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## Original Contribution

# Male Pattern Baldness in Relation to Prostate Cancer–Specific Mortality: A Prospective Analysis in the NHANES I Epidemiologic Follow-up Study

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We used male pattern baldness as a proxy for long-term androgen exposure and investigated the association of dermatologist-assessed hair loss with prostate cancer–specific mortality in the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. From the baseline survey (1971–1974), we included 4,316 men who were 25–74 years of age and had no prior cancer diagnosis. We estimated hazard ratios and used Cox proportional hazards regressions with age as the time metric and baseline hazard stratified by baseline age. A hybrid framework was used to account for stratification and clustering of the sample design, with adjustment for the variables used to calculate sample weights. During follow-up (median, 21 years), 3,284 deaths occurred; prostate cancer was the underlying cause of 107. In multivariable models, compared with no balding, any baldness was associated with a 56% higher risk of fatal prostate cancer (hazard ratio = 1.56; 95% confidence interval: 1.02, 2.37), and moderate balding specifically was associated with an 83% higher risk (hazard ratio = 1.83; 95% confidence interval: 1.15, 2.92). Conversely, patterned hair loss was not statistically significantly associated with all-cause mortality. Our analysis suggests that patterned hair loss is associated with a higher risk of fatal prostate cancer and supports the hypothesis of overlapping pathophysiological mechanisms.

cohort; male pattern baldness; prostate cancer mortality

Abbreviations: CI, confidence interval; HR, hazard ratio; NCHS, National Center for Health Statistics; NHANES I, first National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Follow-up Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

In US men, prostate cancer is the most frequently diagnosed nonskin cancer and the second leading cause of cancer deaths, with an estimated 238,590 new cases and 29,720 deaths in 2013 (1). Established risk factors for prostate cancer are limited to older age, black race, family history of prostate cancer (2), and certain genetic polymorphisms (3), which collectively explain only a fraction of the disease occurrence. More studies are needed to better understand the etiology of prostate cancer, especially lethal malignancies, given that the current screening tests for prostate cancer lead to substantial overdiagnosis (4).

Male pattern baldness (also known as androgenic alopecia) is progressive scalp hair loss due to androgenic miniaturization of hair follicles. Generally, 3 zones of the scalp are

preferentially affected: the bitemporal, frontal, and vertex areas. The prevalence and extent of baldness increase with increasing age (5). Evidence has suggested that male pattern baldness and prostate cancer might share similar pathophysiological mechanisms in terms of heritability and endogenous hormones. For example, heritable factors contribute to approximately 42% of prostate cancer risk (6) and 81% of male pattern baldness (7). Regarding endogenous hormones, androgenic action has been shown to play integral roles in hair loss and prostate cancer progression; both hair follicles and the prostate gland are androgen responsive. However, results from prior epidemiologic studies of circulating sex steroid hormones in relation to prostate cancer risks have been inconsistent (8–12). All of such prior studies only quantitated

sex steroid hormones at a single time point, mainly at midlife or older. Thus, intra-individual variation and/or the etiologically relevant time window of exposure (13, 14) might not have been adequately captured. Male pattern baldness might be a marker of long-term androgen exposure and thus could be useful in aiding our understanding of prostate cancer etiology.

Prior studies of male pattern baldness in relation to prostate cancer risks have been inconsistent in the methods used and the conclusions drawn. In most prior studies, investigators have used a case-control study design, and a meta-analysis of 7 such studies suggested a 25% higher risk of prostate cancer (odds ratio = 1.25; 95% confidence interval (CI): 1.09, 1.44) for men with any vertex balding compared with men with no balding (15). In prospective studies, researchers have found somewhat similarly positive associations between these 2 conditions. An analysis of the Melbourne Collaborative Cohort Study (MCCS) suggested that vertex balding (Norwood-Hamilton scale types III vertex–VII) at 40 years of age might predict earlier onset of prostate cancer (16). In our prior analysis of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) cohort, we found that men with frontal plus moderate vertex balding (Norwood-Hamilton scale types V–VI) at age 45 years had a 39% higher risk of aggressive prostate cancer (hazard ratio (HR) = 1.39; 95% CI: 1.07, 1.80) (17). However, we did not observe associations between classes of baldness and prostate cancer risks in the cohort of Vitamins and Lifestyle (VITAL) Study (18), although vertex balding was captured as a single exposure class—a categorization that produced a similarly null result when assessed in our PLCO analysis. Lastly, results from a former prospective analysis in the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS), which included follow-up until 1992, suggested a 50% higher risk of incident prostate cancer for men with any baldness at baseline compared with men with no balding (19). In that prior analysis of NHEFS data, investigators could not assess the association of baldness with fatal prostate cancer because too few deaths from prostate cancer occurred (19). With an additional 20 years of follow-up, we used the unique resource of the NHEFS, which has the major advantage of data on dermatologically assessed baldness at baseline, to investigate the relationship between male pattern baldness and prostate cancer-specific mortality.

## METHODS

NHANES I is a nationally representative, cross-sectional survey of the US civilian, noninstitutionalized population aged 1–74 years in 1971–1974. The complex survey design of NHANES I is an area-based, multistage, stratified probability cluster sample of persons with oversampling of elderly people, preschool children, persons who live in poverty areas, and women of child-bearing age (20). Sample weights are functions of the probability of selection with adjustment for non-response (within family income groups) and poststratification (calibrated by age-, race-, and sex-specific controls from the US Bureau of the Census) (21). Five variables (age, residence in a poverty area, family income group, race, and sex) were used to calculate sample weights. NHANES I was extended

to 1975 by sampling more adults 25–74 years of age who were selected to undergo a detailed health examination using a similar sample design but without oversampling (known as NHANES I Augmentation) (20). The NHEFS, a longitudinal prospective study, was conducted among individuals who were 25–74 years at the NHANES I or NHANES I Augmentation baselines (21). The NHEFS included a series of follow-up surveys in 1982–1984, 1986, 1987, and 1992 to collect updated data on time-varying exposures, as well as vital and health statuses. Complex survey analytic methods are needed to account for the sampling design and to estimate the appropriate standard errors. Data collection methods for the NHEFS were approved by the US National Center for Health Statistics (NCHS) Ethics Review Board.

## Exposure ascertainment

Baldness was classified at baseline dermatologic examinations only for NHANES I participants (1971–1974). The extent and impression of etiology of baldness were assessed by trained third-year dermatology residents using a standard procedure (22). The extent of baldness was categorized into 4 levels (23): 1) none (no obvious baldness at first encounter or examination); 2) minimum (no obvious baldness at first encounter but baldness detected during the examination); 3) moderate (observable baldness at first encounter); and 4) severe (obvious baldness at first encounter and hair confined to scalp fringes if present). The impression of etiologies determined by dermatology residents included patterned hair loss, alopecia areata, infection, antimetabolites, trauma, and postclimacteric hair loss. Only individuals deemed to have patterned hair loss (“male pattern baldness”) were of interest and were retained for analysis.

## Outcome ascertainment

Vital information was ascertained from death certificates during active follow-up of the NHEFS through 1992; 90% of participants were successfully traced, and death certificates were available for 98% of decedents (24). Additional follow-up has been extended through December 31, 2011, via the linkage of the NHEFS to the National Death Index since 1979, with supplemental data sources (e.g., Social Security Administration, the Centers for Medicare and Medicaid Services, or death certificate review) to aid determination of vital status. The linkage used a probabilistic algorithm and manual reviews at the NCHS (25). The criteria for true matches were calibrated using samples with active follow-up, 98.5% of which were correctly classified (26). Prostate cancer as the underlying cause of death was coded as *International Classification of Diseases, Ninth Revision* code 185 from 1971–1998 (27) and *International Classification of Diseases, Tenth Revision* code C61 from 1999 onward. Classification of prostate cancer as the underlying cause of death remained consistent across revisions (28). Multiple cause of death data were also derived from the original coding of death certificates by the Division of Vital Statistics at NCHS. Each death certificate contains a single underlying cause of death and up to 20 additional multiple causes. Outcome information was assessed through the NCHS Research Data Center,

in which analysis of deidentified restricted data was approved by the NCHS Ethics Review Board.

### Study sample

Of the 4,478 men from the NHANES I (1971–1974) part of the NHEFS, we excluded 49 who had baldness due to reasons other than patterned hair loss, 91 men with a prior cancer diagnosis, and 22 men without a valid National Death Index record match or any other source of mortality information. This resulted in 4,316 men in the NHEFS analytic cohort.

### Statistical analysis

Because of the prior statistical studies in which investigators showed overestimation of standard errors caused by using the highly variable NHEFS sample weights in weighted analyses (21), we used a hybrid framework to account for stratification and clustering of the sampling design while adjusting for 4 applicable variables (age modeled as the time metric, residence in a poverty area (yes vs. no), family income group (<\$3,000; \$3,000–\$6,999; \$7,000–\$9,999; \$10,000–\$14,999; or ≥\$15,000), and race (black vs. nonblack)) that were used in the calculation of sample weights (29). If data were missing for family income (4%), the value was imputed by drawing from a uniform distribution,  $U(0,1)$ , conditioned on the observed income distribution. We used 2 additional frameworks as sensitivity analyses: 1) a model-based framework in which we ignored the complex survey design and 2) a design-based framework into which we incorporated stratification, clustering, and sample weights.

Congruent with the hybrid framework discussed, we used Rao-Scott  $F \chi^2$  statistics to account for clustering and stratification, with each subject's sampling weight set at 1 to test the independence of baseline characteristics relative to degree of baldness and case status. Therefore, unweighted column percentages and standard errors were presented as the main results. We used Cox proportional hazards regressions with age as the time metric and baseline hazard stratified by age at interview (50 one-year strata for ages 25–74 years) (30) to estimate hazard ratios and 95% confidence intervals for associations between male pattern baldness and prostate cancer-specific mortality. Follow-up started at the baseline interview and continued until the time of an event (death from prostate cancer) or of right-censoring (loss of follow-up, death from other causes, or last date of follow-up (December 31, 2011)), whichever occurred first. We also examined male pattern baldness in relation to prostate cancer listed as the underlying cause of death or as 1 of multiple causes of death, as well as in relation to all-cause mortality, using the hybrid framework. Additional potential confounders for multivariable models were determined a priori (family history of prostate cancer) or by including covariates individually (educational level, marital status, region, physical activity level, body mass index (weight (kg)/height (m)<sup>2</sup>), cigarette smoking, and alcohol consumption), with retention requiring a 10% change in the hazard ratios. The proportional hazard assumption was tested by visual inspection of log-log plots and by including interaction terms of exposure and indicators of time intervals based on tertiles of the time-to-event distribution.

Interactions of baldness with race and body mass index (continuous and categorical) were each independently assessed through inclusion of an interaction term in Cox models. Models were stratified by age group (<65 years vs. ≥65 years) to examine whether age at dermatologic examination modified the association of baldness with prostate cancer-specific mortality. Two-sided  $P$  values <0.05 were considered statistically significant. SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina) was used for descriptive analyses. Models were fitted in STATA, version 13 (StataCorp LP, College Station, Texas).

### RESULTS

During follow-up (median, 21 years), 3,284 deaths occurred. Prostate cancer was listed as the underlying cause of death for 107 men and as 1 of multiple causes of death for 22 men. The median age at interview was 54 years (interquartile range, 39–67). Table 1 shows unweighted characteristics by severity of male pattern baldness. The prevalence and extent of male pattern baldness appeared to increase with increasing age and lower educational level. Men with moderate to severe baldness were more likely to have lower family incomes, to abstain from alcohol, to be black, and to be a former smoker. Web Table 1 (available at <http://aje.oxfordjournals.org/>) shows unweighted characteristics by case status. Consistent with literature, advancing age, black race, and family history of prostate cancer were associated with prostate cancer-specific mortality. Differences in prostate cancer-specific mortality were also observed by educational level, smoking status, and frequency of alcohol consumption.

As shown in Table 2, after adjustment for applicable variables used to calculate sample weights, any baldness was associated with a 56% higher risk of prostate cancer-specific mortality (HR = 1.56; 95% CI: 1.02, 2.37), and moderate balding specifically was associated with an 83% higher risk of the outcome (HR = 1.83; 95% CI: 1.15, 2.92), each compared with no balding. The proportional hazard assumption held for male pattern baldness ( $P = 0.709$ ). Conversely, male pattern baldness was unrelated to all-cause mortality. Additional inclusion of potential confounders did not materially change the risk estimates. Estimates for the redefined outcome determined by combining prostate cancer as the underlying cause and as 1 of multiple causes of death were slightly attenuated, although moderate balding was still associated with a 54% higher risk of this composite outcome (HR = 1.54; 95% CI: 1.00, 2.37) compared with no balding (Web Table 2). Results obtained in hybrid Cox models were consistent with those from model-based and designed-based frameworks (Web Table 3). We found no significant interaction of race ( $P = 0.624$ ), body mass index at baseline (continuous  $P = 0.402$ ; categorical  $P = 0.290$ ), or age at dermatologic examination (data not shown) with male pattern baldness.

### DISCUSSION

In the present prospective analysis, any baldness was significantly associated with a 56% higher risk of prostate cancer-specific mortality compared with no balding. The greatest specific risk was conferred by moderate balding, which was

**Table 1.** Unweighted Characteristics of Study Participants by Severity of Male Pattern Baldness, National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, 1971–2011

Characteristic	No Balding			Balding Severity									P Value <sup>c</sup>
				Minimum			Moderate			Severe			
	No. <sup>a</sup>	%	SE <sup>b</sup>										
Age at interview, years													<0.0001
25–44	1,073	47.5	1.57	189	25.2	2.07	153	15.3	0.95	31	10.2	2.14	
45–54	372	16.5	0.91	156	20.8	1.46	182	18.2	1.05	40	13.2	2.40	
55–64	246	10.9	0.78	108	14.4	1.41	163	16.3	1.05	46	15.1	2.08	
65–74	570	25.2	1.39	297	39.6	2.29	503	50.2	1.63	187	61.5	3.07	
Residence in poverty area													0.369
Yes	1,019	45.1	3.03	328	43.7	4.35	490	49.0	3.04	138	45.4	3.87	
No	1,242	54.9	3.03	422	56.3	4.35	511	51.0	3.04	166	54.6	3.87	
Resident region													0.993
Northeast	490	21.7	1.44	161	21.5	2.89	227	22.7	2.64	55	18.1	2.65	
Midwest	540	23.9	1.68	179	23.9	4.55	238	23.8	2.74	74	24.3	3.69	
South	591	26.1	2.43	210	28.0	3.74	250	25.0	2.42	93	30.6	4.50	
West	640	28.3	2.03	200	26.7	3.47	286	28.6	2.20	82	27.0	4.88	
Family income, \$													<0.0001
<3,000	274	12.1	1.27	120	16.0	2.46	164	16.4	1.75	68	22.4	2.80	
3,000–6,999	512	22.6	0.93	166	22.1	1.93	244	24.4	1.41	86	28.3	2.24	
7,000–9,999	499	22.1	1.14	164	21.9	1.72	213	21.3	1.17	51	16.8	2.00	
10,000–14,999	479	21.2	1.05	150	20.0	1.65	164	16.4	1.20	40	13.2	1.73	
≥15,000	405	17.9	1.15	123	16.4	1.52	169	16.9	1.60	40	13.2	1.68	
Race													0.006
Nonblack	1,855	82.0	1.62	656	87.5	2.05	866	86.5	1.77	255	83.9	2.26	
Black	406	18.0	1.62	94	12.5	2.05	135	13.5	1.77	49	16.1	2.26	
First-degree relative(s) with prostate cancer <sup>d</sup>													0.805
No	2,190	96.9	0.45	730	97.3	0.52	966	96.5	0.58	295	97.0	0.88	
Yes	71	3.1	0.45	20	2.7	0.52	35	3.5	0.58	9	3.0	0.88	
Marital status													0.122
Single <sup>e</sup>	404	17.9	0.77	134	17.9	1.54	159	15.9	1.20	66	21.7	2.28	
Married	1,857	82.1	0.77	615	82.0	1.57	839	83.8	1.19	238	78.3	2.28	

Table continues

associated with an 83% higher risk. No association was found between male pattern baldness and all-cause mortality.

To our knowledge, this is the first study in which male pattern baldness has been investigated in relation to prostate cancer-specific mortality. Results obtained in this analysis may be supported by those from prior studies of hair loss patterns and aggressive prostate cancer. In a matched case-control study from Australia, Giles et al. (31) found that vertex balding (Norwood-Hamilton scale types III vertex–V) was associated with a 2-fold increased risk (odds ratio = 2.04, 95% CI: 1.35, 3.08) of high-grade prostate cancer (Gleason score = 8–10) compared with no balding. Our analysis of PLCO data suggested that moderate frontal balding (Norwood-Hamilton scale types V–VI) at 45 years of age was positively associated with “aggressive” prostate cancer (HRs = 1.39–2.02) (17). In addition, in a former NHEFS analysis with follow-up through 1992 (and thus with more than two thirds of the accrual time

in the period before widespread use of the prostate-specific antigen test to diagnose prostate cancer, when symptomatic prostate cancer predominated), researchers reported a 50% increased risk of incident prostate cancer (HR = 1.50; 95% CI: 1.12, 2.00) for men with any baldness and a slightly higher risk estimate for men with moderate baldness (HR = 1.60; 95% CI: 1.15, 2.23) compared with men with no balding (19). Similar to these nonlinear relationships observed within our PLCO analysis and the previous NHEFS analysis, we failed to identify a dose-response relationship between degrees of male pattern baldness and prostate cancer-specific mortality. This could be due to lack of statistical power because there were only 12 deaths in the group with severe baldness. Additionally, it could be explained by the perhaps incorrect assumption that the degree of male pattern baldness is linearly associated with an underlying exposure (e.g., circulating androgen concentrations), which in turn shares a linear

Table 1. Continued

Characteristic	No Balding			Balding Severity									P Value <sup>c</sup>
				Minimum			Moderate			Severe			
	No. <sup>a</sup>	%	SE <sup>b</sup>										
Highest education attainment													<0.0001
Less than high school	669	29.6	1.37	292	38.9	2.76	444	44.4	2.69	144	47.4	3.03	
High school graduate	987	43.7	1.28	301	40.1	2.20	342	34.2	2.00	94	30.9	2.98	
Some college/graduate	573	25.3	1.33	153	20.4	1.69	203	20.3	1.93	63	20.7	2.72	
Usual and recreational physical activity													0.041
Very inactive	179	7.9	0.66	66	8.8	1.34	91	9.1	0.93	36	11.8	1.61	
Inactive	401	17.7	0.95	128	17.1	1.51	219	21.9	1.38	59	19.4	2.03	
Moderate	844	37.3	1.03	294	39.2	1.80	360	36.0	1.54	102	33.6	2.13	
Active	439	19.4	0.95	132	17.6	1.47	188	18.8	1.31	50	16.4	2.25	
Very active	398	17.6	1.18	130	17.3	1.88	143	14.3	1.26	57	18.8	2.36	
Body mass index <sup>f</sup>													0.545
<25.0	1,035	45.8	1.08	322	42.9	2.22	465	46.5	1.48	127	41.8	3.01	
25.0–29.9	934	41.3	0.94	333	44.4	2.07	406	40.6	1.54	133	43.8	2.98	
≥30.0	292	12.9	0.61	95	12.7	0.99	130	13.0	1.00	44	14.5	2.03	
Smoking status													<0.0001
Never	551	24.4	1.02	198	26.4	1.88	254	25.4	1.73	86	28.3	2.33	
Former	514	22.7	0.94	192	25.6	1.63	290	29.0	1.62	84	27.6	2.38	
Current	889	39.3	1.43	265	35.3	1.86	299	29.9	1.60	84	27.6	2.77	
Average number of drinks per week													0.001
None	593	26.2	1.08	212	28.3	1.86	328	32.8	2.48	103	33.9	2.87	
≤2	496	21.9	0.73	129	17.2	1.27	214	21.4	1.47	62	20.4	1.97	
3–7	419	18.5	1.11	158	21.1	1.65	155	15.5	1.36	46	15.1	1.85	
8–14	279	12.3	0.78	87	11.6	1.24	103	10.3	1.16	26	8.6	2.01	
≥15	276	12.2	0.74	70	9.3	0.97	101	10.1	1.00	28	9.2	2.26	

Abbreviation: SE, standard error.

<sup>a</sup> Column percentages may not add up to 100% because of missing values.

<sup>b</sup> Unweighted standard errors were calculated by accounting for clustering and stratification in a hybrid statistical framework.

<sup>c</sup> P value was calculated from Rao-Scott F  $\chi^2$  tests using nonmissing categories to account for clustering and stratification.

<sup>d</sup> In the 1982–1984 or 1992 follow-up survey.

<sup>e</sup> Includes widowed, divorced, separated, and never married.

<sup>f</sup> Weight (kg)/height (m)<sup>2</sup>.

association with aggressive/fatal prostate cancer. An increased understanding of what drives differential susceptibility of hair follicle miniaturization by scalp area might provide a better indication of the exposure(s) that underlies both male pattern baldness and aggressive/fatal prostate cancer. The null associations between male pattern baldness and all-cause mortality might be interpreted to indirectly support our hypothesis of shared exposures between male pattern baldness and prostate cancer, as it shows that it is not merely a risk factor for overall mortality. Deaths with prostate cancer as the underlying cause comprised less than 1% of total deaths among US men in 2011 (32). Ischemic heart disease has previously been reported to be positively associated with male pattern baldness (33, 34); the null result in this study of male pattern baldness and all-cause mortality does not contradict these findings, given the fact that this underlying cause of death accounted for a small fraction (15%) of the total deaths observed.

Despite the inconsistent results from epidemiologic studies of the associations between male pattern baldness and the risk of prostate cancer (15, 16, 19, 31, 35–43), clinical observations and laboratory studies support a link between these 2 conditions. In addition to the fact that both conditions show degrees of heritability, androgenic action appears to be involved in the development of male pattern baldness, as well as prostate carcinogenesis and tumor progression. Men who were born with a congenital deficiency of type II 5 $\alpha$ -reductase, which normally converts testosterone to dihydrotestosterone, or who were prepubertally castrated do not develop prostate cancer and show complete retention of scalp hair (44). Patients with androgen insensitivity due to deleterious mutations in the androgen receptor gene present impaired development of the prostate gland (45) and do not appear bald (46). Balding scalp is characterized by elevated dihydrotestosterone levels (36, 47, 48). Finasteride, a type II 5 $\alpha$ -reductase inhibitor, has been

**Table 2.** Associations of Male Pattern Baldness With Prostate Cancer–Specific Mortality and All-Cause Mortality, National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, 1971–2011

Male Pattern Baldness Severity	No. of Participants	No. of Person-Years	Prostate Cancer–Specific Mortality			All-Cause Mortality		
			No. of Deaths	HR <sup>a</sup>	95% CI	No. of Deaths	HR <sup>a</sup>	95% CI
None	2,261	57,636	38	1.00	Referent	1,500	1.00	Referent
Any	2,055	38,941	69	1.56	1.02, 2.37	1,784	1.04	0.97, 1.12
Minimum	750	15,500	18	1.17	0.62, 2.22	628	1.05	0.96, 1.16
Moderate	1,001	18,565	39	1.83	1.15, 2.92	880	1.03	0.93, 1.15
Severe	304	4,876	12	1.65	0.82, 3.35	276	1.05	0.92, 1.20

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup> Age was modeled as the time metric, with baseline hazard stratified by age at interview. Hazard ratios were estimated by accounting for clustering and stratification in a hybrid statistical framework, with adjustment for variables that were used to calculate the sample weights, including residence in a poverty area (yes or no), family income (<\$3,000, \$3,000–\$6,999, \$7,000–\$9,999, \$10,000–\$14,999, or ≥\$15,000), and race (black or nonblack).

approved by the US Food and Drug Administration to stop hair loss and stimulate hair growth. Similarly, castration has long been shown to shrink the primary cancerous lesion in patients with advanced prostate cancer, whereas injection of androgens aggravates the condition (49). However, associations between concentrations of circulating sex steroid hormones and prostate cancer risk are inconsistent (8–12), possibly because of a combination of variability in the robustness and detection limits of steroid quantitation methods used; assessment of a limited number of metabolites within the sex steroid hormone biosynthesis pathway; and variable case mixes recruited before and/or during the period in which there was widespread use of the prostate-specific antigen test to diagnose prostate cancer. In a pooled analysis of 18 prospective studies in which investigators used study-specific categorization of circulating hormone concentrations, free testosterone concentration was positively associated with incident prostate cancer risk in the period before widespread use of the prostate-specific antigen test to diagnose prostate cancer (9). Moreover, in a recent nested case-control study in the PLCO cohort, Weiss et al. (8) reported that the ratio of serum testosterone to sex hormone-binding globulin was positively associated with aggressive prostate cancer in men older than 65 years of age. However, prediagnostic circulating sex hormone levels were unrelated to lethal prostate cancer (metastasized cancer or death) in a case-control study nested in the Physicians' Health Study (PHS) and the Health Professionals Follow-up Study (HPFS) (10). Nevertheless, prior studies were limited by a single measurement of sex steroid hormones in midlife or later. Fluctuations of sex steroid hormones in early life or cumulative androgen exposure may be more etiologically relevant (50).

There are limitations to our NHEFS analysis. Distinct patterns of baldness were not fully captured by degrees of hair loss. The relationship of these 2 conditions may depend on the scalp areas in which the balding occurs, as we have discussed, and thus a combination of frontal and vertex baldness in NHEFS might have attenuated our risk estimates for fatal prostate cancer. The limited number of men younger than 45 years of age at baseline ( $n = 1,446$ ; 8 cases) precluded

assessment of early-onset baldness in relation to fatal prostate cancer with statistical power. Previous case-control studies have suggested that early-onset baldness may be more strongly associated with incident prostate cancer (38, 42, 43). The limited number of black men in our analytic cohort ( $n = 684$ ; 32 cases) may be the reason why the similar relative risks for fatal prostate cancer in men with any baldness using the full cohort were not statistically significant in this racial group alone (HR = 1.76; 95% CI: 0.75, 4.11). In a previous analysis of NHEFS data, investigators reported that black men with any baldness had a more than 2-fold higher risk of incident prostate cancer (HR = 2.10; 95% CI: 1.04, 4.25), with a slightly lower risk for nonblack men (HR = 1.42; 95% CI: 1.01, 1.98) (19). Results from a case-control study in black men (318 cases, 219 controls) further suggested that frontal baldness at 30 years of age was associated with high-stage (odds ratio = 2.61; 95% CI: 1.10, 6.18) and high-grade (odds ratio = 2.20; 95% CI: 1.05, 4.61) prostate cancer (51). Misclassification of the underlying cause of death may slightly attenuate the true association, given that death certificates were missing for 5% of participants who died (who were thus right-censored when death occurred) and that the estimated agreement for attribution of prostate cancer as the underlying cause of death between medical records review and linkage to death certificates ranged from 87%–97% (52, 53). Information on prostate cancer screening and treatment was incomplete because of the termination of active follow-up in 1992. However, we would expect any effect modification by screening/treatment to be small, given that the most current observational trial data indicate a minimal effect of prostate cancer screening on the reduction of prostate-specific mortality in US men (54) and that we adjusted for covariates of socioeconomic status and accounted for cohort/period effect by stratifying the baseline hazard. Moreover, even if effect modification by screening/treatment exists, we would expect this effect to attenuate the associations observed, assuming that the distribution of screening and/or treatment are mostly likely to be nondifferentially distributed by degree of hair loss. Finally, inferences about the target US population cannot be drawn, given that the unweighted analysis was performed for the appropriate estimation of variances.

In summary, we found that compared with no balding, any baldness was significantly associated with a higher risk of fatal prostate cancer and that moderate balding specifically was associated with the highest risk. Our results support the hypothesis of overlapping pathophysiological mechanisms in the 2 conditions. The moderate association and relatively high prevalence of male pattern baldness in Western populations does not currently support the use of male pattern baldness in prostate cancer screening decisions. In future studies, investigators should aim to confirm the association between male pattern baldness and fatal prostate cancer, as well as evaluate the additional value it may offer to predictive models.

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