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1   **PSA Screening and 15-year Prostate Cancer Mortality: The CAP Randomized Clinical Trial**

2   Richard M. Martin, BM BS PhD[†1,2,3]; Emma L. Turner, PhD[*1]; Grace J. Young, MSc[*1]; Chris Metcalfe,

3   PhD[1]; Eleanor I. Walsh, MSc[1]; J. Athene Lane, PhD[1]; Jonathan A. C. Sterne, PhD[1,2,4]; Sian Noble, PhD[1];

4   Peter Holding, MSc[5]; Yoav Ben-Shlomo[1], MBBS PhD; Naomi J. Williams, PhD[1]; Nora Pashayan, MD

5   PhD[6]; Mai Ngoc Bui, PhD[6]; Peter C Albertsen, MD[7]; Tyler M. Seibert, MD PhD[8,9,10]; Anthony Zietman,

6   MD[11]; Jon Oxley, MD[12]; Jan Adolfsson, MD[13]; Malcolm Mason, MD[14]; George Davey Smith, DSc[1,3];

7   David E. Neal, MD[*5]; Freddie C. Hamdy*, MD[5]; Jenny L. Donovan[*1,], PhD; for the CAP Trial Group.

8   [†]Corresponding author

9   *Contributed equally

10   **Affiliations**

11   1.   Bristol Medical School, Department of Population Health Sciences, University of Bristol,

12   Bristol, BS8 1UD, UK

13   2.   National Institute for Health Research (NIHR) Bristol Biomedical Research Centre, University

14   Hospitals Bristol and Weston NHS Foundation Trust and University of Bristol, Bristol, UK

15   3.   MRC Integrative Epidemiology Unit, University of Bristol, Bristol, BS8 2BN, UK

16   4.   Health Data Research UK South-West, University of Bristol, Bristol, BS8 1UD, UK

17   5.   Nuffield Department of Surgical Sciences, University of Oxford, Oxford, OX3 7DQ, UK

18   6.   Department of Applied Health Research, University College London, London, WC1E 7HB, UK

19   7.   Division of Urology, University of Connecticut Health Center, Farmington, CT, USA

20   8.   Department of Radiation Medicine and Applied Sciences, University of California San Diego, La

21   Jolla, CA, USA

22   9.   Department of Radiology, University of California San Diego, La Jolla, CA, USA

23   10.   Department of Bioengineering, University of California San Diego, La Jolla, CA, USA

24   11.   Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School,

25   Boston MA, USA

26   12.   Department of Cellular Pathology, North Bristol NHS Trust, Bristol, UK

27   13.   Department of Clinical Science, Intervention and Technology- CLINTEC, Karolinska Institutet,

28   Stockholm, Sweden

29   14.   School of Medicine, Cardiff University, Cardiff, Wales, UK

30

31   **Address for correspondence:**

32   Professor Richard Martin

33   Department of Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, BS8

34   1UD, UK

35   Email: Richard.martin@bristol.ac.uk

36   Tel: +44(0)1174553987

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38   **Word count: 3195**

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41   **Key points**

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43   **Question**: In men aged 50-69, does a single invitation for a prostate specific antigen (PSA) screening

44   test reduce prostate cancer mortality at 15-year follow-up, compared to a control group that was

45   not invited for testing?

46

47   **Findings**: In this cluster randomized trial of 415,357 men aged 50-69 randomized to a single

48   invitation for PSA screening (N=195,912) or a control group without PSA screening (N=219,445) and

49   followed-up for a median of 15-years, risks of death from prostate cancer were lower in the group

50   invited to screening (0.69% vs. 0.78%; mean difference: 0.09%), compared to the control group.

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52   **Meaning**: Compared to a control group without routine PSA testing, a single invitation for a PSA

53   screening test reduced prostate cancer mortality at a median follow-up of 15 years, but the absolute

54   mortality benefit was small.

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58   **Abstract (Word count 383)**

59   **IMPORTANCE** The Cluster randomized trial of PSA testing for Prostate cancer (CAP) reported no

60   effect of prostate specific antigen (PSA) screening on prostate cancer mortality at median 10-year

61   follow-up (primary outcome), but the long-term effects of PSA screening on prostate cancer

62   mortality remain unclear.

63   **OBJECTIVE** To evaluate the effect of a single invitation for PSA screening on the pre-specified

64   secondary outcome of prostate cancer-specific mortality at a median of 15 years' follow-up,

65   compared to a control group not invited for screening.

66   **DESIGN, SETTING, PARTICIPANTS** Cluster randomized trial of men aged 50-69 identified from 573

67   primary-care practices in England and Wales. Primary-care practices were randomized between

68   09/25/2001 and 08/24/2007 and men were enrolled between 01/08/2002 and 01/20/2009. Follow-

69   up was completed on 03/31/2021.

70   **INTERVENTION** A single invitation for a PSA screening test with subsequent diagnostic tests if

71   PSA≥3.0ng/ml, compared to standard practice (control).

72   **MAIN OUTCOMES AND MEASURES** The primary outcome was reported previously. Of eight

73   prespecified secondary outcomes, results of four were reported previously. The four remaining pre-

74   specified secondary outcomes at 15-year follow-up were prostate cancer-specific mortality, all-cause

75   mortality, and prostate cancer stage and Gleason grade at diagnosis.

76   **RESULTS** Of 415,357 randomized men (mean [SD] age: 59.0 [5.6] years), 98% were analyzed in these

77   analyses. Overall, 12,013 and 12,958 men with prostate cancers were diagnosed in the intervention

78   and control groups (15-year cumulative risks 7.1% and 6.9% respectively).

79   At a median 15-year follow-up, 1,199 (0.69%) men in the intervention group and 1,451 (0.78%) men

80   in the control group died of prostate cancer (rate ratio [RR] 0.92 [95% CI 0.85, 0.99]; p=0.03).

81   Compared to the control group, the PSA screening intervention increased detection of low-grade

82   (Gleason score [GS]≤6; 2.2% versus 1.6%;p<0.001) and localized (T1/T2; 3.6% versus 3.1%;p<0.001)

83   disease, but not intermediate (GS=7), high-grade (GS≥8), locally-advanced (T3) or distally-advanced

84   (T4/N1/M1) tumors. There were 45,084 all-cause deaths (23.2%) in the intervention group and

85   50,336 deaths (23.3%) in the control group respectively (RR 0.97 [95% CI 0.94, 1.01]; p=0.11). Eight

86   deaths in the intervention and seven deaths in the control group were related to a diagnostic biopsy

87   or prostate cancer treatment.

88   **CONCLUSIONS AND RELEVANCE** A single invitation for PSA screening, compared to standard practice

89   without routine screening, reduced the secondary outcome of prostate cancer deaths at a median

90   follow-up of 15-years. However, the absolute reduction in deaths was small.

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92   **TRIAL REGISTRATION**: ISRCTN92187251

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Introduction

In England, the number of men diagnosed with prostate cancer increased by 68% from 28,216 in 2001 to 47,479 in 2019,[1] reflecting population aging and increased prostate specific antigen (PSA) testing.[2] In the USA, approximately 3.3 million men currently live with a diagnosis of prostate cancer.[3] While low-risk prostate cancer progresses slowly and is associated with a low risk of mortality,[4-7] aggressive prostate cancer currently causes approximately 12,000 deaths in the UK and 34,700 deaths in the U.S. annually.[3,8] The goal of PSA screening is to reduce prostate cancer mortality by early detection of curable disease. However, uncertainty remains regarding the long-term effect of PSA-based screening on mortality.[9-11]

The CAP RCT (N=415,357) showed that, compared to a usual care (unscreened) control group, an invitation to a single PSA screen increased the number of prostate cancers diagnosed during the first 18 months of follow-up (the time period when PSA testing and subsequent biopsies for men with an elevated level of PSA took place). In this trial, rates of diagnosed prostate cancer were 2.2 per 1000 person-years in the control group and 10.4 per 1000 person-years in the intervention group (P<0.001).[10] However, at a median 10-year follow-up, the invitation for a single PSA screen did not reduce prostate cancer mortality, compared to the control group (0.29% vs. 0.30%; rate ratio: 0.96; 95%CI;0.85-1.08;p=0.5).[10] This report describes the effects of this single invitation to a PSA-screening test, with subsequent diagnostic tests if PSA>3.0ng/ml, on the pre-specified secondary outcome of prostate-cancer mortality at 15-year follow-up, compared to standard (unscreened) practice.[12]

Methods

The Derby National Research Ethics Service Committee East Midlands approved the study. The trial **Protocol** and the **statistical analysis plan** are available as Supplementary material to the primary outcome paper.[10] Participants were enrolled between 01/08/2002 and 1/20/2009. Final follow-up occurred 03/31/2021.

120   Men who attended PSA testing in the intervention group gave individual written informed consent

121   via the ProtecT study.[13] Individual consent was not sought from men in the control group or from

122   non-responders in the intervention group. Instead, approval for their identification and linkage to

123   routine electronic records was obtained under Section-251 of the NHS Act 2006 from the UK Patient

124   Information Advisory Group (now Confidentiality Advisory Group).[10] All clinical centers had local

125   research governance approval.

126   **Randomization**

127   The study was a primary-care based cluster RCT that tested the effects of a single invitation for a PSA

128   screening test (**eFigure 1**), compared to usual care (no screening), on the primary outcome of

129   prostate-cancer mortality at a median follow-up of 10 years. The primary outcome has been

130   reported.[10] Between 2001 and 2007, 785 eligible general practices in the catchment area of 8

131   hospitals across England and Wales (located in Birmingham, Bristol, Cambridge, Cardiff, Leeds,

132   Leicester, Newcastle and Sheffield) were randomized before recruitment ('Zelen' design) to

133   intervention or control groups and practices were invited to consent to participate. Randomization

134   was blocked and stratified within groups of 10-12 neighboring practices, using a computerized

135   random number generator. Because allocation preceded the invitation for practices to participate, it

136   was not possible to conceal allocation. 573 (73%) practices, including 68% randomized to the

137   intervention group and 78% randomized to the control group, agreed to participate **(Figure 1).**

138   **Participants**

139   Men aged 50-69 years in each participating randomized general practice were included. Men with

140   prostate cancer on or before the randomization date and those registered as a patient with

141   participating practices on a temporary or emergency basis were excluded.

142   **Intervention**

143   Men in practices randomized to the intervention received a single invitation for a PSA test after

144   counselling. If the resulting PSA was 3.0-19.9ng/ml, they were offered 10-core transrectal

145   ultrasound-guided biopsies. All laboratories participated in the UK National External Quality

146   Assessment Service (UK NEQAS) for PSA testing. Test results that did not meet laboratory quality

147   assurance requirements, were lost, or if consent was ambiguous or if insufficient blood was

148   obtained, were considered non-valid. Men in the intervention group diagnosed with localized

149   prostate cancer were invited to participate in a second RCT, the ProtecT treatment trial

150   (ISRCTN20141297) which randomized participants to active monitoring (consisting of regular PSA

151   testing and clinical review), radical prostatectomy, or radical conformal radiotherapy with neo-

152   adjuvant-androgen-deprivation (**eFigure 1**).[14] Men with a PSA ≥20ng/ml were referred to a urologist

153   and received standard care.

154   Men in practices randomized to the control group received standard NHS management but did not

155   receive a formal invitation for PSA testing as part of this study.[15] We assessed cumulative PSA testing

156   for prostate cancer detection in the control group of CAP by longitudinal analysis of a national

157   primary care database (N=434,236 men from 558 UK GP practices)[2].

158   **Outcomes**

159   The primary outcome of this clinical trial, 10-year prostate cancer mortality, was reported

160   previously.[10] Pre-specified secondary outcomes were: definite or probable prostate cancer mortality

161   at 15-year follow-up; all-cause mortality at 10-year follow-up; all-cause mortality at 15-year follow-

162   up; all-cause mortality at 5-year follow-up; prostate cancer mortality at 5-year follow-up; disease

163   grade and staging; cost-effectiveness; and health related quality of life. The protocol did not indicate

164   the time point for assessing prostate cancer grade and staging; these were measured at median

165   follow-up time points of 10-years and 15-year follow-up. Previously reported outcomes were all-

166   cause mortality at 10-year follow-up,[10] disease grade and stage at 10-year follow-up,[10] cost-

167   effectiveness[16] and health related quality of life.[17] The current report provides results for the

168   remaining secondary outcomes of definite or probable prostate cancer mortality at 15-year follow-

169   up, all-cause mortality at 15-year follow-up, and disease grade and stage at 15-year follow-up. All-

170   cause and prostate cancer mortality at 5-year follow-up were not published separately, but five-year

171   follow-up data are shown in Kaplan Meier curves, both in the current paper and the publication of

172   the 10-year primary outcome.[10]

173   **Outcome ascertainment**

174   Prostate cancer mortality at 15-year follow-up was ascertained with death certificates from the

175   Office for National Statistics (ONS) at NHS England and adjudicated by an independent Cause of

176   Death Evaluation (CoDE) committee using clinical information from hospital medical records and

177   following a standardized protocol.[18,19] Prostate cancer stage and Gleason grade were obtained from

178   the National Disease Registration Service[20] (NDRS, formerly Public Health England) at NHS England

179   and Public Health Wales,[21] up to December 31st 2020.

180   **Exploratory outcomes**

181   Additional outcomes reported here that were described in the published original statistical analysis

182   plan[10] were: i) mean age at diagnosis between allocated groups; and ii) a sensitivity analysis re-

183   defining the primary outcome to include: (a) definite, probable, possible and treatment-related

184   prostate cancer mortality; and (b) definite and treatment-related prostate cancer mortality.

185   **Post hoc outcomes**

186   We estimated differences in the risks of prostate cancer diagnosis between the intervention and

187   control groups at 18-months, 10-years and 15-years, to quantify changes in diagnosis rates over

188   long-term follow-up. We calculated mean sojourn time (the period in which a tumor is asymptomatic

189   but detectable by screening) from microsimulation using estimated transition parameters for single

190   episodes of screening between ages 50 to 69 and over-diagnosis rates as the difference in the

191   cumulative prostate cancer incidence between screened and unscreened groups over a lifetime

192   (further methodological details in **Supplement 1**).[22,23]

193   **Statistical Analysis**

194   The intervention effect at a median 15-years follow-up (at March 31st 2021) was analysed comparing

195   groups as randomized using random-effects Poisson regression to estimate prostate cancer-specific

196   and all-cause mortality rate ratios (RRs) in intervention versus control practices, allowing for

197   clustering within GP practices and randomization strata. To allow for variation in the incidence of

198   prostate cancer with age, follow-up for each participant was divided into periods within five-year

199   age-groups. We present rates (per 1000 person-years) and Kaplan-Meier estimates of the cumulative

200   risk (per 100 men) of prostate cancer diagnosis, and prostate cancer and all-cause mortality.

201   In pre-specified analyses described in the original statistical analyses plan, and available as

202   Supplementary material to the primary outcome paper,[10] we: i) used instrumental methods

203   (generalized method of moments estimator) to estimate the effect of attending the PSA screening

204   clinic at a median 15-years, compared with men in the control group who would have attended the

205   clinic if invited, adjusting for age-group and using robust standard errors to allow for variation

206   between practices; ii) compared mean age, and prostate cancer clinical stage (T1/T2, T3 and

207   T4/N1/M1 disease) and Gleason score (=6 [low-grade]; =7 [intermediate grade]; 8+ [high grade]) at

208   diagnosis between intervention and control groups using ordered logistic regression.

209   Prespecified subgroup analyses investigated variation in the effect of screening on prostate cancer

210   mortality by baseline age-group and quintiles of geographical area-based index of multiple

211   deprivation, a measure of socioeconomic status. An interaction test p-value was used to evaluate the

212   evidence against the null hypothesis of equal intervention effect across sub-groups.

213   In accordance with our original analysis plan,[10] we did not conduct multiple imputation analyses. The

214   statistical analysis plan did not specify an intention to adjust p-values for multiple comparisons:

215   conventional adjustments assumed statistical independence between estimates, which was not the

216   case for analyses of the same outcome at 10 and 15 years. All statistical testing was for superiority

217   and p-values were 2-sided. In interpreting the results, we focused on estimated effects and

218   associated 95% CIs. Results were considered statistically significant if the P value was <.05 or not

219   statistically significant if the P value was ≥.05. All trial analyses were conducted using Stata version

220   16.1 (StataCorp).

221

222

Results

Study Population

911 GP practices were randomized in 99 geographical areas. Of these, 126 were subsequently

excluded as ineligible (**Figure 1**).[12] Consent rates were 68% (271/398) among eligible GP practices in

the intervention group and 78% (302/387) among eligible GP practices in the control group. Overall,

415,357 men registered with these practices were eligible for the intervention (N=195,912) and

control (N=219,445) groups. Follow-up data for cancer diagnosis and mortality at a median of 15

years after randomization were available for 408,721 of the eligible men (98%), including 189,326

(97%) randomized to the intervention and 219,395 (>99%) randomized to control (**Figure 1**).

Baseline characteristics were similar between intervention and control groups at practice and

individual level (**Table 1**). Among people randomized to the intervention who developed prostate

cancer (N=12,013), 9.4% were missing data for cancer stage and 10.4% were missing data for

Gleason grade. Among people randomized to the control group who developed prostate cancer

(N=12,958), 7.8% were missing data for cancer stage and 11.2% were missing data for cancer

Gleason grade.

Rates of PSA testing

Overall, 75,694 (40%) of men randomized to the intervention group underwent PSA-testing and

64,425 (34%) had a valid (as defined in the methods) test result. Of these, 6,855 (11%) had a PSA

value between 3-19.9ng/ml and were eligible for the ProtecT trial. Of these, 5,848 (85%) had a

prostate biopsy. Cumulative PSA testing for prostate cancer detection in the control-group was

indirectly estimated at 10% to 15% over 10-years median follow-up.[2,10]

Prostate cancer deaths

After a median follow-up of 15.4 years (interquartile range, IQR: 14.2-16.4; range: 12.2, 19.2), there

were 1,199 deaths due to prostate cancer (rate: 0.47 per 1000-person years) in the intervention

group and 1,451 deaths (rate: 0.50 per 1000-person years) in the control-group: RR 0.92 (95% CI,

0.85 to 0.99; p=0.03) **(Table 2, Figure 2A)**. At a median of 15-years' follow-up, the cumulative risks of

249 prostate cancer mortality were 0.69% in the intervention group and 0.78% in the control group [risk

250 difference -0.09% (95% CI, -0.15 to -0.03, P=0.02)] (**Table 2, eTable 1**). Using instrumental variable

251 analysis, the prostate cancer mortality rate ratio for the effect of screening amongst men attending

252 PSA-testing clinics was 0.83 (95% CI 0.68, 1.00; p=0.053) (**Table 2**).

Overall survival

254 There were 45,084 total deaths in the intervention group and 50,336 total deaths in the control

255 group (RR 0.97: 95% CI 0.94 to 1.01; p=0.11) (**Table 2, Figure 2B**). Other causes of death were similar

256 between the two groups (**eTable 2**).

Prostate cancer grade and stage

258 Compared to control, men in the intervention group were at higher risk of diagnosis with low-grade

259 (2.2% of men versus 1.6%; risk difference = 0.58%, 95% CI 0.50%, 0.67%), and at lower risk of high-

260 grade (1.2% versus 1.3%; risk difference = -0.15%; 95% CI: -0.22% to -0.08%), prostate cancers over

261 the 15-years follow-up (p for trend <0.001). There was a higher risk of localized (3.6% versus 3.1%;

262 risk difference = 0.56%, 95% CI 0.44%, 0.67%) prostate cancers and a lower risk of advanced-stage

263 tumors (0.9% versus 1.1%; risk difference = -0.16%; 95% CI: -0.22% to -0.10%) over the 15-years

264 follow-up in the intervention versus control group (p for trend <0.001) (**eTable 3; eFigures 2** and **3**).

Exploratory results

266 The mortality results were similar when including in the outcome definition those prostate cancer-

267 specific deaths judged as 'possible' by the Cause of Death Evaluation committee, and when

268 restricting to those judged as 'definite' prostate cancer-specific deaths (**eTable 4**). There was little

269 evidence that the intervention effect differed by age-group or socioeconomic status (p values for

270 interaction ≥0.46) (**Table 3**). Compared to the control group, intervention group men were a mean

271 1.22 years younger at prostate cancer diagnosis (95% CI 1.02, 1.42; p<0.001) (**eTable 3**).

Post hoc results

273 After a median 15-years follow-up, there were 12,013 (4.88 per 1000 person-years [cumulative risk:

274 7.1%]) prostate cancer diagnoses in the intervention group and 12,958 (4.60 per 1000 person-years

12

275   [cumulative risk: 6.9%]) in the control group **(Table 2, Figure 2C)**. Differences in the risks of prostate

276   cancer diagnosis between the intervention and control groups varied markedly during follow-up:

277   cumulative risk differences per 1000 men for the intervention versus control groups were 12.23

278   (95% CI: 11.63, 12.84) at 18-months, 4.80 (95% CI: 3.53, 6.07) at 10-years, 1.38 (95% CI: -0.38, 3.14)

279   at 15-years and 0.86 (95% CI: -1.80, 3.53) at 18-years (**eTable 1**).

280   For age-groups 50-54 compared to 65-69 years, the mean sojourn time increased from 12.1 years to

281   15.3 years, and over-diagnosis from 9.2% to 20.8%, respectively (**eTable 5, eFigures 4-6**).

282   **Adverse Events**

283   Among the deaths due to prostate cancer, 8 (0.7%) in the intervention group and 7 (0.5%) in the

284   control group were related to a diagnostic biopsy or prostate cancer treatment.[10] Other adverse

285   events were reported previously.[9,11]

286

287   **Discussion**

288   In secondary analysis from this cluster RCT of 415,357 men aged 50-69, compared to usual care

289   control, a single invitation to undergo a PSA test led to an absolute reduction in prostate cancer

290   mortality of 0.09% after a median follow-up of 15 years. However, the magnitude of the effect was

291   small. There was no effect on overall survival. Policy-makers considering screening for prostate

292   cancer should consider this small reduction in deaths against the potential adverse effects

293   associated with over-diagnosis and over-treatment of prostate cancer.[6,24]

294   This clinical trial previously reported no benefit of a single invitation to PSA screening on the primary

295   outcome of prostate cancer mortality at a median follow-up of ten years.[10] PSA testing is increasingly

296   common,[2] particularly among men over age 60,[2,25] and definitive evidence on the benefits and harms

297   of PSA screening remain unclear.[24] Analyses reported here are important because of the need for a

298   longer follow up period to evaluate the effect of PSA-detection of prostate cancers,[5] particularly

299   because findings from the ProtecT trial showed no difference in mortality irrespective of treatment

300   over 15 years.[6]

301   The magnitude of reduction in prostate cancer mortality was smaller than the *a priori* defined effect-

302   size considered important for clinical and public health benefit.[12] The harms of PSA testing include

303   over-diagnosis, biopsy complications,[9] adverse treatment-effects on urinary, sexual and bowel

304   function,[11] and the potential to miss an aggressive prostate cancer.[10] This clinical trial's single

305   invitation to a PSA screen aimed to minimize over-diagnosis and over-treatment compared with

306   other screening trials, but overdiagnosis was still observed after 15-years median follow-up. The

307   European Randomized Study of Prostate Cancer Screening (ERSPC) randomized clinical trial

308   (N=162,243), which combined data from 7 centers with different protocols and screening strategies,

309   reported that PSA screening conducted every 2-4 years (mean of 1.4 tests per participant) reduced

310   prostate cancer mortality after 16 years (rate ratio: 0.80; 95% CI:0.72-0.89).[26] The Prostate, Lung,

311   Colorectal and Ovarian (PLCO) randomized clinical trial (N=76,683) reported little evidence of

312   prostate cancer mortality benefit after 17 years with annual PSA testing compared to usual care

313   (rate ratio: 0.93; 95% CI 0.81-1.08),[27] but was limited by high rates of PSA testing in the control group

314   (a mean of 2.7 routine PSA tests over the trial's 6 year intervention period[28]) and only 35%

315   adherence to recommendations for diagnostic biopsy.[29] The Stockholm clinical trial compared one-

316   time PSA screening, and diagnostic investigations if PSA>10ng/ml, with an unscreened control group.

317   It demonstrated over-diagnosis of prostate cancer (persistent excess in cumulative prostate cancer

318   incidence in the screening intervention group throughout follow-up), without reduced prostate

319   cancer mortality after 20 years follow-up.[30] Multiple screens implemented in ERSPC and PLCO

320   increased over-diagnosis,[31] with evidence of a strong positive correlation between the extent of the

321   absolute prostate cancer mortality reduction achieved by the screening intervention and the extent

322   of over-diagnosis (quantified as the risk difference in cumulative incidence of prostate cancer

323   between the trial arms).[32]

324   **Strengths**

325   This study had several strengths. First, compared to randomizing individual patients, recruitment in

326   general practice clusters is expected to minimize volunteer bias and reduce contamination in the

327   control group, in which the intervention effects also cause greater screening in the control group.

328   Cumulative PSA testing in the control-arm of this clinical trial was indirectly estimated at 10% to 15%

329   over 10-years median follow-up, consistent with current UK policy not to recommend screening. A

330   *priori* estimates suggested that the effect on statistical power of ever undergoing PSA testing during

331   follow-up in the control group (contamination) would be minimal unless the PSA testing rate

332   reached 20%.[12] Second, all practices followed the same screening and diagnosis protocol, providing

333   consistent results. Third, among those with an elevated PSA level, adherence with recommendations

334   for biopsy was high at 85%, similar to ERSPC (81%) and higher than PLCO (35%). This feature of the

335   clinical trial would likely improve screening's potential effectiveness, which depends on patients'

336   willingness to undergo subsequent diagnostic tests. Fourth, the large sample size of this trial

337   contributed to excellent statistical power to detect a clinically meaningful effect size (a prostate

338   cancer mortality RR of 0.87), assuming a that PSA testing in the intervention-arm was between 35%

339   and 50% and that less than 20% of the control group had PSA testing.[12] Fifth, the comprehensive

340   national electronic health record linkage of all the men in this clinical trial helped attain a follow-up

341   rate of 98% over the median 15 year follow-up period.

342   **Limitations**

343   This study had several limitations. First, the screening intervention involved a single invitation for a

344   PSA screening test, which is not typical of organized screening programs. Some advanced prostate

345   cancers that might have been identified in subsequent screening rounds were likely missed. Second,

346   NHS electronic records were used to identify prostate cancer, resulting in missing data for clinical

347   characteristics and possible delay in recording diagnoses. Third, prostate cancer mortality at 15 years

348   was a secondary outcome. Fourth, after this clinical trial began, newer diagnostic methods[33] and

349   more effective treatments for advanced and metastatic prostate cancer[34] have been identified. Fifth,

350   few Black men, who are at higher risk of prostate cancer, were included.[35]

351

352

Conclusions

A single invitation for PSA screening, compared to standard practice without routine screening,

reduced the secondary outcome of prostate cancer deaths at a median follow-up of 15-years.

However, the absolute reduction in deaths was small.

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Figure Titles and Footnotes

Figure 1: Recruitment, randomization, and flow of practices and patients in a trial of PSA testing for prostate cancer

Footnotes

Shaded boxes: Flow of GP practices through trial recruitment; unshaded boxes: flow of men through trial recruitment; [a]Pseudo-anonymised follow-up; [b]NHS digital national data opt-outs (previously type-2 opt-outs) preventing NHS data being used for research. https://www.nhs.uk/using-the-nhs/about-the-nhs/opt-out-of-sharing-your-health-records/

*Practices were randomized prior to invitation to take part in the trial. Randomization was blocked and stratified by geographical area based on groups of 10-12 neighboring primary care practices and using a computerized random number generator to allocate near-equal number of practices in each stratum to intervention and comparison groups. The intervention was a single invitation to prostate specific antigen (PSA) screening.

**Numbers of men are as of November 2021 and are subject to small changes over time because of continued updates from NHSD e.g. changes to the trace status of the men (e.g. men newly successfully traced). Note that not all men traced at 15 years were traced at 10 years.

Follow-up was through routine NHS electronic vital status and cancer registry databases for diagnoses and deaths notified by Nov 2021 but that occurred up to 31st March 2021.

Figure 2: The Effect of the Trial Intervention on the Cumulative Incidence of Prostate Cancer Mortality and Diagnosis, and All-Cause Mortality After a Median 15-Years Follow-Up. The intervention was a single invitation to PSA screening.

Figure 2A: Prostate cancer mortality, by group

Figure 2B: All-cause mortality, by group

Figure 2C: Prostate cancer detection, by group

Footnote
P-values from random-effects Poisson model (see Statistical Analysis section).

Table 1: Individual and practice level characteristics at baseline amongst consented GP practices and men included in the analysis (adapted from Turner et al[12] and Martin et al.[10])

	Intervention group	Control group
Individual Characteristics	n= 189,326 men	n= 219,395 men
Median age (IQR)	58.5 (54.3, 63.5)	58.6 (54.3, 63.5)
Median Index of Multiple Deprivation score, England (IQR)	17.5 (10.1, 33.2)	16.9 (9.8, 32.4)
Median Index of Multiple Deprivation score, Wales (IQR)	17.6 (9.2, 29.5)	13.7 (7.1, 29)
Urban area (%)[a]	163,701 (86%)	189,667 (86%)
Race (%White)[b]	98%[b]	Not available
Practice Characteristics	n= 271 practices	n= 302 practices
Median practice list size (IQR) [c]	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 (%)	242 (89%)	267 (88%)
Single partner practices[d]	21 (8%)	29 (10%)
Small practices (2-3)	60 (22%)	61 (20%)
Medium/large practices (4+)	128 (47%)	146 (48%)
Missing	62 (23%)	66 (22%)
Median QOF points achieved (%)[e] (IQR); n	98.9 (97.4, 99.6); 224	99 (97.4, 99.7); 266
Median Index of Multiple Deprivation score, England (IQR); n	21.8 (12.7, 44.1); 231	23.6 (13.3, 46.7); 271
Median Index of Multiple Deprivation score, Wales (IQR); n	18.8 (11.9, 22.9); 40	20.1 (7.6, 34.5); 31
Mean prevalence[f], %		
All cancers (s.d)	0.6 (0.3)	0.5 (0.2)
Diabetes (s.d)	3.6 (1.0)	3.7 (1.0)
Obesity (s.d)	8.0 (2.8)	7.8 (2.8)
Coronary heart disease (s.d)	4.1 (1.4)	3.9 (1.3)

Index of Multiple Deprivation, a measure of relative deprivation for small areas: a higher score indicates more deprivation, range 0-100. English and Welsh IMD scores are not directly comparable and are reported separately. The Index of Multiple Deprivation for the practice refers to the area of the practice not where patients live; QOF = Quality and Outcomes Framework, a system for 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.e. = standard error; [a]Rural/urban classification 2004, a measure of population density and sparseness, urban defined as areas >10,000 people; [b]Race/ethnicity for men attending the intervention group PSA test clinic were ascertained by a nurse using a standardized questionnaire as one of a range of baseline characteristics to assess generalisability.[13] Race/ethnicity were defined using UK Office for National Statistics Census categories and recoded as White and Other (all other categories collapsed due to low numbers of non-White participants). Race/ethnicity data were not available from NHS routine data we had access to at the time, so we could not compute these data for the control group. [c]The total number of individuals registered at GP practices (primary care practices). [d]Single partner GP practices are primary care practices with a single General Practitioner registered and practicing from there. [e]Based on 2007/2008 data,

England only. Quality and Outcomes Framework (QoF) scores are measured from 135 indicators and one measure of depth of care (holistic care) and are split across clinical, organisational, patient experience and additional services domains (maximum score 1,000 points). [f]The prevalence of medical conditions across practices obtained from the clinical domain indicators of QoF: practices reported counts of patients with each condition and practice list size, enabling calculation of mean prevalence.

Table 2: Effect of the trial intervention on prostate cancer specific and all-cause mortality and prostate cancer diagnosis by random allocation and by instrumental variable analysis, after a median 15-years of follow-up (median 10-year estimate can be obtained from Martin et al[10]).

	Intervention group (n=189,326; 2,543,298 person years)			Control group (n=219,395; 2,885,418 person-years)			Estimated effect of intervention versus control		
	Events	Rate/1000 person years (95% CI)	Risk [%] at 15 years (95% CI)[a]	Events	Rate/1000 person years (95% CI)	Risk [%] at 15 years (95% CI)[a]	Risk difference [%] at 15 years (95% CI)	Rate ratio (95% CI)[b]	P value[b,c]
15-year prostate cancer mortality[d]									
As randomized	1,199	0.47 (0.45, 0.50)	0.69 (0.65, 0.73)	1,451	0.50 (0.48, 0.53)	0.78 (0.73, 0.82)	-0.09 (-0.15, -0.03)	0.92 (0.85, 0.99)	0.033
IV analysis[e]	-	-	-	-	-	-	-	0.83 (0.68, 1.00)	0.053
15-year all-cause mortality									
As randomized	45,084	17.7 (17.6, 17.9)	23.2 (23.0, 23.4)	50,336	17.4 (17.3, 17.6)	23.3 (23.1, 23.5)	-0.07 (-0.35, 0.21)	0.97 (0.94, 1.01)	0.11
IV analysis[e]	-	-	-	-	-	-	-	1.01 (0.91, 1.12)	0.85
15-year prostate cancer diagnoses									
As randomized	12,013	4.88 (4.80, 4.97)	7.08 (6.95, 7.21)	12,958	4.60 (4.52, 4.68)	6.94 (6.82, 7.06)	0.14 (-0.04, 0.31)	1.06 (1.02, 1.09)	0.001

CI = confidence interval. IV: Instrumental variable. Median follow-up time was 15.43 years (interquartile range: 14.23-16.43; range: 12.19, 19.23). The intervention was a single invitation to PSA screening. [a]The numbers of deaths for the cumulative 15-year risk by intervention versus control group are 1,018 and 1,288, respectively. [b]Adjusted for current age using a lexis diagram approach; variation between randomisation cluster and GP practice accommodated by random effects in a three-level model. [c]Likelihood ratio test of the null hypothesis "no difference between the groups". [d]Defined as definite or probable prostate cancer death or intervention related death by an independent cause of death committee. [e]Instrumental variable analysis to estimate the effect of screening amongst those attending the PSA testing clinic, using a generalized method of moments (gmm) estimator with random allocation as the instrumental variable.

Table 3: Exploratory analysis of prostate cancer mortality rate ratios comparing intervention versus control groups, by age and deprivation scores, after a median 15-years follow-up

	Intervention group (n=189,326) Person years = 2,543,298			Control group (n=219,395) Person-years = 2,885,418			Estimated effect of intervention versus control		
	Deaths	Rate/1000 person years (95% CI)	Risk [%] at 15 years (95% CI)	Deaths	Rate/1000 person years (95% CI)	Risk [%] at 15 years (95% CI)	Risk difference [%] at 15 years (95% CI)	Rate ratio (95% CI)[a]	P value for interaction[a]
Age at baseline									
50-54	132	0.17 (0.14, 0.20)	0.22 (0.18, 0.27)	154	0.18 (0.15, 0.21)	0.25 (0.21, 0.30)	-0.03 (-0.09, 0.03)	0.96 (0.76, 1.22)	0.75
55-59	251	0.33 (0.29, 0.38)	0.47 (0.41, 0.54)	300	0.35 (0.31, 0.39)	0.54 (0.47, 0.61)	-0.07 (-0.16, 0.02)	0.92 (0.78, 1.10)	
60-64	368	0.64 (0.58, 0.71)	0.97 (0.87, 1.09)	465	0.70 (0.64, 0.77)	1.10 (1.00, 1.22)	-0.13 (-0.28, 0.02)	0.90 (0.77, 1.04)	
65-69+	448	1.05 (0.96, 1.15)	1.61 (1.45, 1.78)	532	1.07 (0.99, 1.17)	1.76 (1.60, 1.93)	-0.15 (-0.38, 0.08)	0.98 (0.86, 1.12)	
IMD area deprivation tertile England[b]									
Most affluent	326	0.44 (0.40, 0.50)	0.61 (0.54, 0.69)	425	0.47 (0.43, 0.52)	0.71 (0.64, 0.79)	-0.11 (-0.21, 0.00)	0.92 (0.79, 1.07)	0.46
Mid-level	373	0.51 (0.46, 0.56)	0.76 (0.68, 0.85)	463	0.53 (0.49, 0.58)	0.84 (0.76, 0.93)	-0.08 (-0.20, 0.04)	0.94 (0.82, 1.07)	
Most deprived	351	0.48 (0.44, 0.54)	0.74 (0.66, 0.83)	444	0.55 (0.50, 0.61)	0.86 (0.77, 0.95)	-0.11 (-0.23, 0.01)	0.85 (0.74, 0.99)	
IMD area deprivation tertile Wales[c]									
Most affluent	45	0.41 (0.31, 0.55)	0.52 (0.37, 0.73)	43	0.34 (0.25, 0.46)	0.47 (0.34, 0.65)	+0.05 (-0.19, 0.28)	1.16 (0.76, 1.77)	0.84
Mid-level	48	0.37 (0.28, 0.49)	0.62 (0.46, 0.84)	36	0.40 (0.29, 0.56)	0.60 (0.43, 0.84)	+0.02 (-0.25, 0.30)	0.89 (0.55, 1.43)	
Most deprived	56	0.49 (0.37, 0.63)	0.66 (0.49, 0.89)	39	0.41 (0.30, 0.56)	0.72 (0.52, 1.02)	-0.07 (-0.38, 0.25)	1.23 (0.82, 1.85)	

[a]Adjustment for age stratum and practice cluster effects apart from age which was not adjusted for age stratum. [b]Index of Multiple Deprivation. Scores range from 0 to 100 with higher scores indicating higher levels of deprivation. Tertile 1 has scores ranging from 1.08 to 12.17, tertile 2 has scores ranging 12.18 to 25.95 and tertile 3 has scores ranging from 25.97 to 79.98. [c]Scores range from 0 to 100 (England and Wales do not share the same scale) with higher scores indicating higher levels of deprivation. Tertile 1 has scores ranging from 1.40 to 10.30, tertile 2 has scores ranging 10.40 to 23.30 and tertile 3 has scores ranging from 23.40 to 78.90.

n=911 Primary care practices randomised (within 99 geographical areas England and Wales)*

26 Practices excluded in 6 geographical areas:
12 No control group practices provided consent in 3 areas
9 No intervention group practices provided consent in 2 areas
5 Not approached because recruiting center had already closed in 1 area

26 Practices excluded in 6 geographical areas:
12 No control group practices provided consent in 3 areas
9 No intervention group practices provided consent in 2 areas
5 Not approached because recruiting center had already closed in 1 area

Practices randomised to **intervention** group n= 440 (93 areas)

Practices randomised to **control** group n= 419 (93 areas)

Practices excluded: 42
Consented but out of time: 13
Involved in other prostate cancer study: 10
Atypical population/unable to produce list: 8
Ceased to exist: 6
Randomised in error: 5

Practices excluded: 32
Ceased to exist: 19
Involved in other prostate cancer study involving screening: 13

Practices eligible for the **intervention** group n= 398 (93 areas)

Practices eligible for the **control** group n= 387 (93 areas)

Refused: 127 (32%)
Did not respond to invitation: 85
Refused to participate: 42

Refused: 85 (22%)
Did not respond to invitation: 45
Refused to participate: 40

Practices participating in **intervention** group n= 271 (68%)
Median list size: 6,883 (IQR: 9,107 − 4,150 = 4,957)
Men 50-69 years in intervention arm practices n= 197,938

Practices participating in **control** group n= 302 (78%)
Median list size: 6,777 (IQR: 9,000 − 3,793 = 5,207)
Men 50-69 years in control arm practices n= 221,644

2026 Men excluded **
Prostate cancer pre-randomisation   n=1,433
No record of registration with NHS digital   n=257
Death pre-randomisation   n=176
Failed to trace at NHS digital   n=160

2199 men excluded **
Prostate cancer pre-randomisation   n=1,688
Death pre-randomisation   n=286
No record of registration with NHS digital   n=127
Failed to trace at NHS digital   n=95
Refused   n=3

Men eligible in **intervention** group n= 195,912

Men eligible in **control** group n= 219,445

6,586 Men excluded from primary analysis**
Did not wish to participate   n=6311[a]
No consent for flagging   n=198
Lost to follow-up including NHS national data opt outs[b] and embarkation   n=62
Event date on list date   n=8
Date of birth missing   n=7

50 Men excluded from primary analysis**
Lost to follow-up including NHS national data opt outs[b]
and embarkation   n=45
Event on list date   n=5

Men analysed in **intervention** group n= 189,326

Men analysed in **control** group n= 219,395

Figure 2: The Effect of the Trial Intervention on the Cumulative Incidence of Prostate Cancer Mortality and Diagnosis, and All-Cause Mortality After a Median 15-Years Follow-Up. The intervention was a single invitation to PSA screening.
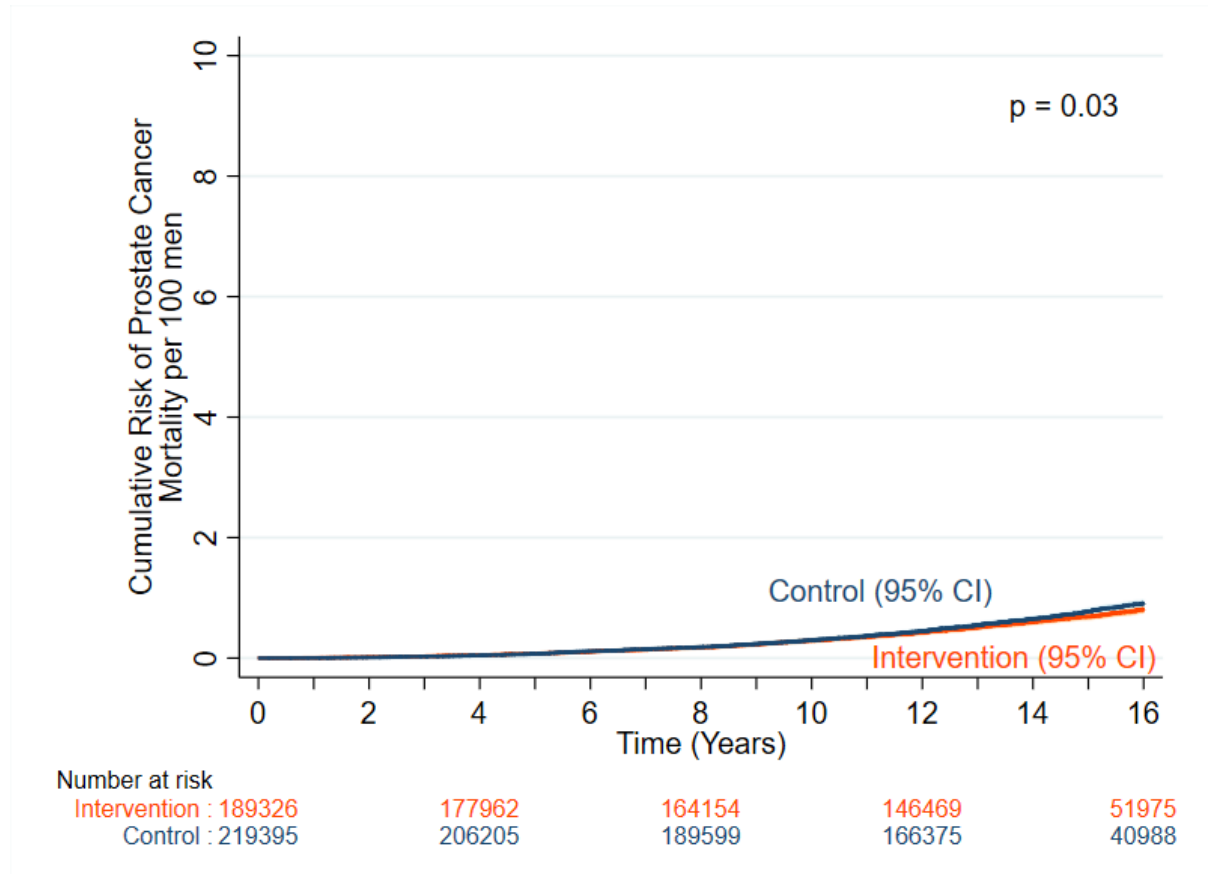
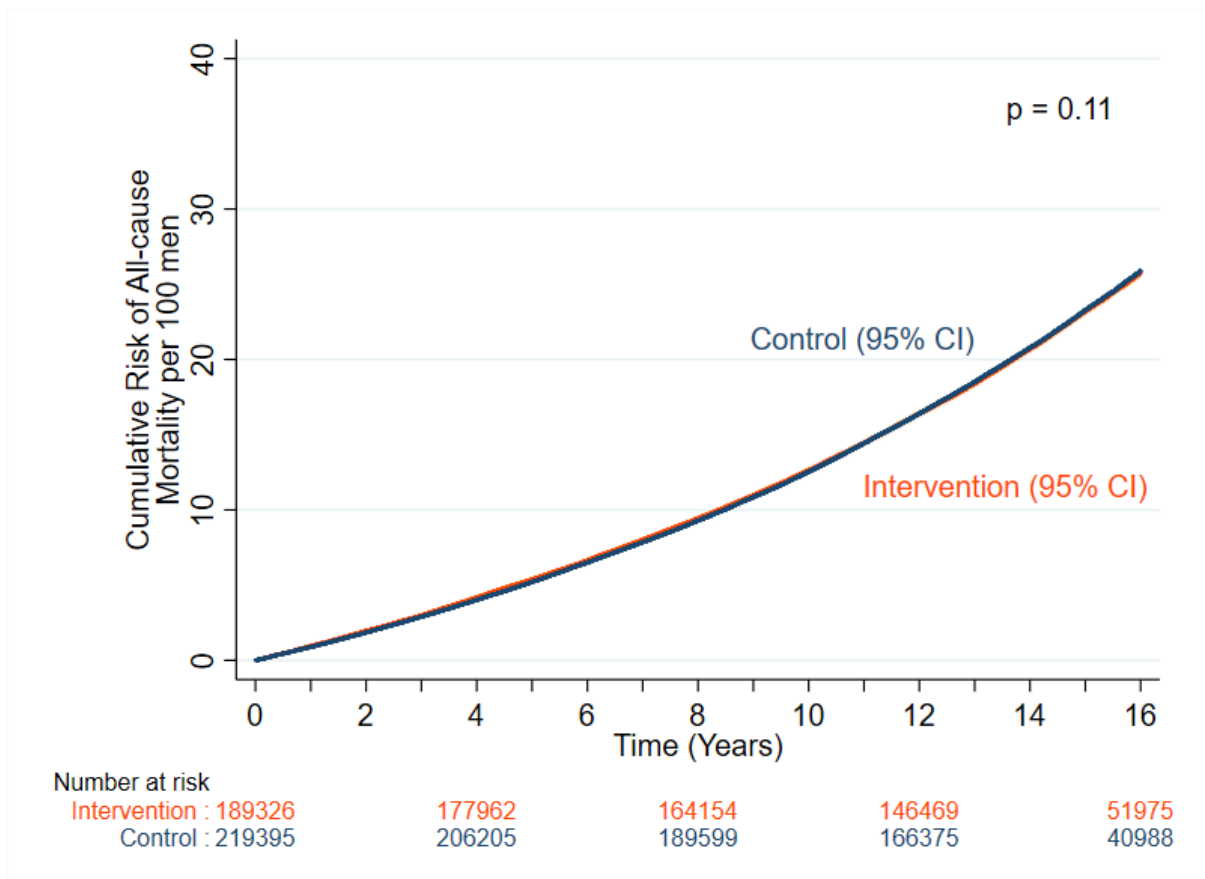**Figure 2A: Prostate cancer mortality, by arm**

Figure 2B: All-cause mortality, by arm

Figure 2C: Prostate cancer detection, by arm

Number at risk
Intervention : 189326   174289   158876   139138   48427
Control : 219395   204203   184887   158863   38396