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Prostate Cancer

Family History of Prostate Cancer and Survival Outcomes in the UK Genetic Prostate Cancer Study

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Abstract

Background: A family history (FH) of prostate cancer (PrCa) is associated with an increased likelihood of PrCa diagnosis. Conflicting evidence exists regarding familial PrCa and clinical outcomes among PrCa patients, including all-cause mortality/overall survival (OS), PrCa-specific survival (PCSS), aggressive histology, and stage at diagnosis.
Objective: To determine how the number, degree, and age of a PrCa patient's affected relatives are associated with OS and PCSS of those already diagnosed with PrCa.
Design, setting, and participants: The UK Genetic Prostate Cancer Study is a longitudinal, multi-institutional, observational study collecting baseline and follow-up clinical data since 1992. We examined OS and PCSS in 16 340 men by degree and number of relatives with prostate and genetically related cancers (breast, ovarian, and colorectal).
Outcome measurements and statistical analysis: The primary outcome was all-cause mortality among PrCa patients. The risk of death with respect to FH was assessed by calculating hazard ratios from Cox proportional hazard regression models, adjusting for relevant factors.
Results and limitations: A stronger FH was inversely associated with the risk of all-cause and PrCa-specific mortality. This association was greater in those with an increasing number (p-trend < 0.001) and increasing closeness (p-trend < 0.001) of the diagnosed relatives. Patients with at least one first-degree relative were at a lower risk of all-cause mortality than those with no FH (hazard ratio = 0.82 [95% confidence interval 0.75–0.89]). The population is largely of European ancestry, and this may cause an issue with representation and generalisation. Data are missing on epidemiological risk factors for death such as smoking and on comorbidities. Recall of family members' diagnoses may affect the classification of FH in unconfirmed cases.
Conclusions: Based on the investigation of the type and timing of relatives' cancers, it is likely that reductions in mortality are due almost completely to a greater awareness of

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the disease. This study provides information for clinicians guiding patients and their relatives based on their familial risk. It shows the importance of screening and awareness programmes, which are likely to improve survival among men with an FH.

Patient summary: We were interested in how a family history of prostate cancer affects survival in prostate cancer patients. We studied 16 340 patients, categorised them according to the strength of their family history, and found that the stronger their family history, the better they did in terms of overall survival. We looked at the type and timing of patients' diagnoses compared with those of their relatives and found that this effect is likely to be explained by awareness, which indicates the importance of screening and awareness programmes.

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1. Introduction

Not all men are at equal risk of developing prostate cancer (PrCa), a polygenic disease with large heritability [1]. The risk of PrCa changes depending on the number and closeness of affected relatives. Men with a brother or father affected by PrCa have at least a two-fold risk of developing PrCa compared with men without a family history (FH), with the risk increasing three- to five-fold if the affected first-degree relative (FDR) had early-onset disease (diagnosed at ages ≤55 yr) [2]. Both rare and common variants for PrCa exist, together explaining approximately 43% of familial disease in men of European ancestry [3].

Conflicting evidence exists for differences in clinical and survival outcomes for PrCa patients with an FH compared with those without [4]. Conflicting reports also exist of inferior oncological outcomes following radical treatment, in addition to a higher incidence of known clinical predictors of poorer prognosis such as Gleason grade [5,6]. While Bagshaw et al [5] found that FH was not an independent predictor of biochemical failure, distant metastasis, PrCa-specific mortality (PCSM), or overall survival (OS) in a retrospective review of PrCa cases receiving radiotherapy, on a further analysis, men with two or more FDRs with PrCa had a higher likelihood of biochemical failure and distant metastasis than those with no FH. In that analysis, men with an FH were also more likely to be younger, have lower prostate-specific antigen (PSA), and have T1 disease.

The discordance in the literature on the effect of FH on the prognosis of PrCa patients may also stem from how FH has traditionally been classified. For example, a simple "yes" or "no" classification of an FH of PrCa will not consider relative family size or structure. To address these issues and investigate the association of the strength of FH with PrCa outcomes, we investigated the role of FH described by degree, number, and age of the affected relatives, and investigated the association with all-cause mortality and PCSM, as well as the relationship with known prognostic factors.

While the relationship between FH and PrCa incidence has been well described [7,8], the relationship with prognosis is more ambiguous, specifically in terms of clinicopathological and survival outcomes. Better information is important to aid clinician decision-making and individualised patient counselling. Our analysis aims to clarify and describe the effect of FH of PrCa on OS, in a unique and large cohort of cases with detailed FH information. We also use the scope of our analysis and available information regarding the timing of the PrCa diagnoses of patients' relatives to discuss the role of awareness in affecting patients' survival.

2. Patients and methods

The UK Genetic Prostate Cancer Study (UKGPCS) [9] was established in 1992, recruiting men from the Royal Marsden NHS Foundation Trust and Collaborative Centres (NHS Trust hospitals) throughout the UK and Northern Ireland, over 180 of whom are from the National Cancer Research Network (NCRN). The study was approved by the relevant ethics committees appropriate to each recruitment centre (REC reference: 06/MRE02/4). All participants gave written informed consent.

Patients were identified by clinicians and self-referrals, consented into the UKGPCS between 1992 and 2019 after a diagnosis of PrCa, and recruited to one of the following three cohorts:

1. PRM: all patients treated at the Royal Marsden NHS Foundation Trust
2. PRY: patients who are diagnosed at age ≤60 yr from the collaborative centres
3. PRS: patients who are diagnosed at age ≤65; who have an FDR, a second-degree relative (SDR), or a third-degree relative diagnosed at age ≤65 yr; or who have a total of three or more relatives with PrCa at any age on the same side of the family

Patients were flagged by the NHS Central Registers (virtually complete registers of the populations of England and Wales, and of Scotland, to which study participants can be linked and on which deaths, cancer registrations, and emigrations are "flagged" and then periodically reported to authorised medical researchers) to confirm date and underlying cause of death, as well as possible emigrations. PrCa diagnoses were confirmed from patient hospital medical records, pathology reports, correspondence with patients' general practitioners, and national cancer registrations.

We extracted the dates of birth, diagnosis, and death if applicable; mode of detection; TNM stage; Gleason score; primary treatment; vital status; geographic region based on referring hospital or treatment hospital if information on the referring hospital was not available; self-reported body mass index (BMI); self-reported ethnicity; and PSA at diagnosis for all patients, as well as for relatives, if available. These data were obtained from recruitment questionnaires and electronic patient records. Information on risk factors for PrCa, demographic characteristics, and clinical data is also collected routinely as part of the medical care and clinical follow-up.

Patients were defined as having an FH of PrCa if any FDR, SDR, or third-degree relative was reported with a diagnosis of PrCa by the proband, at any age, confirmed by medical records or self-reported within

a family (unconfirmed by medical records). Specific details of the FH and pedigree were recorded for all participants. Data were collated and stored using the genetic data management system, Progeny Clinical [10], which also allows for the construction of genetic pedigrees. For the purposes of this study, the proband is defined as the first family member diagnosed with PrCa to enter the study. Other family members with PrCa are excluded, but still contribute to FH information.

2.1. Statistical analysis

The study population in this analysis consisted of PrCa patients consented and NCRN accrued into the UKGPCS, with a confirmed diagnosis of PrCa, who could be traced under the Medical Research Information Service/NHS Digital, and who had provided an FH with coverage over at least two generations. Where more than one family member was present in the UKGPCS, the first family member to consent was taken to be the index case.

To explore fully the nature of an FH of the disease, we investigated whether the number, degree, and age of a patient's affected relatives were associated with OS and PCSM. We also investigated the association of FH with clinical features at diagnosis.

The primary outcome was OS/all-cause mortality. We investigated survival outcomes using a Kaplan-Meier survival analysis. The risk of death with respect to FH was assessed by calculating hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazard regression models, with time since diagnosis (ie, survival) as the underlying timescale. For the survival analysis, patients became at risk at the time of consent or first interview, and the time to event was measured from the date of diagnosis to death. Patients who were still alive at emigration or on June 28, 2019 were censored at the earliest of these dates. The date was chosen because it is the latest date when mortality flagging information is known to be complete.

FH was first defined as a categorical variable based on the number of affected FDRs and SDRs (0, 1, or 2+). We then looked at the highest degree of affected relative (first degree, or second degree or more removed, or no FH). Finally, we looked at the earliest age of a relative's diagnosis as a continuous variable, described by the degree of relative (first degree, or second degree or more removed).

We adjusted for age at diagnosis (linear trend and quadratic term to account for nonlinearity); mode of detection (clinical symptoms, screen detected, or missing indicator); PSA at diagnosis (log-transformed trend or missing indicator); T stage (T1, T2, T3, T4, or missing indicator); N stage (N0, N1, or missing indicator); M stage (M0, M1, or missing indicator); Gleason score at diagnosis (<7, 3 + 4, 4 + 3, 8, >8, or missing indicator); primary treatment (radical prostatectomy, radiotherapy, hormonal therapy, active surveillance, brachytherapy, chemotherapy, watchful waiting, other, or missing indicator); BMI (kg/m^2; trend or missing indicator); year of diagnosis (<1995, 1995–1999, 2000–2004, 2005–2009, 2010–2014, or ≥2015); geographic region (London, South East England, NW, SW, EastMid, GrLondon, WestMid, Wales, NE, NI, Scotland, or missing indicator); ethnicity (White, Black, Asian, other ethnicity, or missing indicator); and recruitment cohort (PRY, PRM, or PRS). We also investigated for effect modification between FH and clinical variables of interest using interaction terms, and likelihood ratio tests between models with and without interaction terms. Likelihood ratio tests were also used to investigate nonlinear terms for continuous variables. Chi-square tests for trend were used to investigate the trends in the FH variables.

To try and separate genetic effects from "true" screening or awareness effects, we also investigated the timing of diagnosis (whether a relative was diagnosed before or after a proband) and an FH of other related cancers (breast, ovarian, or colorectal). By comparing men with affected brothers to those with affected fathers, we are also able to investigate an X-linked (or recessive) model of inheritance [11].

Analyses were repeated to investigate PCSM, and patients were censored at the date of death from non-PrCa mortality. We used competing-risk regression to account for the competing risks of other-cause mortality.

For all analyses, univariable and multivariable associations were investigated. All analyses were conducted in Stata (17.0; StataCorp LLC, College Station, TX, USA) [12]. Further information on the statistical methods can be found in the Supplementary material.

3. Results

3.1. Primary outcomes—strength of FH and risk of death

The analysis included 16 340 index patients (Tables 1 and 2) with PrCa, of whom 6165 (38%) had at least one FDR or SDR with a confirmed (60%) or unconfirmed diagnosis of PrCa, accruing a total of 128 750 person-years of follow-up, and 4380 deaths during follow-up (27% of the total cohort), including 2961 PrCa-specific deaths (18% of the total cohort). A total of 1310 patients have been followed without an event for at least 15 yr (Table 3, and Fig. 1A and B).

In the fully adjusted multivariable Cox analysis, an FH of PrCa in patients with a diagnosis of PrCa was associated with a decreased risk of death from all causes (Table 4). The magnitude of this association was greater in those with an increasing number of affected relatives (p-trend < 0.001) and increasing closeness of the diagnosed relative (p-trend < 0.001). Univariable analyses are presented in Supplementary Table 2.

Having one FDR or SDR was associated with a decreased risk of all-cause mortality compared with those without an FH (HR = 0.85 [95% CI 0.79–0.93]), as was having two or more relatives (HR = 0.80 [95% CI 0.71–0.90]). Having at least one FDR was also associated with a decreased risk of all-cause mortality (HR = 0.82 [95% CI 0.75–0.89]), while for SDRs or further the association was reduced (HR = 0.92 [95% CI 0.81–1.05]).

3.2. Screening and possible mechanisms

There was no evidence to suggest that the risk of dying was related to the relative's age of diagnosis, once the patient's own age at diagnosis is accounted for, or that this risk was different depending on the degree of the relative (Table 4). However, age at diagnosis was strongly correlated with an FDR's age at diagnosis (Supplementary Table 1) with an increase of 0.2 yr (95% CI 0.10–0.30) for every 5-yr increase in the relative's age at diagnosis. The association was not seen among SDRs (or higher-degree relatives); 0.03 yr [95% CI 0.26–0.32], and there was no indication that results from FDRs and SDRs were different (p-int = 0.3). However, numbers available in the SDR category were small.

Screen-detected PrCa was associated with a decreased risk of death with respect to those detected from clinical symptoms (HR = 0.77 [95% CI 0.70–0.84]) irrespective of FH status (Supplementary Table 2). The mode of detection showed some evidence of effect modification by FH (Supplementary Table 3). For men with an FH in an SDR or higher-degree relative with disease detected by clinical symptoms, there was no difference in all-cause mortality

Table 1 – Distribution of family history, by variables of interest (categorical)

	Family history																	
	N, count (% [a])		Y, count (% [a])															
			1st-degree relatives						2nd-degree relatives						3rd-degree relatives					
			1		2		3+		1		2		3+		1		2		3+	
All cases	10175		3871		883		196		880		142		31		136		23		3	
Mode of detection																				
Clinical symptoms	5158	(70)	1655	(57)	327	(48)	66	(43)	439	(67)	72	(69)	15	(60)	66	(70)	9	(53)	3	(100)
Screen detected	2168		1242		355		87		221		33		10		29		8		0	
Missing	2849		974		201		43		220		37		6		41		6		0	
T stage																				
T1	2012	(25)	717	(23)	182	(25)	48	(29)	175	(23)	25	(21)	7	(26)	23	(20)	2	(9.1)	1	(33)
T2	3227	(39)	1365	(44)	340	(46)	72	(44)	286	(40)	56	(48)	10	(37)	50	(44)	9	(41)	0	
T3	2592	(32)	938	(30)	195	(27)	42	(26)	221	(31)	35	(30)	10	(37)	36	(32)	9	(41)	2	(67)
T4	350		102		15		3		27		2		0		4		2		0	
Missing	1994		749		151		31		171		24		4		23		1		0	
M stage																				
M0	5034	(87)	1961	(91)	489	(93)	101	(93)	445	(88)	78	(94)	17	(85)	68	(93)	9	(82)	2	(100)
M1	748		200		39		8		63		5		3		5		2		0	
Missing	4393		1710		355		87		372		59		11		63		12		1	
N stage																				
N0	5437	(88)	2158	(90)	517	(94)	107	(94)	483	(88)	87	(92)	20	(95)	73	(88)	13	(93)	2	(100)
N1	733		238		33		7		64		8		1		10		1		0	
Missing	4005		1475		333		82		333		47		10		53		9		1	
<7	3606	(36)	1419	(37)	345	(39)	77	(40)	334	(38)	57	(40)	12	(39)	46	(34)	9	(39)	2	(67)
3 + 4	2289	(23)	977	(25)	205	(23)	53	(27)	191	(22)	36	(25)	10	(32)	31	(23)	2	(8.7)	0	(0)
4 + 3	1013	(10)	376	(9.8)	79	(9.0)	12	(6.2)	77	(8.8)	15	(11)	1	(3.2)	19	(14)	7	(30)	0	(0)
8	812	(8)	266	(6.9)	65	(7.4)	8	(4.1)	54	(6.2)	7	(4.9)	3	(9.7)	7	(5.2)	2	(8.7)	0	(0)
>8	2367		810		188		45		222		27		5		31		3		1	
Missing	88		23		1		1		2		0		0		2		0		0	
Treatment																				
Radical prostatectomy	2279	(28)	1121	(40)	250	(39)	63	(45)	231	(34)	48	(45)	10	(46)	37	(35)	4	(24)	0	(0)
Radiotherapy	2353	(29)	593	(21)	134	(21)	37	(27)	157	(23)	22	(21)	3	(14)	33	(31)	6	(35)	0	(0)
Hormonal therapy	1620	(20)	419	(15)	86	(14)	12	(8.6)	105	(16)	11	(10)	3	(14)	17	(16)	4	(24)	1	(50)
Active surveillance	1155	(14)	392	(14)	94	(15)	11	(7.9)	113	(17)	15	(14)	3	(14)	11	(10)	1	(5.9)	0	(0)
Brachytherapy	290	(3.6)	179	(6.3)	36	(5.7)	7	(5.0)	28	(4.2)	2	(1.9)	2	(9.1)	2	(1.9)	1	(5.9)	1	(50)
Chemotherapy	209	(2.6)	40	(1.4)	7	(1.1)	3	(2.2)	13	(1.9)	2	(1.9)	1	(4.5)	4	(3.8)	1	(5.9)	0	(0)
Watchful waiting	146	(1.8)	49	(1.7)	20	(3.2)	3	(2.2)	13	(1.9)	3	(2.8)	0		1	(0.9)	0		0	(0)
Other	83		43		7		3		11		4		0		1		0		0	
Missing	2040		1035		249		57		209		35		9		30		6		1	
Vital status																				
Alive	7156	(70)	3042	(79)	662	(75)	149	(76)	685	(78)	117	(82)	27	(87)	102	(75)	19	(83)	1	(33)
Death—PrCa	2044	(20)	552	(14)	137	(16)	32	(16)	147	(17)	19	(13)	2	(6.5)	22	(16)	4	(17)	2	(67)
Death—non-PrCa	868	(8.5)	249	(6.4)	74	(8.4)	11	(5.6)	39	(4.4)	6	(4.2)	2	(6.5)	9	(6.6)	0		0	(0)
Death—unknown	107		28		10		4		9		0		0		3		0		0	
Year of diagnosis																				
<1995	262	(2.6)	122	(3.2)	36	(4.1)	11	(5.6)	18	(2.0)	2	(1.4)	1	(3.2)	4	(2.9)	0		0	
1995–1999	809	(8.0)	276	(7.1)	62	(7.0)	16	(8.2)	47	(5.3)	6	(4.2)	0		7	(5.1)	1	(4.3)	1	(33)
2000–2004	2325	(23)	658	(17)	186	(21)	48	(25)	163	(19)	17	(12)	3	(9.7)	24	(18)	5	(21)	1	(33)
2005–2009	2658	(26)	942	(24)	227	(26)	45	(23)	249	(28)	44	(31)	6	(19)	35	(26)	4	(17)	0	
2010–2014	3562	(35)	1486	(38)	304	(34)	58	(30	350	(40)	59	(42)	19	(61)	56	(41)	9	(39)	1	(33)
≥2015	559		387		68		18		53		14		2		10		4		0	

Table 1 (*continued*)

	Family history																	
	N, count (% [a])		Y, count (% [a])															
			1st-degree relatives						2nd-degree relatives						3rd-degree relatives					
			1		2		3+		1		2		3+		1		2		3+	
Geographic region																				
London	3839	(38)	843	(22)	158	(18)	32	(17)	242	(28)	30	(21)	5	(16)	50	(37)	6	(26)	0	
SE	1068	(11)	621	(16)	156	(18)	35	(18)	120	(14)	16	(11)	8	(26)	14	(10)	1	(4.3)	3	(100)
NW	988	(9.8)	387	(10)	92	(11)	12	(6.2)	87	(10)	11	(7.9)	3	(9.7)	8	(5.9)	0		0	
SW	779	(7.7)	442	(12)	92	(11)	18	(9.3)	79	(9.0)	21	(15)	2	(6.5)	12	(8.8)	3	(13)	0	
EastMid	767	(7.6)	358	(9.3)	98	(11)	23	(12)	73	(8.4)	18	(13)	1	(3.2)	11	(8.1)	2	(8.7)	0	
GrLondon	833	(8.2)	315	(8.2)	48	(5.5)	12	(6.2)	72	(8.2)	6	(4.3)	2	(6.5)	12	(8.8)	4	(17)	0	
WestMid	574	(5.7)	278	(7.2)	57	(6.5)	20	(10)	66	(7.6)	10	(7.1)	4	(13)	7	(5.1)	2	(8.7)	0	
Wales	522	(5.2)	212	(5.5)	63	(7.2)	16	(8.2)	53	(6.1)	11	(7.9)	2	(6.5)	11	(8.1)	4	(17)	0	
NE	453	(4.5)	216	(5.6)	57	(6.5)	10	(5.2)	46	(5.3)	8	(5.7)	2	(6.5)	6	(4.4)	0		0	
NI	182	(1.8)	71	(1.9)	23	(2.6)	9	(4.6)	29	(3.3)	5	(3.6)	1	(3.2)	3	(2.2)	1	(4.3)	0	
Scotland	119		94		29		7		6		4		1		2		0		0	
Missing	51		34		10		2		7		2		0		0		0		0	
Ethnicity																				
White	9243	(92)	3575	(95)	799	(95)	158	(90)	814	(94)	122	(87)	25	(83)	124	(93)	17	(77)	2	(100)
Black	456	(4.6)	141	(3.7)	23	(2.7)	13	(7.4)	36	(4.2)	17	(12)	5	(17)	7	(5.2)	4	(18)	0	
Asian	232	(2.3)	43	(1.1)	10	(1.2)	2	(1.1)	10	(1.2)	1	(0.7)	0		0		0		0	
Mixed ethnicity	68	(0.7)	15	(0.4)	5	(0.6)	1	(0.6)	4	(0.5)	0		0		1	(0.7)	1	(4.5)	0	
Ashkenazi	19		3		3		1		2		0		0		2		0		0	
Missing	157		94		43		21		14		2		1		2		1		1	
Cohort																				
PRY	6410	(63)	2104	(54)	295	(33)	49	(25)	616	(70)	92	(65)	18	(58)	81	(60)	6	(26)	1	(33)
PRM	3713	(37)	702	(18)	108	(12)	20	(10)	209	(24)	26	(18)	5	(16)	51	(38)	7	(30)	0	
PRS	52		1065		480		127		55		24		8		4		10		2	

PrCa = prostate cancer; PRM = patients treated at the Royal Marsden NHS Foundation Trust; PRY = patients who are diagnosed at age ≤60 yr from the collaborative centres; PRS = patients who are diagnosed at age ≤65; who have an first-, second-, or third-degree relative diagnosed at age ≤65 yr; or who have a total of three or more relatives with PrCa at any age on the same side of the family.

[a] Percentages refer to nonmissing data.

Table 2 – Distribution of family history, by variables of interest (continuous)

	Age at diagnosis			Age of diagnosis of youngest relative			PSA			BMI		
	N	Median	(IQR)	*N*	Median	(IQR)	*N*	Median	(IQR)	*N*	Median	(IQR)
All cases	16 340	59	(55, 64)	3698	65	(60, 72)	14 871	8.0	(4.7, 17.9)	2685	27.7	(25.5, 30.5)
Family history												
N	10 175	58	(55, 64)				9349	8.1	(4.5, 19.0)	1711	27.8	(25.5, 30.7)
Y												
1st degree												
1	3871	59	(55, 64)	2423	67	(61, 74)	3469	7.7	(4.8, 15.0)	597	27.6	(25.5, 30.4)
2	883	63	(58, 68)	724	61	(56, 66)	764	8.0	(5.4, 16.0)	126	27.8	(25.6, 30.3)
3+	196	65	(59, 68.5)	168	61	(56, 65)	172	7.6	(5.2, 13.5)	18	29.2	(27.6, 30.3)
2nd degree												
1	880	57	(54, 60)	254	72	(64, 78)	810	7.6	(4.6, 19.0)	172	27.4	(25.5, 29.7)
2	142	58	(55, 61)	50	68	(62, 76)	131	7.9	(4.6, 16.0)	26	28.9	(25.5, 31.4)
3+	31	59	(54, 63)	15	69	(64, 74)	28	7.9	(4.9, 14.6)	5	27.9	(26.2, 28.5)
3rd degree												
1	136	59	(55, 64)	50	66	(60, 71)	124	7.9	(3.9, 20.6)	27	27.5	(24.8, 32.8)
2	23	62	(57, 70)	12	62	(57, 67)	21	10.0	(5.2, 23.5)	3	35.9	(25.5, 43.4)
3+	3	65	(59, 68)	2	60	(59, 60)	3	9.8	(4.1, 123.0)	0	0.0	(0.0, 0.0)

BMI = body mass index; IQR = interquartile range; PSA = prostate-specific antigen.

Table 3 – Survival analysis, by family history status

	Survival, all-cause									
	Median (yr)	(95% CI)	5 yr	(95% CI)	10 yr	(95% CI)	15 yr	(95% CI)	20 yr	(95% CI)
No FH	17.3	(16.1, 18.1)	83.5	(78.9, 87.2)	70.1	(66.4, 73.5)	56.7	(53.6, 59.6)	41.8	(38.9, 44.6)
Number of relatives										
1.	20.1	(19.0, 20.9)	90.2	(89.1, 91.3)	77.4	(75.7, 78.9)	65.0	(62.8, 67.1)	50.7	(47.3, 54.0)
2+	20.4	(19.5, 22.4)	91.7	(90.2, 92.9)	81.1	(78.9, 83.1)	68.9	(65.7, 71.8)	51.5	(46.0, 56.6)
Degree of relative										
≥2nd degree	21.3	(19.1, .)	89.4	(87.2, 91.2)	77.7	(74.7, 80.4)	65.4	(61.3, 69.2)	54.9	(48.9, 60.5)
1st degree	20.1	(19.5, 20.7)	91.0	(90.1, 91.9)	78.7	(77.2, 80.1)	66.1	(64.1, 68.0)	50.5	(47.3, 53.5)
Overall	18.2	(17.6, 19.1)	86.3	(83.7, 88.6)	73.3	(71.1, 75.4)	60.1	(58.1, 62.0)	45.1	(43.1, 47.1)

CI = confidence interval; FH = family history.

compared with men with no FH (HR = 0.97 [95% CI 0.83–1.14]). For men with an FH of PrCa in an SDR or higher-degree relative who had screen-detected disease, we found a lower risk of all-cause mortality (HR = 0.58 [95% CI 0.39–0.87]) than for men without an FH. For other categories of FHs, while point estimates showed a similar pattern, there was no difference in all-cause mortality depending on the mode of detection.

Considering the timing of relatives' cancer as before or after the proband, for an increasing number of relatives, there was no effect on mortality among those who were diagnosed before their relatives (p-trend = 0.5), while for those who were diagnosed after, we saw a reduction in mortality similar to the overall result (p-trend < 0.001; Supplementary Table 4). A similar pattern was suggested when looking by degree of relatives, though numbers were smaller.

Splitting an FH of PrCa into those with (only) affected fathers and those with (only) affected brothers, we find a reduction in mortality for both ($HR_{brother}$ = 0.82 [95% CI 0.71–0.96], HR_{father} = 0.77 [95% CI 0.68–0.88]; Supplementary Table 5). Again, this is only the case where the relative was diagnosed first.

No mortality trend was seen when looking at the effect of an FH of other cancers (breast, ovarian, or colorectal). However, those with affected SDRs or higher-degree relatives had a lower risk of overall mortality (HR = 0.89 [95% CI 0.81–0.98]; Supplementary Table 6).

3.3. *Interaction, confounders, and effect modification*

The main effect holds in subgroups of all cancers and confounders controlled for (Supplementary Tables 7–17). There was some evidence of an effect modification of N stage in patients with only one relative of any degree (Supplementary Table 7). Patients with an FH in one relative with N0 PrCa were at a lower risk of dying than those with no FH (eg, HR = 0.77 [95% CI 0.68–0.87]). This effect was not observed for men with an FH in multiple relatives. However, for patients diagnosed with nodal involvement (N1), there was no difference in OS compared with those with no FH.

There was no evidence to suggest an interaction between T stage and FH, though differences between T1 and T4 disease among those with the weakest FH were observed. For those with SDRs or higher-degree relatives, T4 patients with an FH of PrCa showed no difference in the risk of death from those without an FH (HR = 1.16 [95% CI 0.77–1.75]), and T1 patients with an FH were at a lower risk of death than those without (HR = 0.58 [95% CI 0.37–0.91], p-int: T4 vs T1 = 0.025; Supplementary Table 8).

There was no evidence to suggest an interaction between Gleason score and FH, though there was some suggestion

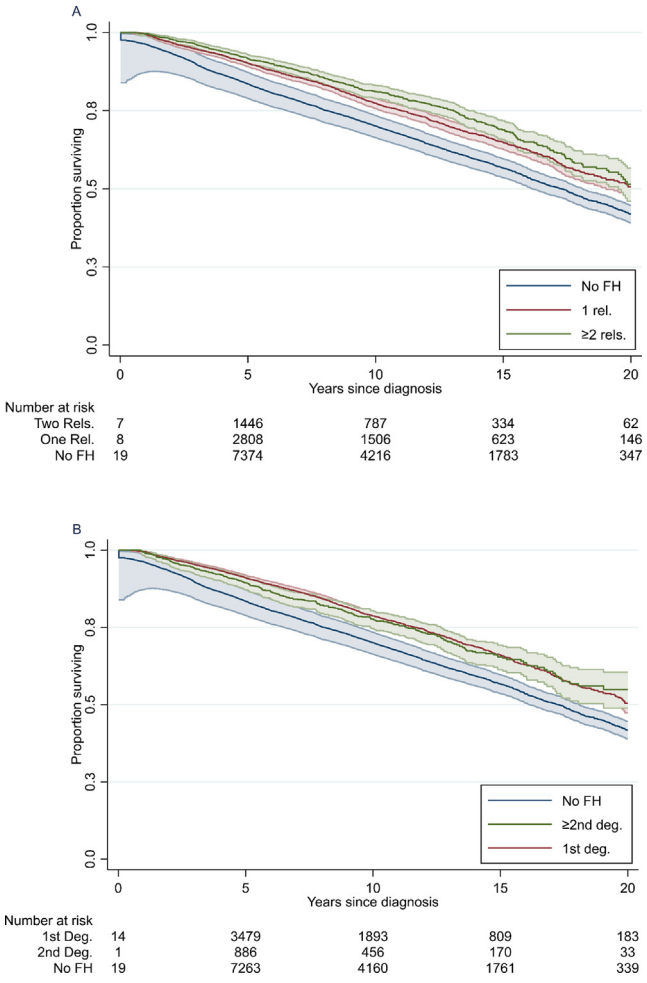

Fig. 1 – All-cause mortality among PrCa patients, by (A) the number of affected relatives and (B) degree of FH of the affected relatives. Deg. = degree; FH = family history; PrCa = prostate cancer; Rel. = relative.

that those with a higher Gleason score and an FH had a similar risk of all-cause mortality risk to those with no FH, while a lower Gleason score was associated with lower all-cause mortality among those with an FH (Supplementary Table 9), for example, for at least one FDR (HR = 0.76 [95% CI 0.65–0.89] and HR = 0.93 [95% CI 0.75–1.14] for Gleason <7 and Gleason 8 disease, respectively).

There was no suggestion of interactions among other covariates of interest: M stage, ethnicity, BMI, PSA, treatment, year of diagnosis, age at diagnosis, and geographic region (Supplementary Tables 9–17).

3.4. *Secondary outcomes*

In our multivariable analysis, after adjusting for FH, worse OS was associated with higher T stage (p-trend < 0.001), M stage (HR = 2.1 [95% CI 1.9–2.3]), N stage (HR = 1.2 [95% CI 1.1–1.4]), Gleason score (p-trend < 0.001), PSA (p-trend < 0.001), higher BMIs (HR = 1.3 [95% CI 1.1–1.6]), and more historic diagnosis (p-trend < 0.001; Supplementary Table 2). Radical prostatectomy was associated with better OS than other treatments (when taking FH status into account, there was no difference in the effect of treatment on survival; Supplementary Table 14). Patients with Black ethnicities were at a lower risk of death than those with European ethnicities (HR = 0.61 [95% CI 0.52–0.72]); 4.6% of the non-FH cohort and 4.0% of the FH cohort were black.

Similar results were seen for PCSM (Supplementary Tables 18 and 19) for both multivariable and univariable associations.

4. Discussion

Our study is one of the largest studies investigating the number, degree, and age of relatives of PrCa patients from multiple centres across the UK, with extensive follow-up and record linkage. The size of our study, coupled with detailed clinical information and follow-up, allows us to break down FH in terms of the number, degree, and age of affected relatives, as well as allowing us to investigate multivariable and subtype analyses. We show a direct "dose-response" relationship between the strength of FH, measured either as the number of relatives or the degree, and OS after diagnosis.

Table 4 – Risk of overall mortality by the number, degree, and age of relatives

	Censored, *N*	Deaths, *N*	Total, *N*	(%)	Person-years of follow-up, *N*	(%)	Haz. Ratio	(95% C. I)	*P*	*P-trend*
Risk of death, by number of first- and second-degree relatives										
No FH	7,278	3,059	10,337	(63)	81,609	(63)	Ref.			
1 Rels	3,071	910	3,981	(24)	31,015	(24)	0.85	(0.79, 0.93)	<0.001	
2+ Rels	1,611	411	2,022		16,125		0.80	(0.71, 0.90)	<0.001	<0.001
							0.1	1		
Risk of death, by degree of relative										
No FH	7,156	3,019	10,175	(89)	80,435	(90)	Ref.			
≥2nd degree	951	264	1,215	(11)	9,244	(10)	0.92	(0.81, 1.05)	0.2	
1st degree	3,853	1,097	4,950		39,072		0.82	(0.75, 0.89)	<0.001	<0.001
							0.1	1		
Risk of death, by age of youngest relative's diagnosis (per five-year increase), by degree of relative										*P-int*
1st degree	2,611	704	3,315	(90)	25,372	(91)	1.00	(0.96, 1.04)	0.9	
≥2nd degree	288	95	383		2,641		1.05	(0.93, 1.17)	0.4	0.4
							0.1	1		

CI = confidence interval; FH = family history; Haz. = hazard; Rel = relatives.

While an FH of PrCa is well known to increase the risk of incidence of all histological grades of PrCa, and appropriate screening should be performed in those with an FH, the effect of FH of PrCa on survival outcomes and clinical presentation among PrCa patients is somewhat contentious. In 2021, Urabe et al [4] published a meta-analysis of 39 716 patients and concluded no impact of FH on cancer-specific survival, OS, or biochemical-free survival among patients with localised PrCa who had undergone radical prostatectomy. However, of the 11 studies selected for the meta-analysis, only three addressed PCSM [5,6,13], of which two investigated OS [5,13]. The study by Westerman et al [13] was of comparable size to our own, with a similarly large FH cohort (32% compared with 38% in our own study), and concluded similarly that men with an FH were significantly more likely to have localised, low-risk disease and higher 10-yr cancer-specific survival (99% vs 97%) and OS (92% vs 85%) than those with no FH, a similar magnitude of difference to our own results (OS 79% for those with at least one FDR vs 70% for those with no FH). Westerman et al [13] reported that the HR for OS was 0.68 (95% CI 0.63–0.75).

Our ability to refine a definition of FH from simply Y/N to a more informative presentation describing the number and closeness of relatives enables us to match those studies described in Urabe et al's [4] meta-analysis. In doing this, we find similar results to our more detailed breakdown (HR PCSM [UKGPCS] = 0.85 [95% CI 0.77–0.94]). While study size is not a panacea for any issues in study design, it is notable that our large study and that by Westerman et al [13] suggest a protective association with FH, while Thalgot et al's [6] study is smaller and reports the result from an unadjusted univariable analysis (Fig. 2)

Regarding screening, although we find some evidence of an interaction with the method of detection (Supplementary Table 3), the difference in survival is not completely explained by a screening effect. Patients with at least one FDR had improved survival compared with those with no FH, but there was no evidence for a difference in survival depending on how the cancer was detected. For those with affected SDRs or higher-degree relatives, there was no difference in survival for those whose cancers were detected clinically, while those detected via screening showed an improvement in survival compared with those with no FH. It is possible that the weaker the FH, the stronger the effect of screening. Increasing the closeness or number of relatives is likely to increase awareness of the disease, producing a protective effect similar to screening. This suggestion is

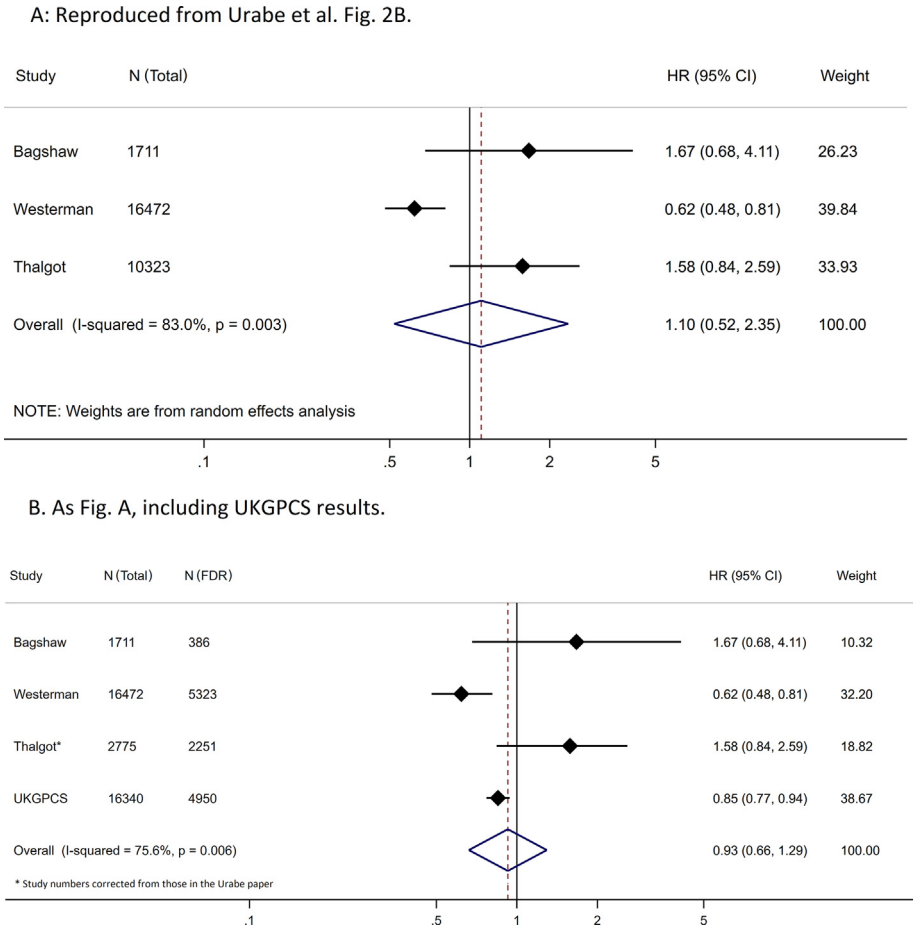

Fig. 2 – Forest plots showing the association of family history with cancer-specific survival. CI = confidence interval; FDR = first-degree relative; HR = hazard ratio; UKGPCS = UK Genetic Prostate Cancer Study.

borne out by the timing of the disease. We saw no reduction in mortality among those whose relatives were diagnosed after the proband, suggesting that the effect could be purely down to awareness. We still see an excess risk among those with affected brothers when compared with those with affected fathers, suggesting room for an x-linked or genetic effect, but this difference is not significant. There was no reduction in mortality among those with an FH of other cancers (breast, ovarian, or colorectal), suggesting that the effect is likely to be down to awareness and screening, rather than germline genetic variants contributing to disease risk.

4.1. Limitations

Our study is comprehensive in its clinical information and follow-up, and most potential confounders have been accounted for; however, we are missing data on other epidemiological risk factors associated with mortality such as smoking. We also lack information on comorbidities, which may be one of the principal predictors of mortality. The population studied here is predominantly of European ancestry (~90%), which is an under-representation of those of other ethnicities. While we did not see evidence of an interaction (Supplementary Table 9), our results suggest that OS was better in Black men after adjusting for FH (HR = 0.61 [95% CI 0.52–0.72]), and this is worth following up in more detail; we made some additional comments in the Supplementary material. We describe "awareness" of an FH of PrCa as a hypothesis for driving improved survival outcomes due to presumed increased PSA testing among "aware" male relatives of the studies' probands and earlier disease detection. Our analysis did not specifically compare those diagnosed (and their relatives' diagnoses) before and after the widespread uptake of PSA testing or before the "PSA era". There is also the possibility that a "healthy screening" effect is taking place. That is, the type of person who takes up screening may be intrinsically healthier and therefore may also avoid other causes of death for longer. Comparing the magnitude of the association between PCSM and non-PCSM and an FH of PrCa indicates that this effect is likely to be small. Further discussion is given in the Supplementary material. FH information may also be missing for family members' diagnoses that occur after the proband.

5. Conclusions

In this study, we have demonstrated a strong relationship between the strength of an FH of PrCa and OS outcomes in men with PrCa, as well as showing that an FH of PrCa is associated with a younger age at diagnosis, but limited evidence to suggest an association between FH and pathological characteristics. We also demonstrate evidence that screening awareness may account for a difference in mortality by assessing the timing of a relative's diagnosis of PrCa.

This study provides information for the benefit of patients and their relatives on which clinicians can guide them based on their familial risk. It may provide some reassurance to patients and clinicians in the UK that OS in PrCa patients with an FH of PrCa is not adversely affected, and provide a platform for further research into better understanding the impact this could have on targeted/risk-adapted screening and risk-stratification algorithms for men with an FH.

***Author contributions*:** Mark N. Brook had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Kote-Jarai, Eeles, Govindasami, Ní Raghallaigh, Dadaev, Rageevakumar, Keating, Hussain, Osborne, UKGPCS Collaborators, Lophatananon, Muir.
Analysis and interpretation of data: Brook, Ní Raghallaigh.
Drafting of the manuscript: Brook, Ní Raghallaigh.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Brook.
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Supervision: Kote-Jarai, Eeles.
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Peer Review Summary

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