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Prostate cancer risk in men with prostate and breast cancer family history: results from the REDUCE study (R1)

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Abstract

Background—To what degree the associations between PCa risk and family history of prostate cancer (PCa) and/or breast cancer (BCa) are attributable to screening biases is unclear. We examined these questions within the REDUCE study, where biopsies were largely independent of prostate specific antigen (PSA) minimizing screening biases.

Methods—Data were from REDUCE, which tested dutasteride 0.5 mg daily for PCa risk reduction in men with PSA 2.5–10.0 ng mL^{−1} and a negative pre-study biopsy. Among men undergoing at least one on-study biopsy with complete data ($n = 6415$; 78.1%), the association

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Conflict of interest statement

Drs Freedland and Andriole are paid consultants to GSK. Drs Freedland, Andriole, and Xu have research support from GSK. Dr Castro is an employee of GSK. All other coauthors have no other conflicts of interest.

Author contributions

Drs. Thomas and Freedland had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Thomas, Freedland, Castro. Acquisition of data: Gerber, Moreira, Andriole, Castro. Analysis and interpretation of data: Thomas, Freedland, Castro, Andriole, Xu, Isaacs, Bañez, Hamilton. Drafting of the manuscript: Thomas, Freedland. Critical revision of the manuscript for important intellectual content: Thomas, Freedland, Hamilton, Castro, Bañez, Xu, Andriole, Castro, Rittmaster, Gerber, Moreira, Issacs. Statistical analysis: Thomas, Freedland. Obtained funding: Freedland, Andriole. Administrative, technical, or material support: Andriole, Castro, Gerber, Moreira. Study super-vision: Freedland, Andriole, Castro.

between family history and PCa risk was tested using multivariate logistic regression adjusting for clinicodemographic characteristics.

Results—A family history of PCa alone was associated with increased PCa diagnosis (OR: 1.47, 95% CI: 1.22–1.77). In North America, PCa family history was not related to PCa diagnosis (OR: 1.02, 95% CI: 0.73–1.44), whereas outside North America, PCa family history was significantly related to diagnosis (OR: 1.72, 95% CI: 1.38–2.15) (P -interaction = 0.01). A family history of both PCa and BCa (OR: 2.54, 95% CI: 1.72–3.75) but not BCa alone (OR: 1.04, 95% CI: 0.84–1.29) was associated with increased PCa risk versus no family history and irrespective of geographical region.

Conclusions—In REDUCE, PCa family history was significantly related to PCa diagnosis, although only for men outside North America. The presence of both PCa and BCa family history significantly increased risk versus PCa family history alone, irrespective of geographical region. Ultimately, our observations may support the need for changes in how we address family history in terms of both risk of PCa diagnosis and general risk stratification.

Keywords

breast cancer; family history; prostate cancer; REDUCE

Introduction

Two meta-analyses reviewing 23 (14 case–control and nine cohort) and 13 (11 case–control and two cohort) studies, respectively, observed a >two-fold increased prostate cancer (PCa) risk in men with an affected first-degree relative with PCa [1, 2]. This risk increased with the number of affected relatives and differed whether the affected individual was a father or brother [3]. Other data suggest increased screening among men with PCa family histories results in an exaggerated impact of PCa family history on risk [4–6]. Yet others suggest high screening rates means true PCa risk factors are obscured where PCa rates are high [4]. Thus, the true association between PCa family history and PCa risk is difficult to know.

Recent data suggest not only does PCa family history influence PCa risk, but perhaps breast cancer (BCa) family history as well. Several studies suggest BCa family history increases PCa risk by 70% [7] and mortality by 16% [8]. However, others found no association between BCa family history and PCa risk [9–11]. To date, only two studies investigated the potential combined effects of PCa and BCa family history on PCa risk versus PCa family history alone with conflicting results [3, 7].

To address these uncertainties, we examined the relationship between PCa and/or BCa family histories and PCa diagnosis in REDUCE, a 4-year placebo-controlled, randomized trial testing the effects of dutasteride on PCa diagnosis [12]. Study participants, all with negative biopsies at baseline, underwent prostate biopsies, regardless of prostate specific antigen (PSA), at 2- and 4 years. Thus, this cohort affords a unique opportunity to test the association between PCa and/or BCa family history and PCa diagnosis minimizing differential screening biases.

Materials and methods

Study population

As previously described, eligible men were aged 50–75 years, with a PSA of 2.5–10 ng mL⁻¹ if aged 50–60 years, or 3–10 ng mL⁻¹ if >60 years, and a single, negative prostate biopsy (6–12 cores) within 6 months prior to the enrolment [13].

Study design

REDUCE was a 4-year, multicenter, double-blind, placebo-controlled study. Eligible subjects were randomized to dutasteride 0.5 mg day⁻¹ or placebo. Visits occurred every 6 months. Total serum PSA (Beckman Coulter Inc., Pasadena, CA, USA) was assessed every 6 months, with doubled PSA values (± 0.1 ng mL⁻¹) reported for men receiving dutasteride. Unscheduled PSA measurements were permitted if obtained through the central study laboratory.

Subjects underwent a 10-core transrectal ultra-sound (TRUS)-guided biopsy at 2- and 4 years regardless of PSA levels ('protocol-dependent'); unscheduled biopsies were performed if clinically indicated ('protocol-independent'). For-cause biopsies obtained during months 19–24 and 43–48 replaced those scheduled for years 2 and 4 and were included in the definition of protocol-dependent biopsies.

At baseline, a detailed history was obtained including family history of PCa or BCa defined as any first-degree relative affected. If there was an affected family member, the age at diagnosis and relationship (sibling versus parent) was ascertained. Race was self-reported. Digital rectal examination (DRE) findings and TRUS prostate volume were reported from the prestudy biopsy.

Statistical analyses

Among 8122 men in the efficacy population, which included all randomly assigned men who took at least one dose of the study medication, 6729 had 1 on-study biopsy (82.8%). There were no differences in the distribution of PCa or BCa family history between men who did and did not undergo biopsy (20.9% vs. 21.4%, χ^2 $P = 0.57$). Men not undergoing a biopsy were similar aged, had similar baseline PSA, body mass index (BMI) and DRE findings (all $P > 0.05$) but were more likely to be black (3.9% vs. 1.9%; $P < 0.001$). Details of the biopsy population have been published [13]. Of the men with 1 on-study biopsy, we excluded those with missing data for prestudy PSA ($n = 15$), BMI ($n = 204$), DRE ($n = 7$) or TRUS volume ($n = 76$), resulting in a final population of 6427 all having family history data. The distribution of PCa and/or BCa family history between arms was similar (χ^2 $P = 0.40$). As treatment arm did not significantly modulate the association between family history and any outcomes, the placebo and dutasteride arms were combined.

Study participants were grouped according to family history as following: no family history, PCa family history only, BCa family history only, or PCa and BCa family history. Men were also categorized according to which family member had PCa or BCa: parent only, sibling(s) only, or parent and sibling(s).

The association between family history and baseline parameters was tested using Kruskal–Wallis and chi-squared for continuous and categorical variables, respectively. The association between PCa/BCa family history and PCa risk was assessed using logistic regression. For the analysis predicting high-grade (Gleason ≥ 7) or low-grade PCa (Gleason < 7) versus no cancer, a multinomial logistic regression was used. Results were adjusted for clinical characteristics associated with PCa risk including age (continuous), race (white, black and other), baseline PSA (log-transformed, continuous), prostate volume (log-transformed, continuous), DRE findings (abnormal versus normal), BMI (log-transformed, continuous), geographic region and treatment arm (dutasteride versus placebo). Biopsy tumour volumes (μL) were known for 1512 (99.7%) men with cancer (see the REDUCE primary article for details regarding tumour volume determination) [12]. We used the Gleason score from the original REDUCE study. We tested the association between PCa and/or BCa family history and tumour volume (continuous, log-transformed) using linear regression adjusting for disease and patient characteristics.

We examined whether the association between PCa and/or BCa family history and PCa risk differed by certain characteristics by performing separate multi-variate analyses stratified by BMI (non-obese versus obese), age (< versus median), TRUS volume (< versus median) and geographic region (North America versus other regions). All analyses were adjusted for patient and disease characteristics. Potential interactions were assessed by including a cross-product term along with both main effect terms in the multi-variate model. There were not enough non-white men or men with an abnormal DRE to test for interactions. All analyses were conducted using Stata 11.1 (College Station, TX, USA).

Results

Study population and baseline characteristics

A total of 1419 (22.1%) men reported a history of PCa and/or BCa family history (Table 1). Men with a PCa and/or BCa family history were younger, had smaller prostates, were more likely to have an abnormal DRE and had lower baseline PSA values versus men with no family history (all P values < 0.05), although the differences were slight.

Family history and overall PCa risk

After adjusting for known PCa risk factors, men with a PCa family history with or without a BCa family history had significantly increased PCa risk versus men with no family history (Table 2). Men with a PCa family history alone were 47% more likely to have cancer whereas men with both BCa and PCa family history were 154% more likely to have cancer on biopsy. Amongst men with a positive PCa family history, also having a BCa family history increased risk by 89% versus PCa family history alone (OR: 1.89, 95%CI: 1.22–2.89, P = 0.004). A BCa family history alone was not associated with PCa risk.

We observed a PCa family history in either father or brother(s) increased cancer risk by 48% and 112%, respectively (Table 2). Although a PCa history in both father *and* brother(s) was not associated with PCa risk, the number of men with both a father and brother(s) affected was small (n = 31). Given that PCa history in a brother or brothers was more strongly related to elevated cancer risk than PCa history in father alone, we postulated that this may result from the possible younger age at diagnosis of the brother (median age 64) versus father (median age 71). To address this, among men with a family history of PCa in either a brother or a father, we examined the age of diagnosis of the affected relative and cancer risk. When this was carried out, we observed that age of diagnosis of the father or brother(s) did not influence PCa risk (P = 0.97). BCa in either mother or sister(s) was not significantly related to PCa risk.

Family history, disease grade and tumour volume

Men who reported a PCa family history only were 46% and 51% more likely to have low- and high-grade disease, respectively, than men without family history (Table 3). The presence of both PCa and BCa family history increased risk of low- and high-grade disease by 119% and 247% relative to men with no PCa or BCa family history. When compared to men with a PCa family history only, those with a PCa and BCa family history were 69% (OR: 1.69, 95% CI: 1.03–2.79, P = 0.04) and 133% (OR: 2.33, 95% CI: 1.24–4.38, P = 0.009) more likely to have low- and high- grade disease, respectively. Additionally, we found PCa and/or BCa family history was not associated with tumour volume (all P > 0.34). These results were similar among men from within and outside North America (all P -interaction > 0.05).

Family history and potential interactions

There were no significant interactions between family history and age, TRUS volume, BMI, and dutasteride use (all P -interactions > 0.05 , data not shown). Given a significant difference in PCa family history prevalence between regions (North America versus Other regions: 18.2% vs. 8.8%; $P < 0.001$), we explored how region influenced our findings. In North American men, PCa family history was not related to overall PCa risk ($n = 1593$; OR: 1.02, 95% CI: 0.73–1.44, $P = 0.91$) or low- (OR: 0.92 95% CI: 0.62–1.37, $P = 0.69$) or high-grade (OR: 1.32, 95% CI: 0.74–2.37, $P = 0.35$) separately. In contrast, for men outside North America, PCa family history was significantly related to overall PCa risk ($n = 4834$; OR: 1.72, 95% CI: 1.38–2.15, $P < 0.001$) as well as low- (OR: 1.79, 95% CI: 1.40–2.30, $P < 0.001$) and high-grade (OR: 1.63, 95% CI: 1.12–2.37, $P = 0.01$) separately. The interaction for overall PCa risk was statistically significant ($P = 0.01$). When ‘North America’ was limited to the United States (US) only, similar results were seen. On the contrary, geographic region did not influence the association (or lack thereof) between BCa family history alone or combined PCa and BCa family history and PCa risk (P -interactions > 0.55).

Discussion

PCa family history is considered a significant PCa risk factor. To what degree this reflects increased screening behaviour versus family history being a ‘true’ risk factor is debated [5]. Additionally, there is growing evidence suggesting that BCa family history may influence PCa risk, although data remain inconclusive [3, 7, 9, 11, 14]. To address these issues, we examined the association between family history of either cancer and PCa diagnosis within REDUCE, where men underwent mandated PSA-independent biopsies. We observed PCa family history was positively associated with increased diagnosis of overall PCa and low- and high-grade disease, though only outside North America. Moreover, a brother’s PCa history alone increased diagnosis more than a father’s PCa history. Finally, BCa family history was associated with increased PCa diagnosis, but only with a concomitant PCa family history.

Early epidemiological data suggest significantly increased PCa risk associated with PCa family history [15–18]. Consequently, the American Urological Association recommended earlier screening for men with PCa family history. Recent studies show a weaker association between PCa family history and PCa risk [3, 19]. Indeed, Giovannucci *et al.* [20] observed a significant yet attenuated PCa risk comparing PCa family history in the pre-PSA period to the PSA-era. Some suggested the risk associated with PCa family history in earlier studies related to increased screening of men with family history [5]. Others propose the weakening in PCa family history’s importance in the PSA-era is secondary to widespread PSA screening [4]. In part related to these uncertainties, modern PCa screening recommendations moved away from earlier screening in those with a family history and now typically recommend screening at younger ages for all men.

We found men with a PCa family history had 47% increased risk of PCa diagnosis, which is modest versus the $>$ two-fold increase in two recent meta-analyses [1, 2], and 83–91% increased risk in two recent large prospective population-based studies [3, 19]. The most comparable study to our own was the Prostate Cancer Prevention Trial (PCPT) wherein PCa family history was associated with 31% increased risk, albeit with differences in biopsy protocols between PCPT and REDUCE [12, 21]. Thus, our findings are consistent with recent studies suggesting increased PCa risk with PCa family history, although the magnitude was smaller than earlier studies [15, 16, 18], but similar to PCPT [21].

Given global differences in screening practices, the increased PCa incidence and elevated prevalence of PCa family history in North American men, we examined whether geographic

region influenced the association between family history and PCa. Amongst men from North America, there was no association between PCa family history and PCa risk or disease grade. However, outside North America, PCa family history remained significantly linked to overall, low- and high-grade disease. Results were similar when limited to US men. Both early and more contemporary studies outside the United States support a strong link between PCa family history and PCa risk [19, 22–24]. In contrast, recent US cohorts have shown attenuated PCa risk with PCa family history compared to earlier studies [7, 11, 21]. This may be explained by the extensive PSA screening in North America [4]. Although the role of PSA was purposefully minimized in the REDUCE trial, PSA screening in North America may have culled prevalent cancers, especially those genetically driven, prior to enrolment in the REDUCE trial. As such, these data suggest that repeated screening as is typical in North America, minimizes and may ultimately eliminate the influence of family history of PCa risk – at least among men with a negative initial biopsy.

Meta-analyses suggest having a brother with PCa increased risk more than an affected father [1, 2]. Recently, Brandt *et al.* [25] found risk more than doubled (HR: 2.12, 95%CI: 2.05–2.20) when an affected father but nearly tripled with an affected brother (HR: 2.96, 95%CI: 2.80–3.13). To what degree screening practices of men with an affected brother versus father differ is unknown. However, in the current study where screening biases were minimized, we found a PCa family history in a brother was more strongly linked with PCa than family history in a father. We hypothesized this may result from younger age at diagnosis of a brother than father. However, in our limited sample, age at diagnosis of the affected relative did not impact PCa risk, suggesting the younger age of diagnosis of the brother was not the likely reason for the stronger association. Alternatively, this observed elevated risk with an affected brother may be explained by an increased number of shared environmental factors amongst siblings. More studies are needed to confirm our observations and to understand the biological basis for these findings.

Despite several studies linking BCa family history to increased risk of overall and fatal PCa [3, 7, 8], we observed no significant association between BCa family history alone and PCa diagnosis and disease grade [8]. However, it is possible that the lack of association between BCa family history and PCa risk was because of limited power. Indeed, previous investigations suggested BCa family history could contribute to PCa risk; however, the reported magnitude was modest versus risk attributable to positive PCa family history [3, 26]. Thus, the current study lacked power to detect modest, but perhaps clinically relevant associations between BCa family history and PCa risk.

To date, only two investigations examined the association between PCa and BCa family history and PCa risk with both finding elevated PCa risk amongst men with such a history versus men with no family history of either cancer [3, 7]. In a cohort from Iowa, having both PCa and BCa family history was linked to a ~six-fold increased risk (RR: 5.8, 95%CI: 2.4–14) whereas risk was doubled for men with either PCa or BCa family history (RR: 2.0, 95%CI: 1.3–3.2) versus men with no family history [7]. Similarly, the Health Professional Follow-up Study found increased PCa risk in men with a family history of both cancers (RR: 1.51, 95%CI: 1.19–2.01) versus men without family history, although this risk was slightly lower than that associated with PCa family history alone (RR: 1.71, 95%CI: 1.53–1.92). In REDUCE, having both PCa and BCa family history was linked to a > 2.5-fold increased PCa diagnosis versus men with no family history and an 89% increased risk versus PCa family history alone. Our data are more consistent with the Iowa cohort in that BCa family history increased PCa risk, but only in men with a concomitant PCa family history. To what degree this elevated risk results from inherited genetic predispositions such as BRCA-1 and BRCA-2 or as yet unidentified genes is unknown [27, 28].

We recognize several limitations. First, more detailed family history data were unavailable (e.g. second-degree relatives, age of family BCa diagnosis). As family history is a summation of genetic and environmental factors, we cannot fully address to what degree shared environmental factors versus genetics dictated the observed associations. We studied cancer diagnosis and grade and cannot address distant PCa outcomes, like PCa-specific mortality. As 97% of men with an affected brother had only one brother affected, we could not assess whether multiple brothers affected increased risk. Because of the limited number of non-white men, we could not examine interactions with race; these findings may only apply to white men. As genotypic data are currently unavailable, we cannot address how our findings relate to specific genotypes. Given few men had Gleason 8 ($n = 46$), we could not test the association between family history and risk of very high-grade disease. Finally, all men in this study had a negative prestudy biopsy. Thus, we cannot exclude the possibility that results may differ from a biopsy-naïve population. Despite these limitations, our study has key strengths. This study is unique in that men underwent biopsies regardless of PSA allowing us to test the association between PCa and/or BCa family history and PCa diagnosis whilst reducing biases from detection/screening. Moreover, because of the large sample size, we could address the link between PCa and BCa family history and PCa diagnosis.

Conclusion

In this multinational cohort, men with PCa family history alone or together with BCa family history were at increased risk for PCa diagnosis. However, the risk attributable to family history varied by region. The lack of association in North America may be a product of extensive PSA screening and if confirmed may lend support to non-risk adapted PSA screening guidelines, although caution must be used in interpreting this secondary analysis of a randomized controlled trial among men who all had a negative biopsy at baseline. The apparent synergistic effects of having both a BCa and PCa family history on PCa risk supports a link between these two cancers, and this should be explored further using genome-wide approaches to identify possible genetic aetiology in these subgroups.

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Table 1

Baseline characteristics of study population

	Family history of prostate and/or breast cancer			
	No family history	Prostate cancer	Breast cancer	Prostate and breast cancer
Number of patients, <i>n</i> (%)	5008 (77.9)	717 (11.1)	581 (9.0)	121 (1.9)
Median age at study enrollment (years)	63 (59–68)	61 (56–65)	62 (56–65)	61 (57–66)
Race, <i>n</i> (%)				<0.001
White	4574 (77.6)	660 (11.2)	564 (9.2)	119 (2.0)
Black	89 (74.8)	17 (14.3)	14 (10.9)	0 (0)
Other	345 (83.3)	40 (9.7)	28 (6.5)	2 (0.5)
Geographic region, <i>n</i> (%)				
North America	1038 (65.2)	290 (18.2)	196 (12.3)	69 (4.3)
South America	504 (80.5)	65 (10.4)	53 (8.5)	4 (0.6)
Europe	3215 (82.5)	341 (8.8)	298 (7.6)	44 (1.1)
Australia/New Zealand	83 (68.0)	11 (9.0)	25 (20.5)	3 (2.5)
Other	168 (89.4)	10 (5.3)	9 (4.8)	1 (0.5)
Body mass index (kg m ⁻²)	26.8 (24.8–29.2)	27.1 (25.1–29.6)	27.0 (24.8–29.4)	26.7 (24.6–29.2)
Median PSA, ng mL ⁻¹ (IQR)	5.8 (4.5–7.4)	5.4 (4.1–7.1)	5.5 (4.3–7.1)	5.4 (4.3–7.1)
Median TRUS, cc (IQR)	43.8 (33.2–56.9)	41.5 (31.5–55.7)	43.5 (33.9–55.2)	41.8 (32.9–52.3)
Abnormal digital rectal exam, <i>n</i> (%)	166 (3.3)	33 (4.6)	28 (4.8)	14 (11.6)
Assigned to dutasteride arm, <i>n</i> (%)				<0.001
No	2576 (78.8)	354 (10.8)	281 (8.6)	59 (1.8)
Yes	2432 (77.0)	363 (11.5)	300 (9.5)	62 (2.0)

Table 2Overall prostate cancer risk and family history of prostate and breast cancer^a

	Odds ratio	95%CI	P-value
Family history of prostate or breast cancer			
No family history	Reference		
Prostate cancer only (<i>n</i> = 717)	1.47	1.22–1.77	<0.001
Breast cancer only (<i>n</i> = 581)	1.04	0.84–1.29	0.71
Prostate and breast cancer (<i>n</i> = 121)	2.54	1.72–3.75	<0.001
Prostate cancer family history			
No family history	Reference		
Father only (<i>n</i> = 455)	1.48	1.18–1.86	0.001
Brother(s) only (<i>n</i> = 162)	2.12	1.52–2.96	<0.001
Father and brother(s) (<i>n</i> = 31)	1.54	0.69–3.42	0.29
Breast cancer family history			
No family history	Reference		
Mother only (<i>n</i> = 316)	1.07	0.80–1.42	0.65
Sister(s) only (<i>n</i> = 215)	1.30	0.95–1.78	0.11
Mother and sister(s) (<i>n</i> = 18)	1.52	0.53–4.33	0.44

DRE, Digital rectal examination.

^aMultivariate logistic regression analyses adjusted for age, race, PSA, BMI, TRUS volume, geographic region, DRE findings and treatment arm.

Table 3

Risk of low- and high-grade disease and family history of prostate and breast cancer^a

	Gleason score <7 [*]		Gleason score 7 [*]	
	Odds ratio	95%CI	P-value	P-value
No family history	Reference			
Prostate cancer only (<i>n</i> = 717)	1.46	1.18–1.80	<0.001	1.10–2.06 0.01
Breast cancer only (<i>n</i> = 581)	1.10	0.86–1.40	0.46	0.62–1.36 0.66
Prostate and breast cancer (<i>n</i> = 121)	2.19	1.39–3.45	<0.001	1.98–6.08 <0.001

DRE, Digital rectal examination.

^aMultivariate multinomial logistic regression model adjusted for age, race, PSA, BMI, TRUS volume, geographic region, DRE findings and treatment arm.

^{*} Relative to no cancer.