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Prostate-specific antigen testing and opportunistic prostate cancer screening in England (1998-2017): a cohort study

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Abstract

Background: Prostate cancer is a leading cause of cancer-related death. Interpretation of results from trials of screening with prostate-specific antigen (PSA) are complex in terms of defining optimal prostate cancer screening policy.

Aims: Assess the rates of, and factors associated with the uptake of PSA testing and opportunistic screening (PSA test in absence of symptoms) in England between 1998 and 2017. Estimate the likely rates of pre-randomisation screening and contamination (unscheduled screening in 'control' arm) of the UK-based Cluster Randomised Trial of PSA Testing for Prostate Cancer ("CAP").

Design and Setting: Open cohort study of men aged 40-75 years at cohort entry (1998-2017) undertaken using the QResearch database.

Method: Eligible men were followed for up to 19-years. Rates of PSA testing and opportunistic PSA screening were calculated and Cox regression was used to estimate associations.

Results: The cohort comprised 2,808,477 men, of whom 631,426 had a total of 1,720,855 PSA tests. We identified that 410,751 men had opportunistic PSA screening. Cumulative proportions of uptake of opportunistic screening in the cohort: 10% at 5yrs, 23% at 10yrs, and 44% at 19yrs of follow-up. The potential rate of contamination in the CAP control arm was estimated at 24.5%.

Conclusions: A substantial number of men in England opt-in to opportunistic prostate cancer screening despite uncertainty regarding the efficacy and harms. The rate of opportunistic prostate cancer screening in the population is likely to have contaminated the CAP trial making it difficult to interpret the results.

Keywords: prostate cancer, screening, prostate-specific antigen, primary health care

How this fits in: Men in the United Kingdom are generally regarded to have a low uptake of prostate cancer screening, and the largest ever screening trial ('CAP') was based in the UK population. We perform the largest and most comprehensive assessment of opportunistic prostate cancer screening behaviours in England in a cohort study of over 2.8 million men. We find that a sizeable proportion of men opt-in to screening with PSA every year, most likely via primary care. Our results suggest that this 'screening on demand' may have significant implications for trial interpretation, screening policy and interpretation of prostate cancer outcomes in the UK.

Introduction

Prostate cancer is a common malignancy and a common cause of cancer-related death in men across many healthcare systems globally [1–5]. The role of screening for prostate cancer using prostate-specific antigen (PSA) testing in asymptomatic men has been evaluated in several randomised controlled trials (RCTs) [6–10], but results are difficult to assimilate into a cohesive narrative regarding the risks and benefits of such screening. Several RCTs also have major methodological limitations, mostly due to contamination of the control groups, i.e. men randomised to a non-screening arm nevertheless undergoing opportunistic screening tests [11–13].

The largest trial to date, the "Cluster Randomised Trial of PSA Testing for Prostate Cancer "(CAP), found no significant difference in prostate cancer-specific mortality between controls and the study arm offered low-intensity screening with a one-off PSA [9]. However, the degree of control arm contamination was not empirically assessed, which is especially important given that the intervention arm's screening uptake was only 36%. If the control arm of the CAP trial was substantially contaminated, then this could have biased the results, potentially masking a true effect of the study intervention.

Although no formal screening programme exists in the United Kingdom, men may effectively opt into screening since they can access PSA screening via shared decision making with their general

practitioner (GP). The uptake of PSA testing and trends therein for some countries, particularly the USA, has been relatively well characterised in several studies [14–16]. The uptake of PSA testing in general in the UK has been studied in several cross-sectional [17–19] and longitudinal studies [20], but these reports are limited since they tend to have narrow time-frames of interest, divergent geographical focusses, restricted evaluation of sociodemographic associations with PSA uptake, and/or do not attempt to distinguish between men having PSA tests for investigation of symptoms indicative of prostatic hypertrophy and asymptomatic men having PSA tests to detect early-stage cancer.

In this study, we undertook a comprehensive analysis of the uptake of PSA testing across England using linked datasets, and also analysed the uptake of opportunistic PSA screening in asymptomatic men. Our primary objective was to quantify the cumulative 'risks' of PSA testing and opportunistic PSA screening between 1998 and 2017. Our secondary objectives comprised identifying associations between PSA testing and opportunistic PSA screening rates with sociodemographic and protective/risk factors for prostate cancer [21,22]. Furthermore, we derive population-based estimates of the potential pre-randomisation testing and control arm contamination of the CAP trial, based on time-period and age-group restricted analyses of the cohort.

Methods

We undertook a cohort study of men identified from the QResearch database (version 42), which has accrued anonymised data on a total of approximately 28 million patients over 25 years, from 1500 UK-based general practices that implement the Egton Medical Information Systems (EMIS) computer system and is representative of the UK population [22–24]. Our extracted dataset (2.8 million) had full linkage to the Office of National Statistics mortality records, Hospital Episode Statistics records for dates of prostate biopsies, operations/treatment, and also to Public Health England cancer registration data regarding date of prostate cancer diagnosis.

Individual practices were eligible for inclusion if they contributed data within the study period of interest: 1st January 1998 to 31st March 2017. Men aged 40-75 at study entry were eligible for

inclusion. Entry to our open cohort was permitted when men had at least 12 months of registration with their practice, when men had their 40th birthday and when the practice had been using EMIS for at least 12 months. The latest of these dates was defined as the cohort entry date. We excluded men that had a pre-existing diagnosis of prostate cancer, prostatic hypertrophy, prostatectomy, anti-androgen therapy or other prostate-directed surgery or biopsy recorded prior to the cohort entry date recorded on any of the linked data sources.

Data regarding multiple risk factors for prostate cancer were extracted (including age, ethnicity, family history of prostate cancer, smoking and co-morbidities, see Tables 1-3), as well as records of PSA tests and dates, urinary symptoms on Read codes (and dates), and cause of death [22]. Read codes are clinical codes inputted by GPs in clinical software during patient consultations or when reviewing case files. To attain a PSA-naïve cohort, we excluded men with a recorded PSA test prior to cohort entry, and also excluded men with a record of any of the following prostate disease focussed parameters prior to their first PSA test when in the cohort: prostate cancer, prostatic hypertrophy, prostatectomy, anti-androgen therapy or other prostate-directed surgery or biopsy. Men with no previous PSA test and no previous prostate disease diagnosis/investigation/treatment were included. The same cohort of men was used for the main analyses, but a subgroup of the cohort was used for analyses relevant to the CAP trial, given the age groups eligible for inclusion and the years in which the trial was conducted. Study outcomes were PSA testing (any man having a PSA test) and opportunistic PSA screening, which we defined as a PSA test in men without urinary symptoms (on Read codes) recorded at any time prior to the test.

Statistical analysis

We used Kaplan-Meier failure functions to estimate cumulative risks of having at least 1 PSA test, and at least one opportunistic screening PSA test during follow-up (1998-2017). For the former, follow-up was calculated from cohort entry date to date of first PSA test or censoring (cohort exit due to earliest of study end date, death, transfer out of practice, or diagnosis of prostate cancer). For the latter, follow-up was calculated from entry to censoring (study end date, death, left practice, or had a

PSA test in the context of urinary symptoms suggestive of prostate pathology as per the aforementioned Read codes). There was no upper age limit for censoring.

Failure functions for both endpoints were stratified by ethnicity, BMI categories, Townsend deprivation quintile, smoking status, diabetes, geographical region, bipolar disorder/schizophrenia, and recorded family history of prostate cancer. Log-rank tests were used to identify significant differences between strata of covariates. Person-year methodology was used to calculate age group-specific rates of PSA testing and opportunistic screening.

Trends in annual rates of men starting PSA testing and opportunistic screening between 1998-2016 (complete years) were analysed by calculating the percentage of men entered in each calendar year undergoing their first PSA test. Times trends in testing and opportunistic screening were assessed using annual percentage changes (APC) calculated using joinpoint regression analyses [25,26]. The parametric method was used for calculation of APC confidence intervals.

We estimated pre-randomisation opportunistic screening in the 3 years prior to the CAP trial (2001-2016) by identifying a subgroup of males aged 50-69 in the study cohort between 1st January 1998 and 31st December 2000 and utilised Kaplan-Meier failure functions therein. We estimated the potential rate of contamination of the control arm of the CAP trial by calculating the cumulative risks of having a PSA test deemed to be for opportunistic screening in men aged 50-69 that entered the cohort between 1st January 2001 and 31st March 2016. The dates and age groups for these sub-analyses correspond to the time frames and inclusion criteria of the CAP trial, respectively. Follow-up and censoring were as defined above.

Cox proportional hazards models were utilised in the whole study cohort to ascertain independent predictors of undergoing a PSA test and opportunistic PSA screening (as complete case analyses). Results are reported as adjusted hazard ratios, with 95% confidence intervals and P-values. The proportional hazards assumption was assessed. All significant risk factors ($p<0.01$) identified in univariate analyses were included in a single multivariable Cox regression model.

Joinpoint regression analyses utilised Joinpoint Regression Program 4.6.0 (National Cancer Institute, USA). All other statistical analyses were executed using Stata V15.1. The significance level was set at $p<0.01$ to account for large sample size and multiple testing.

Results

Study population

The initially extracted cohort comprised 3,211,276 men aged 40 to 74 from a total of 1,457 general practices in England, which represents approximately 19% of all the 7,435 practices in England as of June 2017. After exclusions, the final study cohort comprised 2,808,477 PSA-naïve men (total follow-up: 21,569,176 person-years). Median follow-up was 5.9 years (interquartile range, IQR: 2.2 to 13.3 years) with a maximum of 19 years. The sociodemographic characteristics of the study cohort are summarised in Table 1 but briefly, 54.75% were white (36.66% no recorded ethnicity) and 0.27% had a recorded family history of prostate cancer. During follow-up, there were 50,791 diagnoses of benign prostatic hypertrophy (1.81%), 52,811 diagnoses of prostate cancer (1.88%), and 3,115 deaths from prostate cancer (0.11%).

PSA testing

In total, 631,426 men (22.5%) had at least one PSA test during the follow-up period (total tests= 1,720,855). Estimated cumulative risks of men having at least one PSA test were 2.28% at 1 year (95% CI: 2.23 to 2.32), 13.36% at 5 years (95% CI: 13.32 to 13.41), 29.71% at 10 years (95% CI: 29.64 to 29.79) and 55.25% (95% CI: 55.12 to 55.38) by 19 years. There was a clear association between increasing age and rates of first PSA testing (Table 2).

On univariate analyses, there were significant differences in the cumulative risk of PSA testing when stratified by ethnicity, BMI, deprivation level, smoking status, diabetes status, geographical region, and family history of prostate cancer (all $p<0.0001$, log-rank test, Figure 1). Table 3 demonstrates hazard ratios of multivariable analyses of associations with PSA test uptake.

For 1998-2016, annual rates of first PSA testing ranged between 0.76% and 4.36%. Joinpoint regression analyses demonstrated significant changes in the trends of PSA testing uptake. Between 1998 and 2001, the APC was +41.7% (95% CI: 26.8 to 58.4, $p<0.01$), between 2001 and 2004, it was

+14. 8% (95% CI: 1.5 to 29.8, p<0.01), between 2004 and 2009, it was +5.2% (95% CI: 1.8 to 8.8, p<0.01), and between 2009-2016, it was -2.2% (95% CI: -3.6 to -0.8, p<0.01).

Opportunistic PSA Screening

We identified 410,751 men that were deemed to be undergoing opportunistic screening for prostate cancer, representing 14.6% of all men in the study cohort. Therefore, 65.1% of all first PSA tests in the study period (410,751 out of 631,426) were deemed to be for screening.

Estimated cumulative risks of men undergoing at least one opportunistic screening test were 1.67% (95% CI: 1.66 to 1.69) at 1 year, 9.96% (95% CI: 9.92 to 10.01) at 5 years, 22.70% (95% CI; 22.62 to 22.77) at 10 years, and 44.13% (95% CI; 43.99 to 44.27) by 19 years of follow-up. The cumulative risks of undergoing a screening PSA were significantly associated with increasing age (Table 2), ethnicity (highest in Black Caribbean males), BMI, deprivation level (less screening with increasing deprivation), smoking status, diabetic status, geographical region, and family history of prostate cancer (all p<0.0001, log rank test, Figure 2). Table 3 demonstrates the adjusted hazard ratios in multivariable analyses of associations with opportunistic screening uptake.

Annual percentages for men starting opportunistic prostate screening ranged between 0.46% and 2.87%. On joinpoint analyses, between 1998 and 2004, the APC in screening uptake was +24.7% (95% CI: 15.7 to 24.4, p<0.01), between 2004 and 2014 it was 2.1% (95% CI: -0.3 to 4.5, p>0.05), and between 2014 and 2016, there was a significant decline in screening uptake with an APC of -29.4% (95% CI: -49.9 to -0.5, p<0.01). Throughout this whole period of interest, the average APC was +4.7% (95% CI: 0.4 to 9.2, p<0.01).

Focus on UK-based screening studies

We identified 585,166 men aged 50-69 between 1st January 1998 to 31st December 2000 (three years preceding the CAP trial start date in 2001): 13,580 of these men (2.32%) underwent at least one screening test in this time (pre-randomisation screening estimate).

To estimate control arm contamination, we identified men aged 50-69 during the period of the CAP trial (2001-2009), i.e. those that may have been eligible for inclusion. Of the 848,959 men identified,

208,041 (24.5%) had undergone at least one screening test during the trial period (2001-2016) – the calculated cumulative risk of undergoing screening was 10% by 5 years, 23% at 10 years and 36% at 15 years of follow-up (2001-2016). We estimated that of these men meeting the trial eligibility criteria, by 19 years of follow-up, 45% will have partaken in at least 1 screening PSA.

Discussion

Summary

This is not only the largest study ever reported on the rates of PSA testing and opportunistic PSA screening in the UK population, but also the most comprehensive in terms of time period, geographical coverage and examined risk factors. The potential rate of opportunistic prostate cancer screening in the population 'at large' makes the CAP trial [9] complex to interpret. We found increased rates of opportunistic screening were significantly associated with Black ethnicity, increasing age, increased affluence and family history of prostate cancer.

Strengths and limitations

The major strength of our intentionally contemporaneous study is the use of the QResearch database. The very large representative cohort of over 2.8 million men from across England had high-quality, accurately coded, individual-level data [28] with protracted follow-up, and a low risk of selection, recall and respondent biases. It also had linkages to enable optimal ascertainment of interventions, diagnoses, deaths and laboratory investigation results across the healthcare 'network' [29,30].

Limitations include the extent to which urinary tract symptoms have been recorded by GPs. We mitigated this to the best of our abilities by extracting data based on over 100 Read codes which indicate a comprehensive range of urinary tract symptoms. Other limitations of our study include information bias, missing data (such as for ethnicity), or the influence of the CAP trial itself on our CAP-focussed results as the study period was intentionally identical and some men in our cohort may have been included in the CAP trial. Such influence however should be minimal as whilst 67,313 men

in the CAP trial arm underwent screening [9], we identified 208,041 men aged 50-69 who had undergone at least one screening test during the CAP trial's follow-up period. Assuming the impossible scenario that we included *all* screened men from CAP (QResearch does not cover Cardiff), the estimate of opportunistic screening in the 'remainder' is 17% (140,728/848,959). Even in this flagrant overestimation of the 'worst-case' scenario, a contamination rate of close to 20% can be calculated.

Comparisons with existing literature

Several studies have examined the rates of PSA testing in British men [17–21]. However, these comprise study cohorts smaller than ours [20], have focussed purely on single geographical regions [17] or have limited time frames [18,19,27]. Other studies have identified associations between PSA testing and age, ethnicity, level of deprivation and geographical region [19,20,27], but none have examined as extensive a panel of covariates as the presented study, or comprehensively assessed the associations with opportunistic prostate cancer screening.

Screening uptake was significantly associated with previously established risk factors for prostate cancer diagnosis including ethnicity and positive family history for prostate cancer [22]. Therefore, the status quo of informal, opportunistic screening may be an inadvertent manifestation of a patient-led risk-adapted strategy, or one guided by some GPs.

Implications for research and practice

Men seeking PSA screening in general practice may not be uncommon occurrences, mandating deep clinician awareness of the benefits and harms of PSA screening, which is sometimes limited [19,31,32]. Predictors of screening uptake may be useful for the design of future screening strategies, and our data may impart important context for trends in prostate cancer incidence, stage at diagnosis, treatments and mortality in the UK. We have also identified factors rendering interpretation of the largest-ever prostate cancer screening trial complex. Restricting our focus to an age range-matched contemporaneous sub-cohort, we estimated that 23% of such men in England would have had a screening test by 10 years. This would reduce the trial's power to detect a difference in prostate

cancer-specific mortality between screened and 'non-screened' arms (power calculation assumed a contamination rate of <20%). Statistical analyses adjusting for contamination and screening non-compliance [33] in the CAP trial may be of significant interest for screening policy, as has been done for the PLCO trial results [12,34,35] provided that they are clearly explained and robustly developed [36].

Our results suggest limited plausibility of deriving clear conclusions from trials of PSA screening. The notional conclusion from the trial's findings that one-off PSA screening is not efficacious may be over-simplistic, possibly incorrect, or poorly reflective of a complex situation requiring nuanced interpretation. Contamination of control arms will probably always occur regardless of the trial geographical location and design, which bemires evidence-based practice. Policy makers, researchers, clinicians and patients should accept that we have entered a challenging 'post-trial' world.

Acknowledgements

We acknowledge the contribution of EMIS practices who contribute to QResearch® and EMIS Health and the University of Nottingham for expertise in establishing, developing and supporting the QResearch database. This project involves data derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE). Access to the data was facilitated by the PHE Office for Data Release. The Hospital Episode Statistics data used in this analysis are re-used by permission from NHS Digital who retain the copyright in that data. We thank the Office of National Statistics for providing the mortality data. The NHS Digital, Public Health England and Office of National Statistics bears no responsibility for the analysis or interpretation of the data.

Ethics approval

The QResearch® ethics approval is with East Midlands -Derby Research Ethics Committee [reference 03/4/021].

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This study was not funded.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: JHC is co-director of QResearch® – a not-for-profit organisation which was originally a joint partnership between the University of and EMIS Health (leading commercial supplier of IT for 55% of general practices in the UK) and Nottingham which transferred to Oxford in 2019. JHC was until 2019 also a paid director of ClinRisk Ltd which produces open and closed source software to ensure the reliable and updatable implementation of clinical risk equations within clinical computer systems to help improve patient care. CC is professor of Medical Statistics in Primary Care at the University of Nottingham and a paid consultant statistician for ClinRisk Ltd. AKC has no competing interests to declare. This work and any views expressed within it are solely those of the co-authors and not of any affiliated bodies or organisations.

Data Sharing

Access to the data in the QResearch database is according to the terms on the QResearch website (www.qresearch.org).

Characteristic	N (%)	
Ethnicity		
White	1,537,660	(54.75%)
Indian	44,693	(1.59%)
Pakistani	25,229	(0.9%)
Bangladeshi	18,487	(0.66%)
Other Asian	27,600	(0.98%)
Caribbean	24,835	(0.88%)
Black African	42,405	(1.51%)
Chinese	9,785	(0.35%)
Other	48,299	(1.72%)
Not recorded	1,029,484	(36.66%)
Geographical region (2,808,477, 100% recorded)		
East Midlands	146,179	(5.2%)
East of England	182,864	(6.51%)
London	584,489	(20.81%)
North East	101,938	(3.63%)
North West	445,295	(15.86%)
South Central	365,111	(13%)
South East	230,681	(8.21%)
South West	312,760	(11.14%)
West Midlands	298,113	(10.61%)
Yorkshire & Humber	141,047	(5.02%)
BMI category (2,327,004; 82.9% recorded)		
Underweight (<18.5 kg/m^2)	22,770	(0.98%)
Healthy weight (18.5-24.9 kg/m^2)	731,913	(31.45%)
Overweight (25-29.9 kg/m^2)	1,015,095	(43.62%)
Obese (30-39.9 kg/m^2)	521,124	(22.39%)
Severely obese (>40 kg/m^2)	36,102	(1.55%)
Deprivation quintile (2,799,859; 99.6% recorded)		
1 (most affluent)	548,305	(19.58%)
2	550,816	(19.67%)
3	558,866	(19.96%)
4	565,215	(20.19%)
5 (most deprived)	576,657	(20.6%)
Smoking status (2,579,090; 91.8% recorded)		
Non-smoker	1,212,254	(47%)
Ex-smoker	633,556	(24.57%)
Light smoker (1-9/day)	391,036	(15.16%)
Moderate smoker (10-19/day)	170,700	(6.62%)
Heavy smoker (20+/day)	171,544	(6.65%)
Diabetic status		
No diabetes	2,482,092	(88.38%)
Type 1 diabetes	10,070	(0.36%)
Type 2 diabetes	316,315	(11.26%)
Family history of prostate cancer		
Yes	7,641	(0.27%)
No	2,800,836	(99.73%)
Diagnosis of bipolar disorder or schizophrenia		
Yes	31,717	(1.13%)
No	2,776,760	(98.87%)

Table 1. Basic sociodemographic characteristics of the final study cohort, n=2,808,477.

	PSA Testing Rate			Opportunistic PSA Screening Rate		
Age group	Number having first PSA test (any indication)	PSA testing rate per 1000 person-years	95% CI	Number having first screening test	Screening rate per 1000 person-years	95% CI
40-49	51883	11.86	11.76 - 11.96	36564	8.36	8.27 – 8.44
50-59	203023	31.05	30.92 - 31.19	139656	21.36	21.25 – 21.47
60-69	225227	51.33	51.33 - 51.54	143248	32.65	32.48 – 32.82
70-79	129470	61.39	61.39 - 61.73	77762	36.87	36.61 – 37.13
80-89	21546	68.65	67.74 - 69.58	13347	42.53	41.82 – 43.26
90-100	277	63.25	56.22 - 71.15	147	39.73	34.24 – 46.1
	631,426	**35.62**	**35.53 – 35.79**	**410,751**	**23.17**	**23.1 – 23.24**

Table 2. Age-specific rates per 1000 person-years of men undertaking their first 1st PSA test for any indication (left) or specifically for opportunistic screening (right; a PSA test in the absence of recorded symptoms or recorded prostate-related pathology). PSA = prostate-specific antigen, CI = 95% confidence interval.

	PSA testing			***PSA Screening***		
Characteristic	*Adjusted hazard ratio**	*95% CI*	*P value*	*Adjusted hazard ratio*	*95% CI*	*P value*
Age (per 1-year increase)	1.04	1.04 to 1.04	<0.0001	1.04	1.04 to 1.04	<0.0001
Townsend quintile						
1 (most affluent)	1.00			1.00		
2	0.95	0.94 to 0.96	<0.0001	0.94	0.94 to 0.95	<0.0001
3	0.88	0.88 to 0.89	<0.0001	0.87	0.86 to 0.88	<0.0001
4	0.82	0.81 to 0.82	<0.0001	0.79	0.78 to 0.80	<0.0001
5 (most deprived)	0.74	0.73 to 0.74	<0.0001	0.70	0.69 to 0.71	<0.0001
Ethnicity						
White	1.00			1.00		
Indian	1.14	1.12 to 1.17	<0.0001	1.16	1.13 to 1.18	<0.0001
Pakistani	1.20	1.16 to 1.23	<0.0001	1.12	1.08 to 1.17	<0.0001
Bangladeshi	1.17	1.13 to 1.21	<0.0001	0.99	0.94 to 1.05	0.729
Other Asian	1.15	1.12 to 1.19	<0.0001	1.11	1.07 to 1.15	<0.0001
Caribbean	1.60	1.57 to 1.64	<0.0001	1.55	1.51 to 1.60	<0.0001
Black African	1.44	1.40 to 1.48	<0.0001	1.30	1.26 to 1.35	<0.0001
Chinese	0.84	0.79 to 0.86	<0.0001	0.80	0.75 to 0.86	<0.0001
Other	1.33	1.26 to 1.40	<0.0001	1.28	1.24 to 1.32	<0.0001
Not recorded	0.75	0.74 to 0.75	<0.0001	0.76	0.75 to 0.76	<0.0001
Smoking category						
Non-smoker	1.00			1.00		
Ex-smoker	1.01	1.01 to 1.02	0.003	0.99	0.98 to 0.99	<0.0001
Light smoker	0.87	0.86 to 0.88	<0.0001	0.84	0.83 to 0.85	<0.0001
Moderate smoker	0.81	0.80 to 0.82	<0.0001	0.78	0.77 to 0.79	<0.0001
Heavy smoker	0.80	0.79 to 0.81	<0.0001	0.76	0.75 to 0.77	<0.0001
FH of prostate cancer						
No family history	1.00			1.00		
Family history	3.10	3.00 to 3.19	<0.0001	3.47	3.35 to 3.60	<0.0001
Type of diabetes						
No diabetes	1.00			1.00		
Type 1	0.87	0.83 to 0.92	<0.0001	0.47	0.43 to 0.51	<0.0001
Type 2	0.98	0.97 to 0.99	<0.0001	0.83	0.82 to 0.84	<0.0001
BMI class						
Underweight	1.00			1.00		
Healthy weight	1.09	1.05 to 1.12	<0.0001	1.03	0.99 to 1.06	0.153
Overweight	1.15	1.12 to 1.18	<0.0001	1.07	1.02 to 1.11	<0.0001
Obese	1.15	1.12 to 1.19	<0.0001	1.04	1.01 to 1.08	0.019
Severely obese	1.12	1.08 to 1.16	<0.0001	0.98	0.93 to 1.02	0.276
Geographical region						
East Midlands	1.00			1.00		
East of England	1.04	1.02 to 1.05	<0.0001	1.07	1.05 to 1.09	<0.0001
London	1.25	1.23 to 1.27	<0.0001	1.34	1.32 to 1.37	<0.0001
North East	0.85	0.83 to 0.86	<0.0001	0.86	0.84 to 0.87	<0.0001
North West	1.12	1.10 to 1.13	<0.0001	1.12	1.11 to 1.14	<0.0001
South Central	1.14	1.13 to 1.16	<0.0001	1.21	1.19 to 1.23	<0.0001
South East	1.41	1.39 to 1.43	<0.0001	1.46	1.44 to 1.49	<0.0001
South West	1.11	1.07 to 1.10	<0.0001	1.12	1.10 to 1.14	<0.0001
West Midlands	1.15	1.09 to 1.16	<0.0001	1.20	1.18 to 1.22	<0.0001
Yorkshire & Humber	0.91	0.89 to 0.93	<0.0001	0.90	0.88 to 0.91	<0.0001

Table 3. Cox regression analyses for prostate-specific antigen testing uptake (left) and opportunistic screening uptake (right) in the study cohort: 2,305,998 had complete data and were included. All significant risk factors identified in univariate analyses were included in a single Cox regression model, which is adjusted for all the other variables presented in the above table. CI = confidence interval, FH = family history.

Figure legends

Figure 1. Kaplan-Meier failure functions for factors associated with prostate-specific antigen testing uptake.

Figure 2. Kaplan-Meier failure functions for factors associated with opportunistic prostate cancer screening uptake.

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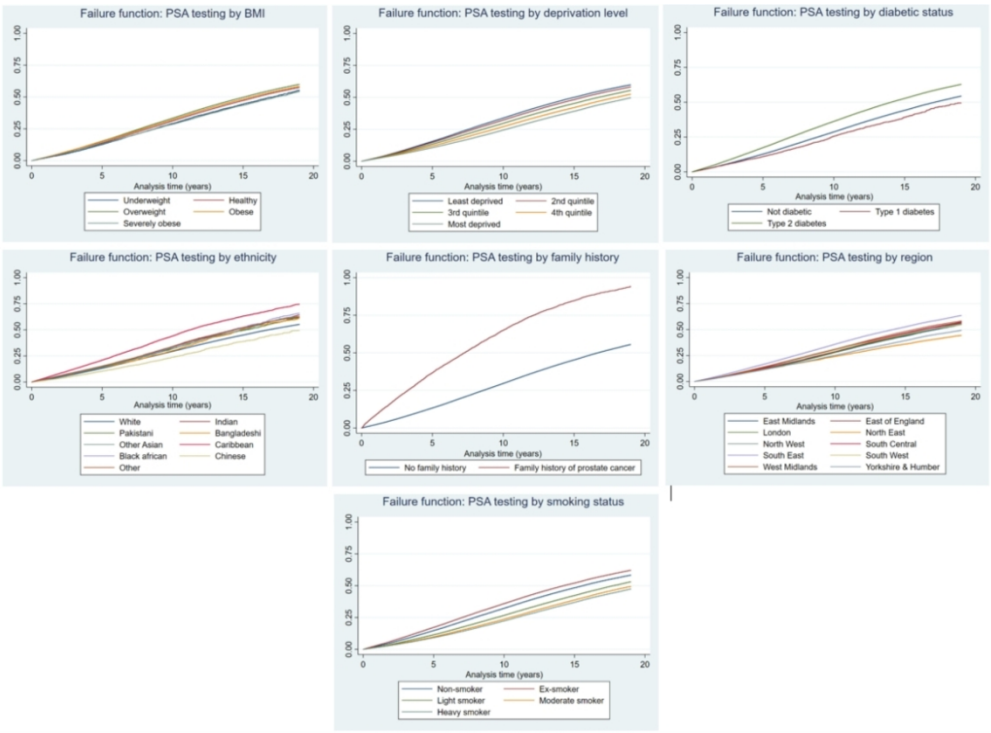

Figure 1. Kaplan-Meier failure functions for factors associated with prostate-specific antigen testing uptake.

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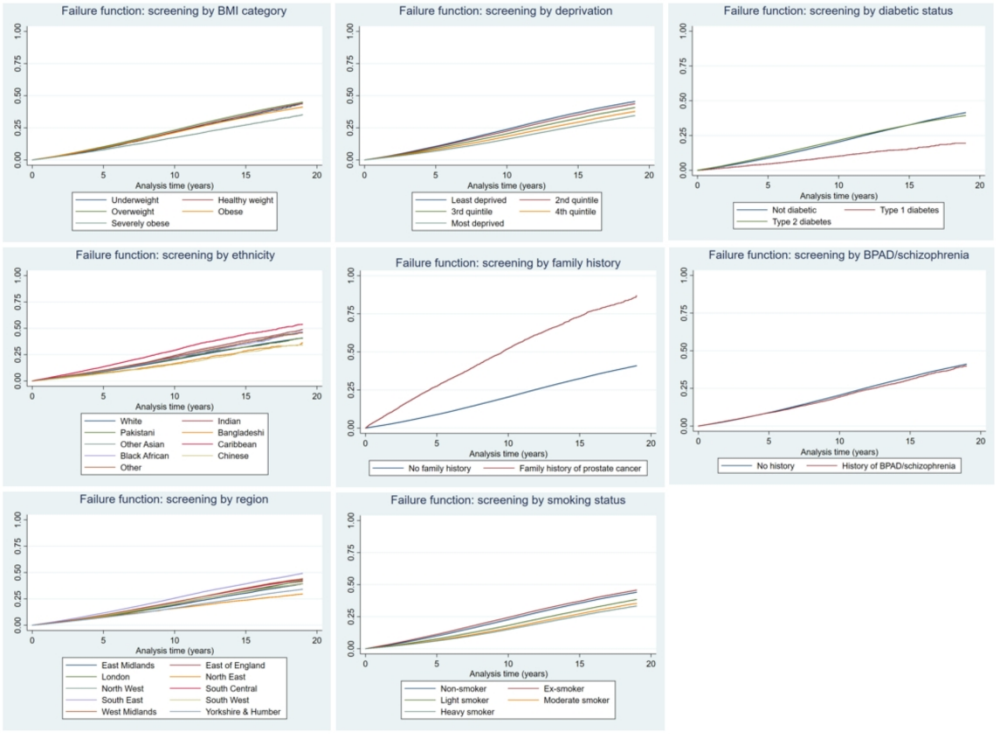

Figure 2. Kaplan-Meier failure functions for factors associated with opportunistic prostate cancer screening uptake.

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Print article summary*	**min 10, max 25 words**	**How would you describe your research in one sentence?** Please avoid saying: "we undertook a randomised controlled trial…", more like "Primary care patients treated with oseltamivir recovered from influenza-like illness one day sooner than usual care."	The uptake of opportunistic prostate cancer screening in the population may make screening trials complex to interpret
How this fits in* (research statement)	**min 50, max 100 words**	**How does your study fit into what is currently known in this field of research?** Summarise, in no more than four short sentences, what was previously known or believed on the topic and what your research adds, particularly focusing on relevance to clinicians.	No formal prostate cancer screening program currently exists in the UK, but men can opt in for a screening PSA test via their GP. A recent randomised trial evaluated low-intensity screening with one-off PSAs in the UK. Our cohort study of 2.8 million men in England aged 40-75 estimates that 14.6% of men opted for a screening PSA test during the study period (1998-2017). Opportunistic screening is associated with
Clinical impact* (clinical statement)	**min 3, max 15 words**	**What is the impact of your research in a clinical settings?** If your findings were implemented, what would be the clinical impact? e.g. 'More accurate diagnosis, fewer antibiotic prescriptions', 'Non-pharmacologic treatment with additional health benefits'. See https://youtu.be/xHmlJG59nZI	Interpretation of trials using PSA to screen for prostate cancer may be complex to interpret.

Press summary*	**min 200, max 300 words (1-2 sentences per question)**	**How would you tell the world about your work?** To help consider whether your research will be considered for a press release please answer the following 3 questions: **1) What is your main message/what have you found?** (e.g. obesity is linked to a sense of smell). **2) So what? Why is it important to a general audience?** (e.g. it contributes to explanations of why some struggle to stay slim). **3) Key background** (e.g. 1/4 of UK adults are obese...). Please structure this as a reversal of the usual research methodology which begins with background. See https://www.bbc.co.uk/news/health-11755995. Include location, number of patients, and method. *Note: Press summary text may be sent to media outlets and also appear as a homepage features on BJGP.org for selected articles.*	1) Using a population-based cohort of over 2.8 million men aged 40-75, we estimated that 14.6% of men opted in to prostate cancer screening via their GP during our study period, despite there being conflicting evidence on prostate screening's harms and benefits, and no formal screening program. 2) There were associations with having an 'opportunistic' screening test and increasing affluence, increasing age, having a family history of prostate cancer, and being of Black or Caribbean ethnicity. This may have implications for the interpretation of prostate cancer outcomes, and also the interpretation of screening trials. 3) There is no formal prostate cancer screening program in the UK, but the world's largest ever prostate screening trial took place in the UK population. The trial randomised men to a one-off PSA blood test or no screening. However, men
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