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Family history of prostate cancer and the incidence of ERG- and PTEN-defined prostate cancer

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Abstract

Family history is among the strongest known risk factors for prostate cancer (PCa). Emerging data suggest molecular subtypes of PCa, including two somatic genetic aberrations: fusions of androgen-regulated promoters with *ERG* and, separately, PTEN loss. We examined associations between family history and incidence of these subtypes in 44,126 men from the prospective Health Professionals Follow-up Study. ERG and PTEN status were assessed by immunohistochemistry. Multivariable competing risks models were used to estimate hazard ratios (HR) and 95%

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confidence intervals (CI) for associations between self-reported family history of PCa and molecular subtypes of disease. Thirteen percent of men had a positive family history of PCa at baseline. During a median follow-up of 18.5 years, 5,511 PCa cases were diagnosed. Among them, 888 were assayed for ERG status (47% ERG-positive) and 715 were assayed for PTEN loss (14% PTEN null). Family history was more strongly associated with risk of ERG-negative (HR: 2.15; 95%CI: 1.71-2.70) than ERG-positive (HR: 1.49; 95%CI: 1.13-1.95) disease ($P_{heterogeneity}$: 0.04). The strongest difference was among men with an affected father ($HR_{ERG\text{-}negative}$: 2.09; 95%CI: 1.64-2.66; $HR_{ERG\text{-}positive}$: 1.30; 95%CI: 0.96-1.76; $P_{heterogeneity}$: 0.01). Family history of PCa was positively associated with both PTEN null (HR: 2.10; 95%CI: 1.26-3.49) and PTEN intact (HR: 1.72; 95%CI: 1.39-2.13) PCa ($P_{heterogeneity}$: 0.47). Our results indicate that PCa family history may be positively associated with PCa in all ERG and PTEN subtypes, suggesting a role of genetic susceptibility in their development. It is possible that ERG-negative disease could be especially associated with positive family history.

Keywords

prostate cancer; *TMPRSS2:ERG*; PTEN; family history; molecular subtypes

INTRODUCTION

Family history of prostate cancer (PCa) is a well-established risk factor for PCa incidence.[1] Men with an affected father have a more than two-fold greater risk of PCa and those with an affected brother have a more than three-fold greater risk.[2] Furthermore, twin studies indicate that nearly 60% of the variability in PCa liability can be attributed to genetic factors,[3,4] making PCa one of the most heritable malignancies.

The past several years have seen progress in defining molecular subtypes of PCa, yet no studies have evaluated the role of family history in specific subtypes of disease. In the most common known molecular subtype (i.e., roughly half of primary PCa),[5] the oncogene *ERG* fuses with androgen-regulated promoter genes, most often *TMPRSS2*.[6] While ERG status is unlikely prognostic by itself,[7] several studies have shown that various risk factors are differentially associated with ERG-defined PCa.[8–16] In particular, preliminary evidence suggests that there are distinct inherited genetic factors associated with the risk of ERG-positive vs. ERG-negative disease,[8–10] lending plausibility to the hypothesis that family history could be differentially associated with the risk of ERG-defined disease.

Loss of phosphatase and tensin homolog (*PTEN*), a tumor suppressor gene, is another common molecular subtype of PCa. Complete PTEN loss is characteristic of approximately one-fifth of primary tumors,[17,18] and it is associated with aggressive clinical features, occurring in nearly 50% of metastatic and castration-resistant disease.[19–22] Given that family history is positively associated with fatal PCa,[23] the evaluation of the role of family history in PCa with PTEN loss has the potential to clarify mechanisms and inform clinical counseling for the risk of aggressive disease. No data exist, however, regarding the inherited genetic susceptibility to PTEN-defined PCa.

Given the substantial heritability of PCa and the high prevalence of both ERG overexpression and PTEN loss, an association between family history and these molecular subtypes is both plausible and potentially valuable for prevention efforts in clinic. Utilizing data from the large prospective Health Professionals Follow-up Study (HPFS), we evaluated whether a positive PCa family history is differentially associated with the incidence of ERG- and/or PTEN-defined disease.

MATERIALS AND METHODS

Study population

The HPFS is an ongoing cohort of 51,529 U.S. male health professionals who were ages 40 to 75 at enrollment in 1986. Cohort data have been updated biennially via questionnaires concerning lifestyle factors, known or suspected contributors to chronic diseases, and various health outcomes. For these analyses, we restricted the cohort to the 47,158 men who responded to a question about family history of PCa on the 1990 questionnaire. We then excluded men who reported cancers other than nonmelanoma skin cancer prior to 1990 (n = 3,013), who were missing data on date of birth (n = 10), who were diagnosed with PCa but missing a diagnosis date (n = 7), or who had a date of death prior to a date of metastases (n = 2). The remaining 44,126 men comprised the study population for these analyses.

Consent and approval

The Institutional Review Board at the Harvard T.H. Chan School of Public Health approved this study. Response to the baseline questionnaire was considered implied consent. Written informed consent was obtained from each study participant to obtain medical records and archival tumor tissue.

Family history assessment

Questionnaires assessed family history of PCa in a father and/or brother (yes/no) in 1990, 1992, and 1996. Family history was considered time-variable, whereby men who initially reported no family history could change to have a positive family history over time. In 1996, participants were asked the age of their affected relatives at the time of diagnosis in five categories (<50, 50–59, 60–69, ≥70 years, unknown). As few relatives were diagnosed under the age of 50 years, we further categorized age of the relative at diagnosis (<60, ≥60 years, unknown).

Case ascertainment, tumor tissue cohort, and immunohistochemistry

PCa diagnoses and deaths were initially identified by self-report or next of kin, and confirmed with medical records, pathology reports, and the National Death Index. Medical records were reviewed to abstract information about clinical characteristics and disease progression. We were thus able to define the following categories of PCa diagnoses: high-grade cancer (Gleason score ≥4+3), low-grade cancer (Gleason score ≤3+4), and lethal disease (distant metastases at diagnosis or during follow-up, or PCa death during follow-up). A total of 5,511 PCa cases were diagnosed during the study period (i.e., between 1990 and 2009).

We collected archival tumor tissue from men who underwent radical prostatectomy (95%) or transurethral resection of the prostate (5%). Hematoxylin and eosin slides were reviewed by study pathologists to confirm PCa and to identify tumor areas for tissue microarray (TMA) construction. We constructed TMAs by sampling at least three 0.6 mm cores of tumor per case from the dominant nodule or nodule with highest Gleason pattern.

Archival tumor tissue was unavailable from some hospitals; hospitals destroy blocks after 10 years, and some do not release tissue outside of their institutions. In addition, tissue for men who were not treated with surgery was not assayed. Among men for whom tissue was available, ERG and PTEN status were measured by immunohistochemistry in a subset, as described in detail previously.[7,24] A case was scored ERG-positive if at least one TMA core had positive ERG staining within PCa epithelial cells.[7] A tissue core was considered to have PTEN protein loss if the intensity of cytoplasmic and nuclear staining was entirely lost (0+ intensity) or decreased (1+ intensity) across more than 10% of tumor cells compared with surrounding benign glands and/or stroma.[24] Among the PCa cases with tissue available, ERG data were available for 888 men and PTEN data were available for 715 men.

Statistical Analysis

Person-time was calculated from the return date of the 1990 questionnaire until PCa diagnosis (regardless of the availability of ERG and PTEN assays), death from any cause, or end of follow-up. Because prostate tumor tissue was available for ERG and PTEN in cases diagnosed through 2009, we ended follow-up at that time. We used Cox proportional hazards models adjusted for age and calendar time to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the association between any family history of PCa and disease incidence (regardless of ERG or PTEN data availability). We also ran separate models for associations with father family history, brother family history, and earliest age at PCa diagnosis in any relative. Multivariable models were adjusted for Caucasian race (yes, no), height (≤68, >68-70, >70-72, >72 inches), body mass index (BMI) at age 21 (<20, 20-<22.5, 22.5-<25, 25+ kg/m^2), current BMI (<21, 21-<25, 25-<30, 30+ kg/m^2), physical activity (quintiles of metabolic equivalent task [MET] hours per week), smoking (never, former/quit >10 years ago, former/quit ≤10 years ago, current), history of diabetes (yes, no), prostate-specific antigen (PSA) testing in the two years prior to the questionnaire date (yes, no; lagged by one period to avoid counting diagnostic PSA tests as screening), total energy intake (quintiles), tomato sauce intake (quintiles), and coffee intake (none, <1, 1-<2, 2-<3, 3+ cups per day). Multivariable models for father family history were additionally adjusted for brother family history and vice versa.

To assess associations with PCa by ERG and, separately, PTEN status, we implemented an extension of Cox modeling as described by Lunn and McNeil.[25] These competing risks models allowed for HR estimation for each molecular subtype of cancer versus no cancer. We examined whether associations between family history and PCa defined by ERG or PTEN status differed using likelihood ratio tests.[26]

Multivariable models were also fit for high-grade and low-grade PCa overall and by subtype. We were also powered to look at the risk of lethal disease for PCa overall.

P-values were calculated with two-sided tests with a significance threshold set at $p<0.05$. Analyses were performed in SAS Version 9.4 (SAS Institute Inc, Cary, NC).

Data Availability

The data that support the findings of this study are available on request. The data are not publicly available due to privacy or ethical restrictions.

RESULTS

Table 1 describes the age-standardized characteristics of the study population by family history of PCa. More men with a known PCa family history were PSA screened in the prior two years (48% in 1994; 75% in 2004) than men without a family history (38% in 1994; 68% in 2004). There were no material differences in any other lifestyle, nutritional, or demographic characteristics between those with and without a PCa family history.

During a median follow-up of 18.5 years, 697,872 person-years were accrued and 5,511 incident PCa cases were diagnosed (Table 2). Among them, 888 were assayed for ERG status (47% ERG-positive) and 715 were assayed for PTEN status (14% PTEN null). Men assayed for a molecular marker were more likely to be diagnosed in earlier years, to be younger at diagnosis, and to have more information regarding their clinical characteristics. Previous studies from our group suggest that statistically accounting for differences between cases with and without molecular marker information does not materially change results.[11,12]

Multivariable results for associations between family history of PCa and incidence of PCa overall and by molecular marker status are presented in Table 3; results from age- and calendar time-adjusted models were materially similar (data not shown). A positive family history was associated with a higher incidence of overall PCa (HR: 1.68; 95% CI: 1.56, 1.80), as well as both high- and low-grade disease. There was also suggestive evidence that men may have an even greater increased incidence of PCa if a family member was diagnosed before age 60: (HR: 2.22; 95% CI: 1.84, 2.68). Results for lethal PCa (HR: 1.65; 95% CI: 1.35, 2.02) were comparable with those for overall PCa.

Family history of PCa was associated with the incidence of ERG-positive (HR: 1.49; 95% CI: 1.13, 1.95) PCa and even more so ERG-negative (HR: 2.15; 95% CI: 1.71, 2.70) PCa ($P_{\text{heterogeneity}}$: 0.04). The strongest difference was among men with an affected father ($HR_{\text{ERG-negative}}$: 2.09; 95% CI: 1.64-2.66; $HR_{\text{ERG-positive}}$: 1.30; 95% CI: 0.96–1.76; $P_{\text{heterogeneity}}$: 0.01). These results were seemingly driven by the association of having an affected father with the incidence of low-grade ERG-negative PCa (HR: 2.31; 95% CI: 1.69-3.16). Indeed, family history overall was more strongly associated with low-grade ERG-negative disease (HR: 2.39; 95% CI: 1.77, 3.22) than low-grade ERG-positive disease (HR: 1.04; 95% CI: 0.69, 1.58; $P_{\text{heterogeneity}}$: 0.001).

Fourteen percent of cases were PTEN null. Analyses of family history and incidence of PCa by PTEN status found similar positive associations for both PTEN null and intact disease

($P_{heterogeneity}$: 0.47). Analyses restricted to subtypes combining both PTEN status and Gleason grade were largely underpowered for meaningful analysis.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate associations between PCa family history and disease incidence by ERG and PTEN status. Our results suggest that family history contributes to the incidence of PCa across the four molecular subtypes. They also indicate the possibility that family history may contribute most strongly to the incidence of ERG-negative PCa, particularly of the low-grade variety.

Twin studies have shown that PCa is among the most heritable cancers,[3,4] and array-based analyses suggest that common genetic variants explain over 33% of PCa heritability.[27] It is thus unsurprising that we found a family history of PCa to be associated with the incidence of PCa overall and with the incidence of each molecular subtype of disease. There is, however, evidence to suggest that the genetic factors that contribute to the incidence of *TMPRSS2:ERG*-positive versus -negative PCa are distinct. One genome-wide linkage analysis revealed several loci that were suggestive of linkage to *TMPRSS2:ERG*-positive PCa.[8] In addition, two studies published in 2016, including one from our group, produced evidence of individual germline variants differentially associated with PCa defined by fusion status.[9,10] Our group further found that shorter CAG repeats in *androgen receptor* are specifically associated with the development of ERG-positive PCa.[28] It should also be noted that the prevalence of the fusion varies across ancestries, suggesting a role for genetics in its development; prevalence of *TMPRSS2:ERG* is higher for Caucasians (~50%) than for individuals of African (16–30%) and Asian (16–30%) descent.[7,29–31] Multi-ancestry genome-wide association studies of PCa defined by molecular subtypes have the potential to more comprehensively elucidate the genetic factors that contribute to the subtypes.

Lifestyle may also play a role in the development of PCa defined by *TMPRSS2:ERG*.[11–16] For example, lycopene consumption from tomato products has been shown to be inversely associated with ERG-positive but not ERG-negative disease,[11] and two studies have shown obesity to be associated with a reduced risk of developing *TMPRSS2:ERG*-positive PCa.[12,13] Given that families often share lifestyle exposures, the association between a family history of PCa and molecular subtypes of PCa could operate through environment.

We found some suggestive evidence that a family history of PCa may be more strongly associated with ERG-negative than ERG-positive PCa. A possible explanation stems from the association between a family history of PCa and increased PSA screening.[32–34] While PSA screening does not seem to wholly account for the association between a family history of PCa and PCa risk,[1,34,35] its increased adoption among men with a family history of PCa means that such men are more likely to be diagnosed with lower stage disease.[36–38] Given that the *TMPRSS2:ERG* gene fusion is associated with higher stage PCa,[7] it is perhaps unsurprising that we found a family history of PCa to be more strongly associated with ERG-negative disease. It is also possible that ERG-negative PCa is more heritable than ERG-positive PCa and/or that lifestyle risk factors shared by families more strongly affect ERG-negative disease. Regardless of the underlying reason, ours is the first study to show a

differential association for PCa family history with PCa defined by ERG status. Fewer explanations come to mind regarding a possible differential association for family history in a father and ERG-defined PCa, or, more accurately, the lack of such a differential association for family history in a brother. The most likely is perhaps insufficient power.

Like *TMPRSS2:ERG*, the frequency of PTEN loss in PCa differs by ancestry, wherein it is lower for African-Americans than for Caucasians.[39] Beyond ancestral differences, little evidence exists regarding the heritability of PTEN loss. Ours is the first study to investigate the relationship between family history and PCa defined by PTEN loss. We found that family history was positively associated with both PTEN intact and PTEN null tumor status. There could be several reasons for the lacking differential association. Many mechanisms may lead to PTEN alterations, including mutations,[40,41] epigenetic changes,[42] microRNA regulation,[43,44] and post-translational modifications.[45] Some PTEN loss may thus be hereditary while other PTEN loss occurs as a result of alternative mechanisms. PTEN loss may even occur subsequent to other genomic alterations, including the *TMPRSS2:ERG* fusion.[46] Additional research is warranted to determine whether family history plays a role in PTEN loss.

This study had some limitations. Given that the HPFS largely consists of Caucasian men and that the prevalence of ERG and PTEN vary by race/ethnicity, results are not generalizable to all racial/ethnic groups. We also acknowledge that most cases assayed for ERG and/or PTEN status were treated with radical prostatectomy, and thus not representative of all men diagnosed with PCa. We found, however, that cases assayed for molecular markers did not substantially differ from other cases with respect to the majority of clinical and demographic characteristics (e.g., stage, Gleason score, and PSA at diagnosis). It is also reassuring that the prevalence of family history was similar among those with and without tissue biomarker data. In addition, two previous studies showed that the use of inverse probability weighting to account for differences between men with and without ERG status available did not materially change results.[11,12] ERG and PTEN status were not available for family members diagnosed with PCa, as these data are not collected in clinical practice. Such information would have provided important data on the heritability of specific subtypes. Lastly, our study was limited by small sample sizes for ERG and PTEN status on rare subsets of PCa.

This study also had several strengths. We utilized longitudinal data from a prospective and well-annotated cohort with ample covariate data to adjust for potential confounders. It is also critical that we had access to a tumor biorepository for assaying ERG and PTEN status given that such data are unavailable from pathology reports. Whereas most epidemiological evaluations are only able to investigate ERG and PTEN status with respect to disease progression,[47–50] our data permitted the assessment of risk factors for development of PCa defined by ERG and PTEN status. In addition, the PCa subtypes in our study were centrally assessed and clinically validated by pathologists, reducing the likelihood of misclassification.

In summary, this is the first study to examine the associations of family history of PCa with respect to ERG and PTEN status. We found evidence suggesting that family history is associated with PCa across molecular subtypes, which indicates that genetic variants may

play a key role in the development of PCa irrespective of *TMPRSS2:ERG* and PTEN status. Our results also imply the possibility that family history may play the largest role in the development of ERG-negative PCa. Additional research is necessary to validate our findings and to further explore the contributions of heritability and environment to the development of molecular subtypes of PCa. Investigators conducting genome-wide association studies might consider integrating data on molecular subtypes to inform the heritability of PCa.

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Abbreviations Used:

BMI	body mass index
CI	confidence interval
HR	hazard ratio
HPFS	Health Professionals Follow-up Study
PTEN	phosphatase and tensin homolog
PCa	prostate cancer
PSA	prostate-specific antigen
TMA	tissue microarray

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Novelty and Impact:

Despite data suggesting molecular subtypes of prostate cancer, little is known about their heritability. We investigated associations between family history of prostate cancer and incidence of prostate cancer defined by fusions of androgen-regulated promoters with *ERG* and, separately, PTEN loss. Our results indicate that family history may be positively associated with prostate cancer in all ERG and PTEN subtypes, suggesting a role of genetic susceptibility. It is possible that ERG-negative disease may be especially associated.

Table 1.

Age-standardized characteristics of the study population at baseline in 1990 by family history of PCa, the Health Professionals Follow-up Study

Characteristic	PCa family history	
	No	Yes
N	38,537	5,589
Mean age, years (SD)[a]	58.0 (9.6)	58.2 (9.5)
Caucasian	95.8%	96.5%
Mean height, inches (SD)	70.1 (2.7)	70.2 (2.7)
Mean BMI at age 21 years, kg/m^2 (SD)	23.0 (2.9)	22.9 (2.9)
Mean BMI, kg/m^2 (SD)	25.7 (3.4)	25.7 (3.4)
Top quintile of physical activity (≥29.7 MET hours/week)	19.9%	21.0%
Smoking status		
Never smoker	44.3%	46.6%
Past smoker quit >10 years	31.7%	31.2%
Past smoker quit ≤10 years	9.6%	8.7%
Current smoker	8.3%	8.0%
Smoking unknown	6.1%	5.5%
History of diabetes	4.4%	4.0%
PSA screening[b]		
1994	38.1%	48.2%
2004	67.7%	75.2%
Mean total energy intake, kcal/day (SD)	1,953 (558)	1,972 (554)
Mean tomato sauce intake, servings/day (SD)	0.1 (0.1)	0.1 (0.1)
Mean coffee intake, cups/day (SD)	1.9 (1.7)	1.9 (1.7)
Father with PCa	–	80.6%
Brother(s) with PCa	–	23.6%
Earliest age at family member PCa diagnosis		
Age <60 years	–	7.9%
Age 60+ years	–	60.0%
Age unknown	–	32.1%

Abbreviations: BMI, body mass index; MET, metabolic equivalent task; PCa, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation

[a]Value is not age-standardized

[b]Reported having a PSA test in the two years before the questionnaire date

Table 2.

Age-standardized characteristics of participants with PCa by ERG and PTEN status, the Health Professionals Follow-up Study, 1990-2009

	Cases by ERG status			Cases by PTEN status		
Characteristic	**Positive**	**Negative**	**Unavailable**	**Null**	**Intact**	**Unavailable**
N	417	471	4,623	100	615	4,796
Mean age at diagnosis, years (SD)[a]	65.2 (6.1)	66.2 (5.7)	70.9 (7.5)	66.4 (6.3)	65.7 (5.9)	70.7 (7.5)
Year of diagnosis						
1990-1994	34.7%	27.9%	21.5%	32.9%	26.0%	22.3%
1995-1999	36.3%	33.1%	25.3%	39.8%	28.6%	26.4%
2000-2004	15.0%	25.2%	30.4%	16.9%	26.3%	29.4%
2005-2009	14.0%	13.7%	22.8%	10.4%	19.0%	21.9%
Mean PSA at diagnosis (SD)[b]	9.9 (10.8)	10.0 (11.1)	15.5 (117)	9.4 (7.8)	9.9 (11.2)	15.4 (116)
% Missing	5.6%	9.5%	16.0%	13.9%	6.8%	15.8%
TNM clinical stage						
T1 / T2[b]	93.4%	96.0%	92.8%	92.1%	96.0%	92.9%
T3[b]	4.7%	2.0%	2.8%	2.3%	3.3%	2.8%
T4 / N1 / M1[b]	1.9%	2.0%	4.4%	5.6%	0.7%	4.3%
% Missing	0.0%	0.0%	11.8%	0.0%	0.0%	11.5%
Gleason grade						
Gleason 2-6[b]	58.1%	59.0%	61.5%	33.1%	60.5%	61.7%
Gleason 3+4[b]	19.1%	16.9%	16.1%	21.0%	17.9%	16.1%
Gleason 4+3[b]	12.0%	12.6%	7.5%	17.4%	12.8%	7.5%
Gleason 7, breakdown unknown[b]	1.5%	0.7%	3.7%	3.7%	0.2%	3.6%
Gleason 8-10[b]	9.3%	10.8%	11.2%	24.8%	8.7%	11.0%
% Missing	0.0%	0.1%	15.3%	0.0%	0.1%	14.8%
Lethal PCa	9.6%	8.8%	14.2%	24.8%	5.0%	14.1%
Family history of PCa	21.6%	21.8%	20.0%	25.7%	19.8%	20.2%
Father with PCa	14.3%	16.7%	15.4%	14.8%	15.2%	15.5%

Characteristic	Cases by ERG status			Cases by PTEN status		
	Positive	Negative	Unavailable	Null	Intact	Unavailable
Brother(s) with PCa	8.5%	6.2%	5.9%	12.3%	5.5%	6.0%
Earliest age at family member PCa diagnosis[c]						
Age <60 years	14.0%	5.9%	10.3%	15.3%	5.3%	10.5%
Age 60+ years	59.1%	63.2%	63.1%	58.6%	63.7%	63.0%
Age unknown	26.9%	30.8%	26.6%	26.1%	31.0%	26.5%

Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation

[a]Value is not age-standardized

[b]Values are among those with data available

[c]Among cases with a positive family history of PCa

Table 3.

Multivariable hazard ratios (HR) and 95% confidence intervals (CI) for the incidence of PCa, overall and by ERG and PTEN status, the Health Professionals Follow-up Study, 1990-2009

	PCa Overall		By ERG Status				By PTEN Status			
	N cases	HR (95% CI)[a]	N Cases		HR (95% CI)[a]		N Cases		HR (95% CI)[a]	
			ERG+	ERG−	ERG+	ERG−	PTEN Null	PTEN Intact	PTEN Null	PTEN Intact
Total PCa	**5,511**		**417**	**471**			**100**	**615**		
Family history of PCa										
No	4,554	1 (ref)	354	375	1 (ref)	1 (ref)	80	509	1 (ref)	1 (ref)
Yes	957	1.68 (1.56, 1.80)	63	96	1.49 (1.13, 1.95)	2.15 (1.71, 2.70)	20	106	2.10 (1.26, 3.49)	1.72 (1.39, 2.13)
$P_{heterogeneity}$					0.04				0.47	
Father with PCa										
No	4,738	1 (ref)	368	388	1 (ref)	1 (ref)	86	525	1 (ref)	1 (ref)
Yes	773	1.65 (1.53, 1.78)	49	83	1.30 (0.96, 1.76)	2.09 (1.64, 2.66)	14	90	1.60 (0.88, 2.91)	1.63 (1.30, 2.05)
$P_{heterogeneity}$					0.01				0.96	
Brother(s) with PCa										
No	5,279	1 (ref)	402	455	1 (ref)	1 (ref)	94	597	__[b]	__[b]
Yes	232	1.51 (1.32, 1.73)	15	16	1.96 (1.16, 3.29)	1.71 (1.03, 2.86)	6	18		
$P_{heterogeneity}$					0.72					
Earliest age at family member PCa diagnosis										
No family history	4,400	1 (ref)	332	361	1 (ref)	1 (ref)	75	489	__[b]	__[b]
Age <60 years	114	2.22 (1.84, 2.68)	11	9	2.58 (1.42, 4.72)	2.40 (1.22, 4.74)	3	10		
Age 60+ years	693	1.76 (1.62, 1.91)	49	65	1.65 (1.22, 2.22)	1.99 (1.53, 2.60)	15	73		
Age unknown	304	1.57 (1.40, 1.77)	25	36	1.65 (1.09, 2.48)	2.25 (1.59, 3.17)	7	43		
$P_{heterogeneity}$					0.57					
High grade PCa (Gleason ≥4+3)	**1,207**		**181**	**213**			**76**	**269**		
Family history of PCa[c]										
No	997	1 (ref)	144	177	1 (ref)	1 (ref)	59	219	1 (ref)	1 (ref)
Yes	210	1.68 (1.44, 1.96)	37	36	2.14 (1.48, 3.10)	1.75 (1.21, 2.53)	17	50	2.43 (1.39, 4.26)	1.94 (1.41, 2.66)

	PCa Overall		By ERG Status				By PTEN Status			
	N cases	HR (95% CI)[a]	N Cases		HR (95% CI)[a]		N Cases		HR (95% CI)[a]	
			ERG+	ERG−	ERG+	ERG−	PTEN Null	PTEN Intact	PTEN Null	PTEN Intact
$P_{heterogeneity}$					0.45				0.49	
Father with PCa[c]										
No	1,039	1 (ref)	155	182	1 (ref)	1 (ref)	65	228	1 (ref)	1 (ref)
Yes	168	1.64 (1.39, 1.94)	26	31	1.62 (1.06, 2.48)	1.69 (1.14, 2.51)	11	41	1.64 (0.83, 3.26)	1.75 (1.24, 2.47)
$P_{heterogeneity}$					0.89				0.87	
Brother(s) with PCa[c]										
No	1,154	1 (ref)	169	208	__[b]	__[b]	70	259	__[b]	__[b]
Yes	53	1.57 (1.18, 2.08)	12	5			6	10		
$P_{heterogeneity}$										
Low grade PCa (Gleason ≤3+4)	**3,434**		**235**	**253**			**24**	**344**		
Family history of PCa[c]										
No	2,808	1 (ref)	209	195	1 (ref)	1 (ref)	21	290	__[b]	__[b]
Yes	626	1.73 (1.58, 1.89)	26	58	1.04 (0.69, 1.58)	2.39 (1.77, 3.22)	3	54		
$P_{heterogeneity}$					0.001					
Father with PCa[c]										
No	2,928	1 (ref)	212	203	1 (ref)	1 (ref)	21	297	__[b]	__[b]
Yes	506	1.67 (1.52, 1.84)	23	50	1.06 (0.69, 1.65)	2.31 (1.69, 3.16)	3	47		
$P_{heterogeneity}$					0.004					
Brother(s) with PCa[c]										
No	3,286	1 (ref)	232	243	__[b]	__[b]	24	337	__[b]	__[b]
Yes	148	1.61 (1.36, 1.91)	3	10			0	7		
$P_{heterogeneity}$										

Abbreviations: CI, confidence interval; HR, hazard ratio; PCa, prostate cancer

[a]Models adjusted for age, calendar time, Caucasian race (yes, no), height (≤68, >68-70, >70-72, >72 inches), body mass index (BMI) at age 21 years (<20, 20-<22.5, 22.5-<25, 25+ kg/m^2), current BMI (<21, 21-<25, 25-<30, 30+ kg/m^2), physical activity (quintiles of metabolic equivalent task [MET] hours per week), smoking (never, former / quit >10 years ago, former / quit ≤10 years ago, current), history of diabetes (yes, no), prostate-specific antigen (PSA) testing in the two years prior to the questionnaire date (yes, no; lagged by one period to avoid counting diagnostic PSA tests as screening), total

energy intake (quintiles), tomato sauce intake (quintiles), and coffee intake (none, <1, 1-<2, 2-<3, 3+ cups per day); models for father family history were additionally adjusted for brother family history and vice versa

[b] Sample size insufficient to yield meaningful results

[c] Of any grade

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