Baldness and Risk of Prostate Cancer in the Health Professionals Follow-up Study

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ABSTRACT

Background: The association between male pattern baldness and prostate cancer has been inconsistent. We prospectively investigated the association between baldness at age 45 and prostate cancer risk in the Health Professionals Follow-up Study (HPFS), focusing on clinical and molecular markers.

Methods: Baldness was self-reported on the 1992 questionnaire using the modified Norwood–Hamilton scale prior to diagnosis. We estimated HRs between baldness and prostate cancer risk among 36,760 men, with follow-up through 2014. We also investigated whether baldness was associated with prostate cancer defined by tumor protein expression of androgen receptor and the presence of the TMPRSS2:ERG fusion.

Results: During 22 years, 5,157 prostate cancer cases were identified. Fifty-six percent of the men had either frontal or vertex baldness. No significant associations were found between baldness and prostate cancer risk. Among men younger than 60 years, there was a statistically significant association between frontal and severe vertex baldness and overall prostate cancer (HR: 1.74; 95% confidence interval: 1.23–2.48). Baldness was not significantly associated with expression of molecular subtypes defined by AR and TMPRSS2:ERG IHC of prostate tumors.

Conclusions: This study showed no association between baldness at age 45 and prostate cancer risk, overall or for clinical or molecular markers. The association between baldness and overall prostate cancer among younger men is intriguing, but caution is warranted when interpreting this finding.

Impact: The null findings from this large cohort study, together with previous literature's inconclusive findings across baldness patterns, suggest that baldness is not a consistent biomarker for prostate cancer risk or progression.

Introduction

Male pattern baldness and prostate cancer are both androgen-related conditions with potentially similar epidemiologic risk factors, including advanced age (1). As such, several studies have investigated the association between baldness and prostate cancer risk. Prior results from case–control studies are inconsistent, with some citing male pattern baldness as a significant risk factor for prostate cancer, either overall or more aggressive (2–7), and others reporting null or protective associations (8–10). Findings from cohort studies have also been mixed, with results differing for aggressive versus overall prostate cancer, and patterns of baldness [any, frontal, or vertex (baldness at the crown of the head)]. Two studies found an increased risk of aggressive or fatal prostate cancer (11, 12), and one showed an increased risk for early-onset (before age 40 years) prostate cancer (13), comparing any or, frontal plus vertex baldness, with no baldness. Another study found moderate balding compared with none was associated with overall prostate cancer. (14) Two other cohort studies found no association between any baldness and any prostate cancer outcome (15, 16). A meta-analysis of nine case–control studies and two cohort studies found no association between baldness and overall prostate cancer risk; however, among five case–control studies with information on more aggressive prostate cancer, there was a 60% increased risk of aggressive prostate cancer comparing any baldness with no baldness. In the same meta-analysis, vertex baldness was associated with an 18% increased risk of overall prostate cancer and a 62% increased risk of aggressive prostate cancer (17). A separate meta-analysis conducted in 2018 among 15 studies found no association between baldness and prostate cancer, but found a 24% increased risk of prostate cancer for those with vertex baldness compared with no baldness. (18) In addition, significant heterogeneity was seen across studies.

This study utilizes data from a large, prospective cohort of men, the Health Professionals Follow-up Study (HPFS), to evaluate the association between baldness and risk of overall, advanced, and lethal prostate cancer. We hypothesized there would be a positive association between baldness, and particularly vertex baldness, and prostate cancer, and that the association would be stronger for advanced or lethal prostate cancer. To extend previous research, we examine this relationship in a large sample with robust clinical and covariate information and long-term follow-up, evaluate different subtypes of baldness. Furthermore, given associations of hair pattern and androgen signaling, we also examined the association for different clinical and molecular subtypes defined by AR and *TMPRSS2:ERG* IHC of prostate cancer, the androgen receptor (AR) and the *TMPRSS2:ERG* fusion.

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Materials and Methods

Study population

The HPFS is an ongoing prospective cohort of 51,529 males ages 40–75 years at baseline in 1986 (19). The participants have been followed with biennial questionnaires to obtain updated demographic, lifestyle, and disease endpoint information. Dietary information is collected every 4 years using a validated food frequency questionnaire.

In 1992, the participants provided information about their hair pattern at age 45. We excluded men who had died before 1992 ($n = 2{,}019$), were diagnosed with any cancer, including prostate, prior to the 1992 questionnaire ($n = 3{,}958$), missing the 1992 questionnaire ($n = 3{,}099$), missing date of birth ($n = 6$), missing date of cancer diagnosis ($n = 6$), and improbable metastatic cancer date ($n = 2$). In addition, we excluded those who returned the 1992 questionnaire, but were missing information on baldness from the 1992 questionnaire ($n = 5{,}679$). Our final study population included 36,760 men who were followed prospectively for prostate cancer incidence and progression through 2014. The characteristics of men who responded to the baldness question ($n = 36{,}760$) and those who did not respond to the baldness question ($n = 5{,}679$) were similar. The mean age was 59.4 years and 59.6 years, respectively. Those who did not respond were slightly more likely to have a higher body mass index (BMI; 26.3 kg/m^2 vs. 25.8 kg/m^2) and were more likely to be current smokers (10.3% vs. 6.8%). In relation to prostate cancer outcomes, those without baldness information were slightly more likely to have lethal (13.2% vs. 11.7%) and advanced (7.9% vs. 6.7%) prostate cancer.

The study protocol was approved by the Institutional Review Board at the Harvard T.H. Chan School of Public Health (Boston, Massachusetts), and those of participating cancer registries as required.

Assessment of hair patterns

Men were asked to indicate their "hair pattern at age 45" based on a modified Norwood–Hamilton scale. The possible patterns are shown in **Fig. 1**. For our primary analysis, we compared frontal balding (pattern 2) and any vertex balding (patterns 3–5) with no balding (pattern 1). We also individually compared: frontal baldness (pattern 2), frontal plus mild vertex baldness (pattern 3), frontal plus moderate vertex baldness (pattern 4), and frontal plus severe vertex baldness (pattern 5), respectively, with no baldness pattern (pattern 1) as the reference group. Finally, we dichotomized the baldness patterns and compared any baldness (patterns 2–5) with no baldness (pattern 1).

Prostate cancer ascertainment

Prostate cancer cases were initially obtained by self-report from the participants or their next of kin on biennial questionnaires. Medical records and pathology reports were obtained to confirm diagnoses and extract clinical information, including Gleason score and stage. Deaths for the whole HPFS cohort were ascertained from family members and the National Death Index, and cause of death was assigned by an endpoints committee of study physicians using medical and death reports. Follow-up for cancer incidence (96%) and mortality (>99%) was quite complete. Men with prostate cancer were followed with additional biennial prostate cancer–specific questionnaires to obtain information on treatments, disease progression, and diagnosis of metastases. For the current analysis, we assessed total prostate cancer incidence (excluding stage T1a disease), lethal (death from prostate cancer or metastasis at diagnosis or over follow-up), advanced stage (stage T3b, T4, N1, or M1 at diagnosis or lethal disease), and high grade (defined as Gleason grade 4+3 or above). In a sensitivity analysis, we also defined high grade as Gleason 8 or above.

Molecular subtypes defined by AR and TMPRSS2:ERG IHC

We examined protein tumor tissue expression of AR and ERG, as a marker of *TMPRSS2:ERG* on a subset of prostate cancer specimens from patients in HPFS, as described previously (20). Briefly, it included men diagnosed with prostate cancer between 1986 and 2005 in HPFS for whom archival tumor tissue materials from radical prostatectomy or transurethral resections of the prostate (TURP). We performed IHC on 5-μm sections of tumor tissue microarrays were constructed from archival radical prostatectomy and TURP specimens. Detailed descriptions of the IHC methods have been provided by previous studies (20, 21). Briefly, AR was measured [Upstate (Millipore); catalog no. 06–680; 1:100) and scored by the Ariol and ChromaVision (ChromaVision Medical Systems, Inc.) systems as a continuous variable. We dichotomized expression at the median. We characterized *TMPRSS2:ERG* using ERG protein expression with a mAb (clone EPR3864, Epitomics, Inc.; ref. 22). Tumors were classified ERG-positive if at least one core stained positive for ERG, and ERG-negative if all cores stained negative for ERG. Among the men diagnosed with prostate cancer, 696 men were assayed for ERG and 351 were assayed for AR.

Statistical analysis

Cox proportional hazards regression models were used to calculate age-adjusted and multivariable-adjusted HRs and 95% confidence intervals (CI) for total, lethal, advanced, and high-grade cancers. Follow-up began on the date of return of the 1992 questionnaire and continued until prostate cancer diagnosis, death from any other

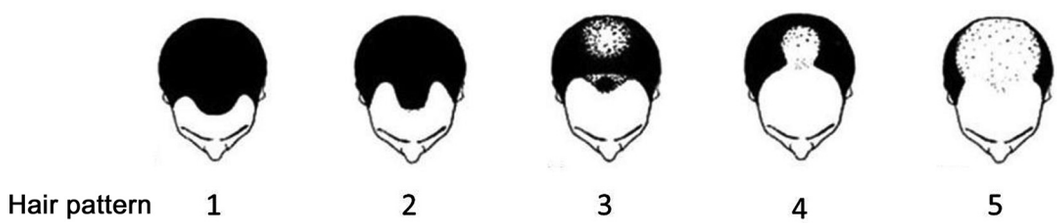

Figure 1.

Hair pattern scale used in the HPFS questionnaire, modeled after the Norwood–Hamilton Baldness Scale. Participants reported which pattern best described their hair pattern at age 45. Hair pattern 1 represents no baldness, hair pattern 2 represents frontal baldness, hair pattern 3 represents frontal and mild vertex baldness, hair pattern 4 represents frontal and moderate vertex baldness, and hair pattern 5 represents frontal and severe vertex baldness.

causes, or end of follow-up (January 1, 2014), whichever came first. All models were stratified by age and calendar time. In multivariable models, we additionally adjusted for race (White, African American, Asian American, other), height (<68 inches, 68–70 inches, 70.1–72 inches, >72 inches), BMI at age 21 (<20 kg/m^2, 20–22.4 kg/m^2, 22.5–25 kg/m^2, >25 kg/m^2), family history of prostate cancer in father or brother (yes or no), and history of PSA testing (yes or no). Inclusion of smoking, BMI, physical activity, diabetes, and diet (tomato sauce intake, coffee, and energy intake) in our models did not change estimates, so we present the most parsimonious models. Because other studies have suggested varying associations between baldness and prostate cancer by age at diagnosis, we repeated the analysis, restricting it to men less than 60 years old.

To assess the association between baldness and risk of prostate cancer defined by tissue biomarkers, we implemented an extension of Cox modeling as described by Lunn and McNeil (23) that allows for exposure associations to vary by disease subtype, as described previously (24, 25). These models allowed for the estimation of HRs separately for ERG-positive and ERG-negative cancer versus no cancer, respectively; similar models were conducted for AR. We tested for heterogeneity across HRs using likelihood ratio tests (26). Follow-up began on the date of return of the 1992 questionnaire and continued until diagnosis of prostate cancer, death from other causes, or end of follow-up (January 1, 2009—when the last case of IHC diagnosed prostate cancer was made), whichever came first. Because tissue markers were measured in a smaller subset of cases, we did not evaluate risk of ERG-, AR-defined lethal or advanced disease due to low sample sizes.

All analyses were performed using SAS version 9.4 (SAS Institute, Inc), and P values were two-sided, with <0.05 considered to be statistically significant.

Results

Among the study population of 36,760 men with information on hair pattern at age 45, 16,070 (44%) reported no balding at age 45; 9,374 reported (25%) frontal balding; 6,300 (17%) reported frontal and mild vertex balding; 2,929 (8%) reported frontal and moderate vertex balding; and 2,087 (6%) reported frontal and severe vertex balding. We confirmed 5,157 total prostate cancer cases during the 22 years of follow-up. Of these, 606 were lethal, 780 advanced, and 1,206 high-grade (Gleason score 4+3 or higher). **Table 1** shows the characteristics of the study population in 1992 according to categories of baldness as assessed at age 45. Men who reported frontal and severe vertex baldness (pattern 5) tended to be slightly shorter, had a higher BMI at age 21 and were less likely to currently smoke, compared with those who reported no baldness. Participant characteristics were otherwise similar across the baldness categories.

There was a suggestion of an inverse association between frontal and moderate vertex baldness, compared with no baldness, and risk of overall prostate cancer (HR: 0.89; 95% CI: 0.80–1.00). However, none of the other hair patterns were associated with overall prostate cancer risk and overall vertex baldness was slightly (nonsignificantly) associated with increased risk (**Table 2**). We also found no association between baldness patterns and risk of lethal, advanced, or high-grade disease (**Table 2**). Furthermore, any baldness (dichotomized) was not associated with risk of overall or for more aggressive stage or grade disease (lethal—HR: 0.99; 95% CI: 0.84–1.17; advanced—HR: 1.01; 95% CI: 0.88–1.17). We found similar results defining lethal disease as Gleason 8 or above (Supplementary Table S1). We did find a statistically significant association between frontal and severe vertex baldness and risk of overall prostate cancer among men younger than 60 years old (HR: 1.74; 95% CI: 1.23–2.48; **Table 3**). We were unable to evaluate lethal, advanced, or high-grade disease in the younger age group due to small numbers.

We then assessed whether baldness patterns at age 45 were associated with risk of prostate cancer defined by molecular subtypes defined by AR and *TMPRSS2:ERG* IHC. There was no association between hair pattern at age 45 and risk of ERG-positive or ERG-negative prostate tumors, nor with disease characterized by AR expression (**Table 4**).

Discussion

In this prospective cohort study of U.S. male health professionals, we found that hair pattern at age 45 was not associated with risk of prostate cancer. While we hypothesized there would be a positive association between baldness, and particularly vertex baldness, and prostate cancer, we found no clear evidence of associations with overall, or more aggressive disease. Furthermore, we also did not observe an association between male pattern baldness and risk of ERG- or AR-defined prostate cancers. A positive association between frontal and severe vertex baldness and overall prostate cancer among men younger than 60 years old suggests a potential association between baldness and early-age onset prostate cancer, though absence of a positive risk trend across baldness severity groups suggest that caution is warranted when interpreting this finding.

Previous studies on this subject have yielded conflicting results (2–17, 27). A 2018 meta-analysis of 11 studies found no association between male pattern baldness and overall prostate cancer risk; however, among the five case–control studies with information on more aggressive disease, there was a 60% increased risk of aggressive prostate cancer, comparing any baldness with no baldness (17). Similarly, among two of these case–control studies, vertex baldness was associated with an 18% increased risk of overall and 62% risk of aggressive prostate cancer (17). A separate meta-analysis among 15 studies found a 24% increased risk of overall prostate cancer comparing vertex balding with no balding; however, significant heterogeneity was noted between studies (18). An analysis of 39,070 men nested in the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial found a 39% increased risk of aggressive prostate cancer (defined as Gleason ≥7, clinical stage ≥III or fatal disease) comparing frontal plus moderate vertex baldness with no baldness; however, the association between frontal plus severe vertex baldness and aggressive prostate cancer was null (HR: 0.97; 95% CI: 0.68–1.39; ref. 11). Similarly, a study of 4,316 men, including 107 prostate cancer deaths, in the National Health and Nutrition Examination Survey (NHANES), found a 56% increased risk of fatal prostate cancer for any dermatologically confirmed baldness compared with none, with the highest risk (83%) when comparing moderate baldness with no baldness (12). A previous analysis in NHANES conducted among 4,421 men and 214 prostate cancer cases similarly found an increased risk of prostate cancer (HR: 1.60; 95% CI: 1.15–2.23) comparing moderate with no baldness (14). Conversely, analyses in the Vitamins and Lifestyle (VITAL) cohort study and a Finnish study found no association between any baldness pattern and prostate cancer (15, 16). In our study of over 5,000 prostate cancer cases, including 780 advanced, we did not find any associations between hair patterns and advanced, lethal or high grade, prostate cancer. The sample demographics in previous studies (11–13, 15) were similar to ours, and included mainly white men of similar age distribution. However, the number of prostate cancer cases in our study (5,157) was significantly more than the previous studies.

Table 1. Age-standardized characteristics of the study population at baseline by hair pattern at age 45 years, the Health Professionals Follow-up Study, 1992.

N (%)	No baldness 16,070 (44%)	Frontal baldness 9,374 (25%)	Frontal + mild vertex baldness 6,300 (17%)	Frontal + moderate vertex baldness 2,929 (8%)	Frontal + severe vertex baldness 2,087 (6%)
Mean baseline age, years (SD)[a]	59.5 (9.4)	59.9 (9.6)	59.1 (9.5)	60.3 (9.7)	59.8 (9.8)
Race/ethnicity, %					
White	95.6	96.7	96.6	96.7	96.9
Black	0.8	0.6	0.8	0.6	1.0
Asian	2.2	1.3	1.1	1.0	0.3
Other race	1.5	1.4	1.5	1.7	1.8
Height, %					
Less than 68 inches	24.3	26.8	28.3	27.4	29.2
68–70 inches	28.8	28.9	29.5	29.8	29.3
70–72 inches	28.3	27.3	26.1	26.4	27.0
Over 72 inches	18.6	17.1	16.1	16.4	14.5
BMI at age 21 years, %					
Less than 20 kg/m^2	12.9	12.4	11.0	10.3	9.5
20–<22.5 kg/m^2	31.8	31.5	30.6	29.2	27.0
22.5–<25 kg/m^2	34.7	35.6	36.0	38.0	36.3
25+ kg/m^2	20.5	20.5	22.5	22.5	27.2
BMI, %					
Less than 21.0 kg/m^2	3.3	3.1	2.8	2.5	3.2
21–<25 kg/m^2	35.0	35.6	32.9	31.9	29.9
25–<30 kg/m^2	39.0	39.4	41.0	41.0	41.2
30+ kg/m^2	8.6	7.6	8.3	9.7	10.8
PSA screening in prior 2 years					
1994, %	41.8	42.5	43.7	42.1	43.6
2000, %	75.6	75.0	76.3	77.1	76.9
2004, %	73.0	72.5	73.8	74.1	73.6
Smoking status, %					
Never smoker	43.5	44.3	45.5	47.1	46.1
Past smoker, quit >10 years	31.8	31.9	30.9	30.6	30.6
Past smoker, quit ≤10 years	11.6	10.9	10.8	10.2	11.3
Current smoker	7.2	6.8	6.4	5.6	5.9
History of diabetes, %	4.8	4.4	4.5	5.4	6.1
Family history of prostate cancer, %	13.7	13.7	13.2	13.6	12.2
Mean total physical activity, MET-hours/week (SD)	25.8 (22.6)	25.5 (22.2)	25.3 (22.4)	25.6 (22.8)	24.7 (21.9)
Mean total energy intake, kcal/day (SD)	1955 (551)	1973 (551)	1959 (558)	1951 (548)	1965 (563)
Mean tomato sauce intake, servings/week (SD)	0.9 (0.9)	0.9 (0.9)	1.0 (1.0)	0.9 (1.0)	0.9 (1.0)
Mean coffee intake, cups/day (SD)	1.9 (1.7)	1.9 (1.7)	1.9 (1.6)	1.9 (1.7)	1.9 (1.6)

Note: Values are means (SD) for continuous variables, percentages or ns or both for categorical variables, and standardized to the age distribution of the study population. Values may not sum to 100% due to rounding and missingness.
[a]Value is not age-adjusted.

Some studies have suggested an age-dependent association between hair pattern and prostate cancer risk. A cohort study done in 2013 among 9,448 participants and 476 prostate cancer cases evaluated the association between balding, categorized as no balding, frontal balding, and vertex balding, and early-onset prostate cancer. They found that men with vertex balding (compared with no balding) at age 40 had an increased risk of early-onset prostate cancer and a lower risk of late-onset prostate cancer (13). At age 55, men with vertex balding had an 81% increased risk of overall prostate cancer; at age 60–70 years, there was no association; and at age 75 years, those with vertex balding had a 44% reduced risk. We similarly found a significant association between frontal and severe vertex baldness and overall prostate cancer risk among men younger than 60 years. When comparing vertex with no balding, there was a 12% increased, but not statistically significant, risk of overall prostate cancer among younger men.

Common risk factors, such as age and endogenous hormone levels, have been highlighted as potential explanation for an association between male pattern baldness and prostate cancer (1). Advancing age, for example, increases the incidence of both conditions (1, 28). Androgen levels have also been associated with both baldness and prostate cancer; however, associations between circulating androgen levels and prostate cancer have been varied (2, 9, 10, 29, 30). Testosterone is responsible for overt sexual development in men, while DHT causes maturation of the prostate tissue and appearance of facial,

Table 2. HRs and 95% CIs of the association between hair pattern at age 45 years and risk of prostate cancer, the Health Professionals Follow-up Study, 1992–2014.

		Age-adjusted		Full model[a]	
	Cases, *n*	HR (95% CI)	*P*	HR (95% CI)	*P*
Overall prostate cancer					
Hair pattern					
No baldness	2,238	1.00 (ref)		1.00 (ref)	
Frontal baldness	1,303	1.00 (0.93–1.07)	0.89	0.99 (0.93–1.06)	0.83
Vertex baldness	1,616	1.03 (0.97–1.10)	0.33	1.03 (0.97–1.10)	0.33
Hair pattern					
No baldness	2,238	1.00 (ref)		1.00 (ref)	
Frontal baldness	1,303	1.00 (0.93–1.07)	0.89	0.99 (0.93–1.06)	0.83
Frontal + mild vertex baldness	935	1.08 (1.00–1.17)	0.05	1.08 (1.00–1.17)	0.05
Frontal + moderate vertex baldness	371	0.90 (0.80–1.00)	0.05	0.89 (0.80–1.00)	0.04
Frontal + severe vertex baldness	310	1.09 (0.97–1.23)	0.15	1.10 (0.98–1.24)	0.12
Lethal prostate cancer					
Hair pattern					
No baldness	267	1.00 (ref)		1.00 (ref)	
Frontal baldness	163	1.04 (0.85–1.27)	0.71	1.04 (0.85–1.27)	0.69
Vertex baldness	176	0.94 (0.78–1.14)	0.56	0.95 (0.78–1.15)	0.61
Hair pattern					
No baldness	267	1.00 (ref)		1.00 (ref)	
Frontal baldness	163	1.04 (0.85–1.27)	0.71	1.04 (0.85–1.27)	0.69
Frontal + mild vertex baldness	98	0.98 (0.78–1.24)	0.87	0.99 (0.78–1.25)	0.92
Frontal + moderate vertex baldness	42	0.81 (0.58–1.12)	0.21	0.81 (0.58–1.12)	0.20
Frontal + severe vertex baldness	36	1.04 (0.73–1.48)	0.83	1.07 (0.75–1.52)	0.72
Advanced prostate cancer					
Hair pattern					
No baldness	339	1.00 (ref)		1.00 (ref)	
Frontal baldness	202	1.01 (0.85–1.21)	0.91	1.01 (0.85–1.21)	0.90
Vertex baldness	239	1.01 (0.85–1.19)	0.93	1.02 (0.86–1.20)	0.86
Hair pattern					
No baldness	339	1.00 (ref)		1.00 (ref)	
Frontal baldness	202	1.01 (0.85–1.21)	0.91	1.01 (0.85–1.21)	0.90
Frontal + mild vertex baldness	136	1.06 (0.87–1.30)	0.55	1.07 (0.88–1.31)	0.50
Frontal + moderate vertex baldness	57	0.88 (0.66–1.17)	0.37	0.87 (0.66–1.16)	0.35
Frontal + severe vertex baldness	46	1.04 (0.76–1.42)	0.81	1.07 (0.78–1.46)	0.69
High-grade prostate cancer					
Hair pattern					
No baldness	537	1.00 (ref)		1.00 (ref)	
Frontal baldness	306	0.97 (0.85–1.12)	0.72	0.97 (0.84–1.12)	0.71
Vertex baldness	363	0.98 (0.86–1.13)	0.81	0.99 (0.86–1.13)	0.87
Hair pattern					
No baldness	537	1.00 (ref)		1.00 (ref)	
Frontal baldness	306	0.97 (0.85–1.12)	0.72	0.97 (0.85–1.12)	0.72
Frontal + mild vertex baldness	207	1.01 (0.86–1.19)	0.92	1.02 (0.86–1.19)	0.86
Frontal + moderate vertex baldness	89	0.90 (0.72–1.13)	0.38	0.90 (0.72–1.13)	0.37
Frontal + severe vertex baldness	67	1.03 (0.79–1.33)	0.84	1.04 (0.81–1.35)	0.75

Abbreviations: Lethal cancer, distant metastases at diagnosis, or development of metastases or death over follow-up; advanced cancer, T3b, T4, or N1, or M1 at diagnosis or lethal; high-grade cancer, Gleason 4+3, 8–10.

[a]Full model adjusted for age, calendar time, race (white, African American, Asian, other), height (≤68, >68–70, >70–72, >72 inches), BMI at age 21 years (<20, 20–<22.5, 22.5–<25, 25+ kg/m^2), and family history of prostate cancer, PSA testing history (yes/no in prior 2 years, lagged by one period to avoid counting diagnostic PSA tests as screening), PSA testing intensity (reported testing in ≥50% or <50% of possible time periods, lagged by one period).

axillary, and pubic hair, along with male pattern baldness. Men with vertex baldness had higher levels of total and free testosterone, compared with those with no balding (10). In addition, another study showed a positive association between any balding and levels of serum testosterone, DHT, estradiol, and sex hormonebinding globulin, and a weak association with elevated intraprostatic testosterone (31). A large Finnish study showed that initiation of endogenous androgen production, as occurs in late puberty (defined as puberty onset after 15 years of age), was associated with a lower prostate cancer risk compared with earlier onset (16). Furthermore, a study using data from a tertiary hospital found that compared with patients with stable testosterone over one year, men with an annual testosterone reduction of more than 30 ng/dL had 5-fold increased risk of prostate cancer (32). Future robust and large-scale

Table 3. Association between hair pattern at age 45 years and overall prostate cancer among men <60 years old (early-onset prostate cancer), Health Professionals Follow-up Study.

		Age-adjusted		Full model[a]	
	Cases, *n*	HR (95% CI)	*P*	HR (95% CI)	*P*
Any baldness					
No	182	1.00 (ref)		1.00 (ref)	
Yes	239	1.02 (0.84–1.24)	0.84	1.02 (0.84–1.24)	0.82
Hair pattern					
No baldness	182	1.00 (ref)		1.00 (ref)	
Frontal baldness	94	0.90 (0.70–1.16)	0.43	0.90 (0.70–1.16)	0.42
Vertex baldness	145	1.11 (0.89–1.39)	0.34	1.12 (0.90–1.40)	0.30
Hair pattern					
No baldness	182	1.00 (ref)		1.00 (ref)	
Frontal baldness	94	0.90 (0.70–1.16)	0.43	0.90 (0.70–1.16)	0.42
Frontal + mild vertex baldness	78	1.02 (0.78–1.33)	0.90	1.02 (0.78–1.33)	0.91
Frontal + moderate vertex baldness	28	0.91 (0.61–1.37)	0.66	0.93 (0.62–1.40)	0.73
Frontal + severe vertex baldness	39	1.69 (1.19–2.40)	0.003	1.74 (1.23–2.48)	0.002

[a]Full model adjusted for age, calendar time, race (white, African American, Asian, other), height (≤68, >68–70, >70–72, >72 inches), BMI at age 21 years (<20, 20–<22.5, 22.5–<25, 25+ kg/m^2), and family history of prostate cancer, PSA testing history (yes/no in prior 2 years, lagged by one period to avoid counting diagnostic PSA tests as screening), PSA testing intensity (reported testing in ≥50% or <50% of possible time periods, lagged by one period).

studies of the fluctuations in androgen levels at multiple points in life may help explain previous findings for an association between male pattern baldness and prostate cancer.

We also found men who reported frontal and severe vertex balding tended to be slightly shorter. Genome-wide association studies indicate a high degree of heritability for both early- and late-onset baldness, with most variants located in androgen-related pathways (33). A variant in the AR gene (*AR*-E211 A allele) has been associated with both a lower risk of metastatic prostate cancer and baldness (34). Genetic variants associated with baldness have also been associated with height and waist-hip ratio (35) such that variants associated with increased risk of baldness were also associated with shorter height (33, 35). Strengths of this study include a large sample size and a long-term and complete follow-up for prostate cancer incidence

Table 4. HRs and 95% CIs for risk of ERG-positive and ERG-negative and high and low expression of androgen receptor by hair pattern at age 45 years, Health Professionals Follow-up Study.

	ERG-positive		ERG-negative		
	Cases, *n*	Multivariable HR (95% CI)	Cases, *n*	Multivariable HR (95% CI)	$P_{heterogeneity}$
Hair pattern					
No baldness	139	1.00 (ref)	163	1.00 (ref)	0.38
Frontal baldness	99	1.22 (0.94–1.58)	97	1.03 (0.80–1.32)	
Vertex baldness	87	0.89 (0.68–1.17)	111	1.00 (0.78–1.27)	
Hair pattern					
No baldness	139	1.00 (ref)	163	1.00 (ref)	0.67
Frontal baldness	99	1.22 (0.94–1.58)	97	1.03 (0.80–1.32)	
Frontal + mild vertex baldness	48	0.85 (0.61–1.18)	63	1.02 (0.76–1.37)	
Frontal + moderate vertex baldness	22	0.91 (0.58–1.43)	26	0.87 (0.58–1.32)	
Frontal + severe vertex baldness	17	1.00 (0.61–1.64)	22	1.11 (0.71–1.75)	
	AR-positive		**AR-negative**		
	Cases, *n*	Multivariable HR (95% CI)	Cases, *n*	Multivariable HR (95% CI)	$P_{heterogeneity}$
Hair pattern					
No baldness	69	1.00 (ref)	83	1.00 (ref)	0.25
Frontal baldness	38	0.96 (0.65–1.43)	56	1.15 (0.82–1.61)	
Vertex baldness	55	1.17 (0.82–1.68)	50	0.88 (0.62–1.25)	
Hair pattern					
No baldness	69	1.00 (ref)	83	1.00 (ref)	0.15
Frontal baldness	38	0.96 (0.65–1.43)	56	1.15 (0.82–1.61)	
Frontal + mild vertex baldness	35	1.34 (0.88–2.04)	24	0.77 (0.49–1.20)	
Frontal + moderate vertex baldness	9	0.73 (0.36–1.46)	17	1.09 (0.65–1.83)	
Frontal + severe vertex baldness	11	1.31 (0.69–2.46)	9	0.89 (0.45–1.79)	

and mortality. Furthermore, our exposure assessment and large sample size allowed for investigations of male pattern baldness, dichotomized as well as by the type of baldness (frontal, vertex, and none), and the degree of baldness (mild, moderate, or severe vertex). We were also able to investigate clinical subtypes of prostate cancer (advanced, lethal, and high-grade disease), to attempt to validate prior findings regarding aggressive prostate cancer. In addition, we evaluated the associations molecular subtypes defined by AR and *TMPRSS2:ERG* IHC. Finally, we had detailed covariate information to adjust for potential confounding.

A limitation of our study was the use of a single measure of pattern of baldness at a specific age point (45 years). Further research evaluating baldness at different ages may reveal differing results. In addition, the use of the modified Norwood–Hamilton scale to recall the type and severity of baldness may have introduced recall bias as the participants ranged from age 45 to over 75 and were asked about hair patterns at age 45. Self-reported balding pattern has been shown to be fairly accurate and reliable (36, 37); however, balding pattern was self-reported by participants instead of trained observers. Therefore, misclassification of the exposure cannot be ruled out, but would be expected to be nondifferential with respect to prostate cancer outcomes. The study is restricted to a homogeneous group of European descent men; thus, the relevance of these findings to other populations with higher risk of prostate cancer and different distributions of baldness, testosterone, and age of diagnosis of prostate cancer is uncertain. We were also limited by a smaller sample size to assess the associations between male pattern baldness and prostate tumor biomarkers in more aggressive forms of prostate cancer.

In this study, we did not find an association between male pattern baldness at 45 years of age and prostate cancer risk. Similarly, no association was found between male pattern baldness and subtypes of prostate cancer defined by clinical and molecular features.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Development of methodology: S.C. Markt

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