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Family History of Breast or Prostate Cancer and Prostate Cancer Risk

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Abstract

Purpose: Breast and prostate cancer co-occur in families, and women with a family history of prostate cancer are at increased breast cancer risk. Prostate cancer is among the most heritable cancers, but few studies have investigated its association with familial breast cancer. The objective of this study is to investigate the extent to which familial breast or prostate cancer in first-degree relatives increases prostate cancer risk.

Experimental Design: A prospective study of 37,002 U.S. men in the Health Professionals Follow-up Study. During the 16-year follow-up to 2012, 4,208 total and 344 lethal cases were diagnosed. Using cause-specific hazards regression, we estimated the multivariable HRs and 95% confidence intervals (CI) for associations between familial breast or prostate cancer and total and lethal prostate cancer.

Results: Those with familial breast cancer had a 21% greater risk of prostate cancer overall (95% CI, 1.10–1.34), and a 34% greater risk of lethal disease (HR 1.34; 95% CI, 0.96–1.89). Family history of prostate cancer alone was associated with a 68% increased risk of total disease (95% CI, 1.53–1.83) and a 72% increased risk of lethal disease (95% CI, 1.25–2.38). Men with a family history of both cancers were also at elevated risk.

Conclusions: Our study found that men with a family history of breast or prostate cancer had elevated prostate cancer risks, including risk of lethal disease. These findings have translational relevance for cancer risk prediction in men.

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Introduction

Prostate cancer is among the most heritable cancers, and twin studies estimate that 57% of the variation in risk can be attributed to the genetic factors (1). Men with a brother or father diagnosed with prostate cancer have 2- to 4-fold greater risk of developing prostate cancer (2–4), with risk higher if a brother is diagnosed (2, 3, 5, 6).

Moreover, prostate cancer risk increases with the number of affected relatives and decreases with the relative's age at diagnosis (5).

The role of family history with respect to prostate cancer risk may be broader, given the observation that prostate and breast cancer can co-occur in families. Prospective studies have found statistically significant (5, 7), null (4, 6), or nonsignificant (8) associations between familial breast cancer and prostate cancer risk. Men with a family history of both cancers have greater prostate cancer risk than those without history of either cancer (2, 5).

A detailed understanding of the role of family history and prostate cancer risk is a key component of cancer risk prediction. Few studies have investigated associations between familial prostate or breast cancer and aggressive prostate cancer. One study observed the elevated risks of aggressive and high-grade prostate cancer among men with familial prostate cancer (5). Another found that familial breast cancer increased the fatal disease by 16% (7). Given prostate cancer's biological heterogeneity (9), such evaluations are important in understanding the prostate cancer etiology, given the increased prevalence of indolent cancer likely resulting from PSA screening and differences in the associations of risk factors with aggressive versus total prostate cancer.

In this study, we leveraged data from a cohort of men followed for 16 years to comprehensively assess the associations between familial prostate or breast cancer and risk of total and lethal prostate cancer. Because women of Ashkenazi Jewish heritage have elevated breast cancer risk due to a high prevalence of *BRCA* mutations, and given the emerging role of *BRCA* in advanced prostate cancer (10), we also investigated interactions between religion, a proxy for Ashkenazi Jewish descent, and family history. Uniquely, this study includes a large number of prostate cancer cases, information on relatives' age at diagnosis, and PSA-screening history, which allowed us to explore whether the underlying associations with family history were due to the diagnostic bias from PSA screening.

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Translational Relevance

Prostate cancer is among the most heritable cancers. However, few studies have adequately investigated its association with familial breast cancer. Our data show that familial breast cancer and familial prostate cancer are strong independent risk factors for total and lethal prostate cancer. Our findings shed light on the shared genetic link between prostate cancer and breast cancer and provide evidence that could be used clinically to better identify potentially at-risk populations of men, improve family counseling of patients, and improve prostate cancer screening practices to reduce overtreatment.

Materials and Methods

Study population

The Health Professionals Follow-up Study is a prospective cohort of 51,529 predominantly white (97%) U.S. men ages 40 to 75 years at enrollment in 1986. Study participants completed a baseline questionnaire on health and lifestyle, biennial follow-up questionnaires, and dietary questionnaires every 4 years.

Participants completing the 1996 questionnaire, which first collected information on family history of breast cancer, form the study population ($N = 42{,}034$). We excluded men with prior cancer diagnoses, except nonmelanoma skin cancer ($n = 5{,}013$), men dying before 1996 ($n = 10$), or whose birthdate ($n = 4$) or diagnosis date ($n = 5$) was unavailable, leaving 37,002 men who were followed prospectively until 2012.

Cancer ascertainment

Primary outcomes were total and lethal prostate cancer, which were identified from biennial follow-up questionnaires and confirmed through medical and pathology records. Data on cancer characteristics were abstracted from the medical and pathology records. Additional clinical follow-up was conducted through biennial prostate cancer patient questionnaires. Death status was obtained from the National Death Index, postal system, and/or next-of-kin. An Endpoints Committee assigned cause of death based on all available data. Cases who were diagnosed with or developed metastases during follow-up, or died from prostate cancer were considered lethal cases.

The Human Subjects Committee at Harvard T.H. Chan School of Public Health (Boston, MA) approved this study. Written informed consent was obtained from each subject.

Exposure ascertainment

Familial prostate and breast cancer were ascertained from the 1996 questionnaire, where participants reported relation (mother, father, sister, one brother, additional brother, neither) and relatives' age at diagnosis (<50, 50–59, 60–69, ≥70 years, unknown). We dichotomized relative's age into <60 and ≥60 years. Because of small numbers, we combined "additional brother" and "one brother" into ≥1 brothers diagnosed. We excluded the non–first-degree relative family history data.

Statistical analysis

Because all-cause mortality increases with age, and prostate cancer is slow-progressing, death from another cause may hinder observation of prostate cancer incidence. Therefore, we employed cause-specific hazards regression, a competing risks method, with no independent assumption (11, 12), that models the hazard of each competing event separately using standard Cox regression for the primary event and censoring all other observations (13, 14).

Fitting separate cause-specific hazard models for each endpoint, we estimated HRs and 95% confidence intervals (CI) for associations between family history and prostate cancer risk, assuming the competing events were independent of family history. For both endpoints, participants accrued follow-up time from the date of their 1996 questionnaire to the date of prostate cancer diagnosis, death from other causes, or were censored at the end of follow-up in January 2012, whichever came first. Death from other causes was classified as a competing event. Lethal disease was similarly modeled, except that the nonlethal cases were classified as separate competing events. Independence of competing events was assessed by modeling the subdistribution hazards, an alternative competing risk method with no independence assumption (13, 14), and comparing overall HRs to cause-specific HRs.

We calculated age-adjusted and multivariable HRs adjusted for age, race (White, Black, Asian, other), body mass index (quartiles), smoking status (never smoker, past smoker quitting >10 years ago, past smoker quitting ≤10 years ago, current smoker), PSA screening (yes/no in prior questionnaire cycle), PSA testing intensity (testing in >50% of time periods), alcohol intake (quartiles), vigorous physical activity (quartiles), total energy intake (quartiles), tomato sauce consumption (quartiles), and red meat consumption (quartiles). All covariates, except race, were updated with each questionnaire.

We modeled family history as no family history of either cancer, familial prostate cancer only, familial breast cancer only, familial breast and prostate cancer. In analyses specifying relation or relative's age at diagnosis as the exposure, we mutually adjusted for familial breast or prostate cancer.

Because men with a family history are more likely to have PSA testing (15), we evaluated the extent to which PSA screening drove the observed associations by conducting a sensitivity analysis among subjects reporting prior PSA testing on the 1996 questionnaire.

To determine whether the associations varied by age, we included an interaction term between family history and a man's age (<60 and ≥60 years). Given the high prevalence of *BRCA* mutations in those of Ashkenazi Jewish descent, we assessed the association between family history and total prostate cancer by religious affiliation, as a proxy for Ashkenazi Jewish ethnicity. We dichotomized religion, reported on the 1998 questionnaire [Catholic, Protestant, Sephardic Jewish, Eastern (e.g., Buddhist or Hindu), Muslim, other Christian, other religion], into Ashkenazi Jewish and other religious affiliation.

Significance of interactions was assessed using Wald tests. Reported *P* values were two-sided with a 0.05 significance level. Analyses were performed in SAS Version 9.3 (SAS Institute Inc.).

Results

During follow-up, 254,626 person-years and 4,208 prostate cancer cases, of which, 344 were lethal, were accrued. Table 1 describes study population characteristics in 1996. The average age at baseline was 63 years. Eleven percent of men had a positive

Table 1. Age-standardized characteristics of the Health Professionals Follow-up Study cohort by prostate and breast cancer family history in 1996[a]

	Prostate cancer family history		Breast cancer family history	
	No ($n = 33,154$)	Yes ($n = 3,848$)	No ($n = 32,962$)	Yes ($n = 4,040$)
Age, mean (SD), years[b]	62.8 (9.2)	63.1 (9.3)	62.8 (9.2)	63.0 (9.3)
Race/ethnicity, %				
Caucasian	96	97	96	97
African-American	1	1	1	0
Asian	2	1	2	1
Other race	1	1	1	1
Smoking status, %				
Never smoker	40	45	40	44
Past smoker, quit >10 years ago	33	31	32	33
Past smoker, quit ≤10 years ago	11	10	11	11
Current smoker	6	6	7	5
Missing smoking status	10	7	10	7
Body mass index, mean (SD), kg/m^2	26.1 (3.6)	26.0 (3.6)	26.09 (3.6)	25.89 (3.4)
Vigorous physical activity, mean (SD), METs	13.9 (25.4)	14.4 (23.9)	14.0 (25.6)	13.6 (22.5)
Total energy intake, mean (SD), kcal/day	1,974 (549)	1,998 (538)	1,976 (548)	1,978 (544)
Alcohol consumption, mean (SD), g/day	10.8 (13.7)	10.9 (13.4)	10.8 (13.7)	10.6 (13.0)
Red meat consumption, mean (SD), servings/day	0.9 (0.6)	0.9 (0.6)	0.9 (0.6)	0.9 (0.6)
Tomato sauce consumption, mean (SD), servings/day	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
Men reporting PSA test in past 2 years, %	57	75	58	71

[a]Values are means (SD) or percentages and are standardized to the age distribution of the study population in 1996.
[b]Value is not age adjusted.

family history of breast cancer; 10% had a positive family history of prostate cancer. Men with a family history of prostate or breast cancer were more likely to have had PSA testing in the prior 2 years than men with no family history. Age and other lifestyle factors did not differ appreciably by family history.

Total prostate cancer

The rate of overall prostate cancer during the 16-year follow-up was 16.5 cases/1,000 person-years. Men who only had a family history of breast cancer had a statistically significant increased risk of total prostate cancer (HR = 1.21; 95% CI, 1.10–1.34) compared with those with no family history (Table 2). The association was independent of PSA screening patterns in multivariable analysis. Relative risks for familial breast cancer were similar regardless of whether a mother or sister was diagnosed. Intriguingly, the positive association between familial breast cancer and prostate cancer risk was limited to those whose relative was diagnosed at <60 years.

Table 2. Family history and risk of total prostate cancer among 37,002 male health professionals, 1996–2012

Variable	Prostate cancer cases Total ($N = 4,208$)	Age-adjusted HR[a] (95% CI)	Multivariable HR[b] (95% CI)	Multivariable *P*
Overall family history				
None	3,071 (73%)			
Breast cancer only	460 (10.9%)	1.26 (1.14–1.39)	1.21 (1.10–1.34)	<0.001
Prostate cancer only	582 (13.8%)	1.76 (1.60–1.92)	1.68 (1.53–1.83)	<0.001
Breast and prostate cancer	95 (2.3%)	1.68 (1.37–2.07)	1.61 (1.30–1.98)	<0.001
Breast cancer family history				
None	3,653 (86.8%)			
Mother only	334 (8%)	1.21 (1.08–1.35)	1.14 (1.01–1.27)	0.03
Sister only	195 (4.6%)	1.26 (1.09–1.46)	1.20 (1.04–1.39)	0.02
Mother & sister	26 (0.6%)	1.27 (0.86–1.88)	1.22 (0.82–1.80)	0.32
Age of mother or sister at breast cancer diagnosis				
No breast cancer family history	3,653 (86.8%)			
<60 years	282 (6.7%)	1.32 (1.17–1.49)	1.25 (1.11–1.42)	<0.001
≥60 years	215 (5.1%)	1.09 (0.95–1.26)	1.03 (0.89–1.18)	0.70
Age unknown	58 (1.4%)	1.39 (1.07–1.81)	1.32 (1.02–1.72)	0.04
Prostate cancer family history				
None	3,531 (83.9%)			
Father only	514 (12.2%)	1.73 (1.58–1.90)	1.65 (1.50–1.81)	<0.001
Brother only	138 (3.3%)	1.57 (1.32–1.86)	1.50 (1.26–1.78)	<0.001
Father & brother	25 (0.6%)	1.81 (1.21–2.70)	1.76 (1.17–2.63)	0.006
Age of father or brother at prostate cancer diagnosis				
No prostate cancer family history	3,531 (83.9%)			
<60 years	73 (1.7%)	1.89 (1.49–2.39)	1.78 (1.40–2.25)	<0.001
≥60 years	513 (12.2%)	1.66 (1.51–1.82)	1.58 (1.44–1.74)	<0.001
Age unknown	91 (2.2%)	1.79 (1.45–2.21)	1.72 (1.39–2.12)	<0.001

NOTE: Follow-up: 254,626 person-years, 1996–2012.
[a]HR adjusted for age.
[b]Multivariable HR adjusted for: age, race (White, Black, Asian, other), body mass index, smoking status (never smoker, past smoker who quit >10 years ago, past smoker who quit ≤10 years ago, current smoker), PSA screening (yes/no in prior questionnaire cycle), PSA testing intensity (variable indicating subjects who had testing in >50% of time periods), alcohol intake, vigorous physical activity, total energy intake, consumption of tomato sauce, and red meat.

Table 3. Family history and risk of lethal prostate cancer among 37,002 male health professionals, 1996–2012

Variable	Lethal prostate cancer cases Total ($N = 344$)	Age-adjusted HR[a] (95% CI)	Multivariable HR[b] (95% CI)	Multivariable *P*
Overall family history				
None	248 (72.1%)			
Breast cancer only	41 (11.9%)	1.33 (0.93–1.86)	1.34 (0.96–1.89)	0.09
Prostate cancer only	47 (13.7%)	1.68 (1.22–2.31)	1.72 (1.25–2.38)	0.001
Breast and prostate cancer	8 (2.3%)	1.70 (0.83–3.50)	1.84 (0.89–3.80)	0.10
Breast cancer family history				
None	295 (85.8%)			
Mother only	27 (7.8%)	1.40 (0.93–2.09)	1.42 (0.95–2.13)	0.09
Sister only	21 (6.1%)	1.26 (0.80–1.98)	1.25 (0.79–1.97)	0.34
Age of mother or sister at breast cancer diagnosis				
No breast cancer family history	295 (85.8%)			
<60 years	20 (5.8%)	1.14 (0.72–1.82)	1.16 (0.73–1.85)	0.52
≥60 years	21 (6.1%)	1.26 (0.81–1.98)	1.25 (0.80–1.97)	0.33
Age unknown	8 (2.3%)	2.00 (0.97–4.10)	2.01 (0.97–4.17)	0.06
Prostate cancer family history				
None	289 (84%)			
Father only	35 (10.2%)	1.63 (1.14–2.33)	1.68 (1.17–2.42)	0.005
Brother only	16 (4.6%)	1.48 (0.88–2.49)	1.49 (0.88–2.52)	0.14
Father & brother	4 (1.2%)	2.51 (0.91–6.96)	2.49 (0.89–7.01)	0.08
Age of father or brother at prostate cancer diagnosis				
No prostate cancer family history	289 (84%)			
<60 years	4 (1.2%)	1.20 (0.44–3.29)	1.26 (0.46–3.49)	0.65
≥60 years	43 (12.5%)	1.66 (1.20–2.30)	1.70 (1.22–2.36)	0.002
Age unknown	8 (2.3%)	1.73 (0.84–3.54)	1.75 (0.85–3.60)	0.13

NOTE: Follow-up: 254,626 person-years, 1996–2012. Lethal prostate cancer: metastatic, or fatal disease.

[a]HR adjusted for age.

[b]Multivariable HR adjusted for: age, race (White, Black, Asian, other), body mass index, smoking status (never smoker, past smoker who quit >10 years ago, past smoker who quit ≤10 years ago, current smoker), PSA screening (yes/no in prior questionnaire cycle), PSA testing intensity (variable indicating subjects who had testing in >50% of time periods), alcohol intake, vigorous physical activity, total energy intake, consumption of tomato sauce, and red meat.

Familial breast cancer diagnosis at ≥60 years was not associated with prostate cancer.

Men with a family history of prostate cancer had a 68% (95% CI, 1.53–1.83) greater risk of developing total prostate cancer compared with men with history of neither cancer. This association was independent of PSA screening or other potential confounding factors. Relative risks of prostate cancer associated with a family history of prostate cancer were similar regardless of a relative's relation or age at diagnosis.

A history of both prostate and breast cancer was associated with a 61% (95% CI, 1.30–1.98) increased total prostate cancer risk compared with men with neither family history.

Lethal prostate cancer

The incidence rate of lethal prostate cancer during the 16 years of follow-up was 1.4/1,000 person-years. Men with only a family history of breast cancer had a borderline significant 34% (95% CI, 0.96–1.89) increased risk of lethal prostate cancer (Table 3). The relative risk did not differ by a relative's relation or age at diagnosis.

A positive family history of prostate cancer increased risk of lethal disease by 72% (95% CI, 1.25–2.38). Relative risks were comparable for diagnosis in a father or brother, and did not differ by relation.

Men with a family history of both cancers had a nonstatistically significant increased risk of lethal disease (HR = 1.84; 95% CI, 0.89–3.80).

Sensitivity analysis: PSA-screened population

Of the full cohort, 21,886 participants reported prior PSA testing on the 1996 questionnaire. These men were included in a sensitivity analysis to further assess whether PSA screening influenced our results. During 149,186 person-years of follow-up, 2,860 total and 216 lethal cases were diagnosed. The associations between familial breast or prostate cancer and prostate cancer risk were quite similar to the full cohort analysis (Table 4). If anything, the association between a positive family history of both breast and prostate cancer and lethal disease was stronger (HR = 2.19; 95% CI, 0.98–4.89).

Effect modification by age and religion

The associations between family history and prostate cancer risk overall were mostly stronger among men <60 years old at baseline (615 men, 1.7%; $P_{\text{interaction}} = 0.04$; Table 5). In this younger group, men with familial breast cancer had a 62% (95% CI, 1.20–2.18) increased prostate cancer risk. Familial prostate cancer increased a man's own risk by 2.19-fold (95% CI, 1.67–2.88). A positive family history of both cancers was associated with a 2.44-fold (95% CI, 1.39–4.29) prostate cancer risk among subjects age <60 years.

Among Ashkenazi Jewish men (4,818 men, 13%), total prostate cancer risk increased by 67% (95% CI, 1.27–2.21) if men reported familial prostate cancer, and approximately 30% if men reported familial breast cancer (95% CI, 1.00–1.66; Table 6). Associations were similar among men with other religious affiliations (P for interaction = 0.87).

Discussion

In this large prospective study of men with long-term follow-up, we found a positive family history of breast and prostate cancer were each independent predictors of a man's risk of

Table 4. Sensitivity analysis: Total or lethal prostate cancer risk among 21,886 participants reporting PSA testing in 1996

	Total prostate cancer risk			Lethal prostate cancer risk		
Variable	**Cases ($N = 2,860$)**	**Multivariable HR[a] (95% CI)**	**Multivariable *P***	**Cases ($N = 216$)**	**Multivariable HR[a] (95% CI)**	**Multivariable *P***
Overall family history						
None	1,959			146		
Breast cancer only	361	1.25 (1.11–1.40)	<0.001	32	1.36 (0.91–2.02)	0.13
Prostate cancer only	464	1.68 (1.51–1.86)	<0.001	31	1.57 (1.05–2.35)	0.03
Breast and prostate cancer	76	1.56 (1.23–1.97)	<0.001	7	2.19 (0.98–4.89)	0.06
Breast cancer family history						
None	2,423			177		
Mother only	253	1.13 (0.99–1.29)	0.08	22	1.60 (1.00–2.54)	0.05
Sister only	163	1.27 (1.08–1.49)	0.004	16	1.23 (0.71–2.08)	0.47
Mother & sister	21	1.19 (0.77–1.85)	0.43	1	N/A	N/A
Age of mother or sister at breast cancer diagnosis						
No breast cancer family history	2,423			177		
<60 years	224	1.28 (1.11–1.47)	<0.001	16	1.21 (0.71–2.06)	0.48
≥60 years	163	1.02 (0.86–1.19)	0.86	16	1.28 (0.75–2.17)	0.37
Age unknown	50	1.43 (1.08–1.92)	0.01	7	2.41 (1.07–5.41)	0.03
Prostate cancer family history						
None	2,320			178		
Father only	393	1.60 (1.43–1.78)	<0.001	24	1.60 (1.02–2.49)	0.04
Brother only	124	1.58 (1.31–1.91)	<0.001	11	1.39 (0.74–2.62)	0.31
Father & brother	23	1.95 (1.27–2.98)	0.002	3	2.70 (0.81–9.02)	0.11
Age of father or brother at prostate cancer diagnosis						
No prostate cancer family history	2,320			178		
<60 years	61	1.79 (1.38–2.32)	<0.001	2	0.86 (0.20–3.67)	0.84
≥60 years	411	1.58 (1.42–1.76)	<0.001	31	1.71 (1.16–2.54)	0.007
Age unknown	68	1.58 (1.23–2.03)	<0.001	5	1.32 (0.53–3.34)	0.55

NOTE: Follow-up: 149,186 person-years, 1996–2012. Lethal prostate cancer: metastatic, or fatal disease.

[a]Multivariable HR adjusted for: age, race (White, Black, Asian, other), body mass index, smoking status (never smoker, past smoker who quit >10 years ago, past smoker who quit ≤10 years ago, current smoker), PSA screening (yes/no in prior questionnaire cycle), PSA testing intensity (variable indicating subjects who had testing in >50% of time periods), alcohol intake, vigorous physical activity, total energy intake, consumption of tomato sauce, and red meat.

developing overall prostate cancer. Moreover, family history of these cancers was positively associated with a man's risk of lethal disease. Observed associations were not explained by differences in the PSA screening patterns or other covariates. Taken together, these data provide compelling evidence that a man's prostate cancer risk assessment should integrate the information on both familial breast and prostate cancer.

Our results found that familial breast cancer on its own was associated with a 21% higher risk of total prostate cancer. Although previous studies have reported similar estimates (5, 8), others have observed relative risks as high as 1.7 (2). Our finding is comparable with reported associations between familial prostate cancer and breast cancer risk in women in both the Iowa Health Study (16) and Women's Health Initiative (17). In line with the previous studies (5, 6, 18), we found a history of familial prostate cancer increased a man's total prostate cancer risk by 68%. Some studies have reported estimates greater than 2-fold (2–4, 8, 19), although these did not take into account the PSA screening patterns that may have led to a higher estimate of prior findings. Family history of both cancers was as important as familial prostate cancer alone, increasing risk by 60%. This is consistent with results in some studies (5, 17), although others reported greater estimates (2, 6).

One of the novel components of our study was our ability to study family history of both breast and prostate cancer in relation to lethal prostate cancer given the more than 15 years of follow-up. Familial prostate cancer was statistically significantly associated with the increased lethal prostate cancer risk, whereas familial breast cancer was borderline associated. Indeed, in the subcohort of men who were PSA-screened, the relative risk of lethal prostate cancer was 2-fold higher in men with both a positive breast and prostate cancer family history compared with those with neither. However, the number of cases was small ($n = 7$).

In line with prior studies (3, 5, 6), we found a man's prostate cancer risk either increased or remained constant as the number of diagnosed relatives increased. The magnitude of risk associated with an affected brother versus father was not notably different in our study, given the closeness of the point estimates and the overlapping confidence intervals. Others have found a higher risk when diagnoses occurred in a brother versus father (2, 5, 19). Although the underlying reason for this is unclear, our study accounted for potential differences due to screening practices. Furthermore, participants with an affected mother versus sister also had similar risks of total prostate cancer. Previous studies observed higher risk among men with breast cancer in a mother (2, 7), sister (6, 8, 20), or equivalent risk estimates (5). Higher risk among siblings versus parents may be explained by shared environmental factors, which we were able to assess (6).

In general, total prostate cancer risk was greater when the relative was diagnosed at age <60 versus ≥60 years, as observed by Grill and colleagues (21; $P_{\text{interaction}} = 0.04$). Similar differences by age group have been observed for familial prostate cancer (2, 8), but not breast cancer (2). These findings are in line with the hypothesis that earlier onset cancers are more likely to have an inherited cause (22).

Ashkenazi Jewish men and men of other faiths with familial prostate or breast cancer had similar elevated prostate cancer risk, suggesting no modification by religion. Increased prostate cancer risk was reported in male Ashkenazi Jewish *BRCA*

Table 5. Association between family history and total prostate cancer risk stratified by a man's age

	Age < 60		Age ≥ 60	
Variable	**Cases unexposed/exposed**	**Multivariable HR[a] (95% CI)**	**Cases unexposed/exposed**	**Multivariable HR[a] (95% CI)**
Overall family history[b]				
None				
Breast cancer only	270/54	1.62 (1.20–2.18)	2,801/406	1.17 (1.06–1.30)
Prostate cancer only	270/66	2.19 (1.67–2.88)	2,801/516	1.63 (1.48–1.79)
Breast and prostate cancer	270/13	2.44 (1.39–4.29)	2,801/82	1.52 (1.22–1.91)
Breast cancer family history[c]				
None				
Mother only	336/54	1.55 (1.15–2.08)	3,317/280	1.08 (0.96–1.23)
Sister only	336/11	1.36 (0.74–2.51)	3,317/184	1.19 (1.02–1.38)
Mother & sister	336/2	1.52 (0.37–6.17)	3,317/24	1.20 (0.80–1.80)
Age of mother or sister at breast cancer diagnosis[d]				
No breast cancer family history				
<60 years	336/29	1.39 (0.94–2.05)	3,317/253	1.24 (1.09–1.41)
≥60 years	336/32	1.65 (1.14–2.40)	3,317/183	0.97 (0.83–1.12)
Age unknown	336/6	1.44 (0.63–3.31)	3,317/52	1.31 (0.99–1.73)
Prostate cancer family history[e]				
None				
Father only	324/75	2.09 (1.62–2.70)	3,207/439	1.59 (1.44–1.76)
Brother only	324/4	2.32 (0.84–6.35)	3,207/134	1.48 (1.24–1.77)
Father & brother	324/0	N/A	3,207/25	1.80 (1.20–2.69)
Age of father or brother at prostate cancer diagnosis[f]				
No prostate cancer family history				
<60 years	324/10	3.36 (1.77–6.37)	3,207/63	1.65 (1.28–2.13)
≥60 years	324/58	1.91 (1.44–2.54)	3,207/455	1.55 (1.40–1.71)
Age unknown	324/11	2.34 (1.27–4.30)	3,207/80	1.66 (1.32–2.08)

NOTE: Follow-up: 254,626 person-years, 1996–2012.

[a]Multivariable HR adjusted for: age, race (White, Black, Asian, other), body mass index, smoking status (never smoker, past smoker who quit >10 years ago, past smoker who quit ≤10 years ago, current smoker), PSA screening (yes/no in prior questionnaire cycle), PSA testing intensity (variable indicating subjects who had testing in >50% of time periods), alcohol intake, vigorous physical activity, total energy intake, consumption of tomato sauce, and red meat.

[b]Overall family history–age interaction: $P = 0.04$.

[c]Breast cancer family history–age interaction: $P = 0.18$.

[d]Age of relative at breast cancer diagnosis–age interaction: $P = 0.07$.

[e]Prostate cancer family history–age interaction: $P = 0.23$.

[f]Age of relative at prostate cancer diagnosis–age interaction: $P = 0.09$.

mutation carriers (23, 24). However, this does not explain our findings.

Findings from our study and others on family history put into context genome-wide association studies in prostate cancer, which has implicated several potential susceptibility genes (25) and identified more than 180 independent SNPs associated with prostate cancer risk (26, 27). Intriguingly, these SNPs explain only 33% of familial disease risk (26). Given the link between *BRCA* and breast cancer and evidence of increased prostate cancer risk among male *BRCA* carriers, inherited *BRCA* mutations may provide one biological mechanism for familial clustering of prostate and breast cancer (5, 28). The important role of inherited mutations in *BRCA* and metastatic prostate cancer has been demonstrated more recently.

Strengths of our study include its prospective design, long-term follow-up, and large number of cases including lethal disease. Our ability to study lethal prostate cancer is a unique and powerful attribute of our cohort given the marked biologic heterogeneity of the disease. We had detailed information on relatives' age at cancer diagnosis and relation. Our updated data on PSA-screening patterns allowed us to disentangle the contribution of screening to the positive association with family history. No study has

Table 6. Association between family history and prostate cancer risk and stratified by religious affiliation

	Ashkenazi Jewish religion		Other religion	
Variable	**Cases unexposed/exposed**	**Multivariable HR[a] (95% CI)**	**Cases unexposed/exposed**	**Multivariable HR[a] (95% CI)**
Overall family history[b]				
None				
Breast cancer only	370/76	1.29 (1.00–1.66)	2,701/384	1.20 (1.08–1.34)
Prostate cancer only	370/60	1.67 (1.27–2.21)	2,701/522	1.67 (1.52–1.84)
Breast and prostate cancer	370/9	1.30 (0.66–2.54)	2,701/86	1.65 (1.32–2.05)

NOTE: Follow-up: 254,626 person-years, 1996–2012. Total prostate cancer: $n = 4,208$.

[a]Multivariable HR adjusted for: age, race (White, Black, Asian, other), body mass index, smoking status (never smoker, past smoker who quit >10 years ago, past smoker who quit ≤10 years ago, current smoker), PSA screening (yes/no in prior questionnaire cycle), PSA testing intensity (variable indicating subjects who had testing in >50% of time periods), alcohol intake, vigorous physical activity, total energy intake, consumption of tomato sauce, red meat, religion, and religion–family history interaction.

[b]Overall family history–religion interaction: $P = 0.87$.

previously explored family history associations by Ashkenazi Jewish heritage.

Both family histories were only reported in 1996, precluding us from updating exposure status. Exposure misclassification is possible because family history was self-reported. However, given our study population and prospective design, it is likely modest and nondifferential, which would have diluted associations. Although we had more than 4,000 prostate cancer cases and 344 lethal cases, we had limited statistical power in some of our subgroup analyses. We could not examine the impact of biopsy detection bias (29) on our results, although this was somewhat mitigated in our sensitivity analysis. Moreover, this potential bias cannot explain our lethal prostate cancer findings because men with a family history would be more likely to have a biopsy, and thus, more likely to be diagnosed with early-stage disease. Finally, our results may only be generalizable to populations of white men, and thus, should be replicated in other more diverse populations.

In summary, we found that a man's family history of breast and prostate cancer independently was associated with total and lethal prostate cancer risk. Our findings shed light on the shared genetic link between prostate and breast cancer and provide data to better identify at-risk populations of men. In addition, these results can be translated clinically to better guide effective genetic counseling and screening practices.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L. Barber, S.C. Markt, E. Giovannucci, G. Parmigiani, L.A. Mucci

Development of methodology: L. Barber, L.A. Mucci

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Giovannucci, L.A. Mucci

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Barber, T. Gerke, S.C. Markt, S.F. Peisch, T. Ahearn, L.A. Mucci

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