

Family History and Prostate Cancer Risk in a Population-Based Cohort of Iowa Men¹

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Abstract

A family history of prostate cancer has been associated with prostate cancer risk in most prior studies, and more limited data suggest that a family history of breast cancer may also be important; however, there are no data from a population-based cohort study of prostate cancer incidence that adjusts for major confounders. We conducted follow-up through 1995 on 1557 men, ages 40–86 years, who were randomly selected (81% response rate) as cancer-free controls for a population-based case-control study conducted in Iowa from 1987–1989. Family history of cancer in parents and siblings was obtained using a mailed questionnaire. Incident cancers and deaths were ascertained through linkages to state and national databases; 101 incident cases of prostate cancer were identified. At baseline, 4.6% of the cohort reported a family history of prostate cancer in a brother or father, and this was positively associated with prostate cancer risk after adjustment for age [relative risk (RR) = 3.2; 95% confidence interval (CI), 1.8–5.7] or after multivariate adjustment for age, alcohol, and dietary factors (RR = 3.7; 95% CI, 1.9–7.2). Risk was greater if a brother had prostate cancer (RR = 4.5; 95% CI, 2.1–9.7) than if a father had prostate cancer (RR = 2.3; 95% CI, 1.0–5.3). Also at baseline, 9.6% of the cohort had a family history of breast and/or ovarian cancer in a mother or sister, and this was positively associated with prostate cancer risk (age-adjusted RR = 1.7; 95% CI, 1.0–3.0; multivariate RR = 1.7; 95% CI, 0.9–3.2). Men with a family history of both prostate and breast/ovarian cancer were also at increased risk of prostate cancer (RR = 5.8; 95% CI, 2.4–14). There was no association

with a family history of colon cancer. Exclusion of well-differentiated, localized tumors did not alter these findings. These data from an incidence study confirm that a family history of prostate cancer is a strong prostate cancer risk factor after adjustment for dietary and other risk factors, and suggest that selection and recall bias have not had an important influence on most case-control study results. These data also support the idea that a family history of breast cancer may also be a prostate cancer risk factor.

Introduction

There are few well-established risk factors for prostate cancer, but one of the most consistently identified has been a family history of prostate cancer (1). Hospital-based (2–10) and population-based (11–19) case-control studies, cross-sectional studies (20, 21), and family studies (22–27) have almost universally found that men with a first-degree relative with prostate cancer are at a 2–4-fold risk of developing prostate cancer. A single cohort study of prostate cancer mortality also reported a positive association with family history of prostate cancer (28). In addition, cancers of the prostate and breast seem to cluster in families (3, 17, 22, 24, 26, 29–32). Some data suggest that a family history of prostate cancer is a risk factor for breast cancer in women (3, 22, 31) and that a family history of both breast and prostate cancer is an even stronger risk factor, stronger than a family history of breast cancer alone (29–32). There are also data that suggest that a family history of breast cancer is a risk factor for prostate cancer (17, 24, 26, 33). Finally, there are some limited data that a family history of colon cancer may also be a risk factor for prostate cancer (17, 26).

Although family history represents both shared genetic and environmental factors and their interaction, only four studies have addressed confounding beyond the role of age (16–18, 28), and only three studies have specifically addressed potential confounding by dietary factors (16, 18, 28). Case-control studies are also susceptible to selection bias. Although hospital-based case-control studies are particularly susceptible to selection bias, population-based case-control studies can also be affected by this type of bias due to low overall response rates. Only five of the case-control studies have specifically reported response rates of >70% for both cases and controls (7, 8, 17–19), and only three of these were population-based (17–19). Selection bias may also occur if controls with a family history of cancer are more likely to participate. Finally, case-control studies are susceptible to recall bias. Cases may differentially report their family cancer history compared with controls, particularly healthy controls. The cohort study design can overcome these potential biases, but to our knowledge there are no published cohort studies of family history of cancer and prostate cancer incidence. We present data on this association using a population-based cohort of 1557 Iowa men, ages 40–86

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years, at baseline whose cancer experience over an average of 6.1 years of follow-up was determined by linkage to a statewide cancer registry.

Materials and Methods

Study Population. This study was reviewed and approved by the institutional review board of the University of Iowa. From 1987 to 1989, a population-based, case-control study of six cancer sites was conducted in Iowa (34). Controls were frequency matched to the case series by sex and 5-year age groups. Male controls, ages 40–64 years, were randomly selected from computerized Iowa driver's license records, whereas male controls, ages 65–86 years, were randomly selected from listings provided by the United States HCFA.³ Each sampling frame covers over 95% of the population in its respective age group (35, 36). Of the 1989 men selected as controls, 1601 participated (80.5%). We further excluded men who were incompetent, no longer alive when the questionnaire was received by study staff, and/or had proxy data for other reasons ($n = 24$), leaving 1577 men in the at-risk cohort. All controls at the time of their enrollment were Iowa residents and had not been previously diagnosed with a cancer. The date of return of the study questionnaire (or telephone interview) served as the entry date for men in this retrospective cohort study, with follow-up through 1995.

Data Collection. Respondents in the at-risk cohort completed a mailed questionnaire (89.9%), a full-length telephone interview (4.4%), or an abbreviated interview (5.6%). Data collected included demographics, education, and occupational history; weight and height; a detailed smoking history, including use of cigarettes, cigars, pipes, snuff, and chewing tobacco; a food frequency questionnaire assessing usual adult consumption of 55 items including beer, wine, and liquor use; number of brothers and number of sisters related by blood; and family history of cancer among biological parents and siblings, including type of cancer(s). BMI was calculated as weight (kilograms) divided by height (meters) squared. Nutrient intake values were calculated using the consumption frequency data from the questionnaire, and sex-specific portion sizes and food consumption data from the NHANES II nutrient database (37).

Follow-up. We linked to several databases to passively follow this cohort of men. Computer linkages were based on a combination of social security number, first and last name, birthdate, sex, baseline city, and zip code. Cancer incidence from 1986 through 1995 was ascertained by linking to the State Health Registry of Iowa's statewide cancer database, which is part of the National Cancer Institute's SEER Program (38). The Iowa Cancer Registry collects cancer data, including identifying information, tumor site, morphology, histological grade, and extent of disease on all persons who are Iowa residents at the time of their diagnosis. All tumor stage and grade data were derived from pathology reports of the diagnosing pathologist, and there was no centralized review of the tumor material. Topographic and morphological data were coded using the *International Classification of Diseases for Oncology, Second Edition* (39). Through 1995, 274 men were diagnosed with cancer, including 103 men with prostate cancer (International Classification of Diseases for Oncology code 61.9). Two of the prostate cancers were diagnosed before the questionnaire was

received by the study staff, and exclusion of these two prevalent cases reduced the at-risk cohort to 1575.

The stage of the prostate cancer was categorized using the following SEER summary staging codes (40): localized (confined to the gland, no extracapsular extension), regional (extracapsular extension and into adjacent tissue or lymph node involvement), distant (metastatic), and unstaged. The tumor grade was also based on the pathology report, and was categorized according to SEER rules (41) into well, moderately, or poorly differentiated, or unknown. Similar to West *et al.* (42), we also categorized prostate cancers into a subset that we termed "significant disease," which was defined as all prostate cancers that were moderately or poorly differentiated or were staged as regional or distant (irrespective of grade); this eliminated 22 well-differentiated and localized tumors and 9 tumors with insufficient stage and/or grade data to be classified.

The vital status of the cohort was ascertained using three approaches. First, all men were linked to a database of Iowa death certificates housed at the State Health Registry of Iowa, and 456 Iowa deaths were identified through August 1996. Second, all men who were not identified in the Iowa mortality database ($n = 1121$) were linked to the state of Iowa driver's license database, which includes the social security number (usually the driver's license number). This database also includes persons with Iowa identifications for those who do not or no longer drive. The Driver's license database includes the date of issue and most recent (February 1997) status of the license (or identification; *i.e.*, valid, revoked, surrendered, suspended, or expired). One thousand ninety men (97.2% of 1121) linked to this database. Finally, all men who were not identified in the Iowa mortality database ($n = 1121$) were also linked to the HCFA Medicare enrollment database in September 1996. This database contains the names of all persons enrolled in Medicare, and includes date of death for recent decedents. Eight hundred fifty men (75.8% of 1121) linked to this database, 9 of whom were deceased (death occurred outside of Iowa) and 97 of whom were alive but did not link to the Iowa driver's license database. Three men did not link to any of these databases and were excluded, leaving 1572 men in the at-risk cohort.

Statistical Analysis. Because we could only identify prostate cancers occurring in Iowa residents, each man in the at-risk cohort was allocated person-years of follow-up from the date of receipt of the questionnaire to one of the following events (in order of priority): (a) date of prostate cancer diagnosis; (b) date of death, if the death occurred in Iowa; (c) date last identified with a valid Iowa driver's license; or (d) the midpoint between the baseline date and June 30, 1996, for persons identified only in the HCFA enrollment database. Because the cancer data were complete only through December 31, 1995, this was the closing date for these analyses. We also excluded an additional 15 men who had no data on family history of cancer, leaving an at-risk cohort 1557. Of this at-risk cohort, 60 (3.9%) were censored for a presumed move out of Iowa (*i.e.*, death occurred outside Iowa, a surrendered Iowa Driver's license), 22 (1.4%) were censored because they were only identified in the HCFA database, and 371 (23.8%) were censored because of death in Iowa.

Family history and other variables of interest were categorized into natural categories. Dietary variables were categorized into three levels of consumption based on tertile cutpoints in the cohort. Alcohol use was categorized into no present use, use below the median (6.4 g/day), or use at or above the median. Tobacco use was defined as use of cigarettes, cigars, pipes, chewing tobacco, or snuff for >6 months. RRs and 95%

³ The abbreviations used are: HCFA, Health Care Financing Administration; BMI, body mass index; RR, relative risk; CI, confidence interval; SEER, Surveillance, Epidemiology and End Results.

Table 1 Baseline descriptive characteristics of the study participants by family history of prostate cancer in a father or brother

Characteristic	Family history of prostate cancer ^a	
	No (n = 1423)	Yes (n = 71)
Age (years) ^b	67.9 ± 9.7	69.4 ± 9.5
Number of brothers ^b	2.0 ± 1.7	2.4 ± 1.7
Number of sisters ^b	2.0 ± 1.7	1.8 ± 1.7
Height (m) ^b	1.77 ± 0.06	1.79 ± 0.06
BMI (kg/m ²) ^b	25.8 ± 3.7	25.6 ± 2.7
Total energy (kcal/day) ^b	1972 ± 783	1947 ± 474
Dietary intake ^c		
Carbohydrate (g/day)	214 ± 1.2	214 ± 5.5
Saturated fat (g/day)	30.2 ± 0.2	31.1 ± 0.9
Linoleic acid (g/day)	10.3 ± 0.1	10.1 ± 0.4
Lycopene (μg/day)	527 ± 11	504 ± 49
Red meat (servings/week)	7.05 ± 0.14	7.57 ± 0.62
Marital status		
Current	87%	89%
Former	10%	8%
Never	3%	3%
Alcohol use at baseline		
None	43%	42%
<6.4 g/day	28%	33%
≥6.4 g/day	29%	25%
Tobacco use		
Never	27%	31%
Former	49%	54%
Current	24%	15%

^a Does not sum to 1557 due to missing values.

^b Mean ± SD.

^c Mean ± SE. Mean is adjusted for total energy.

CI's were used as the measure of association between these exposure categories and prostate cancer incidence. The Mantel-Haenszel procedure (43) was used to estimate age-adjusted RRs, and Cox proportional hazards (44) regression was used to estimate multivariate-adjusted RRs. The following independent risk factors in this dataset were included in the final model: age (continuous); alcohol intake (none, <6.4, ≥6.4 g/day); and consumption of carbohydrate (<200, 200–227, >227 g/day), saturated fat (<75.5, 75.5–84.7, >84.7 g/day), linoleic acid (<9.3, 9.3–11.0, >11.0 μg/day), lycopene (<244, 244–557, >557 μg/day), and red meat (<4.8, 4.8–7.4, >7.4 servings/week). We adjusted all dietary factors for total energy intake, and used the residual method for adjustment of macronutrients (45). Height, body mass, and tobacco use were also considered and eventually removed from the final multivariate model.

Results

The mean age at entry into the cohort was 68.1 years (median age, 69 years), and 99% of the participants were white. At baseline, 87% of the men were married; 26% had greater than a high school education; 24% were using some tobacco product; and 57% consumed alcoholic beverages. There were few differences in baseline characteristics between men with a family history of prostate cancer in a father or brother compared with men without such a history (Table 1).

Through 1995 (9509 person-years; median of 6.8 years of follow-up), there were 101 incident cases of prostate cancer. The mean age at diagnosis of prostate cancer for men with a family history of prostate cancer was 74.1 years compared with 73.4 years for men with no such history ($P = 0.7$). On the basis of the SEER summary staging codes, 63% of the tumors were

Table 2 Descriptive characteristics of the incident prostate cancers by family history of prostate cancer in a father or brother

Characteristic	Family history of prostate cancer	
	No (n = 84)	Yes (n = 13)
Age at diagnosis (years) ^a	73.5 ± 6.1	74.1 ± 5.7
Stage at diagnosis		
Local	61%	84%
Regional	12%	8%
Distant	12%	8%
Missing	15%	0%
Tumor grade		
Well differentiated	26%	16%
Moderately differentiated	42%	46%
Poorly differentiated	25%	23%
Missing	7%	15%

^a Mean ± SD.

localized, 11% were regional, 11% were distant, and 15% were unstaged. Men with a family history were somewhat more likely to have localized disease, but the overall distribution of stage at diagnosis by family history (Table 2) was not statistically significant ($P = 0.3$). Tumor grade was distributed as follows: 25% well differentiated, 42% moderately differentiated, 24% poorly differentiated, and 9% missing, and there were no significant differences in these distributions by family history (Table 2; $P = 0.8$).

Table 3 presents the age-adjusted and multivariate-adjusted associations between family history and prostate cancer risk. At baseline, nearly 50% of the cohort reported a history of cancer in one or more first-degree relatives, and having any family history of cancer was positively associated with prostate cancer risk (RR = 1.6; 95% CI, 1.1–2.4); this estimate changed little after multivariate adjustment for age, alcohol use, total energy, and consumption of carbohydrate, saturated fat, linoleic acid, lycopene, and red meat (RR = 1.5; 95% CI, 1.0–2.4). There was a weak and not statistically significant association with a family history of colorectal cancer, although if a sibling had colorectal cancer, the risk of prostate cancer was elevated (RR = 2.0); but, this estimate lacked precision (95% CI, 0.8–4.9) and attenuated after multivariate adjustment (RR = 1.7; 95% CI, 0.6–4.8).

Compared with men with no family history of prostate cancer, men with a history of prostate cancer in a father (RR = 2.3; 95% CI, 1.0–5.3), brother (RR = 4.5; 95% CI, 2.1–9.7), or father or brother (RR = 3.2; 95% CI, 1.8–5.7) were all at elevated prostate cancer risk. These point estimates were not attenuated after multivariate adjustment (Table 3). Most men with a family history of prostate cancer had either a father or one brother affected; only five men had more than one of these relatives with prostate cancer. Therefore, we were unable to estimate prostate cancer risk for increasing number of first-degree relatives with the disease.

We were also interested in whether a family history of breast and/or ovarian cancer in the mother or sisters was associated with prostate cancer risk. We included a history of ovarian cancer because breast and ovarian cancer aggregate in families and may be genetically linked, particularly by the *BRCA1* gene. Compared with men with no history of breast/ovarian cancer in a mother or sister, men with a family history of a breast/ovarian cancer in a mother (RR = 2.0; 95% CI, 1.0–4.1) or a mother or sister (RR = 1.7; 95% CI, 1.0–3.0) were at elevated risk of prostate cancer, and these point esti-

Table 3 Age-adjusted and multivariate-adjusted RRs of prostate cancer by family history of cancer in a parent or sibling, Iowa, 1987–1995

Family history of cancer	n ^c	Prevalence (per 100) ^d	Cases	Person years	Age model ^a		Multivariate model ^b	
					RR	95% CI	RR	95% CI
Any cancer								
No family history	786		40	4865	1	Referent	1	Referent
Family history	771	49.5	61	4644	1.6	1.2–2.4	1.5	1.0–2.4
Colorectal cancer								
No family history	1387		88	8483	1	Referent	1	Referent
Any first-degree relative	107	6.8	9	659	1.4	0.7–2.8	1.3	0.6–2.9
Parent(s)	74	4.7	4	478	0.9	0.3–2.5	0.8	0.2–2.5
Sibling(s)	41	2.6	5	231	2.0	0.8–4.9	1.7	0.6–4.8
Prostate cancer								
No family history	1423		84	8717	1	Referent	1	Referent
Father or brother(s)	71	4.6	13	425	3.2	1.8–5.7	3.7	1.9–7.2
Father	45	2.9	6	281	2.3	1.0–5.3	2.3	0.9–5.9
Brother(s)	27	1.7	7	150	4.5	2.1–9.7	6.5 ^e	2.6–16
Breast/ovarian ^f cancer								
No family history	1345		82	8311	1	Referent	1	Referent
Mother or sister(s)	149	9.6	15	832	1.7	1.0–3.0	1.7	0.9–3.2
Mother	77	4.9	9	440	2.0	1.0–4.1	2.2	1.1–4.7
Sister(s)	79	5.1	6	436	1.3	0.5–2.9	1.1 ^e	0.4–3.1
Prostate or breast/ovarian ^f								
No family history	1286		74	7958	1	Referent	1	Referent
Family history	208	13.4	23	1184	2.0	1.3–3.2	2.1	1.2–3.6
Prostate and breast/ovarian ^f								
No family history	1482		92	9069	1	Referent	1	Referent
Family history	12	0.8	5	73	5.8	2.4–14	9.2	3.2–27

^a Adjusted for age (40–64, 65–69, 70–74, 75–79, 80+) by the method of Mantel and Haenszel.

^b Adjusted for age (continuous), alcohol intake (none, <6.4 g/day, ≥6.4 g/day), and the following energy-adjusted nutrients or foods: carbohydrate, saturated fat, linoleic acid, lycopene, and red meat.

^c Does not sum to 1557 due to missing values.

^d Prevalence is calculated as number with selected family history divided by 1557.

^e Also adjusted for number of brothers (prostate cancer) or sisters (breast/ovarian cancer).

^f Family history of breast and/or ovarian cancer.

mates were not materially changed after multivariate adjustment (Table 3). There was only a slight, not statistically significant, increase in risk in men with a family history of a breast/ovarian cancer in a sister (RR = 1.3; 95% CI, 0.5–2.9), which attenuated after multivariate adjustment. Only 13 men had more than one first-degree female relative with a history of breast/ovarian cancer, so we could not estimate prostate cancer risk according to number of family members with breast/ovarian cancer.

Men with a history of either breast/ovarian or prostate cancer had a doubling in the risk of prostate cancer (95% CI, 1.3–3.2), whereas men with a family history of both breast and prostate cancer were 5.8 times more likely to develop prostate cancer (95% CI, 2.4–14). Multivariate adjustment did not attenuate these point estimates.

A second set of multivariate models, adjusting for the same factors listed in Table 3 as well as tobacco use, BMI, height, and farming occupation, did not materially affect the point estimates reported in Table 3 (data not shown).

We next stratified the cohort into two baseline age groups (40–69 years and 70–86 years) and evaluated the association of prostate and breast/ovarian family histories with risk of prostate cancer (Table 4). RR estimates were stronger for a history of prostate cancer in the father or father or brother among younger men, but were similar for men with one or more brothers with prostate cancer among both younger (RR = 4.8; 95% CI, 1.5–16) and older (RR = 4.2; 95% CI, 1.5–12) men. In contrast, a family history of breast/ovarian cancer in the mother was a stronger risk factor among older men, whereas a family history of breast/ovarian cancer in a sister was only a

risk factor among younger men. Finally, a family history of prostate and breast/ovarian was a stronger risk factor among older (RR = 7.8; 95% CI, 2.9–22) compared with younger (RR = 2.5; 95% CI, 0.3–18) men, although these RRs were based on only four cases and one case, respectively.

To evaluate whether a family history was associated with “significant” prostate cancer, we next excluded all of the well-differentiated, localized prostate cancers and cancers missing stage and grade data ($n = 31$; see “Materials and Methods”). As seen in Table 5, the RRs for significant disease were not materially different from those for all prostate cancer presented in Table 3.

A potential concern is whether a detection bias might explain our findings. In this context, men with a family history of prostate cancer might be more motivated to undergo regular screening and have their prostate cancers detected earlier compared with men with no such history. We, unfortunately, did not have any data on screening behaviors or on medical care use in general. When we stratified the outcome by stage of disease at diagnosis, we found that the RRs were generally stronger for localized disease, but were still elevated for regional or distant disease (Table 5). It should be noted that the latter RRs were based on only a small number of cases and, thus, could not be estimated with great precision.

Discussion

In this population-based cohort of Iowa men, we found that a family history of prostate cancer in a father or brother was associated with a 220% increase in prostate cancer risk, and that

Table 4 Age-adjusted RRs of prostate cancer by family history of cancer, stratified by age at baseline, Iowa, 1987–1995

Family history of cancer	Age at baseline					
	40–69 years			70–86 years		
	Cases	RR ^a	95% CI	Cases	RR	95% CI
Prostate cancer						
No family history	42	1	Referent	42	1	Referent
Father or brother(s)	7	4.3	1.9–9.7	6	2.4	1.0–5.7
Father	4	4.0	1.4–11	2	1.2	0.3–5.1
Brother(s)	3	4.8	1.5–16	4	4.2	1.5–12
Breast/ovarian ^b cancer						
No family history	43	1	Referent	39	1	Referent
Mother or sister(s)	6	1.8	0.8–4.4	9	1.7	0.8–3.6
Mother	3	1.5	0.5–4.9	6	2.7	1.2–6.5
Sister(s)	3	2.3	0.7–7.3	3	0.9	0.3–2.8
Prostate or breast/ovarian ^b						
No family history	37	1	Referent	37	1	Referent
Family history	12	3.0	1.5–5.7	11	1.5	0.8–3.0
Prostate and breast/ovarian ^b						
No family history	48	1	Referent	44	1	Referent
Family history	1	2.5	0.3–18	4	7.8	2.9–22

^a Age-adjusted RR and 95% CI.^b Family history of breast and/or ovarian cancer.

Table 5 Age-adjusted RRs of prostate cancer for significant, localized, and regional/distant disease, Iowa, 1987–1995

Family History of Cancer	Stage at diagnosis											
	Significant disease ^a			Localized disease						Regional/distant disease		
	Cases	RR ^b	95% CI	Cases	RR	95% CI	Cases	RR	95% CI			
Prostate cancer												
No family history	59	1	Referent	51	1	Referent	20	1	Referent			
Father or brother(s)	9	3.1	1.5–6.3	11	4.3	2.3–8.3	2	2.1	0.5–9.0			
Father	5	2.6	1.0–6.5	5	3.1	1.2–7.7	1	1.5	0.2–11			
Brother(s)	4	4.3	1.5–12	6	6.5	2.7–15	1	4.5	0.6–35			
Breast/ovarian ^c cancer												
No family history	60	1	Referent	54	1	Referent	18	1	Referent			
Mother or sister(s)	8	1.4	0.7–2.9	8	1.5	0.7–3.2	4	2.2	0.8–6.6			
Mother	5	1.7	0.7–4.2	6	2.2	0.9–5.1	3	3.3	1.0–11			
Sister(s)	3	0.9	0.3–2.9	2	0.7	0.2–3.0	1	1.0	0.1–7.6			
Prostate or breast/ovarian ^c												
No family history	54	1	Referent	48	1	Referent	16	1	Referent			
Family history	14	1.8	1.0–3.3	14	2.0	1.1–3.7	6	2.5	1.0–6.5			
Prostate and breast/ovarian ^c												
No family history	65	1	Referent	57	1	Referent	22	1	Referent			
Family history	3	5.8	1.8–19	5	9.7	3.8–24	0					

^a Excludes well differentiated and localized tumors.^b Age-adjusted RR and 95% CI.^c Family history of breast and/or ovarian cancer.

risk was greater if a brother had prostate cancer (350% increase) than if a father had prostate cancer (130% increase). These associations were not affected after multivariate adjustment for alcohol, usual adult diet (total energy, consumption of carbohydrate, saturated fat, linoleic acid, lycopene, and red meat), BMI or tobacco use, or after exclusion of well-differentiated, localized tumors. We also found that men with a family history of breast and/or ovarian cancer were at a 70% increased risk of prostate cancer, and that risk was greater if a mother had breast/ovarian cancer (100% increase) than if a sister had breast/ovarian cancer (30% increase). If there was a history of both prostate and breast/ovarian cancer, risk of prostate cancer was increased 480%.

To our knowledge, this is the first population-based cohort study of family history and risk of incident prostate cancer that

also adjusts for major confounding factors. In the only other cohort study published to date, Rodriguez *et al.* (28) found that a family history of prostate cancer in a first-degree relative was associated with an increased risk of fatal prostate cancer after adjustment for age, race, education, BMI, physical activity, intake of vegetables and fat, smoking status, and vasectomy (RR = 1.60; 95% CI = 1.31–1.97). Our results for a family history of prostate cancer confirm results from case-control (2–19), cross-sectional (20, 21), and family (22–27) studies and suggest that these studies were not greatly affected by selection or recall biases. In addition, our prevalence estimates for a family history of prostate cancer in a father or brother (4.6%) agree well with estimates for whites in other population-based studies, which have ranged from 2.8–8.3% (13, 16–18, 21, 28). Finally, our results are consistent with the limited number of

studies that have found that the family history and prostate cancer association is not likely to be confounded by dietary or other lifestyle factors (16, 18, 28). However, no study, including ours, has measured lifestyle factors among members of a family, and there is evidence, for example, that adult siblings living apart share dietary patterns as much alike as has been described for monozygotic twins or familial correlations of serum cholesterol (46).

We found that the family history was a stronger risk factor for younger men (40–69 years) than older men, although the risks were still elevated in the latter group, consistent with some, but not all, published data (16–19, 28). Consistent with prior studies, there was little difference in the mean age at diagnosis between family history positive and negative cases (7–9, 16, 20). Increasing numbers of first-degree relatives with prostate cancer (7, 16, 25, 28), younger age at onset of prostate cancer among affected relatives (18, 25, 28), and a family history of prostate cancer among second-degree relatives (7, 8, 24) have also been associated with elevated prostate cancer risk. We were unable to address these issues due to the lack of a sufficient number of families with multiple affected relatives as well as not having family history data on relatives beyond parents and siblings or the age of diagnosis of the cancers, and these are important limitations of this study.

One concern in a study of family history and prostate cancer incidence is that a detection bias might inflate the observed association. In this context, men with a family history of prostate cancer might be more likely to undergo regular screening or seek medical care for early symptoms of prostate cancer and, thus, have their tumors detected earlier than men without a family history. Indeed, our data, consistent with other population-based case-control studies (17, 18), suggest that this may be occurring to some extent because the association with family history is somewhat stronger for local disease at diagnosis compared with regional or distant disease. Nevertheless, the risk is still elevated (RRs >2.0) for regional/distant disease in these studies, suggesting that a detection bias could only account for a portion of the observed association.

Other studies also support the idea that familial prostate cancer is likely to have a genetic component and is not due solely to bias or confounding. Carter *et al.* (25) conducted a segregation analysis of 691 families ascertained through a prostate cancer proband with localized disease suitable for radical prostatectomy and seen at a United States tertiary care hospital. Familial clustering in their data were best explained by an autosomal dominant gene, with a rare allele ($q = 0.0030$) that was highly penetrant (88% of the carriers were predicted to develop disease by age 85 years). Gronberg *et al.* (47) conducted a segregation analysis using a population-based sample of 2,857 nuclear families selected through a father diagnosed with prostate cancer in Sweden from 1959–1963. They found that the best explanation for the observed clustering was also autosomal dominant transmission, but with an allele with a high population frequency ($q = 0.0167$) and a moderate lifetime penetrance (63%). The latter authors suggested that the difference in gene frequency and penetrance found in their study may be due to the different populations studied, different ascertainment procedures, or that there may be multiple prostate cancer genes. Consistent with the last explanation, a linkage study of 91 hereditary prostate cancer families (48) found a major susceptibility locus on chromosome 1q24–25 (*HPC1*), but only 33% of the families were linked to this region, suggesting that other prostate cancer genes must exist. Other linkage studies have been directed at sites with known tumor suppressor genes or loci showing loss of heterozygosity in prostate cancer (*e.g.*,

8p, 10q or 16q); however, they have not yet identified a prostate cancer susceptibility locus (49–51).

Prostate cancer has also been hypothesized to have an X-linked or recessive mode of inheritance. Narod *et al.* (20), in a cross-sectional study of a Canadian screening program, noted that participants with one or more brothers with prostate cancer had a 2.6-fold greater risk of prostate cancer compared with those with no affected first-degree relatives (95% CI, 1.7–4.1), whereas participants with a father with prostate cancer had a 1.2-fold increase in risk (95% CI, 0.8–1.9). They suggested that this was consistent with a recessive or X-linked model of inheritance. Monroe *et al.* (21), in a cross-sectional study, found an excess risk of prevalent prostate cancer in men with brothers affected with prostate cancer compared with men with affected fathers (RR = 2.07; $P < 0.00005$). We found that prostate cancer risk was greater if a brother had a history of prostate cancer (RR = 4.5; 95% CI, 2.1–9.7) than a father (RR = 2.3; 95% CI, 1.0–5.3), although our study was too small to evaluate whether the two RRs differed from a statistical perspective. Most (11, 13, 16–21), but not all (7, 8, 14, 28), previous studies have shown stronger RR estimates for a history of a brother having a prostate cancer than a father. The X-linked hypothesis is of interest because the gene for the androgen receptor is located on the X-chromosome and polymorphisms in this gene have been linked to prostate cancer risk (52–54).

These data are also consistent with most previous studies that suggest that a family history of breast cancer may also be a prostate cancer risk factor (17, 24, 26, 33), although one clinic-based study of highly selected patients found no association (10). Although we found that the risk of prostate cancer was greater if the mother had breast/ovarian cancer than if the sister was affected, a population-based case-control study (17) found that family history of breast cancer was a stronger prostate cancer risk factor if a sister had breast cancer (OR = 1.8; 95% CI, 1.1–3.0) than if the mother had breast cancer (OR = 1.0; 95% CI 0.6–1.7). The latter associations need further evaluation, including the need for studies that include breast as well as ovarian cancer in the family history definition.

We found little evidence that a family history of colorectal cancer was associated with prostate cancer risk. One previous family study (26) found that relatives of prostate cancer probands were at elevated risk of colon cancer (familial relative risk = 1.26; 95% CI, 1.1–1.4), whereas one population-based case-control study found that a family history of colon cancer was a weak, nonsignificant prostate cancer risk factor among blacks but not whites (17).

There are several limitations to this study not yet discussed. Family history of cancer was based on self-reports that were not verified. However, self-report of cancer in a first-degree relative, particularly breast and prostate, has been shown to be relatively accurate (16, 55). Family history of cancer was assessed only at a single point in time, and misclassification of family history could bias our estimates, although likely toward the null. In addition, given the relatively short period of follow-up (median of 6.8 years), any such bias should be small.

The strengths of this study include a cohort study design, the use of a SEER cancer registry for case ascertainment, nearly complete follow-up of the at-risk cohort, adjustment for major potential confounding factors, and the use of a population-based sample with a high participation rate. On the basis of Iowa age-specific prostate cancer rates for the years 1988–1995 (56), we would have expected approximately 95 prostate cancers in this cohort compared with the 101 identified. The latter point gives this study a high generalizability to other white men of European descent, but must be balanced against the lack of

data on minorities, particularly African Americans, who have the highest rates of prostate cancer.

In summary, these data from an incidence study confirm findings from other study designs that a family history of prostate cancer is a strong prostate cancer risk factor, and also support the idea that a family history of breast/ovarian cancer may also be a prostate cancer risk factor.

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References

- Ross, R. K., and Schottenfeld, D. Prostate cancer. In: D. Schottenfeld and J. F. Fraumeni Jr. (eds.), *Cancer Epidemiology and Prevention*, Ed. 2, pp. 1180–1206. New York: Oxford University Press, 1996.
- Steele, R., Lees, R. E. M., Kraus, A. S., and Rao, C. Sexual factors in the epidemiology of cancer of the prostate. *J. Chronic Dis.*, *24*: 29–37, 1971.
- Thiessen, E. U. Concerning a familial association between breast cancer and both prostatic and uterine malignancies. *Cancer (Phila.)*, *34*: 1102–1107, 1974.
- Krain, L. S. Some epidemiologic variables in prostatic carcinoma in California. *Prev. Med.*, *3*: 154–159, 1974.
- Schuman, L. M., Mandel, J., Blackard, C., Bauer, H., Scarlett, J., and McHugh, R. Epidemiologic study of prostatic cancer: preliminary report. *Cancer Treat. Rep.*, *61*: 181–186, 1977.
- Jackson, M. A., Kovi, J., Heshmat, M. Y., Ogunmuyiwa, T. A., Jones, G. W., Williams, A. O., Christian, E. C., Nkposong, E. O., Rao, M. S., Jackson, A. G., and Ahluwalia, B. S. Characterization of prostatic carcinoma among blacks: a comparison between a low-incidence area, Ibadan, Nigeria, and a high-incidence area, Washington. *D.C. Prostate*, *1*: 185–205, 1980.
- Steinberg, G. D., Carter, B. S., Beaty, T. H., Childs, B., and Walsh, P. C. Family history and the risk of prostate cancer. *Prostate*, *17*: 337–347, 1990.
- Spitz, M. R., Currier, R. D., Fueger, J. J., Babaian, R. J., and Newell, G. R. Familial patterns of prostate cancer: a case-control analysis. *J. Urol.*, *146*: 1305–1307, 1991.
- Aprikian, A. G., Bazinet, M., Plante, M., Meshref, A., Trudel, C., Aronson, S., Nachabe, M., Pélouin, F., Déssureault, J., Narod, S., Bégin, L., and Elhilali, M. M. Family history and the risk of prostatic carcinoma in a high risk group of urological patients. *J. Urol.*, *154*: 404–406, 1995.
- Isaacs, S. D., Kiemeny, L. A. L. M., Baffoe-Bonnie, A., Beaty, T. H., and Walsh, P. C. Risk of cancer in relatives of prostate cancer probands. *J. Natl. Cancer Inst.*, *87*: 991–996, 1995.
- Woolf, C. M. An investigation of the familial aspects of carcinoma of the prostate. *Cancer (Phila.)*, *13*: 739–744, 1960.
- Kolonel, L. N., Yoshizawa, C. N., and Hankin, J. H. Diet and prostatic cancer: case-control study in Hawaii. *Am. J. Epidemiol.*, *127*: 999–1012, 1988.
- Honda, G. D., Bernstein, L., Ross, R. K., Greenland, S., Gerkins, V., and Henderson, B. E. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br. J. Cancer*, *57*: 326–331, 1998.
- Fincham, S. M., Hill, G. B., Hanson, J., and Wijayasinghe, C. Epidemiology of prostatic cancer: a case-control study. *Prostate*, *17*: 189–206, 1990.
- Ghadirian, P., Cadotte, M., Lacroix, A., and Perret, C. Family aggregation of cancer of the prostate in Quebec: the tip of the Iceberg. *Prostate*, *19*: 43–52, 1991.
- Whittemore, A. S., Wu, A. H., Kolonel, L. N., John, E. M., Gallagher, R. P., Howe, G. R., West, D. W., Teh, C. Z., and Stamey, T. Family history and prostate cancer risk in black, white and Asian men in the United States and Canada. *Am. J. Epidemiol.*, *141*: 732–740, 1995.
- Hayes, R. B., Liff, J. M., Pottern, L. M., Greenberg, R. S., Schoenberg, J. B., Schwartz, A. G., Swanson, G. M., Silverman, D. T., Brown, L. M., Hoover, R. N., and Fraumeni, J. F., Jr. Prostate cancer risk in U. S. blacks and whites with a family history of cancer. *Int. J. Cancer*, *60*: 361–364, 1995.
- Lesko, S. M., Rosenberg, L., and Shapiro, S. Family history and prostate cancer risk. *Am. J. Epidemiol.*, *144*: 1041–1047, 1996.
- Andersson, S., Baron, J., Bergström, R., Lindgren, C., Wolk, A., and Adami, H. Lifestyle factors and prostate cancer risk: a case-control study in Sweden. *Cancer Epidemiol. Biomark. Prev.*, *5*: 509–513, 1996.
- Narod, S. A., Dupont, A., Cusan, L., Diamond, P., Gomez, J.-L., Suburu, R., and Labrie, F. The impact of family history on early detection of prostate cancer. *Nat. Med.*, *1*: 99–101, 1995.
- Monroe, K. R., Yu, M. C., Kolonel, L. N., Coetzee, G. A., Wilkens, L. R., Ross, R. K., and Henderson, B. E. Evidence of an X-linked or recessive genetic component to prostate cancer risk. *Nat. Med.*, *1*: 827–829, 1996.
- Cannon, L., Bishop, D. T., Skolnick, M., Hunt, S., Lyon, J. L., and Smart, C. R. Genetic epidemiology of prostate cancer in the Utah Mormon genealogy. *Cancer Surv.*, *1*: 47–69, 1982.
- Meikle, A. W., Smith, J. A., and West, D. W. Familial factors affecting prostatic cancer risk and plasma sex-steroid levels. *Prostate*, *6*: 121–128, 1985.
- Tulinus, H., Egilsson, V., Ólafsdóttir, G. H., and Sigvaldason, H. Risk of prostate, ovarian and endometrial cancer among relatives of women with breast cancer. *Br. Med. J.*, *305*: 855–857, 1992.
- Carter, B. S., Beaty, T. H., Steinberg, G. D., Childs, B., and Walsh, P. C. Mendelian inheritance of familial prostate cancer. *Proc. Natl. Acad. Sci. USA*, *89*: 3367–3371, 1992.
- Goldgar, D. E., Easton, D. F., Cannon-Albright, L. A., and Skolnick, M. H. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J. Natl. Cancer Inst.*, *86*: 1600–1608, 1994.
- Gronberg, H., Damber, L., and Damber, J.-E. Familial prostate cancer in Sweden. A nationwide register cohort study. *Cancer (Phila.)*, *77*: 138–143, 1996.
- Rodriguez, C., Calle, E. E., Miracle-McMahill, H. L., Tatham, L. M., Wingo, P. A., Thun, M. J., and Heath, C. W., Jr. Family history and risk of fatal prostate cancer. *Epidemiology*, *8*: 653–657, 1997.
- Anderson, D. E., and Badzioch, M. D. Breast cancer risks in relatives of male breast cancer patients. *J. Natl. Cancer Inst.*, *84*: 1114–1117, 1992.
- Anderson, D. E., and Badzioch, M. D. Familial breast cancer risks. Effects of prostate and other cancers. *Cancer (Phila.)*, *72*: 114–119, 1993.
- Sellers, T. A., Potter, J. D., Rich, S. S., Drinkard, C. R., Bostick, R. M., Kushi, L. H., Zheng, W., and Folsom, A. R. Familial clustering of breast and prostate cancers and risk of postmenopausal breast cancer. *J. Natl. Cancer Inst.*, *86*: 1860–1865, 1994.
- Andrieu, N., Clavel, F., Auquier, A., Gairard, B., Bremond, A., Lansac, J., Piana, L., Flamant, R., and Renaud, R. Association between breast cancer and family malignancies. *Eur. J. Cancer*, *27*: 244–248, 1991.
- Ford, D., Easton, D. F., Bishop, D. T., Narod, S. A., Goldgar, D. E., and the Breast Cancer Linkage Consortium. Risks of cancer in BRCA1-mutation carriers. *Lancet*, *343*: 692–695, 1994.
- Cantor, K. P., Lynch, C. F., Hildesheim, M. E., Dosemeci, M., Lubin, J., Alavanja, M., and Craun, G. Drinking water source and chlorination byproducts: I. Risk of bladder cancer. *Epidemiology*, *9*: 21–28, 1998.
- Lynch, C. F., Logsdon-Sackett, N., Edwards, S. L., and Cantor, K. P. The driver's license list as a population-based sampling frame in Iowa. *Am. J. Public Health*, *84*: 469–472, 1994.
- Hartge, P., Cahill, J. I., West, D., Hauck, M., Austin, D., Silverman, D., and Hoover, R. Design and methods in a multi-center case-control interview study. *Am. J. Public Health*, *74*: 52–56, 1984.
- Dresser, C. M. From nutrient data to a data base for a health and nutrition examination survey organization, coding, and values—real or imputed. Proceedings of the Eighth International Nutrient Data Base Conference, Minneapolis, MN, July 1983.
- Ries, L. A. G., Kosary, C. L., Hankey, B. F., Miller, B. A., Harras, A., and Edwards, B. K. (eds.). *SEER Cancer Statistics Review, 1973–1994: Tables and Graphs*, National Cancer Institute. NIH Pub. No. 97-2789. Bethesda, MD: NIH, 1997.
- Percy, C., Van Holten, V., and Muir, C. (eds.). *International Classification of Diseases for Oncology*, Ed. 2. Geneva: WHO, 1990.
- Cunningham, J., Hankey, B., Lyles, B., Percy, C., Lynn, R., and Seiffert, P. *The SEER Program Code Manual*. Rev. Ed. Bethesda, MD: National Cancer Institute, 1992.
- Shambaugh, E. M., Gloeckler Ries, L., Young, J. L., and Kruse, M. A. *SEER Extent of Disease 1988 Codes and Coding Instructions*. Rockville, MD: National Cancer Institute, 1992.
- West, D. W., Slaterry, M. L., Robison, L. M., French, T. K., and Mahoney, A. W. Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. *Cancer Causes Control*, *2*: 85–94, 1991.
- Breslow, N. E., and Day, N. E. *Statistical methods in cancer research: The Design and Analysis of Cohort Studies*, Vol. 2, pp. 76–79. New York: Oxford University Press, 1989.
- Cox, D. R. *Regression models and life tables (with discussion)*. *J. R. Stat. Soc. B*, *34*: 187–220, 1972.
- Willett, W. C. *Nutritional Epidemiology*. New York: Oxford University Press, 1990.

46. Sellers, T. A., Kushi, L. H., and Potter, J. D. Can dietary intake patterns account for the familial aggregation of disease? Evidence from adult siblings living apart. *Genet. Epidemiol.*, 8: 105–112, 1991.
47. Gronberg, H., Damber, L., Damber, J-E., and Iselius, L. Segregation analysis of prostate cancer in Sweden: support for dominant inheritance. *Am. J. Epidemiol.*, 146: 552–557, 1997.
48. Smith, J. R., Freije, D., Carpten, J. D., Gronberg, H., Xu, J., Isaacs, S., Brownstein, M. J., Bova, G. S., Guo, H., Bujnovszky, P., Nusskern, D. R., Damber, J. E., Bergh, A., Emanuelsson, M., Kallioniemi, O. P., Walker-Daniels, J., Bailey-Wilson, J. E., Beaty, T. H., Meyers, D. A., Walsh, P. C., Collins, F. S., Trent, J. M., and Isaacs, W. B. Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science (Washington DC)*, 274: 1371–1374, 1996.
49. Carter, B. S., Ewing, C. M., Ward, W. S., Treiger, B. F., Aalders, T. W., Schalken, J. A., Epstein, J. I., and Isaacs, W. B. Allelic loss of chromosomes 16q and 10q in human prostate cancer. *Proc. Natl. Acad. Sci. USA*, 87: 8751–8755, 1990.
50. Bergerheim, U. S., Kunimi, K., Collins, V. P., and Ekman, P. Deletion mapping of chromosomes 8, 10, and 16 in human prostatic carcinoma. *Genes Chromosomes Cancer*, 3: 215–220, 1991.
51. Hunchareck, M., and Muscat, J. Genetic characteristics of prostate cancer. *Cancer Epidemiol. Biomark. Prev.*, 4: 681–687, 1995.
52. Ingles, S. A., Ross, R. K., Yu, M. C., Irvine, R. A., La Pera, G., Haile, R. W., and Coetzee, G. A. Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. *J. Natl. Cancer Inst.*, 89: 166–170, 1997.
53. Stanford, J. L., Just, J. J., Gibbs, M., Wicklund, K. G., Neal, C. L., Blumenstein, B. A., and Ostrander, E. A. Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk. *Cancer Res.*, 57: 1194–1198, 1997.
54. Giovannucci, E., Stampfer, M. J., Krithivas, K., Brown, M., Brufsky, A., Talcott, J., Hennekens, C. H., and Kantoff, P. W. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. *Proc. Natl. Acad. Sci. USA*, 94: 3320–3323, 1997.
55. Love, R. R., Evans, A. M., and Josten, D. M. The accuracy of patient reports of a family history of cancer. *J. Chronic Dis.*, 38: 289–293, 1985.
56. Karnell, L. H., Kelley, S. L., Olson, D. B., McKeen, K. M., Platz, C. E., and Lynch, C. F. (eds). *Cancer in Iowa: 1973–1992*. State Health Registry of Iowa. Iowa City: The University of Iowa Press, 1995.