Research Article

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Relationship of Early-Onset Baldness to Prostate Cancer in African-American Men

Charnita Zeigler-Johnson, Knashawn H. Morales, Elaine Spangler, Bao-Li Chang, and Timothy R. Rebbeck

Abstract

Background: Early-onset baldness has been linked to prostate cancer; however, little is known about this relationship in AfricanAmericans who are at elevated prostate cancer risk.

Methods: We recruited 219 African-American controls and 318 African-American prostate cancer cases. We determined age-stratified associations of baldness with prostate cancer occurrence and severity defined by high stage (T3/T4) or high grade (Gleason 7+.) Associations of androgen metabolism genotypes (*CYP3A4, CYP3A5, CYP3A43, AR-CAG*, *SRD5A2 A49T*, and *SRD5A2 V89L*), family history, alcohol intake, and smoking were examined by baldness status and age group by using multivariable logistic regression models.

Results: Baldness was associated with odds of prostate cancer [OR = 1.69; 95% confidence interval (CI), 1.05–2.74]. Frontal baldness was associated with high-stage (OR = 2.61; 95% CI, 1.10–6.18) and high-grade (OR = 2.20; 95% CI, 1.05–4.61) tumors. For men diagnosed less than the age of 60 years, frontal baldness was associated with high stage (OR = 6.51; 95% CI, 2.11–20.06) and high grade (OR = 4.23; 95% CI, 1.47–12.14). We also observed a suggestion of an interaction among smoking, median age, and any baldness ($P = 0.02$).

Conclusions: We observed significant associations between early-onset baldness and prostate cancer in African-American men. Interactions with age and smoking were suggested in these associations. Studies are needed to investigate the mechanisms influencing the relationship between baldness and prostate cancer in African-American men.

Impact: African-American men present with unique risk factors including baldness patterns that may contribute to prostate cancer disparities. *Cancer Epidemiol Biomarkers Prev; 22(4); 589–96. ©2013 AACR.*

Introduction

Few definitive prostate cancer risk factors have been identified, but those that are clearly associated with prostate cancer risk include advancing age, family history of prostate cancer, and African-American race (1, 2). Among African-American men, prostate cancer has the highest incidence of any noncutaneous tumor and is a leading cause of cancer-related mortality (3). African-American men suffer from among the highest rates of prostate cancer in the world, with an age-adjusted incidence of 233.8 per 100,000. This rate is substantially higher than that in European-Americans (age-adjusted incidence of 149.5 per 100,000; ref. 4). African-American men also present with more advanced disease at initial diagnosis and have a worse prognosis than European-American men (5–7). Studies to date have not completely determined the reasons for these apparent ethnic disparities, but it is likely that they are multifactorial and complex.

Baldness has been investigated for a number of years as a potential risk factor for prostate cancer etiology. Also known as androgenetic alopecia, this age-dependent genetic disorder is characterized by patterned permanent hair loss (8, 9). Baldness affects about 50% to 70% of men during their lifetime (10, 11). Although the incidence of both prostate cancer and baldness increases with age, and both have been connected to androgen metabolism, the association between the 2 remains unclear. Genes involved in androgen metabolism have been suggested to be associated with the etiology of both baldness and prostate cancer. Although studies have shown a null relationship (9, 10) and others suggest an inverse relationship (12, 13), some have reported a positive association between prostate cancer and baldness (10, 11, 14).

To date, little is known about the relationship of baldness, prostate cancer, and androgen metabolism genotypes in African-American men. The aim of this study was to conduct a case–control study to examine the relationship between early-onset baldness and prostate cancer in African-American men. This study also included measures of polymorphic variation in candidate androgen metabolism genes to assess differences in baldness association with prostate cancer by genotype.

Authors' Affiliation: Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

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Corresponding Author: Charnita Zeigler-Johnson, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, 220 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104. Phone: 215-573-5264; Fax: 215-573-1050; E-mail: czj@mail.med.upenn.edu

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Materials and Methods

Study participants and data collection

We identified a sample of 219 African-American male controls (ages 33–93) and 318 African-American prostate cancer cases (ages 39–86) with baldness data through the University of Pennsylvania Health System (UPHS; Philadelphia, PA) and Philadelphia Veterans Affairs (VA) Hospital (Philadelphia, PA) recruited to the Study of Clinical Outcomes, Risk and Ethnicity (SCORE) between 1998 and 2010. SCORE is a hospital-based prostate cancer case–control study to examine genetic and other risk factor associations for prostate cancer etiology and progression in a diverse population of patients from the Philadelphia region. Cases were histologically confirmed patients with prostate cancer from UPHS and VA urology clinics. Controls were ascertained through UPHS primary care facilities. The participation rate was 98% for cases and controls approached to participate in the SCORE study. Case and control status was confirmed by medical records review using a standardized abstraction form. Participants were excluded from this analysis if they reported having exposure to finasteride (for treatment of baldness or prostate-related issues) at the time of their prostate cancer diagnosis. Participants with a prior diagnosis of cancer at any site other than the prostate were also excluded.

We used the Hamilton-Norwood Hair Baldness Patterns Scale arranged according to "no baldness (stages I and II), frontal baldness (stages IIa, III, IIIa, IVa), and any vertex baldness (stages III-vertex, IV, V, Va, VI, VII)" categories (15). These were categories similar to those used in studies by Faydaci and colleagues and Demark-Wahnefried and colleagues (9, 16). All baldness data were self-reported. Patients were asked to recall their hair pattern at the age of 30 years.

Risk factor, medical history, and prostate cancer diagnostic information were obtained by using a standardized questionnaire and review of medical records. Information collected included personal history of previous cancer diagnoses, demographic information, prostate cancer screening history, tumor characteristics at diagnosis, and cancer treatments. All study participants provided written informed consent for participation in this research with guarantees of confidentiality under a protocol approved by the Committee for Studies Involving Human Subjects at the University of Pennsylvania.

Biosample collection and genotype analysis

Genomic DNA for the present study was self-collected by each study participant using sterile cheek swabs (Cyto-Pak Cytosoft Brush, Medical Packaging Corporation), and processed using either a protocol modified from Richards and colleagues (17) as described previously (18), or using a modified protocol on the Qiagen 9604 robot with the QIAamp 96 DNA Buccal Swab Biorobot Kit (Qiagen). The methods used to determine each of the genotypes have been reported previously (19–21).

Statistical methods

This study investigated the relationship between male pattern baldness and odds of developing prostate cancer. We considered the presence of any baldness as well as type of baldness. Type of baldness was defined as "frontal only" or "any vertex" (either vertex only or frontal with vertex.) To compare demographics by prostate cancer case–control status, we computed frequency tables and χ^2 statistics for categorical variables. The Wilcoxon rank-sum test was used to test for significant case–control differences in median age and median body mass index (BMI).

For age-stratified associations, which were also adjusted for age, we calculated OR to determine the relationship between type of baldness and prostate cancer severity compared with controls in the same baldness and age category. Prostate cancer severity was defined by higher tumor stage (T1/T2 vs. T3/T4) or Gleason score (<7 vs. 7+) at diagnosis. The median age at diagnosis among cases (age 60 years) was used as the point of age stratification.

Additional analyses considered risk factors that have been reported in previous studies of baldness and prostate cancer (family history, alcohol use, smoking history, and prostate-specific antigen; PSA) and genotypes associated with testosterone metabolism (9, 14, 22, 23). Patient knowledge of any family history of prostate cancer (first-degree or second-degree relatives diagnosed with prostate cancer), any weekly alcohol intake in the year before study entry, and ever-smoking status were all categorized as "positive" or "negative" for these analyses. PSA was grouped as high (≥10 ng/mL) and low (<10 ng/mL) among cases. The median number of repeats for our sample was used as a cut-off points for the androgen receptor repeat polymorphism to optimize the sample size in the comparisons. For genotype analyses, we coded genotypes according to phenotypically relevant groups based on previous reports in the literature. For *AR-CAG*, we compared more than 21 repeats with 21 or less repeats (21, 24). We also coded the other genotypes by the presence of the known variant (homozygote or heterozygote): *CYP3A43 *3, CYP3A4 *1B, CYP3A5 *1, SRD5A2 A49T (T)*, and *SRD5A2 V89L* (*L*; refs. 19, 20). Each risk factor was modeled in a separate logistic regression model adjusting for age at diagnosis for cases and age at study entry for controls. We explored age as an effect modifier by testing for interactions between age group (age 60, cut-off points) and all risk factors of interest (family history, alcohol use, smoking history, and genotypes) in baldness-stratified analyses. Statistical heterogeneity among groups was tested using the Mantel–Haenszel test of independence.

Analyses were conducted in STATA version 11.0 (STATA Corporation). A 2-sided *P* value of 0.05 or less was considered statistically significant. We corrected for multiple testing by controlling the false discovery rate in the analysis of risk factors.

Results

Table 1 reports the demographics for our sample. Median age at study entry for controls was 57 years and for patients with prostate cancer was 60 years ($P = 0.001$). Cases were significantly more likely to report a family history of prostate cancer (36% vs. 27%; $P = 0.033$) and more likely to report any baldness (20% vs. 13%, $P = 0.038$) based upon findings from the Hamilton-Norwood Hair Baldness Patterns Scale (baldness reference age 30 years.) There were no significant differences in completion of high school education, median BMI, ever smoking, any weekly alcohol intake, or type of baldness (Table 1).

Associations with prostate cancer severity by baldness and age group are presented in Table 2. In most cases, baldness was associated with an increased risk of prostate cancer. Significant associations were observed for men with any balding and all prostate cancer [OR = 1.69; 95% confidence interval (CI), 1.05–2.74] and low-grade cancer (OR = 1.82; 95% CI, 1.07–3.10). Frontal baldness was associated with high-stage (OR = 2.61; 95% CI, 1.10–6.18) and high-grade cancer (OR = 2.20; 95% CI, 1.05–4.61). Any vertex balding was associated with low-grade prostate cancer (OR = 1.45; 95% CI, 1.01–2.07).

Among younger men (men under the age of 60 years), baldness was associated only with more severe disease. Men with any balding had more than 3 times the odds of being diagnosed with high-stage cancer (OR = 3.43; 95% CI, 1.37–8.61) and more than twice the odds of being diagnosed with high-grade prostate cancer (OR = 2.33; 95% CI, 1.03–5.28). Frontal baldness particularly increased the odds of severe disease. The OR associated with frontal baldness was 6.51 (95% CI, 2.11–20.06) for high-stage and 4.23 (95% CI, 1.47–12.14) for high-grade disease.

No significant associations between baldness and prostate cancer severity were observed for older men (age of 60 years or more) in this sample.

Controlling the false discovery rate in Table 3, we analyzed the risk factor associations with prostate cancer by presence of baldness. We observed a significant relationship between positive family history of prostate cancer in men with no baldness (OR = 1.74; 95% CI, 1.14–2.67). There was also an inverse relationship between the presence of *CYP3A43 *3* and prostate cancer in men with no baldness (OR = 0.32; 95% CI, 0.15–0.70). No associations with prostate cancer were observed for men with any baldness.

Table 3 also presents these associations stratified by age group. We observed effects for younger men with no baldness for 3 variables. Younger men with a prostate cancer family history were twice as likely to develop prostate cancer (OR = 2.04; 95% CI, 1.14–3.65). Younger men who ever smoked (OR = 0.37; 95% CI, 0.20–0.69) or carried the *CYP3A43*3* variant (OR = 0.21; 95% CI, 0.07–0.63) had a significantly lower odds of developing prostate cancer. There was also a suggestion of an interaction between smoking, median age, and any baldness ($P = 0.02$). However, tests of heterogeneity showed no significant differences between estimates by baldness group.

We also determined associations of baldness and prostate cancer by high and low PSA at prostate cancer diagnosis (results not shown.) The results showed an association of any baldness with prostate cancer in younger men (diagnosed before the age 60 years) among cases with high PSA at diagnosis ($\geq$ 10 ng/mL, OR = 3.08; 95% CI, 1.28–7.40, $P<0.001$). For men with frontal-only baldness, the association with prostate cancer in younger men among cases with high PSA was even stronger (OR = 5.29; 95% CI, 1.70–16.53, $P<0.001$). These multivariable models were adjusted for age. No significant associations were observed for cases with lower PSA at diagnosis (<10 ng/mL), nor for models including any vertex or older men stratified by PSA group.

Discussion

Key finding

This study aimed to determine the association between early-onset baldness, prostate cancer risk factors, and prostate cancer occurrence in a sample of African-American men. We observed a greater prevalence of early-onset baldness among prostate cancer cases with no significant

Table 1. Demographics of African-American SCORE sample

Variables	Controls ($N = 219$)	Cases ($N = 318$)	P
Median age, y	57	60	0.001
% High school education	80%	84%	0.196
Median BMI	29	27.8	0.215
% Ever smokers	68.0%	63.6%	0.290
% Family history prostate cancer	27%	36%	0.033
% Any weekly alcohol intake	31%	39%	0.078
% Any baldness at the age of 30 years	13%	20%	0.038
% Frontal baldness only at the age of 30 years	7%	13%	0.053
% Any vertex baldness at the age of 30 years	7%	10%	0.283
% High Gleason (7–10)	—	40%	—
% High stage (III/IV)	—	22%	—

Table 2. Prostate cancer case–control associations of baldness with prostate cancer by age group–adjusted for age

Reference group $N = 219$			All prostate cancer ($N = 318$)		Low stage ($N = 231$)		High stage ($N = 63$)[a]		Low grade ($N = 182$)		High grade ($N = 122$)[b]	
	Baldness type at the age of 30 years	Controls (*n*)	Cases (*n*)	OR (95% CI)	Cases (*n*)	OR (95% CI)	Cases (*n*)	OR (95% CI)	Cases (*n*)	OR (95% CI)	Cases (*n*)	OR (95% CI)
All ages	No balding	190 (87%)	254 (80%)	1.00	187 (81%)	1.00	49 (78%)	1.00	143 (79%)	1.00	100 (82%)	1.00
	Any balding	29 (13%)	64 (20%)	1.69 (1.05–2.74)	44 (19%)	1.60 (0.95–2.67)	14 (22%)	1.93 (0.94–3.95)	39 (21%)	1.82 (1.07–3.10)	22 (18%)	1.15 (0.82–2.79)
	Frontal only	15 (7%)	37 (12%)	1.86 (0.99–3.51)	24 (10%)	1.63 (0.82–3.22)	10 (16%)	2.61 (1.10–6.18)	18 (10%)	1.57 (0.77–3.25)	17 (14%)	2.20 (1.05–4.61)
	Any vertex	14 (6%)	27 (8%)	1.23 (0.88–1.73)	20 (9%)	1.25 (0.87–1.80)	4 (6%)	1.10 (0.61–1.96)	21 (12%)	1.45 (1.01–2.07)	5 (4%)	0.87 (0.51–1.48)
Age <60	No balding	116 (87%)	117 (80%)	1.00	82 (82%)	1.00	20 (67%)	1.00	64 (87%)	1.00	44 (75%)	1.00
	Any balding	17 (13%)	29 (20%)	1.79 (0.90–3.55)	18 (18%)	1.69 (0.77–3.70)	10 (33%)	3.43 (1.37–8.61)	14 (18%)	1.68 (0.75–3.78)	15 (25%)	2.33 (1.03–5.28)
	Frontal only	7 (5%)	17 (12%)	2.60 (1.00–6.79)	9 (9%)	2.12 (0.70–6.44)	8 (27%)	6.51 (2.11–20.06)	6 (8%)	1.76 (0.54–5.76)	11 (19%)	4.23 (1.47–12.14)
	Any vertex	10 (8%)	12 (8%)	1.10 (0.69–1.75)	9 (9%)	1.18 (0.70–1.98)	2 (7%)	1.09 (0.49–2.42)	8 (10%)	1.28 (0.76–2.14)	4 (7%)	1.00 (0.53–1.89)
Age 60+	No balding	74 (86%)	137 (80%)	1.00	105 (80%)	1.00	29 (88%)	1.00	79 (76%)	1.00	56 (89%)	1.00
	Any balding	12 (14%)	35 (20%)	1.23 (0.58–2.57)	26 (20%)	1.19 (0.55–2.59)	4 (12%)	0.68 (0.19–2.37)	25 (24%)	1.53 (0.70–3.38)	7 (11%)	0.59 (0.21–1.65)
	Frontal only	8 (9%)	20 (12%)	1.07 (0.43–2.63)	15 (11%)	1.05 (0.41–2.69)	2 (6%)	0.51 (0.10–2.68)	12 (12%)	1.12 (0.41–3.03)	6 (10%)	0.78 (0.24–2.51)
	Any vertex	4 (5%)	15 (9%)	1.25 (0.70–2.22)	11 (8%)	1.23 (0.67–2.24)	2 (6%)	1.01 (0.41–2.45)	13 (13%)	1.53 (0.85–2.78)	1 (2%)	0.49 (0.16–1.51)

[a]26 cases missing stage.
[b]16 cases missing grade.

difference in the type of baldness (frontal only vs. any vertex.) We also observed positive associations between baldness and prostate cancer occurrence. The greatest odds and the most severe disease occurred in men with frontal only baldness and those younger than age of 60 years with frontal only baldness.

Baldness prevalence

The prevalence of baldness, especially vertex and frontal with vertex baldness, increases with age (8, 12, 25). In the Washington State Surveillance Epidemiology and End Results (SEER) registry, the frequency of any hair loss by the age 30 of years was reported in 20% of prostate cancer cases and 25% of controls ($P = 0.005$). Fifty-five percent of cases and controls reported hair loss in their 50s, whereas 66% of cases and 74% of controls aged 65 years or more reported any hair loss. The prevalence of frontal baldness was 47% in controls and 32% in prostate cancer cases (12). The prevalence of frontal baldness was also 33% in Australian men aged 40 to 69 years (8). We observed 13% of controls and 20% of cases with any baldness, whereas 7% for controls and 13% for cases in our sample suffered from frontal baldness only.

Our results are opposite to the Washington State SEER data and other reports, which suggest that the prevalence of baldness is greater among controls compared with cases (12–14). Although most studies show some variability in prevalence depending on age, ethnic composition of the sample, and study design (population-based vs. hospital-based and reference age for baldness), our results are similar to several other studies that support an increased prevalence of early-onset baldness among prostate cancer cases and an association of baldness with early-onset prostate cancer (10, 16, 26). Unfortunately, the prevalence of early pattern baldness types among African-American prostate cancer cases and controls has not been documented.

Our prevalence of baldness was expected to be lower for an African-American sample and is similar (11, 12) or slightly higher (27) to the rates described previously for African-Americans. Results from the National Health and Nutrition Survey (NHANES) and Washington State SEER and hospital-based Washington, D.C. studies describe an increased prevalence of baldness among Caucasian patients with prostate cancer compared with African-Americans (11, 12, 27). According to our calculations using data provided in the report of Washington State SEER (12), prevalence rates of any hair loss at the age of 30 years are higher for Caucasian cases (Caucasian: 21%; African-American: 15%, $P = 0.112$) compared with controls (Caucasians: 26%; African-Americans: 16%, $P = 0.033$) in the population-based study.

Associations between baldness and prostate cancer

Male-patterned baldness was associated with prostate cancer in Black men in the NHANES cohort [relative risk (RR) = 2.10; 95% CI, 1.04–4.25] and non-Blacks (RR = 1.42; 95% CI, 1.01–1.98; ref. 11). In NHANES, men with

Table 3. Risk factor associations with prostate cancer by baldness pattern in African-American men–adjusted for age

Age group		No baldness at the age of 30 years		Any baldness at the age of 30 years	
	Variables of interest	***N***	**OR (95% CI)**	***N***	**OR (95% CI)**
All ages	Prostate cancer family history	430	1.74 (1.14–2.67)[a]	87	1.26 (0.48–3.35)
	Alcohol (any weekly intake)	426	1.42 (0.94–2.13)	78	1.52 (0.56–4.09)
	Ever smokers	439	0.80 (0.53–1.21)	93	0.80 (0.32–1.99)
	AR-CAG (≤21 repeats)	193	1.42 (0.77–2.62)	45	2.31 (0.41–12.93)
	SRD5A2 A49T (any T)	165	1.34 (0.13–13.43)	36	—
	SRD5A2 V89L (any L)	187	1.09 (0.58–2.04)	41	0.83 (0.16–4.30)
	CYP3A43 (any *3)	163	0.32 (0.15–0.70)[a]	36	0.38 (0.04–3.97)
	CYP3A4 (any *1B)	126	0.44 (0.17–1.20)	28	0.17 (0.02–1.70)
	CYP3A5 (any *1)	136	0.64 (0.26–1.58)	31	2.52 (0.33–19.02)
< Age 60, y	Prostate cancer family history	226	2.04 (1.14–3.65)[a]	43	1.26 (0.32–4.97)
	Alcohol (any weekly intake)	223	1.56 (0.88–2.76)	39	1.06 (0.27–4.14)
	Ever smokers	230	0.37 (0.20–0.69)[a]	46	2.51 (0.66–9.57)
	AR-CAG (≤21 repeats)	91	1.14 (0.46–2.82)	22	1.45 (0.10–22.02)
	SRD5A2 A49T (any T)	—	—	—	—
	SRD5A2 V89L (any L)	94	1.79 (0.70–4.58)	19	0.17 (0.01–4.25)
	CYP3A43 (any *3)	80	0.21 (0.07–0.63)[a]	—	—
	CYP3A4 (any *1B)	74	0.56 (0.18–1.78)	12	0.95 (0.05–17.36)
	CYP3A5 (any *1)	80	0.57 (0.19–1.70)	13	2.39 (0.14–39.95)
≥ Age 60, y	Prostate cancer family history	204	1.36 (0.68–2.73)	44	2.82 (0.46–17.31)
	Alcohol (any weekly intake)	203	1.05 (0.56–1.99)	39	2.08 (0.35–12.25)
	Ever smokers	209	1.30 (0.68–2.49)	47	0.12 (0.02–0.80)
	AR-CAG (≤21 repeats)	102	2.34 (0.92–5.96)	23	3.04 (0.21–43.42)
	SRD5A2 A49T (any T)	—	—	—	—
	SRD5A2 V89L (any L)	93	0.72 (0.27–1.88)	22	1.39 (0.11–16.84)
	CYP3A43 (any *3)	83	0.65 (0.20–2.09)	20	0.54 (0.04–6.54)
	CYP3A4 (any *1B)	52	0.11 (0.01–1.40)	—	—
	CYP3A5 (any *1)	56	0.87 (0.11–6.70)	18	2.37 (0.10–55.07)

NOTE: Tests of heterogeneity of estimates showed no significant differences by baldness group.
[a]Significance levels: a = adjusted $P \leq 0.05$ controlling the false discovery rate.

baldness were at higher risk for prostate cancer in all age strata, but only significantly so for men in the oldest stratum when prostate cancer was most common for this cohort study (ages 65–74 years, RR = 1.69; 95% CI, 1.14–2.46). This differs from our case–control study as we had similar number of cases in both the older and younger age groups. This enabled us to capture differences that may only occur in a younger age group because we had a sufficient sample size to detect significant differences in our age-group analyses. A case–control study of 669 subjects in France also found a positive association between prostate cancer and baldness at the age 20 of years (OR = 2.01; 95% CI, 1.07–3.79). Interestingly, this trend was lost when baldness at the age of 30 and 40 years was recalled (10). The authors suggested that it may be more difficult to see the effects of baldness in older men as baldness prevalence increases similarly in cases and controls with aging. Contrary to their findings, a recent large prospective study of 9,448 Australian men found that baldness at the age of 40 years rather than the age of 20 years was predictive of early-onset prostate cancer (26). It has been suggested that the age of 20 years may be too early to observe associations of baldness on prostate cancer, as many men that will experience early-onset baldness have not yet begun balding by that age. An age range between 30 to 40 years seems more appropriate as a reference point to avoid misclassification of early pattern baldness and is also a closer timepoint to prostate cancer diagnosis and related processes. Type of baldness has also been investigated for differential associations with prostate cancer risk. An Australian study showed that only vertex baldness was positively associated with prostate cancer occurrence (OR = 1.54; 95% CI, 1.19–2.00; ref. 14). Additional studies from Washington state and the Netherlands found protective effects of baldness on prostate cancer risk, particularly for men with a combination of

early-onset frontal–vertex balding (12, 13). We noted no significant inverse associations in this African-American sample of patients or significant effects related to vertex baldness. It remains unclear whether there are differences in the biologic significance of type of baldness as it relates to prostate cancer and whether different patterns of baldness reflect genetic predisposition to hormonal milieu that might alter risk for disease. However, frontal baldness clearly is more significant for our sample of African-American patients and is particularly relevant for severe disease.

It remains unclear why men bald differently (frontal vs. vertex) and how the mechanisms that influence baldness type contribute differentially to prostate cancer onset. This is the first study to report the association of frontal baldness with aggressive disease in younger prostate cancer cases. However, it is also the first study to examine these associations stratified by age group and baldness type in an all African-American sample. This study is unique in that respect and cannot be easily compared with previous studies. These results will have to be validated using similar methods in a similar sample of patients. Given that prostate cancer outcomes are worse for African-American men than other ethnic groups, future confirmatory studies may suggest frontal baldness by the age of 30 years as an important risk factor for early diagnosis of this high-risk group.

There are also limited data concerning the effect of PSA values on baldness and prostate cancer associations. We found significant associations of any baldness and frontal baldness with early prostate cancer among men with high PSA levels (PSA $\geq$ 10 ng/mL.) However, a study by Yassa and colleagues showed no associated early pattern baldness (by the age of 40 years) in French prostate cancer cases with a much higher PSA cutoff point of more than 20 ng/mL ($P = 0.63$; ref. 10).

Baldness and prostate cancer are linked by their relationship to androgen metabolism (22). There are differences in the prevalence of genotypes that metabolize testosterone and influence dihydrotestosterone (DHT) levels (19, 20). High DHT levels have been associated with both early pattern baldness and prostate cancer processes, including increases in PSA levels. Perhaps the underlying mechanisms that influence these associations by race are genetically determined. Genetic studies to date have found genes associated with early-onset baldness that are also involved in pathways of androgen metabolism, hair development/hair cycling, and neurodegenerative diseases that increase with aging (28–30). However, little is known about the associations of many of these pathways in men of African descent. Interestingly, not all studies with predominately Caucasian samples show consistent effects of baldness on prostate cancer, so there is heterogeneity in the reports that have been published in recent years. Much more research in this area is needed to confirm our results and the previous results of other investigators.

Smoking

Although only alcohol intake and not smoking has been previously associated with baldness (8), we observed no association of alcohol intake with prostate cancer in the context of baldness. However, we were surprised to find an association that others had not reported with smoking. By extending our analytic design to examine smoking results stratified by age group and baldness type, we observed significant protective smoking effects for particular subgroups of African-American men. We also observed in our study significant interactions of smoking, median age, and baldness. Although smoking has not been a consistent risk factor in prostate cancer, recent studies have shown significant positive associations for prostate cancer incidence, prostate cancer mortality, and risk of biochemical recurrence in patients with prostate cancer (31, 32). Although smoking may have a direct biologic consequence on promoting carcinogenesis and increasing prostate cancer risk and progression (33), for individuals with particular predisposition, smoking may yield a protective effect for cancer (34), similar to what we observed in certain subgroups of our sample.

Both ever-smoking and the *CYP3A43* *3 genotype in particular showed protective effects with prostate cancer in young men with no balding at the age of 30 years. This could suggest that hypoandrogenism, mediated by the combination of smoking and the expression of *CYP3A43* *3, may lower the risk of disease for hormonally driven cancers. It is unclear what the mechanisms might be that invoke such protection in this subgroup of men or whether the mechanism for smoking and *CYP3A43* may be connected in some way. Little is known about the interplay of these variables and how they may jointly contribute to prostate cancer risk.

This "phenotype-limited" pattern of association (i.e., where the genetic association is only observed on the background of a specific phenotype) is consistent with other studies evaluating genotype and phenotype associations simultaneously. For example, Kanetsky and colleagues observed that *MC1R* genotypes only affect risk of melanoma among individuals with "low-risk" phenotypes (i.e., dark hair color; ref. 35). Similarly, we observe here that genotypes have their primary effect in men with a "low-risk" prostate cancer phenotype (i.e., no baldness). To better understand the etiology of common diseases, it may be necessary to explore the phenotype-limited effects of susceptibility genotypes.

However, it is important to note that our sample sizes for the individual baldness groups by smoking and genotype were small and may thus have been underpowered to detect some associations. We computed tests of heterogeneity and determined that there were no significant differences in the estimates that were obtained for these risk factors by baldness status. Therefore, we must view these results with caution, as there may be little difference in the smoking and genotype effects on prostate cancer in men with and without baldness. It is also clear that the health risks of smoking far outweigh any interesting

biologic "benefits" that may occur for a subset of patients in this particular context. In general, it seems that more research is needed in this area before we can conclude what the true relationships among baldness, smoking, and androgen genotypes may be. This study suggests that we take a closer look at these variables in other populations before we discount them, especially among younger patients with prostate cancer.

Study limitations and strengths

Our study lacked the power to study associations with frontal-vertex/vertex baldness, a pattern shown to be a predictive factor in some other studies. However, this pattern seems to be less common among African-Americans, so it may not be an important risk factor for this population. There may also have been recall bias in remembering baldness pattern at a younger age accurately. However, this is unlikely, as most men would likely remember when they developed alopecia due to psychosocial effects that it might have on the individual patient (10, 36). Aside from finasteride, we did not ask about other treatments for baldness, such as Rogaine. Future studies may also take a more thorough look at exposure to smoking.

The strength of our study is that we were able to analyze genotypes, PSA, and other risk factors with baldness in an understudied high-risk population of men, African-Americans. All of the studies reported in the literature, except for NHANES (11), either were homogenous samples, did not correct for race, or adjusted for race without reporting the results for African-Americans separately. There is tremendous variation in associations of early-onset baldness and prostate cancer by race, but it is very difficult to compare studies because of differing methodology. Study designs vary by age groups, sample populations, community-based versus hospital-based, and differing assessment of baldness with varying age of reference and categories of baldness type. Early-onset baldness also has been associated with several cardiovascular risk factors for which African-Americans are at increased risk, including diabetes and central adiposity (37–39). Our ability to observe stronger associations in our sample may also be linked to underlying biology and higher prevalence of risk factors that place African-Americans at increased risk for a variety of chronic diseases involving disturbances in androgen metabolism. Although we have a limited number of patients in our analyses, our results are thought provoking and provide evidence for building larger follow-up studies that examine interactions among genotypes, lifestyle factors, baldness, and prostate cancer.

Conclusions

The mechanistic relationship between baldness, genotypes, smoking, and prostate cancer etiology/severity is not yet well defined. However, our findings support the need to study these interactions and their effects on the underlying hormones that impact prostate cancer risk.

Given the high prevalence of prostate cancer in African-Americans, early-onset baldness may be a particularly relevant indicator of risk that deserves attention in future studies as we seek to advance our knowledge about high-risk populations. Future studies examining magnitude of risk and consistency compared with other risk factors may suggest whether early-onset baldness is an important predictor of early-onset prostate cancer. Furthermore, knowledge of both *CYP3A43* genotype and baldness pattern may provide predictive information about the risk of prostate cancer in African-American men.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Authors' Contributions

Conception and design: T.R. Rebbeck, C. Zeigler-Johnson
Development of methodology: T.R. Rebbeck, C. Zeigler-Johnson
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Zeigler-Johnson, E. Spangler, T.R. Rebbeck
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.H. Morales, Bao-Li Chang, T.R. Rebbeck, C. Zeigler-Johnson
Writing, review, and/or revision of the manuscript: C. Zeigler-Johnson, K. H. Morales, T.R. Rebbeck
Administrative, technical, or material support (i.e., reporting or organizing data, constructing: databases): C. Zeigler-Johnson, T.R. Rebbeck, T.R. Rebbeck
Study supervision: C. Zeigler-Johnson, E. Spangler, T.R. Rebbeck

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