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Family History of Prostate and Breast Cancer and the Risk of Prostate Cancer in the PSA era

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Abstract

Background—A family history of prostate cancer (PCa) or breast cancer (BCa) has been associated with the risk of PCa, but the risks were inconsistent in terms of the affected family members, and data in the PSA era are limited.

Methods—This study included a subcohort of the Health Professionals Follow-Up Study composed of a highly PSA screened population from 1986 to 2004 with 3,695 PCa cases identified. Questionnaires and a food frequency questionnaire were administered every other and every four years, respectively. Family history of PCa and BCa was ascertained in 1990, 1992, and 1996. All statistics were two-sided.

Results—A family history of PCa in both a father and brother(s) was associated with a 2.3-fold increased risk of PCa [95% confidence interval (CI)=1.76–3.12]. Men with a father or brother(s) with a PCa diagnosis at age<60 and ≥60 had 2.16- and 1.95-fold increased risk of PCa, respectively. A family history of PCa was related to early-onset PCa (<65 years: RR=2.25, 95% CI=1.95–2.60) and weakly to late-onset PCa (≥65 years: RR=1.67, 95% CI=1.52–1.85). History of BCa in a mother or a sister was associated with a 1.22-fold increased risk of PCa (95% CI=1.08–1.38).

Conclusion—A family history of PCa or BCa significantly increases PCa risk. These associations are evident in a population with widespread PSA screening.

Keywords

Family history; prostate cancer; breast cancer; PSA era

INTRODUCTION

The risk of prostate cancer (PCa) incidence or progression has been related to several factors, e.g., obesity (1–3), diet (4,5), family history of PCa and/or breast cancer (BCa) (2,6–10), and steroid hormones (4). A large twin study reported that 42% of PCa cases up to age

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70 years can be explained by heritable factors, supporting a role for family history in PCa (11).

Most studies reported an association of PCa family history with higher risk of PCa (7,9,12,13), but one study found no such association (10). A meta-analysis, which included 14 case-control studies and 9 cohort studies, indicated that prostate cancer family history of first-degree relatives was associated with a higher risk of prostate cancer [relative risk (RR)=2.22]; the risk was slightly lower among those who had any affected family member (RR=1.93) or those who had affected second-degree relatives (RR=1.88) (14). In addition, men with an affected brother (RR=2.87) showed higher risk than those with an affected father (RR=2.12) (14). Family history of BCa also may affect the risk of PCa. A study of the Utah Mormon genealogy found that PCa coaggregated with cancer at several other sites (e.g., breast, brain, and central nervous system) (7). In addition, a family history of BCa or ovarian cancer in female family members increased the risk of PCa in male family members [odds ratio (OR)=1.7, 95% confidence interval (CI)=1.0–3.0](9). Early-onset PCa among family members was linked to increased risk of PCa in some studies (7,12,13,15) but not others (8,16). The effect of family history of BCa in a mother or sister(s) on age at BCa onset has not been fully explored. Only one study (9) explored the risk of PCa considering the combined effect of family history of both PCa and BCa and found a markedly elevated risk of PCa (OR=5.8, 95% CI=2.4–14), but the sample size of this study was relatively small (n=1,601). Factors in addition to family history of PCa or BCa and the age at onset of PCa in a relative that are suspected of modifying the association between family history and PCa risk include the number of relative(s) with PCa (12,13,17), ethnicity (18,19), and religion (e.g., Mormonism) (20,21).

In this report, we examined the association between family history of PCa and BCa and the risk of PCa, and the effect modification by age, stage, and grade of PCa. Prostate-specific antigen (PSA) screening identifies a pool of generally less aggressive PCa (15), which may not necessarily have the same risk factors that have been identified in non-PSA settings. Since screening for PSA has come into common use, association studies have often found a weak or even null relationship between either genetic susceptibility or environmental exposures and PCa risk. Previous studies evaluated how family history of PCa affects the behavior of PSA screening and found that men with a positive family history may be more likely to undergo PSA screening than those without a family history (10,22). However, the effect of PSA screening on the association between family history of PCa or BCa and the risk of PCa has yet to be investigated. We thus performed additional analyses that included only men who underwent PSA screening to assess this association, which will provide clinicians useful information for evaluating the risk of PCa in the context of widespread PSA screening.

MATERIALS AND METHODS

The Study Population

In 1986, 51,529 U.S. male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians aged 40 to 75 years completed and returned a mailed questionnaire to initiate the Health Professionals Follow-Up Study (HPFS) cohort. This cohort is predominantly white (>91%). Through the 1986 baseline questionnaire, we elicited information on age, marital status, height, weight, ancestry, medications, smoking history, disease history, physical activity, and diet. Every two years, follow-up questionnaires were mailed to surviving cohort members requesting information on new medical diagnoses and lifestyle factors and updating data on family disease history. Deaths were reported by family members or by the postal system in response to the mailed questionnaires or were ascertained through the National Death Index (23). Through these various methods, we have

ascertained over 98% of the deaths and 96% of the incident PCa. The conduct of this cohort study and the analyses were approved by the Human Subjects Committee of the Harvard School of Public Health. Completion of the self-administered questionnaire was considered to imply informed consent.

Identification of Cases of Prostate Cancer

On the follow-up questionnaires, the study participants (or next-of-kin for decedents) reported any new diagnoses of PCa. For newly reported cases, we then asked for permission to obtain hospital records and pathology reports for further details on diagnosis and treatment. From 1990 to the end of this study period (January 31, 2004), including 277,503 person-years for 43,494 eligible participants, we documented 3,695 cases of prostate adenocarcinoma after excluding cases of stage T1a cancer (incidental histologic cancer found in ≤5% of resected tissues). Stage T1a cancer, accounting for only 2% of the total diagnosed prostate cancer cases, is relatively innocuous and especially prone to detection bias. We documented approximately 90% of the 3,695 cases using medical records and pathology reports; for most of the remaining 10% of cases, participants provided information regarding the diagnosis and subsequent treatment. From the pathology report, we abstracted information on Gleason histologic grade, which was available for 2,718 cases (74%).

Ascertainment of Family History and Other Exposure Variables

Family histories of PCa, including age at diagnosis, were obtained from follow-up questionnaires. Data related to family history of PCa were available in 1990, 1992, and 1996. A positive family history should not change over time, but a negative family history in 1990 could change into a positive family history in 1992 or 1996. Therefore, we checked the consistency of data across these time periods and used the updated information in 1996 for analyses. The information of family history of BCa was available only in 1996, and completely coded data were available until 2004. Therefore, the 1990–2004 and 1996–2004 data were used for statistical analyses related to family history of PCa and BCa, respectively. For information regarding relative's age at diagnosis of PCa or BCa, we asked whether a relative was diagnosed at age <50, 50–59, 60–69, ≥70, no family history, and unknown. Because few relatives were diagnosed under age 60, we combined age groups and used age 60 as a cut point for this variable. To obtain prospective diet data, we used diet information in 1990 for analyses, because this is the earliest time that family disease history was available.

Statistical Analysis

Because results were similar before and after exclusion of non-whites, we included all ethnic groups in this population. Each man accrued follow-up time beginning the month he returned the baseline questionnaire. For men diagnosed with PCa (stage T1b and above), follow-up ended the month of diagnosis, the month of death from other causes, or January 31, 2004, whichever came first. We calculated incidence rates of PCa by dividing the number of incident cases by the number of person-years. The endpoints were total, advanced stage (T3c or T4 or N1 or M1), non-advanced (T1b–T3b), high-grade (Gleason sum≥7), low-grade (Gleason sum<7), and fatal PCa. Aggressive PCa represented cases with advanced PCa and death due to PCa (24).

We computed RR, defined as the incidence rate of disease in one category (e.g., positive family history) divided by the incidence rate in a specified reference category (e.g., negative family history). We used the Mantel-Haenszel summary estimator to adjust for age (across five-year categories) and Cox proportional hazards modeling to control for multiple variables simultaneously and to compute RR and 95% CI. Age (one-month intervals) and

follow-up period (two-year intervals) were controlled for as stratification variables in the Cox model. The following covariates were included in the models because they were previously associated with the risk of PCa: family history of BCa or PCa; ethnicity; body mass index (BMI); total calorie intake; vigorous physical activity; cigarette smoking; and consumption of tomato sauce, calcium, alpha-linolenic acid, fish, and red meat. Modifiable variables were updated periodically. All reported p-values were two-sided. All analyses were performed using SAS 9 (SAS Institute Inc, Cary, NC).

RESULTS

The average age, number of brothers and sisters, height, BMI, total energy intake, dietary intake, prior vasectomy, marital status, average alcohol and tobacco use, ethnicity, vigorous physical activity (Table 1), and religion (data not shown) were similar by family history status. Men with a family history of cancer were more likely to have been screened for PSA (family history of PCa: 92%=4,838/5,236, family history of BCa: 95%=3,932/4,139) than those without a family history (84%=31,139/36,908 and 92%=30,784/33,494, respectively); note: the higher percentage of men screened for PSA than for BCa is due to the fact that this figure is based on the subpopulation who responded to this question in 1996. Family history data on PCa and BCa were available for 97% (42,144 of 43,494) and 87% (37,633 of 43,494) of participants, respectively; 12% and 11% of them had a positive PCa and BCa family history, respectively.

The distribution of clinical stage and Gleason score did not vary by family history of PCa or BCa (Table 2). Slightly more men with than without a positive PCa family history had early-onset PCa (<65 years) (33%=251/759 vs. 28%=804/2,907). This difference was not shown for men with vs. without a BCa family history (28%=80/288 vs. 29%=546/1,875).

Table 3 details the association between disease family history and the risk of PCa and BCa. After the exclusion of healthy men without a PSA screening, the RRs decreased slightly, but the results were not appreciably different. PCa in a father and brother(s), a father or brother(s), a father only, or brother(s) only was significantly associated with elevated risks of PCa (RR 1.78 to 2.34). The increased risk was similar for brother(s) (RR=1.84) or a father (RR=1.78) with the history of PCa. Men with a father or brother(s) diagnosed with PCa before age 60 had a significantly higher risk of PCa (RR=2.16) than men without a family history. The risk of PCa was similar for family members diagnosed with PCa at an older age (≥60, RR=1.95). For men with a family history of PCa, the risk of early-onset PCa was significantly elevated (RR=2.25), but this association was weaker for late-onset PCa (RR=1.67). Family history of PCa significantly increased the risk of both aggressive PCa (RR=1.76) and non-aggressive PCa (RR=1.84). Men with either high- or low-grade PCa and positive family history of PCa had a significantly higher risk of PCa than men without a family history of PCa (RRs=1.74 and 1.87, respectively, Table 3).

For men whose mother had BCa, the risk of PCa was significantly higher (RR=1.24) than for men without a BCa family history (Table 3). The younger age of a female family member at diagnosis of BCa (<60 years old) was associated with higher PCa risk (RR=1.35). The results stratified by age group remained significant when we restricted them to the mother only (RR=1.38). A positive family history of BCa was similarly associated with early-onset (RR=1.20) and late-onset (RR=1.23) PCa. A family history of BCa was associated with an elevated risk of non-aggressive (RR=1.24), but not with aggressive, PCa risk, though our power to examine aggressive cases here was low (n=10 cases in men with a positive family history). Low-grade PCa and high-grade PCa were similarly associated with family history of BCa (RR=1.21 and 1.24, respectively). Men with a family history of PCa only had the highest risk (RR=1.71), followed by men with a family history of both PCa and

BCa (RR=1.51), and the lowest increased risk was among men with a family history of BCa only (RR=1.30), all compared with men without a family history of either cancer.

DISCUSSION

This study found increased risks of PCa for men with a family history of PCa (RRs=1.78–2.34), which was consistent with the risk estimated in previous meta-analyses (2–2.5) (14,25). The risk of PCa has been found to increase with the number of relatives affected by PCa (12,13,17), which was consistent with our findings. A family history of PCa and younger onset age among relatives were significantly associated with the risk of PCa, which was consistent with previous studies (7,12,13). Some studies found that PCa risk was higher among men with an affected brother than among those with an affected father (9,12,16,26–30), but this was not evident in the present study [brother(s): 1.84 vs. father: 1.78] or in others (13,17,31–33). Regarding BCa family history and PCa risk, our finding suggests that X-linked or recessive mode of inheritance may not be the major mode of conferring family history of PCa risk (33). The combination of PCa and BCa family history (RR=1.51) did not increased the risk of PCa further than only one of the family histories (1.71 and 1.30 for family history of PCa and BCa, respectively), and the magnitude of PCa risk was not as high as in a previous study (RR=5.8) (9). Although PSA screening was related to identification of occult prostate cancer (15), exclusion of healthy men without a PSA test only slightly weakened the association. In addition, disease aggressiveness and tumor grade were not related to the risk of PCa when we compared men with PCa family history with those without. However, a positive BCa family history was significantly associated with an elevated the risk of non-aggressive or low-grade PCa.

We also observed that having a female family member(s) (especially a mother) with BCa was related to increased PCa risk (RR=1.24), which was consistent with one of the previous studies (RR=1.34) (13) but not another study (28). However, mortality, instead of incidence, was the outcome of the study with the significant finding (13), and therefore the endpoints are not directly comparable. One study found the risk of PCa significantly elevated (RR=2.7) when a mother had a positive family history of BCa and/or ovarian cancer (9). However, in that study (9), we are unable to dissect whether the risk of PCa resulted from the family history of BCa or ovarian cancer. The biological mechanism relating the mother's BCa family history to PCa risk has also not been investigated, and a role of *BRCA1* and *BRCA2* was speculative (34,35). However, results from the whole-genome association study of Cancer Genetic Markers of Susceptibility, National Cancer Institute (https://caintegrator.nci.nih.gov/cgems/aboutSetup.do) did not support the association between SNPs in the *BRCA2* gene and the risk of PCa. Another possibility was that the inclusion of sib sets without any girls resulted in a null association between a sister's history of BCa and the risk of PCa. While statistically significant, the association with BCa was much weaker than that of family history of PCa.

Familial PCa tends to be diagnosed at a younger age than sporadic PCa (36). This study lends credence to that finding, because we found that men with a family history of PCa had a higher risk of early-onset PCa than those without a family history of PCa. As in previous studies (12,13), we found that the risk of PCa was higher in men whose relatives were diagnosed with PCa when they were <60 years old (Table 3). We also observed that, a family history of PCa was equally related to aggressive and non-aggressive PCa (Table 3), which conflicted with previous findings (13,37,38). Similarly, men with a family history of PCa had a significantly higher risk of PCa than men without a family history of the disease, regardless of tumor grade. Therefore, we did not confirm the findings from previous studies (2,39) that men with a family history of PCa were less likely to have high-grade disease. However, the family history of BCa was only significantly associated with the risk of non-

aggressive or low-grade PCa, although our power for aggressive PCa was limited; this association has not been reported previously.

In the United States, PSA screening started in the early 1990s and has led to more frequent identification of PCa in its early stages. PCa family history (15,22), higher educational level (40), and older age (41) are associated with frequency of undergoing PSA screening and thus could bias the study results. No study has explored the effect of PSA screening on the association between family history and the risk of PCa. In our study, a higher proportion of men with a PCa or BCa family history than men without a family history had a PSA screening [PCa family history (yes vs. no): 92% vs. 84%; BCa family history (yes vs. no): 95% vs. 92%, Table 1]. About 8% of men with a positive PCa family history had elevated PSA levels, which was consistent with a previous study in asymptomatic men from families at high risk for PCa in a Finnish population (10%) (15). When we conducted an analysis that excluded healthy men without PSA screening, our findings did not change appreciably. In addition, family history status did not affect the propensity for diagnostic tests. For example, on the 1994 questionnaire, we had asked men if they ever had an elevated PSA test and a prostate biopsy; among men with an elevated PSA level, the likelihood of having had a biopsy did not vary by family history status: 70% vs. 72% for men with a family history of PCa vs. without, and 73% vs. 71% for men with a family history of BCa vs. without. Thus, our findings suggest that detection bias did not appreciably affect our results.

A strength of this study is that it is one of the largest to date (3,695 PCa cases) and is of prospective design, which avoids recall bias and allows the assessment of PCa risk by age at onset in both the family members and the “proband.” Family history data were available in 87–97% of participants and were updated over time for family history of PCa. Although family history of PCa was self-reported, previous studies found such data to be highly accurate (86.2% in a US population (42) and 92% in a Swedish population) (43). Our participants are health professionals and likely report family history accurately. PSA screening has changed the epidemiologic patterns of diagnosed PCa (e.g., average age, incidence, proportion that are aggressive), but most studies were not conducted in the PSA era. Disease aggressiveness is available with a relatively large number of events in the aggressive category to obtain stable risk estimates. In addition, fewer studies have been able to assess the association with a family history of BCa, so this study adds additional important data to the literature.

However, our study had some limitations. We did not have complete data on age at diagnosis of PCa or BCa among relatives. PCa and BCa are diseases with a relatively late onset, and some siblings of the study participants may have been too young to develop the disease during follow-up. In addition, the incidence of PCa is higher among African Americans than among whites (19), and African Americans reported a family history of PCa more often than did whites (18) and were younger at PCa diagnosis (18). However, this study had limited power to test our hypothesis for groups other than whites. Because this study was composed of a highly PSA screened population (cumulative percentage between 1994 and 2004>84%), the results should be generalized to similar populations.

Individuals from the same family share part of their genetic makeup and some of their environmental exposures (e.g., diet, carcinogens, socioeconomic status, and lifestyle) during part of their lives. Except for a common variant found in 3 case-control series of European ancestry (44), no other major susceptibility genes for PCa have been consistently found across populations. We found that a positive PCa family history was related to early-onset PCa, with associations similar for a paternal or fraternal history. In addition, BCa family history in a mother or a sister was significantly but modestly associated with PCa. There was not an appreciable difference according to stage or grade of the disease according to PCa

family history, but BCa family history was associated with increased risk of non-aggressive or low-grade PCa. Exclusion of healthy men without PSA screening did not change our findings, and family history of PCa and BCa was unlikely to alter the likelihood of a man with an elevated PSA undergoing biopsy. These findings may provide important information for primary care providers and urologists. Further study is warranted to identify potential mechanisms and modifiers of these associations.

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Table 1

Characteristics of the study participants in HPFS at baseline 1990

	Family history of prostate cancer		Family history of breast cancer	
	Negative (n=36,908)	**Positive (n=5,236)**	**Negative (n=33,494)**	**Positive (n=4,139)**
Average age (years)	56.5	56.7	55.9	56.4
Average number of brothers in 1996	1.8	1.9	1.8	1.9
Average number of sisters in 1996	1.8	1.9	1.8	1.8
Average height (in)	70.2	70.2	70.2	70.2
Average BMI* (kg/m^2)	24.9	25.0	24.9	24.9
Average total energy (kcal/day)	1,917	1,940	1,923	1,918
Average dietary intake				
Alpha-linolenic fatty acid (g/d)	1.04	1.05	1.04	1.04
Calcium (mg/d)	908	916	909	907
Red meat (servings/d)	.45	.52	.46	.50
Tomato sauce (servings/week)	.94	.90	.94	.93
Lycopene (μg/d)	7,274	7,061	7,347	7,208
Prior vasectomy (%)	(11)	(11)	(11)	(10)
Marital status in 1992 (%)				
Married	(77)	(84)	(80)	(84)
Divorced/separated	(5)	(5)	(5)	(5)
Widowed	(2)	(2)	(2)	(2)
Never married	(2)	(1)	(2)	(2)
Average alcohol use (g/day)	10.0	10.3	10.1	9.9
Tobacco use (%)				
Never	(45)	(48)	(46)	(47)
Former	(43)	(41)	(42)	(42)
Current 0 –15 (cigarettes/day)	(2)	(3)	(2)	(2)
Current ≥15 (cigarettes/day)	(4)	(4)	(4)	(4)
PSA screening prior to 1994 (%)				
Not elevated	(82)	(81)	(82)	(82)
Unknown	(9)	(11)	(9)	(8)
Elevated	(9)	(8)	(9)	(10)
PSA screening, n (%)				
1994	18,495 (50)	3,314 (63)	18,468 (55)	2,603 (63)
1996	19,113 (52)	3,508 (67)	19,635 (57)	2,980 (72)
1998	20,874 (57)	3,546 (68)	21,352 (64)	2,932 (71)
2000	21,382 (58)	3,548 (68)	24,531 (73)	3,140 (76)
2002	19,857 (54)	3,234 (62)	21,667 (65)	2,977 (72)
2004	21,066 (57)	3,436 (66)	21,320 (64)	2,860 (69)
Cumulative % to 2004	31,139 (84)	4,838 (92)	30,784 (92)	3,932 (95)
Race/ethnicity, n (%)				

	Family history of prostate cancer		Family history of breast cancer	
	Negative (n=36,908)	**Positive (n=5,236)**	**Negative (n=33,494)**	**Positive (n=4,139)**
White	35,497 (96)	5,075 (97)	32,277 (96)	4,035 (97)
African American	344 (1)	60 (1)	304 (1)	21 (1)
Asian	663 (2)	55 (1)	584 (2)	50 (1)
Other origin	878 (2)	109 (2)	753 (2)	88 (2)
Vigorous physical activity (METs)	8.8	9.6	9.2	9.9

* BMI denotes body mass index.

Most variables are from 1990 data set except average number of brothers/sisters, marital status, and PSA screening prior to 1994.

METs denotes the metabolic equivalent of sitting at rest for 1 hour.

Table 2

Clinical characteristics of prostate cancer cases and family history in the HPFS

	Family history of prostate cancer		Family history of breast cancer	
	Negative (n=2,907)	**Positive (n=759)**	**Negative (n=1,875)**	**Positive (n=288)**
Clinical stage, n (%)				
T1b–T3a	1,748 (85)	470 (84)	1,242 (94)	194 (95)
T3b or T4 or N1 or M1 or death due to PCa	307 (15)	78 (16)	84 (6)	10 (5)
Gleason score, n (%)				
2–4	160 (7)	44 (8)	53 (4)	5 (3)
5–7	1,769 (82)	461 (82)	1,252 (86)	201 (87)
≥8	228 (11)	56 (10)	144 (10)	24 (10)
Patient's age at PCa diagnosis, n (%)				
<65	804 (28)	251 (33)	546 (29)	80 (28)
≥65	2,103 (72)	508 (67)	1,329 (71)	208 (72)

Exclude PCa cases with stage T1a.

The information on PCa family history was collected in 1990, 1992, and 1996; we used the follow-up period 1990 to 2004. The information on BCa family history was collected in 1996; we used the follow-up period 1996 to 2004.

Table 3

Association between family history and the risk of prostate cancer

		Relative Risk (95% CI)	
	Cases (n)	**Include healthy men without PSA test**	**Exclude healthy men without PSA test**
PCa family history			
No family history	2,907	1.00	1.00
Father or brother(s)	759	1.83 (1.69–1.98)	1.72 (1.59–1.86)
Father and brother(s)	48	2.34 (1.76–3.12)	2.16 (1.62–2.88)
Father	511	1.78 (1.62–1.95)	1.69 (1.54–1.86)
Brother(s)	197	1.84 (1.59–2.12)	1.68 (1.45–1.95)
Father or brother(s)' age at diagnosis of PCa			
No family history	2,907	1.00	1.00
<60	71	2.16 (1.70–2.73)	2.10 (1.82–2.42)
≥60	492	1.95 (1.77–2.15)	1.78 (1.62–1.96)
Case's age at diagnosis of PCa <65 years PCa family history			
No	804	1.00	1.00
Yes	251	2.25 (1.95–2.60)	2.13 (1.85–2.45)
Case's age at diagnosis of PCa ≥65 years PCa family history			
No	2,103	1.00	1.00
Yes	508	1.67(1.52–1.85)	1.57 (1.43–1.73)
Aggressive PCa PCa family history			
No	307	1.00	1.00
Yes	78	1.76 (1.37–2.26)	1.61 (1.25–2.06)
Non-aggressive PCa PCa family history			
No	2,600	1.00	1.00
Yes	681	1.84 (1.69–2.00)	1.73 (1.59–1.89)
High-grade PCa PCa family history			
No	893	1.00	1.00
Yes	223	1.74 (1.50–2.02)	1.66 (1.43–1.92)
Low-grade PCa PCa family history			
No	2014	1.00	1.00
Yes	536	1.87 (1.70–2.06)	1.75 (1.59–1.93)
BCa family history			
No family history	1,875	1.00	1.00
Mother or sister(s)	288	1.22 (1.08–1.38)	1.19 (1.05–1.35)
Mother and sister(s)	14	1.25 (0.74–2.12)	1.21 (0.71–2.04)
Mother	168	1.24 (1.06–1.45)	1.21 (1.03–1.42)

	Cases (n)	Relative Risk (95% CI)	
		Include healthy men without PSA test	Exclude healthy men without PSA test
Sister(s)	106	1.19 (0.98–1.45)	1.16 (0.96–1.42)
Mother or sister(s)' age at diagnosis of BCa			
No family history	1,875	1.00	1.00
<60	150	1.35 (1.15–1.60)	1.31 (1.11–1.55)
≥60	106	1.04 (0.85–1.26)	1.02 (0.84–1.24)
Mother's age at diagnosis of BCa			
No family history	1875	1.00	1.00
<60	78	1.38 (1.10–1.74)	1.16 (0.92–1.48)
≥60	82	1.11 (0.89–1.38)	1.08 (0.87–1.35)
Case's age at diagnosis of PCa <65 years BCa family history			
No	546	1.00	1.00
Yes	80	1.20 (0.95–1.52)	1.18 (0.93–1.49)
Case's age at diagnosis of PCa ≥65 years BCa family history			
No	1,329	1.00	1.00
Yes	208	1.23 (1.06–1.42)	1.20 (1.04–1.39)
Aggressive PCa BCa family history			
No	84	1.00	1.00
Yes	10	0.95 (0.49–1.83)	0.92 (0.48–1.77)
Non-aggressive PCa BCa family history			
No	1,791	1.00	1.00
Yes	278	1.24 (1.09–1.40)	1.21 (1.06–1.37)
High-grade PCa BCa family history			
No	604	1.00	1.00
Yes	95	1.24 (1.00–1.54)	1.22 (0.98–1.51)
Low-grade PCa BCa family history			
No	1271	1.00	1.00
Yes	193	1.21 (1.04–1.41)	1.18 (1.02–1.38)
PCa and BCa family history	49	1.51 (1.19–2.01)	1.46 (1.10–1.94)
PCa family history only	368	1.71 (1.53–1.92)	1.66 (1.48–1.86)
BCa family history only	239	1.30 (1.13–1.49)	1.26 (1.10–1.45)
No PCa and BCa family history	1507	1.00	1.00

All models additionally adjusted for ethnicity, BMI, total calories, vigorous activity, cigarette smoking, and consumption of tomato sauce, calcium, alpha linolenic fatty acid, fish, and red meat.

Aggressive PCa indicates cases with stage T3b or T4 or N1 or M1 or death due to PCa.

High-grade PCa indicates cases with Gleason sum≥7; low-grade PCa indicates cases with Gleason sum<7