

Family History of Prostate Cancer in a Black Population

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Abstract Although family history of prostate cancer (PC) is an established risk factor for the disease, few studies have investigated this relationship among men with an African heritage. The Prostate Cancer in a Black Population (PCBP) study is a large, nationwide case–control study conducted in Barbados, West Indies from 2002 to 2011. In the PCBP study, a family history of PC in fathers or brothers was associated with a threefold increased risk of disease (OR = 3.04, 95 % CI (2.18, 4.22)) and a strong positive relationship was noted for the number of affected first degree relatives. Tumor grade did not generally influence the relationship between family history and PC. The magnitude of risks associated with having a father affected with the disease was slightly higher in the PCBP study compared to other populations. It remains unclear whether this finding is the result of an increased genetic susceptibility in African-Barbadian men.

Keywords Family history · Prostate cancer · African ancestry · Familial aggregation

Introduction

Prostate cancer (PC) is presently the most common malignancy and second leading cause of death (following lung cancer) affecting men in the United States [1]. The incidence of PC is more than 1.5 times higher among African-American (AA) than White-American (WA) males (230.8 vs 142.8 per 100,000, respectively) and mortality from PC in AAs is more than 2 times the rate reported for WA men (54.9 vs 22.4 per 100,000, respectively) [1]. In addition to race, family history of disease has been implicated as one of only a limited number of risk factors associated with prostate carcinogenesis to date. Three meta-analyses have confirmed that affected first degree relatives confer more than a twofold increased risk of PC [2–4], however these systematic reviews included predominantly Caucasian populations. Investigations across the African diaspora may assist in elucidating reasons for racial disparities in PC, as well as the role of particular risk factors, including family history, by providing additional data in African-origin populations known to have higher rates of disease.

The Prostate Cancer in a Black Population (PCBP) study [5] was designed to evaluate epidemiologic and genetic factors associated with PC in an African population of relatively low admixture [6]. A recent report by Hennis et al. indicated that the incidence rate for PC among African-Barbadian (AB) men was 160.6 per 100,000 (standardized to the US population), with very high mortality rates, ranging from 63.2 to 101.6 per 100,000, exceeding those of AA men [7]. Given the high rates of PC in Barbados, as well as the reduced admixture (and perhaps higher predominance of African genes than in AAs), the PCBP study may be able to provide a better understanding of the role of familial aggregation as a risk factor for the

The study was conducted by the Prostate Cancer in a Black Population Study Group and the article was written for the group.

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disease. The purpose of this report is to describe the relationship between family history and PC in a population of predominantly African origin.

Methods

The infrastructure of the PCBP study included a Coordinating Center (Stony Brook Medicine, Stony Brook, NY), Clinical Center (Ministry of Health and University of the West Indies, Bridgetown, Barbados), Local Laboratory Center (University of the West Indies, Bridgetown, Barbados), a center at the National Human Genome Research Institute (NHGRI, Bethesda, MD) and a Gene Discovery Center (Translational Genomics Research Institute, Phoenix, AZ). The design and protocols of the study have been detailed elsewhere [5] and are summarized below.

The PCBP study is a nationwide case–control study conducted in Barbados, West Indies between July, 2002 and January, 2011. Eligible cases included all male citizens of the country with newly diagnosed, histologically confirmed PC identified during the study period, while controls were randomly selected residents of Barbados chosen from a national database and frequency age-matched (by 5-year age groups) to the cases. All study participants provided informed consent and the study's protocols conformed to the Declaration of Helsinki. A total of 1,007 PC cases and 1,005 controls consented and participated in the PCBP study, of which 963 cases and 941 controls self-reported their race as African-Barbadian. Of those, 641 cases and 630 controls provided complete family history information and represent the basis for this investigation.

A standardized protocol was followed to collect the data that included demographic and lifestyle information, anthropometric and other measurements, blood samples to assess PSA, HbA1c and selected genetic variants, and a complete medical and family history. As part of a comprehensive study questionnaire administered by trained nurse interviewers, family history data were collected for prostate, breast and any other types of cancer among parents, siblings, children and parent's siblings (aunts and uncles).

Statistical Analyses

The present investigation is based on a subset of participants who provided complete family history information. The demographic characteristics of these cases and controls are described as mean \pm SD (median) for continuous variables and percentages for categorical factors. Multivariate logistic regression analyses were performed to evaluate the relationship between family history and PC. Due to the infrequency of PC among offspring, this investigation did not include them in the analyses. The

regression models controlled for potential risk factors including age, marital status, religion, occupation and waist-hip ratio. Additional analyses, stratified by tumor grade of the cases, were also performed with categories of low- and high-grade cancer defined by Gleason scores of <7 and ≥ 7 , respectively. All regression results are presented as odds ratios (ORs) with 95 % confidence intervals (CIs). The Statistical Analysis System (SAS Institute, Cary, NC) was used for these analyses.

Results

The demographic characteristics for the 641 cases and 630 controls of African origin providing complete family history information are presented in Table 1. The average age of the study participants was 67 years and more than half were married or living with a partner. Approximately one-third of the men smoked and two-thirds reported ever drinking alcohol. Waist-hip ratio, an established risk factor for PC in this population [5], was significantly higher among cases than controls (0.93 vs. 0.91). In Barbados, families tend to be large, as is evidenced by the finding that more than half of the study participants reported having 3 or more brothers.

Table 2 presents the data relating to family history of cancer and PC. More than one-quarter of cases reported having a family history of PC in a father, brother or uncle, whereas only 12.7 % of controls reported such history. A threefold multivariate-adjusted increased risk (OR = 3.02, 95 % CI (2.22, 4.10)) was found if any such family member was reported as having PC. The ORs for having an affected father, brother or uncle were 3.02, 2.70 and 2.31, respectively. When only first degree relatives were considered, a threefold risk (OR = 3.04, 95 % CI (2.18, 4.22)) was found. Risk positively increased with the number of first degree affected relatives (father or brothers) yielding a multivariate-adjusted OR of 2.76 (95 % CI (1.94, 3.92)) for those with one affected relative (father or brother) and more than a fivefold increased risk (OR = 5.24, 95 % CI (2.24, 12.30)) among men with 2 or more affected first degree relatives.

To evaluate the impact of having only a father or only a brother with PC, we conducted additional analyses for these mutually exclusive categories. Having an affected father with PC (in the absence of an affected sibling) yielded a threefold increased risk (OR = 3.15, 95 % CI (1.95, 5.07)), which was similar to that of having only an affected sibling (OR = 2.78, 95 % CI (1.76, 4.39)). A fourfold increased risk was noted if both a father and brother had PC.

Gleason scores were available on 607 (95 %) of the 641 cases. Of these, 327 (54 %) and 280 (46 %) were classified

Table 1 Characteristics of study participants

Demographic factors	Cases (n = 641)	Controls (n = 630)	P value*
Age (years), mean ± SD (median)	67.6 ± 9.0 (68.0)	66.5 ± 9.1 (67.0)	0.03
Religion, %			0.11
Anglican	50.5	44.1	
Pentecostal	11.7	13.3	
None	7.8	7.5	
Other	30.0	35.1	
Marital status, %			0.001
Single and never married	15.4	22.3	
Married or living together	61.0	52.0	
Separated or divorced	10.0	14.0	
Widowed	8.6	7.3	
Education (years), mean ± SD (median)	11.9 ± 3.9 (11)	11.6 ± 3.3 (11)	0.21
Occupation, %			0.15
Prof/admin/manag	25.9	22.5	
Waist-hip ratio, mean ± SD (median)	0.93 ± 0.07 (0.92)	0.91 ± 0.06 (0.91)	0.002
Number of brothers, %			0.86
0	10.1	9.2	
1	17.5	19.5	
2	20.0	20.8	
3+	52.4	50.5	

* χ^2 test was used for categorical variables; *t* test was used for continuous variables

as low- and high-grade, respectively. Table 3 presents the logistic regression results for the family history data stratified by tumor grade. The elevated risk of PC when any family history of PC was present (in father, brother(s) or uncle(s)) was similar for low-grade (OR = 3.22, 95 % CI (2.27, 4.56)) and high-grade (OR = 2.87, (1.97, 4.18)) cancer cases compared to controls. A total of 15.3 % of participants with low-grade cancer and 10.4 % with high-grade disease reported a father with PC. Although a family history of PC in a parent appeared to be slightly higher in men with low-grade (OR = 3.46) compared to high-grade (OR = 2.87) tumors, this difference was not statistically significant. While both groups showed higher risks with increasing number of affected family members, men with

Table 2 Family history and prostate cancer

	Cases (n = 641) %	Controls (n = 630) %	Multivariate-adjusted OR (95 % CI)
Family history of prostate cancer	27.8	12.7	3.02 (2.22, 4.10)*
Father	12.3	5.4	3.02 (1.95, 4.68)*
Brother(s)	13.6	5.7	2.70 (1.77, 4.11)*
Parent's brother(s)	8.1	4.1	2.31 (1.40, 3.83)*
First degree relatives (father or brothers)	23.6	10.3	3.04 (2.18, 4.22)*
0	76.4	89.7	1.0 (reference)
1	19.2	9.2	2.76 (1.94, 3.92)*
2+	4.4	1.1	5.24 (2.24, 12.30)*

OR odds ratio, CI confidence interval

* *P* < 0.05 based on logistic regression models adjusting for age, marital status, religion, occupation, waist-hip ratio

Table 3 Family history and prostate cancer by tumor grade

	Multivariate-adjusted OR (95 % CI)	
	Low-grade (n = 327) ^a	High-grade (n = 280) ^a
Family history of prostate cancer	3.22 (2.27, 4.56)*	2.87 (1.97, 4.18)*
Father	3.46 (2.13, 5.62)*	2.87 (1.66, 4.95)*
Brother(s)	2.49 (1.54, 4.03)*	2.94 (1.80, 4.80)*
Parent's brother(s)	2.48 (1.41, 4.36)*	2.10 (1.11, 3.95)*
First degree relatives (father or brothers)	3.28 (2.26, 4.76)*	2.87 (1.92, 4.29)*
0	1.0 (reference)	1.0 (reference)
1	3.20 (2.16, 4.75)*	2.34 (1.50, 3.63)*
2+	3.90 (1.47, 10.34)*	7.33 (2.90, 18.50)*

OR odds ratio, CI confidence interval

* *P* < 0.05 based on logistic regression models adjusting for age, marital status, religion, occupation, and waist-hip ratio

^a n = 630 for controls; 34 with missing data on Gleason scores

high-grade tumors and 2 or more affected first degree relatives had a higher risk of PC (OR = 7.33 (2.90, 18.50)) than cases with low-grade tumors and multiple affected family members (OR = 3.90, 95 % CI (1.47, 10.34)). However, these estimates were based on very small numbers of men reporting 2+ affected relatives.

Discussion

Prostate cancer is prevalent in Barbados. Ten percent of controls and approximately one-quarter of cases reported a

family history of PC among first degree relatives in the PCBP study, with affected fathers and brothers, respectively, found to have an approximate threefold increased risk of disease. Study results also indicated a higher risk as the number of affected family members increased. The association between family history of PC and disease was comparable regardless of tumor grade. Overall, the magnitude of association between family history of disease in a father and PC risk appeared to be higher in Barbados than in some other populations, yet it remains unclear whether or not this result is attributable to a possible increased genetic susceptibility in AB men.

Three meta-analyses have reported on the association of PC with family history of an affected first degree relative and the pooled risk ratios ranged from 2.2 to 2.5 [2–4]. These analyses primarily included men of European descent, as data in African-derived populations are relatively limited. Of those that have included men of African origin, two reported slightly higher PC risks than those reported in Whites. The first included 472 PC cases and 583 controls and reported an OR = 3.4 (95 % CI (1.5, 7.5)) if a first degree relative (father, brothers or sons) was affected [8] and the second reported a threefold increased risk among 472 cases and 512 controls [9]. The risks were somewhat lower in two smaller studies, one including 166 cases and 166 controls in South Carolina (OR = 2.4) [10] and another including 263 cases and 263 controls in Jamaica (OR = 2.1) [11]. The noted threefold increased risk in the present investigation is consistent with reports given by the 2 larger investigations [8, 9]. These slightly higher risks compared to those reported among men of European descent suggest that African men may have a genetic predisposition to PC. This postulate, however, requires further investigation, as existing data are not sufficient to confirm or refute the presence of an increased genetic susceptibility among men of African origin.

Numerous studies have reported on the risks associated with having either a father or brother affected with PC (as opposed to a family history in any relative as described above) and the results have been mostly consistent. The three systematic reviews reported pooled risks associated with having an affected brother ranging from 2.8 to 3.4, while estimates based on having a father affected with PC ranged from 2.1 to 2.5 [2–4]. Lesko et al. also reported a threefold increased risk when a brother alone had the disease [12]. However, one study found that having only an affected sibling did not significantly increase the risk of PC [13]. On the other hand, results from these two studies indicated a statistically significant twofold increased risk of PC if only a father was affected [12, 13]. The risk estimates in these reports were based on primarily Caucasian men. Only one case–control study, to our knowledge, presented data stratified by familial relationship in an African-origin

population. The study included 121 AA men with PC and 179 controls and found age-adjusted ORs (95 % CI) of 1.71 (0.80, 3.71) and 4.80 (2.01, 11.44) for affected fathers and brothers, respectively [14]. The lack of statistical significance of the OR for men with an affected father, as well as the wide confidence limits noted for the association of PC with having an affected sibling, likely reflect the limited sample size in that investigation.

While other studies have reported a higher risk of PC when a brother, rather than a father, is affected [2–4, 12, 14], the risk associated with having an affected father (OR = 3.0) did not differ appreciably from that of having a brother with PC (OR = 2.7) in the PCBP study. The magnitude of risk noted for a sibling with PC in the present investigation was lower than in one small study conducted among AA men [14] but was comparable with estimates in other predominantly Caucasian populations. The risk among AB men with an affected parent seemed to suggest a slightly higher magnitude than other reported estimates [2–4]. One's ability and accuracy for recalling family history may fare better in siblings than in parents, especially among relatively older populations with late onset disease such as PC. It is unclear whether the higher risk estimate for fathers in the PCBP study is due to a genetic influence in AB men, possible reporting biases or some other factor(s). Further studies are necessary to fully elucidate the underlying reasons for such findings.

Several studies have documented higher PC risks among men who report having more than one affected relative [3, 9, 11–13, 15–17]. Although the associated risks ranged in magnitude from 2.8 to 9.4, a meta-analysis found a pooled RR (95 % CI) of 3.5 (2.6, 4.8) associated with having 2 or more affected family members [3]. Additionally, a trend of increasing risk with the number of affected relatives has been documented. In a large case–control study in Baltimore, including 691 PC cases and 640 spouse controls, those with 2 affected first degree family members had a fivefold increased risk of PC, while having 3 or more affected relatives conferred an 11-fold increased risk [13].

Among men of African origin, a similar increased risk has been observed for those with multiple affected relatives. Whittemore et al. reported an OR (95 % CI) of 9.6 (2.2, 42.0) in AA men with a history of disease in more than one family member [9], however, the wide confidence limits for this result reflect the limited number of men in that study reporting 2 or more relatives with PC. A second study conducted in Jamaica also reported a significant increasing linear trend in risk associated with a larger number of affected first degree relatives ($P = 0.005$) [11]. However the Jamaican study did not present data on the magnitude of the risks associated with multiple affected family members. The PCBP study found a fivefold increased risk for men with 2 or more affected first degree

relatives, which is consistent with results from other studies, as detailed above.

Two studies in the US evaluating the association of PC family history with risk of disease reported that the average (nuclear) family included 2 brothers [18, 19]. Since Barbadian families tend to be larger (Table 1) and this may influence the amount of medical history information AB men possess about their siblings, we conducted additional analyses controlling for the number of brothers in the family. The findings were very similar to those reported in the main analysis. For example, the OR associated with having 2 or more affected first degree relatives was 5.27 compared to 5.24. One must consider, however, that larger family sizes may pose additional challenges for members to maintain complete information on one another. This inverse relationship between the awareness of one's family history and the number of members in the family would result in an underestimate of the actual risks. On the other hand, one can not discount the possibility that larger sibship sizes may bias the results in the opposite direction, as having more brothers may increase the probability of identifying one that is affected, especially if genetic susceptibility for PC is present in the family. These potential biases (both negative and positive) may account for some of the differences observed between studies, yet the true effect of the influence of larger family sizes on these types of analyses continues to remain unclear.

Several studies have reported an inverse relationship between PC risk and age at diagnosis for men with a family history of disease [3, 4, 8, 12, 19]. As such, we controlled for age in all regression models in the present investigation. Additionally, we re-analyzed the data, stratifying by age, and found that younger men (≤ 65 years) reported a father or brother with PC more often than older (> 65 years) men (30.7 vs. 18.8 % among younger and older cases, respectively; 13.0 vs. 8.1 % among controls, respectively). The associated risks, however, in both groups, were similar. These findings may simply reflect better recall among younger men.

PC risks associated with having a family history of disease were similar for men with low- and high- grade tumors in the PCBP study (3.2 and 2.9 for low- and high-grade cancer, respectively). The similarity in risks is consistent with other reports, although the magnitude of the risks in Barbados is somewhat higher. For example, results from the Health Professionals Follow-Up Study found the risk of PC associated with having a family history was 1.87 and 1.74 among men with low- and high-grade cancer, respectively [19].

Although tumor severity did not generally appear to influence the relationship between family history of PC and disease in the present investigation, one exception was noted for men with multiple affected relatives. A sevenfold

(OR = 7.33, 95 % CI (2.90, 18.50)) increased risk was found for men with high-grade cancer and 2 or more affected family members compared to an approximate fourfold (OR = 3.90, 95 % CI (1.47, 10.34)) elevated risk among men with low-grade tumors and more than one affected first degree relative. Although this difference was statistically significant, only 11 men with low-grade tumors, 17 with high-grade tumors and 7 controls reported having 2 or more family members with PC. It should also be noted that the average age of men in the PCBP study with low-grade disease was significantly lower than the mean age of those with high-grade PC (66 vs. 69 years, respectively). As such, the relationship between cancer grade and PC risk among men with a family history of disease may be confounded by age, as younger men may have better recall than those who are older. A second possible explanation for the noted finding in this population is that high-grade cancer may not necessarily be synonymous with aggressive disease in Barbados and may more likely be the result of poor screening and a longer duration of affectation. Given these considerations, the estimated magnitude between tumor grade and PC risk among men with multiple affected relatives should be interpreted with caution.

Strengths and Weaknesses

The PCBP study includes the largest population-based sample of incident, histologically-confirmed PC cases among men of African origin to date. The standardized protocols and high participation rates also add to the strengths and value of the study.

As with other case-control studies, the PCBP study was subject to certain inherent limitations. Difficulties in recalling family history, particularly in older parents and in families with large sibships, may have contributed to the approximately one-third of participants with unknown responses in this population. To account for the under-reporting of these unknowns, which were found to be similar among cases and controls, the present investigation included only those participants who provided complete family history information, thereby resulting in a somewhat reduced sample size. Recall bias was also a possibility in the PCBP study, as following diagnosis, men with PC may become more knowledgeable about their family's cancer history than controls and may tend to be older and perhaps less familiar with the health history of their family members (particularly a father or older brothers). Additionally, self-selection bias may have played a role in the study, since men with a family history may be more likely to respond to family history questions than those without any affected relatives.

Of note, the family history information obtained in this study was given by self-report and it was beyond the scope

of this investigation to verify the information provided. Although this may reduce the validity of the data to some degree, the accuracy of self-reported family history information in first degree relatives has been shown to be highly reliable [20, 21] and is therefore not likely to significantly change the outcome.

Conclusions

In the Afro-Caribbean population of Barbados, West Indies, a family history of PC was found to significantly increase the risk of PC and the threefold elevated risk was similar whether a father or brother was affected. Additionally, there was a strong positive association between the number of affected relatives and the risk of developing PC, whereas tumor grade did not appear to influence the relationship. Men with a family history of disease represent a high-risk group that may benefit from earlier screening and closer monitoring.

Acknowledgments We would like to acknowledge the Barbados National Cancer Study Group:

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Consultant Urologists: Dr. Jerry Emtage, MBBS, FRCS(C); Dr. Dave Padmore, MBBS, FRCS(C); Dr. Irving Smith, MBBS, FRCS.

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This project was supported by the Intramural Research Program of the NIH, National Human Genome Research Institute (contract N01HG25487) and the National Cancer Institute (Grant R01CA114379).

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