectiveness also were prespecified secondary end points but are not reported in this article.

Statistical Analysis

The primary analysis followed the intention-to-screen principle, comparing outcomes among eligible men at primary care practices randomized to the intervention group with outcomes for eligible men at primary care practices

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randomized to the control group.[17] Kaplan-Meier plots were used to display cumulative incidence of the primary and secondary outcomes. Estimated rate ratios (RRs) were used to compare prostate cancer incidence and mortality in intervention vs control practices using mixed-effects Poisson regression, which allows for clustering of men within primary care practices and of neighboring primary care practices within randomization strata.

Because the incidence of prostate cancer varies greatly by age, each man's follow-up was divided into periods defined by his age using a lexis diagram approach[19] (≤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 prespecified secondary analysis was estimation (using random allocation as an instrumental variable) of the effect of the trial intervention in those accepting the PSA clinic invitation and attending the clinic, using a generalized method of moments estimator.[17,20,21] Prespecified 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.

Prespecified sensitivity analyses were (1) adjustment of the primary analysis for baseline measures observed to differ between the intervention and control groups (not required because baseline measures did not differ between groups) and (2) estimation of the intervention effect on the primary outcome if all patients treated within the ProtecT trial had undergone the treatment shown to be superior (not required because no treatment was shown to be superior). In exploratory analyses, differences in the 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 evidence that the prostate cancer mortality rate ratio changed over time by testing for nonproportional hazards using scaled Schoenfeld residuals derived from Cox models.

Because there were few missing data, and in accordance with our statistical analysis plan, we did not conduct multiple imputation analyses. All *P* values are 2-sided. In interpreting the results, we focused on estimated effects of the intervention vs the control and the associated 95% CIs.[22] Results are described as statistically significant if the *P* value was <.05 or not statistically significant if the *P* value was ≥.05. All analyses were conducted using Stata version 14.2 (StataCorp).

Power

The original power calculations were based on the estimated 10-year incidence of prostate cancer mortality using 1994 data for England and Wales, assuming a plausible between-practice coefficient of variation of 0.2 (additional information appears in the trial protocol in Supplement 1). Calculations predicted that 209 000 men in each group would yield 1720 prostate cancer deaths during a median follow-up of 10 years, and allow a prostate cancer mortality RR of 0.87 to be detected with 80% power at a significance level of .05. Assuming an uptake in PSA testing of between 35% and 50%, this corresponds to RRs between 0.62 and 0.73 among men actually undergoing PSA testing.

These RRs are similar to those assumed in the power calculations for the ERSPC.[23] Estimates of the effect on power of ever undergoing PSA testing during follow-up in the control group suggested that the effect would be minimal unless reaching 20%.

Results

Study Population

There were 911 primary care practices randomized within 99 geographical areas. Of these, 126 were subsequently excluded as ineligible (**Figure 1**).[14] Consent rates among the remaining eligible primary care practices in the intervention group (n = 398) and the control group (n = 387) were 68% (n = 271) and 78% (n = 302), respectively. There were 573 eligible practices (73%) that agreed to participate and there were 195 912 men eligible for the intervention group and 219 445 men eligible for the control group. Among these 415 357 randomized men (mean [SD] age, 59.0 [5.6] years), there were 189 386 in the intervention group and 219 439 in the control group after exclusions who were included in the analysis (n = 408 825; 98%).

There are some differences between the numbers of participants in the intervention group of this trial[14] and the published ProtecT trial study population[5] (eTable 1 in Supplement 2). There were no important differences comparing measured characteristics of practices that did vs did not agree to participate.[14] There were 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 men in the intervention group, 75 707 (40%) attended the PSA testing clinic, 67 313 (36%) had a blood sample taken, and 64 436 had a valid PSA test result. Of these 64 436 men, 6857 (11%) had a PSA level between 3 ng/mL and 19.9 ng/mL (eligible for the ProtecT trial) of whom 5850 (85%) had a prostate biopsy. Men in the intervention group who attended PSA testing clinics were sociodemographically similar to those who did not attend the clinics.[24] Cumulative contamination (PSA testing in the control group) was indirectly estimated at approximately 10% to 15% over 10 years, which is based on previously reported diagnostic referral rates and approximately 20% of follow-up being subsequent to a PSA test undertaken for screening.[25-27]

Primary Analysis

After a median follow-up of 10 years, 549 men (0.30 per 1000 person-years) died of prostate cancer (including intervention-related deaths) in the intervention group compared with 647 men (0.31 per 1000 person-years) in the control group (**Figure 2**A) (rate difference, −0.013 per 1000 person-years [95% CI, −0.047 to 0.022]; RR, 0.96 [95% CI, 0.85 to 1.08];

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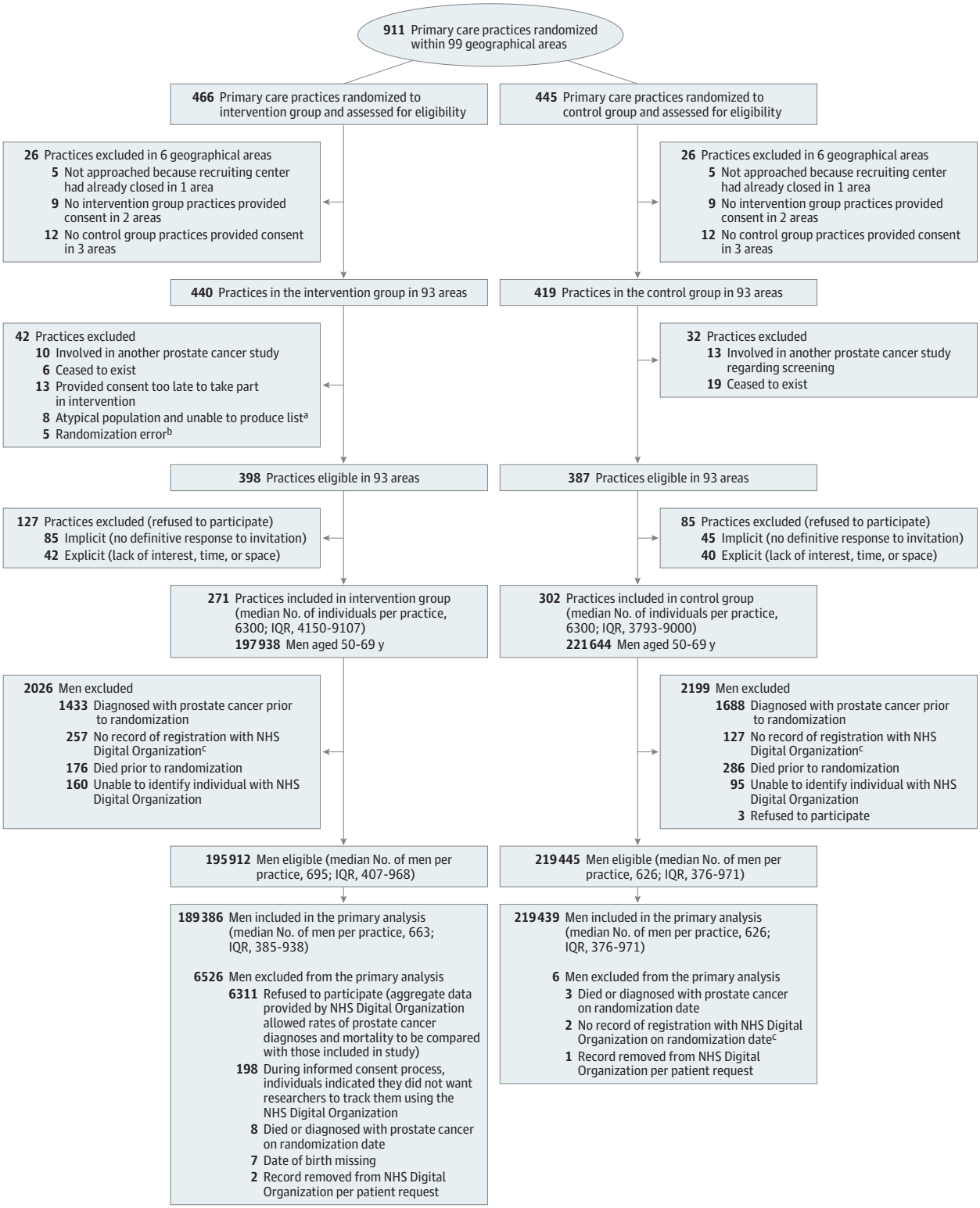
Figure 1. Recruitment and Retention of Practices and Patients in the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP)



Adapted from Turner et al[14] with updated data from the National Health Service (NHS) Digital Organization as of June 2017. IQR indicates interquartile range; PSA, prostate-specific antigen.

[a] Indicates that the practice could not provide a list of men aged 50 to 69 years registered at the practice usually because it treated a subset of the UK population (eg, homeless, elderly care home).

[b] These practices took part in the feasibility study for the intervention and therefore were not eligible for inclusion in the main trial.

[c] Due to emigration out of the United Kingdom or other reasons.

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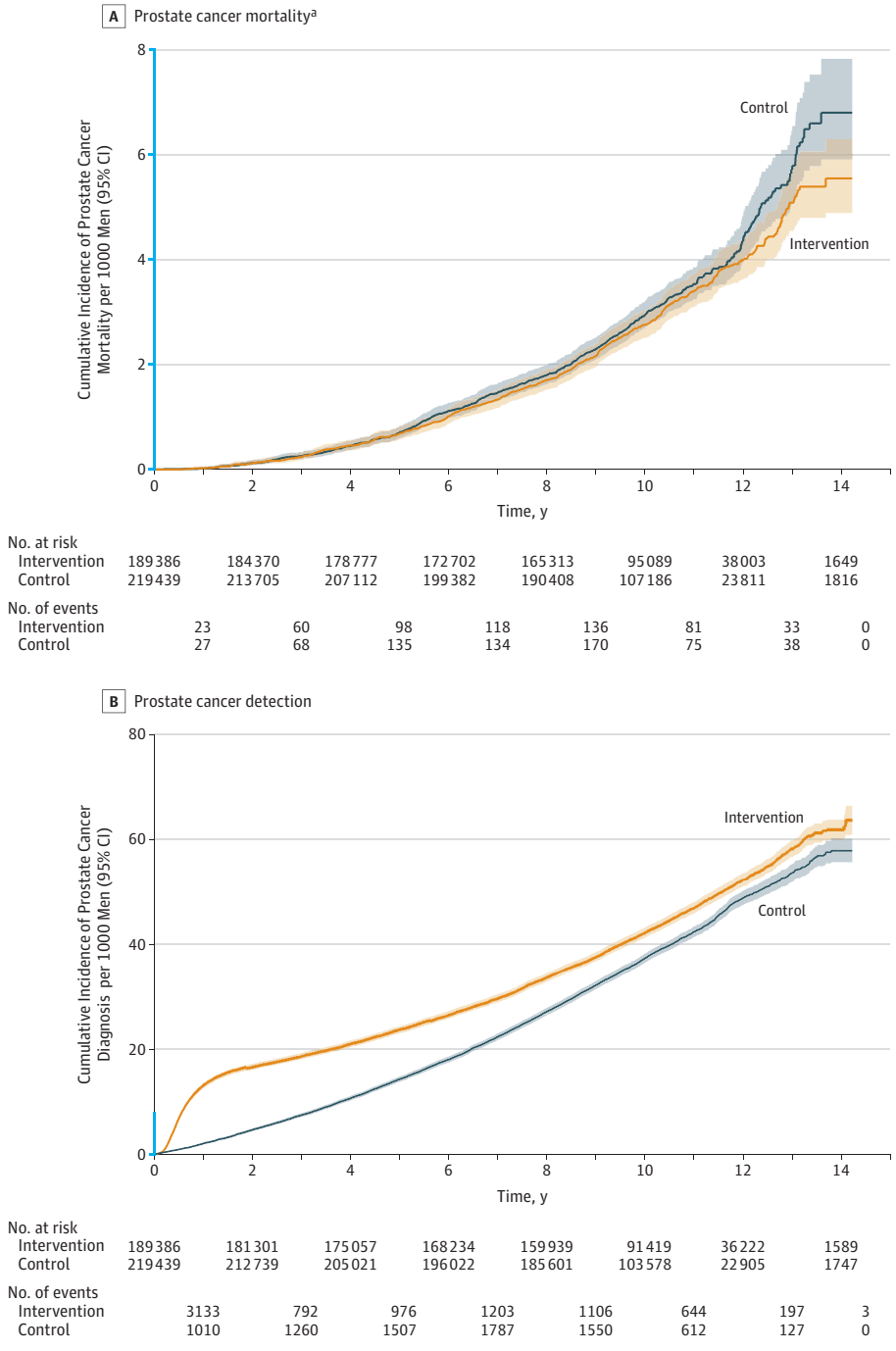
Figure 2. Cumulative Incidence of Prostate Cancer Detection and Mortality in the Single Prostate-Specific Antigen Testing Intervention Group vs Standard Practice (Control)



Y-axis shown in blue indicates range from 0 to 8 events per 1000 men. For part A, the median follow-up was 10.03 years (interquartile range [IQR], 8.80 to 11.50) for the intervention group vs 9.92 years (IQR, 8.74 to 10.93) for the control group (crude rate difference, −0.01 per 1000 person-years; 95% CI, −0.05 to 0.02). For part B, the median follow-up was 9.85 years (IQR, 8.61 to 11.43) for the intervention group vs 9.82 years (IQR, 8.67 to 10.92) for the control group (crude rate difference, 0.65 per 1000 person-years; 95% CI, 0.52 to 0.78).

[a] Defined as definite, probable, or intervention-related prostate cancer death as determined by an independent cause of death committee.

P = .50; **Table 2**) (P = .38 in the exploratory analysis for nonproportional hazards).

Secondary Analyses

After a median follow-up of 10 years, the number of men diagnosed with prostate cancer was higher in the intervention group (n = 8054; 4.3%) than in the control group (n = 7853; 3.6%) (**Table 3**) (RR, 1.19 [95% CI, 1.14-1.25]; P < .001). The between-group difference for incidence rate was 0.65 per 1000 person-years (95% CI, 0.52-0.78; P < .001). The incidence rates were 4.45 per 1000 person-years (95% CI, 4.36-4.55) in the intervention group and 3.80 per 1000 person-years (95% CI, 3.72-3.89) in the control group (Figure 2B).

Compared with the control group, men in the intervention group were younger at diagnosis of prostate cancer

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Table 2. Prostate Cancer-Specific and All-Cause Mortality in the Single Prostate-Specific Antigen (PSA) Testing Intervention Group vs Standard Practice (Control)

	Intervention Group (n = 189 386)[a]		Control Group (n = 219 439)[b]					
	No. of Deaths	Rate/1000 Person-Years (95% CI)	No. of Deaths	Rate/1000 Person-Years (95% CI)	Rate Difference/1000 Person-Years (95% CI)	Rate Ratio (95% CI)[c]	*P* Value	Rate Ratio (95% CI)[d]	*P* Value
Primary Outcome: Prostate Cancer Mortality[e]									
Intention-to-screen cohort	549	0.30 (0.27 to 0.32)	647	0.31 (0.29 to 0.33)	−0.013 (−0.047 to 0.022)	0.96 (0.85 to 1.08)	.50	0.93 (0.67 to 1.29)	.66
Secondary Outcome: All-Cause Mortality									
Intention-to-screen cohort	25 459	13.74 (13.57 to 13.91)	28 306	13.51 (13.35 to 13.67)	0.229 (−0.001 to 0.460)	0.99 (0.94 to 1.03)	.49	1.07 (0.93 to 1.23)	.35

[a] There were 1 853 167 person-years, calculated as the time until death or censoring.

[b] There were 2 095 405 person-years, calculated as the time until death or censoring.

[c] Likelihood ratio test of the null hypothesis (ie, no difference in prostate cancer mortality between the groups) adjusted for randomization cluster and age stratum.

[d] Analysis to obtain the causal effect of screening among those attending the PSA testing clinic using a generalized method of moments estimator with random allocation as an instrumental variable.

[e] Defined as definite, probable, or intervention-related prostate cancer death as determined by an independent cause of death committee.

(−1.34 years; 95% CI, −1.59 to −1.10; *P* < .001). The proportion of men with low-grade prostate cancer (Gleason grade of ≤6) was 1.7% in the intervention group vs 1.1% in the control group (between-group difference, 6.11 per 1000 men [95% CI, 5.38 to 6.84]; *P* < .001); localized prostate cancer (stage T1 or T2), 2.6% vs 1.9%, respectively (between-group difference, 6.97 per 1000 men [95% CI, 6.05 to 7.89]; *P* < .001); high-grade prostate cancer (Gleason grade of ≥8), 0.7% vs 0.7% (between-group difference, −0.58 per 1000 men [95% CI, −1.09 to −0.06]; *P* = .03); and advanced-stage cancer (stage T4, N1, or M1), 0.5% vs 0.6% (between-group difference, −0.91 per 1000 men [95% CI, −1.36 to −0.46], *P* < .001; Table 3 and eFigure 2 and eFigure 3 in Supplement 2).

Thus, as a proportion of detected cancers, the prostate cancer tumors in the intervention group were less likely to be high grade (≤6 vs 7 vs ≥8; odds ratio, 0.68 [95% CI, 0.64-0.73]; *P* < .001) or advanced stage (T1 or T2 vs T3 vs T4, N1, or M1; odds ratio, 0.68 [95% CI, 0.62-0.75]; *P* < .001). The clinical characteristics of prostate cancer tumors among men in the intervention group who did not attend the PSA testing clinic were not significantly different from men in the control group (Table 3 and eFigure 4 and eFigure 5 in Supplement 2).

In the instrumental variable analysis for prostate cancer mortality, the adherence-adjusted causal RR was 0.93 (95% CI, 0.67-1.29, *P* = .66; Table 2). This represents an increase of the effect estimate compared with the intention-to-screen analysis (relative reduction from 4% to 7%), 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 the rates of all-cause mortality between these groups (RR, 0.99 [95% CI, 0.94-1.03], *P* = .49; Table 2 and eFigure 6 in Supplement 2). Prostate cancer-specific mortality effect estimates were consistent when based on alternative definitions of prostate cancer mortality (eTable 2 in Supplement 2).

Prespecified 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 that were related to diagnostic biopsy or prostate cancer treatment (eTable 3 in Supplement 2).

Exploratory Analysis

After a median follow-up of 10 years, 4687 of 75 707 (6.2%) men in the intervention group were diagnosed with prostate cancer after attending the PSA testing clinic compared with 3367 of 113 679 (3.0%) men who did not attend the clinic (Table 3). Among the 4687 incident cases of prostate cancer among those who attended the PSA clinic, 4160 cases of prostate cancer were found following a valid PSA test result, of which 1172 (28%) were among men with a baseline PSA level of less than 3 ng/mL (eTable 1 in Supplement 2). These 1172 initially PSA test-negative cases of prostate cancer were diagnosed a mean of 7.9 years after randomization. Prostate cancer detection was lower among men who did not attend

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Table 3. Characteristics of Prostate Cancer Cases at Diagnosis

	Intervention Group			Control Group (n = 219 439)	Between-Group Difference (95% CI)
	Total (n = 189 386)	Attended PSA Clinic (n = 75 707)	Did Not Attend PSA Clinic (n = 113 679)		
Prostate cancer, No. (%)	8054 (4.3)	4687 (6.2)	3367 (3.0)	7853 (3.6)	
Person-years of follow-up[a]	1 808 031	750 573	1 057 458	2 063 912	
Incidence rate per 1000 person-years	4.45 (4.36 to 4.55)	6.24 (6.07 to 6.43)	3.18 (3.08 to 3.29)	3.80 (3.72 to 3.89)	0.65 (0.52 to 0.78)[b]
Age, median (IQR), y	66.3 (62.1 to 70.0)	65.3 (61.2 to 69.0)	67.9 (63.7 to 71.5)	67.7 (63.6 to 71.6)	−1.37 (−1.56 to −1.19)[c]
Time from randomization to diagnosis, median (IQR), y	4.3 (0.8 to 7.9)	1.2 (0.5 to 7.0)	6.2 (3.4 to 8.7)	6.2 (3.6 to 8.4)	−1.49 (−1.61 to −1.37)[c]
Gleason grade recorded, No./total (%)	7276/8054 (90.3)	4388/4687 (93.6)	2888/3367 (85.8)	6899/7853 (87.9)	
≤6	3263/189 386 (1.7)	2297/75 707 (3.0)	966/113 679 (0.8)	2440/219 439 (1.1)	6.11 (5.38 to 6.84)[d]
7	2710/189 386 (1.4)	1526/75 707 (2.0)	1184/113 679 (1.0)	2823/219 439 (1.3)	1.44 (0.73 to 2.16)[d]
≥8	1303/189 386 (0.7)	565/75 707 (0.7)	738/113 679 (0.6)	1636/219 439 (0.7)	−0.58 (−1.09 to −0.06)[d]
Cancer stage recorded, No./total (%)	7197/8054 (89.4)	4299/4687 (91.7)	2898/3367 (86.1)	7009/7853 (89.3)	
T1 or T2	4938/189 386 (2.6)	3308/75 707 (4.4)	1630/113 679 (1.4)	4192/219 439 (1.9)	6.97 (6.05 to 7.89)[d]
T3	1329/189 386 (0.7)	690/75 707 (0.9)	639/113 679 (0.6)	1540/219 439 (0.7)	0 (−0.51 to 0.51)[d]
T4, N1, or M1	930/189 386 (0.5)	301/75 707 (0.4)	629/113 679 (0.6)	1277/219 439 (0.6)	−0.91 (−1.36 to −0.46)[d]

Abbreviations: IQR, interquartile range (25th to 75th percentile); PSA, prostate-specific antigen.

[a] Person-years of follow-up were calculated as the time until diagnosis, death, or censoring. These figures are lower than those in Table 2 because they exclude person-years after diagnosis.

[b] Difference in incidence rate.

[c] Difference in medians calculated using the generalized Hodges-Lehmann method.[28]

[d] Difference per 1000 men.

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Table 4. Prostate Cancer Mortality Rate Ratios According to Age and Deprivation Scores

	Intervention Group (n = 189 386; 1 853 167 Person-Years)		Control Group (n = 219 439; 2 095 405 Person-Years)		Rate Difference/1000 Person-Years (95% CI)	Rate Ratio (95% CI)[a]	P Value
	Deaths/Person-Years	Rate/1000 Person-Years (95% CI)	Deaths/Person-Years	Rate/1000 Person-Years (95% CI)			
Age group at baseline, y							
50-54	46/563 086	0.08 (0.06 to 0.11)	64/628 611	0.10 (0.08 to 0.13)	−0.02 (−0.05 to 0.01)	0.79 (0.49 to 1.10)	
55-59	110/547 996	0.20 (0.17 to 0.24)	125/613 997	0.20 (0.17 to 0.24)	0 (−0.06 to 0.05)	0.98 (0.72 to 1.23)	.14
60-64	166/421 111	0.39 (0.34 to 0.46)	222/481 235	0.46 (0.40 to 0.53)	−0.07 (−0.15 to 0.02)	0.85 (0.68 to 1.03)	
65-69	227/320 974	0.71 (0.62 to 0.81)	236/371 563	0.64 (0.56 to 0.72)	0.07 (−0.05 to 0.20)	1.11 (0.90 to 1.32)	
Index of Multiple Deprivation Area[b]							
England							
Tertile 1 (1.08-12.17)	132/525 973	0.25 (0.21 to 0.30)	196/651 184	0.30 (0.26 to 0.35)	−0.05 (−0.11 to 0.01)	0.84 (0.64 to 1.03)	
Tertile 2 (12.18-25.95)	174/529 621	0.33 (0.28 to 0.38)	189/628 337	0.30 (0.26 to 0.35)	0.03 (−0.04 to 0.09)	1.10 (0.86 to 1.33)	.22
Tertile 3 (25.96-79.98)	176/540 949	0.33 (0.28 to 0.38)	208/593 187	0.35 (0.31 to 0.40)	−0.03 (−0.09 to 0.04)	0.93 (0.73 to 1.12)	
Wales							
Tertile 1 (1.40-10.30)	20/80 425	0.25 (0.16 to 0.39)	21/91 112	0.23 (0.15 to 0.35)	0.02 (−0.13 to 0.17)	1.02 (0.38 to 1.66)	
Tertile 2 (10.31-23.30)	21/92 373	0.23 (0.15 to 0.35)	16/63 855	0.25 (0.15 to 0.41)	−0.02 (−0.18 to 0.13)	0.88 (0.30 to 1.47)	.79
Tertile 3 (23.31-78.90)	26/83 826	0.31 (0.21 to 0.46)	17/67 729	0.25 (0.16 to 0.40)	0.06 (−0.11 to 0.23)	1.22 (0.45 to 1.98)	

[a] Adjusted for age stratum and practice cluster effects apart from age, which was not adjusted for age stratum.

[b] A measure of relative deprivation for small areas; a higher score indicates more deprivation (range, 0-100). English and Welsh scores are not directly comparable; therefore, they are reported separately.

the PSA clinic in the intervention group compared with men in the control group (between-group difference, −6.17 per 1000 person-years [95% CI, −7.42 to −4.91], $P < .001$; eFigure 7A in Supplement 2).

During the first 18 months following recruitment (the screening phase), the rate of prostate cancer detection was 10.42 per 1000 person-years (95% CI, 10.05 to 10.81) in the intervention group compared with 2.18 per 1000 person-years (95% CI, 2.02 to 2.34) in the control group (rate difference, 8.25 [95% CI, 7.83 to 8.66], $P < .001$; eTable 4 in Supplement 2). In contrast, the rate of prostate cancer detection after the screening phase was 3.36 per 1000 person-years (95% CI, 3.27 to 3.46) in the intervention group vs 4.11 per 1000 person-years (95% CI, 4.02 to 4.21) in the control group (rate difference, −0.75 [95% CI, −0.61 to −0.88]; $P < .001$). When the analysis was restricted to men in the intervention group who attended the PSA clinic vs men in the control group, the rate of prostate cancer was 3.41 (95% CI, 3.27 to 3.56) (rate difference, −0.70 per 1000 person-years [95% CI, −0.87 to −0.53], $P < .001$; eFigure 7B in Supplement 2).

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 (eFigure 2, eFigure 3, and eTable 4 in Supplement 2). In contrast, the proportions of all categories of Gleason grade and TNM stage prostate cancer diagnosed more than 18 months after randomization were lower in the intervention group than in the control group (eTable 4 in Supplement 2).

Among the 549 men in the intervention group who died of prostate cancer, 188 (34%) had attended the PSA screening clinic and 59 deaths occurred 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%). Of these 129 men, 42 had not undergone PSA testing at all, 15 eligible men had not received a prostate biopsy, 68 had a PSA level of less than 3.0 ng/mL at screening (and therefore were below the threshold for recommending biopsy), and 4 had a benign prostate biopsy result (eTable 1 in Supplement 2). Other causes of death were similarly distributed between the trial groups (eTable 5 in Supplement 2).

Discussion

In this cluster randomized clinical trial among men aged 50 to 69 years, 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 cancer.

This trial provides new evidence that complements published trials such as ERSPC and PLCO[1,2] (eTable 6 in Supplement 2). First, recruitment was based on primary care practice clusters, minimizing volunteer bias and lessening PSA testing contamination among controls[25] compared with trials that individually randomized men. The lower

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proportion of prostate cancer cases detected, and the greater proportion of higher stage and Gleason grade prostate cancer tumors detected among men in the control group (compared with the ERSPC and PLCO trials), suggest low background PSA testing rates during follow-up, which is consistent with current UK policy.[16]

Second, diagnostic pathways were standardized, and men in the intervention group with localized prostate cancer were randomized into the ProtecT trial to determine the effectiveness of treatment following screening.[5,10] Because there was little evidence of a difference in mortality between the ProtecT trial groups after a median follow-up of 10 years,[5] it is unlikely that the randomization to the ProtecT trial within the intervention group in the CAP trial had any effect on the primary mortality results in the CAP trial.

Third, screening was less intensive than in the ERSPC or PLCO trials, aiming to reduce overdetection. The higher age, Gleason grade, and cancer stage at diagnosis in the CAP trial's intervention group compared with in the ERSPC and PLCO trials reflect adherence to the low-intensity strategy.

Fourth, the CAP trial recruited patients during a more recent PSA testing era between 2001 and 2009 compared with between 1993 and 2003 in the ERSPC trial and 1993 and 2001 in the PLCO trial. Participants had access to similar advances for treatments of all stages of prostate cancer, 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 among those with an increased PSA level, and 10-core rather than sextant biopsy to improve prostate cancer detection. Sixth, compared with the ERSPC and PLCO trials, the CAP trial included a much greater number of participants following a single randomization and recruitment process, allowing for more precise estimates of the effect of the intervention. In addition, the CAP trial's design enabled the follow-up of all men in the source population for key outcomes.

It has been hypothesized that screening men in their early 50s may be more effective than at a later age[29]; however, 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-center analysis of the ERSPC trial suggested that more intensive screening reduces mortality relative to no screening, but also that intensive screening strategies detect higher numbers of low-risk prostate cancer cases and have a strong positive correlation between the extent of the benefits gained and the harms caused.[30] The results of the CAP trial show that even a low-intensity strategy aiming to reduce overdetection leads to an increased detection of low-risk prostate cancer cases, without benefit in reducing mortality from the disease (Table 3 and eTable 4 in Supplement 2).

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

This trial also identified the underdetection of lethal cancer in initial screening and among nonresponders (eTable 1 in Supplement 2). Even though this may be related in part to the low-intensity intervention, it raises the question of whether underdetection of clinically important cancer also occurs with more intensive screening strategies in other trials, but has not been evident in trials lacking comprehensive follow-up and identification of the target population.

The diagnostic pathway for prostate cancer detection is changing, with advances in imaging (eg, multiparametric magnetic resonance imaging) being introduced with prostate biopsy to improve the identification and targeting of clinically important cancer,[33] and blood-based biomarkers to enhance the specificity of the serum PSA test, including genetic testing.[34] A PSA test alone with transrectal ultrasound-guided biopsy may no longer be the standard of care in the early detection of prostate cancer. Furthermore, offering multiparametric magnetic resonance imaging or novel biomarkers to men based on PSA thresholds will still miss cases of potentially lethal cancer.

Limitations

This study has several limitations. First, the single PSA screening may fail to reflect the long-term effect of multiple PSA testing rounds seen in the ERSPC and PLCO trials. Nevertheless, we observed both a Gleason grade and cancer stage shift, and a reduction in long-term prostate cancer incidence following a single screening round. In PLCO[35] and ERSPC centers,[36,37] tumors identified during second and subsequent screening rounds were more likely to be localized, small volume, and with favorable histological grading compared with those found during the first round of screening, supporting model-based estimates that suggest overdetection increases with repeated screening.[37]

Second, an important number of incident and lethal prostate cancer cases were not identified through the initial screening intervention (eg, among men with an initial PSA level <3 ng/mL or among men in the intervention group who did not attend the PSA screening clinic; eTable 1 in Supplement 2), suggesting the inadequacy of conventional PSA testing followed by transrectal ultrasound-guided biopsy. These prostate cancer cases were clinically comparable with those in the control group, suggesting similar routes to diagnosis. The single PSA testing protocol followed by 10-core transrectal ultrasound-guided biopsy in this trial may have led to the underdetection of some lethal cases. Prebiopsy multiparametric magnetic resonance imaging 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), which was also noted in the Swedish center of ERSPC.[38]

Third, in this trial there was 40% adherence with the intervention. This compares with 59% to 69% in ERSPC centers

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using consent obtained after randomization; however, adherence was higher in ERSPC centers with consent obtained prior to randomization.[39] Consistent with the primary analysis, the instrumental variable analysis found no evidence that attending the PSA screening clinic reduced prostate cancer mortality. Men in the intervention group who attended the PSA screening clinic were sociodemographically similar to men who did not attend,[24] although the measures were somewhat crude, and nonattendees had lower rates of incident prostate cancer than controls. Therefore, men not entering the trial might be less likely to subsequently seek a PSA test. The similarity of non-prostate cancer-related deaths between the intervention group and the control group indicates the success of randomization (eTable 5 in Supplement 2).

Fourth, a median follow-up of 10 years may be too short to identify the effect of screening. More than half the deaths due to prostate cancer in the intervention group occurred during the first 7 years after randomization, a period during which it is unlikely that PSA screening would have an effect (Figure 2A). 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 follow-up of 10 years, with no evidence of a difference between randomized groups.[5]

However, the rate of metastatic disease was reduced by 2.4 per 1000 person-years with surgery and by 3.0 per 1000 person-years with radiotherapy vs by 6.3 per 1000 person-years with active monitoring. Given the very low disease-specific mortality at 10 years and the long lead time for the development of prostate cancer (approximately 12 years in the United Kingdom[31]), extended follow-up of the CAP 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 follow-up of 12.7 years, the Prostate Intervention vs Observation Trial (PIVOT) reported little evidence of a difference in disease-specific or all-cause mortality, but showed intermediate-risk disease may benefit from early intervention.[40] Nevertheless, there was no significant effect of the CAP trial intervention on the prespecified primary outcome of prostate cancer mortality at a median follow-up of 10 years.

Fifth, while postrandomization exclusions have the potential to lead to bias (Figure 1), there were no differences between excluded practices in the intervention group and the control group for key variables such as primary care practice size, Index of Multiple Deprivation, or urban vs rural location.[14] Furthermore, the cumulative incidence of all-cause mortality was similar in both the intervention and control groups. Therefore, it seems unlikely that the postrandomization exclusions biased our results.

Conclusions

Among practices randomized to a single PSA screening intervention vs standard practice without screening, there was no significant difference in prostate cancer mortality after a median follow-up of 10 years but the detection of low-risk prostate cancer cases increased. Although longer-term follow-up is under way, the findings do not support single PSA testing for population-based screening.

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REFERENCES

1. Schröder FH, Hugosson J, Roobol MJ, et al; ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360(13):1320-1328.

2. Andriole GL, Crawford ED, Grubb RL III, et al; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial [published correction appears in *N Engl J Med*. 2009;360(17):1797]. *N Engl J Med*. 2009;360(13):1310-1319.

3. Moyer VA; US Preventive Services Task Force. Screening for prostate cancer: US 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. *N Engl J Med*. 2017;376(13):1285-1289.

5. Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):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. https://legacyscreening.phe.org.uk/prostatecancer. Accessed February 9, 2018.

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;167(7):449-455.

9. Schröder FH, Hugosson J, Roobol MJ, et al; ERSPC Investigators. 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; ProtecT Study Group. Patient-reported outcomes after

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monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med*. 2016;375(15):1425-1437.

11. Heijnsdijk EAM, Wever EM, Auvinen A, et al. Quality-of-life effects of prostate-specific antigen screening. *N Engl J Med*. 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. *Int J 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. *Eur Urol*. 2015;68(3):354-360.

14. Turner EL, Metcalfe C, Donovan JL, et al; CAP Trial Group. 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; ProtecT Study Group. 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 Oncol*. 2014;15(10):1109-1118.

16. Burford D, Kirby M, Austoker J. Prostate Cancer Risk Management Programme: information for primary care and PSA testing in asymptomatic men. http://webarchive.nationalarchives.gov.uk/20150505144744/http://www.cancerscreening.nhs.uk/prostate/pcrmp02.pdf. Accessed February 6, 2018.

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. https://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 December 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*. New York, NY: John Wiley & Sons Ltd; 2005.

20. Baum CF, Schaffer ME, Stillman S. Instrumental variables and GMM: estimation and testing. *Stata J*. 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. *Eur Urol*. 2014;65(2):329-336.

22. Sterne JAC, Davey Smith G. Sifting the evidence—what's wrong with significance tests? *BMJ*. 2001;322(7280):226-231.

23. de Koning HJ, Liem MK, Baan CA, Boer R, Schröder FH, Alexander FE; ERSPC. Prostate cancer mortality reduction by screening: power and time frame with complete enrollment in the European Randomised Screening for Prostate Cancer (ERSPC) trial. *Int J Cancer*. 2002;98(2):268-273.

24. Walsh EI, Turner EL, Lane JA, et al; and the CAP & ProtecT Trial Groups. 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 Int*. 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):e017729.

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. Altman DG, Bryant TN, Gardner MJ. *Statistics With Confidence*. 2nd ed. London, England: BMJ Books; 2000.

29. Carlsson S, Assel M, Ulmert D, et al. Screening for prostate cancer starting at age 50-54 years: a population-based cohort study. *Eur Urol*. 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. *Clin Cancer Res*. 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. *Br J Cancer*. 2009;100(7):1198-1204.

32. Loeb S, Bjurlin MA, Nicholson J, et al. Overdiagnosis and overtreatment of prostate cancer. *Eur Urol*. 2014;65(6):1046-1055.

33. Ahmed HU, El-Shater Bosaily A, Brown LC, et al; PROMIS Study Group. 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 [published online November 9, 2017]. *Eur Urol*. doi:10.1016/j.eururo.2017.10.036

35. Grubb RL III, 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 Int*. 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. *J Natl Cancer Inst*. 2003;95(12):868-878.

37. Postma R, Schröder 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. *Eur Urol*. 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 Sanchez A, et al; European Randomized Screening for Prostate Cancer (ERSPC) Trial; International Prostate Cancer Screening Trials Evaluation Group. 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. *Int J 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. *N Engl J Med*. 2017;377(2):132-142.

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