

Short Communication

Male Pattern Baldness and Clinical Prostate Cancer in the Epidemiologic Follow-Up of the First National Health and Nutrition Examination Survey

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Abstract

Male pattern baldness (MPB) and prostate cancer are common in American males; however, MPB is clinically observable decades earlier. Aging, androgens, and heritability are risk factors for both conditions. We prospectively studied the association between MPB and clinical prostate cancer in a cohort representative of the United States male population. A total of 4,421 men 25–75 years old without a history of prostate cancer were examined for baldness in the Epidemiologic Follow-up Study of the first National Health and Nutrition Examination Survey. Participants were followed from baseline (1971–1974) through 1992. Incident cases of prostate cancer were identified by interviews, medical records, and death certificates. Age-standardized incidence rates and proportional hazards models were used to examine the association between MPB and clinical prostate cancer. Prostate cancer was diagnosed in 214 subjects over 17–21 years of follow-up. The age-standardized incidence of prostate cancer was greater among men with baldness at baseline (17.5 versus 12.5 per 10,000 person-years). The adjusted relative risk for prostate cancer among men with baldness was 1.50 (95% confidence interval, 1.12–2.00) and was similar regardless of the severity of baldness at baseline and was independent of other risk factors, including race and age. MPB seems to be a risk factor for clinical prostate cancer.

Introduction

MPB² and prostate cancer are prevalent in American men (1–5). Cosmetically significant MPB (Hamilton type III or

greater) occurs in as many as 70% of men by the age of 80, and prostate cancer is the most common cancer diagnosed in American men. However, MPB, a clearly observable trait, generally precedes the diagnosis of clinical prostate cancer by decades (4–6). The precise mechanisms leading to the development of MPB and prostate cancer are largely unknown; however, both conditions share epidemiological and biological risk factors, including aging, heritable genetic factors, and androgenic metabolism (7–10).

Because of the commonalities between MPB and prostate cancer and yet their differences with regard to the timing of phenotypic expression, we hypothesized that MPB would predict for prostate cancer. We used data from the NHEFS to examine the relationship between MPB and incident prostate cancer in a prospective manner.

Materials and Methods

The NHANES I, a nationally representative cross-sectional survey of the civilian, noninstitutionalized United States population, was conducted in 1971–74; an augmentation survey was conducted in 1974–75 to supplement the NHANES I. The NHEFS is a prospective cohort study composed of participants who were 25–74 years of age at their baseline NHANES I or NHANES I augmentation interview ($n = 14,407$; male $n = 5,811$). Our NHEFS-based study uses data from males ($n = 4,479$) interviewed in the 1971–74 NHANES I survey only; at baseline, each participant had an in-person interview and a medical examination including a comprehensive dermatological assessment (data from the augmentation survey were not used because the primary variable of interest, baldness, was not ascertained in that survey). The cohort has been periodically followed-up in 1982–84, 1986, 1987, and 1992 for vital and health status of its participants, although no additional assessments of baldness were conducted. By the end of the 1992 follow-up, about 90% of the subjects in the cohort had been successfully traced; median follow-up of the subjects was 18.2 years. Additional details about the NHEFS have been presented elsewhere (11–14).

Assessment of MPB. The extent and apparent cause of baldness in the men was determined during a dermatological examination performed by physician dermatology residents (15). As reported previously, baldness was characterized as: (a) none, no baldness on initial encounter or directed examination; (b) mild, no obvious baldness on initial encounter but baldness on directed examination; (c) moderate, observable baldness on initial encounter; and (d) severe, obvious baldness on initial encounter and hair, if present, limited to scalp fringes (16). Men with mild, moderate, or severe baldness were queried regarding the etiology of their baldness (*i.e.*, male pattern, alopecia areata, trauma, antimetabolites, postclimacteric, infections). Because of our uncertainty related to the use of the term “postclimacteric” in these men, we performed analyses with and without

Received 8/10/99; revised 1/10/00; accepted 1/24/00.

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² The abbreviations used are: MPB, male pattern baldness; NHEFS, Epidemiologic Follow-up Study of the NHANES I; NHANES I, first National Health and Nutrition Examination Survey; RR, relative risk; CI, confidence interval.

this subset of men. No substantial differences were found between these analyses.

Prostate Cancer Ascertainment. Cases of prostate cancer were determined by asking participants about medical conditions diagnosed by physicians, overnight hospitalizations, and stays in nursing homes during the study period. Permission was obtained to abstract primary data from medical records on admission and discharge dates, diagnoses, and medical procedures. Trained coders reviewed the medical records and determined the International Classification of Disease Codes (ICD-9-CM) for medical conditions including prostate cancer. Deaths were identified by using the National Death Index, records from the Health Care Financing Administration, and other tracing sources. A death certificate was available for about 98% of decedents in the cohort (14). For each male having the codes ICD 185 (invasive prostate cancer), ICD 233.4 (prostate carcinoma *in situ*), v 10.46 (personal history of malignant prostate neoplasm), or 60.3–60.5 (prostatectomy surgical procedures), archived summaries of interviews, records from health care facilities, and histopathology reports at the National Center of Health Statistics in Hyattsville, Maryland were reviewed (17). For the purposes of this study, only men with invasive prostate cancer were categorized as cases—approximately two-thirds from histopathology reports or medical records and most of the remainder from interviews. Less than 5% of the cases were determined by death certificates. Additional details on case ascertainment have been presented elsewhere (17).

Analytic Cohort. Of the 4479 men in the cohort from the NHANES I part of the NHEFS at baseline, we excluded 10 men with prevalent prostate cancer at baseline and 48 men who exhibited balding that was attributed to causes other than MPB, including alopecia areata, infections, postclimacteric, antime-tabolites, or trauma. Thus, our analytic cohort consisted of 4421 men (cases, $n = 214$; noncases, $n = 4207$).

Statistical Analyses. Associations between potential confounding covariates of age, race, education, region, family history of prostate cancer, and degree of balding were determined by χ^2 tests of independence or ANOVA. Age-adjusted prostate cancer incidence rates were derived by direct standardization within 10-year-age groups from 25 years of age, using the age distribution of the 1980 United States male population. Standard methods were used to compute CIs for these rates (18). Adjusted relative hazard rates for clinical prostate cancer, referred to as RRs throughout the paper, were estimated using proportional hazard regression analyses. For these analyses, the response was age to cause-specific incidence of clinical prostate cancer (19). Individuals who died during, or survived free of prostate cancer throughout, the follow-up period were censored at age of death or last interview, respectively. The baseline hazards in the proportional hazard regressions were stratified by year of age at baseline examination to adjust for the age at which baldness was determined (*i.e.*, there were 50 strata for ages 25–75 at baseline; Ref. 19). The proportional hazard assumption was tested and not rejected.

The NHEFS has a complex design that involves sample weighting, stratification, and clustering. To account for sample weights, design variables [age < 65 versus 65+, residence or nonresidence in a poverty census enumeration district, family income (<\$3,000; \$3,000–\$6,999; \$7,000–\$9,999; \$10,000–\$14,999; \$15,000+), and race (black and nonblack)] were included in all of the proportional hazard regression analyses (20). The SEs for the adjusted RRs were computed in two ways: (a) design-based SEs that take into account the stratification and cluster sampling of the complex sample design; and (b)

Table 1 Subject characteristics by MPB at baseline (1971–1975) in the NHEFS

	MPB			
	None $n = 2310$		Any $n = 2111$	
	<i>n</i>	%	<i>n</i>	%
Age				
25–34	640	27.7	153	7.2
35–44	437	18.9	221	10.5
45–54	376	16.3	380	18.0
55–64	261	11.3	332	15.7
65–74	596	25.8	1025	48.6
$P < 0.01$				
Race				
White	1856	80.3	1799	85.2
Black	414	17.9	284	13.4
Other	40	1.7	28	1.3
$P < 0.01$				
Education ^a				
<12 years	1029	44.5	1235	58.5
12 years	667	28.9	433	20.5
>12 years	581	25.2	423	20.0
$P < 0.01$				
Region				
Northeast	500	21.6	453	21.4
Midwest	551	23.8	502	23.8
South	605	26.2	570	27.0
West	654	28.3	586	27.8
$P = 0.94$				
Family history of prostate cancer, 1982 or 1992				
Yes	77	3.3	64	3.0
No	2233	96.7	2047	97.0
$P = 0.57$				

^a Data missing on 33 (1.4%) subjects in the “None” category and on 20 (0.9%) subjects in the “Any” category.

model-based SEs that assume that the sample was a simple random sample (19, 20). We chose to use the larger of the two SEs in all of the statistical tests and CIs. All of the tests of significance were two-tailed with the level of significance set at 5%. Descriptive analyses were performed using SAS v. 6.11 (SAS Institute, Cary, North Carolina). Proportional hazard regressions were performed using in-house software, which is available via the internet³ (19). Cumulative incidence curves were compared by the log-rank test.

Results

The median age at baseline of the 4421 men in our cohort was 55.1 years (range, 25.0–74.4; Table 1). Consistent with prior studies, the prevalence of MPB was strongly associated with aging, involving 19, 33, 50, 56, and 63% of the cohort within progressive ten-year strata from the lowest age at entry, 25 years old. Men with MPB were more likely to be white ($P < 0.001$) and less educated ($P < 0.001$), though there were no differences in region of residence ($P = 0.94$). Relatively few men reported a family history of prostate cancer, regardless of their degree of baldness at baseline (3%); this is lower than others’ estimates of the frequency of positive family histories

³ “Cox Regression for Survey Data” at, <http://dcp.nci.nih.gov/BB/Software.html#cox>.

Table 2 Age-standardized incidence and adjusted RR of prostate cancer by level of baldness in the NHEFS, 1971–1974 through 1992^a

	N	Person-years	No. of cases	Incidence (95% CI) ^b	Adjusted RR with 95% CI ^c
None	2,310	33,585	70	12.5 (9.5–15.6)	1.00 ^d
Any	2,111	27,490	144	17.5 (14.3–20.7)	1.50 ^e
Mild	772	10,553	47	18.0 (12.5–23.5)	1.40
Moderate	1,030	13,225	75	17.1 (12.9–21.3)	1.60 ^e
Severe	309	3,712	22	18.3 (7.5–29.2)	1.40

^a Incidence rates standardized to the age distribution of the 1980 United States male population.

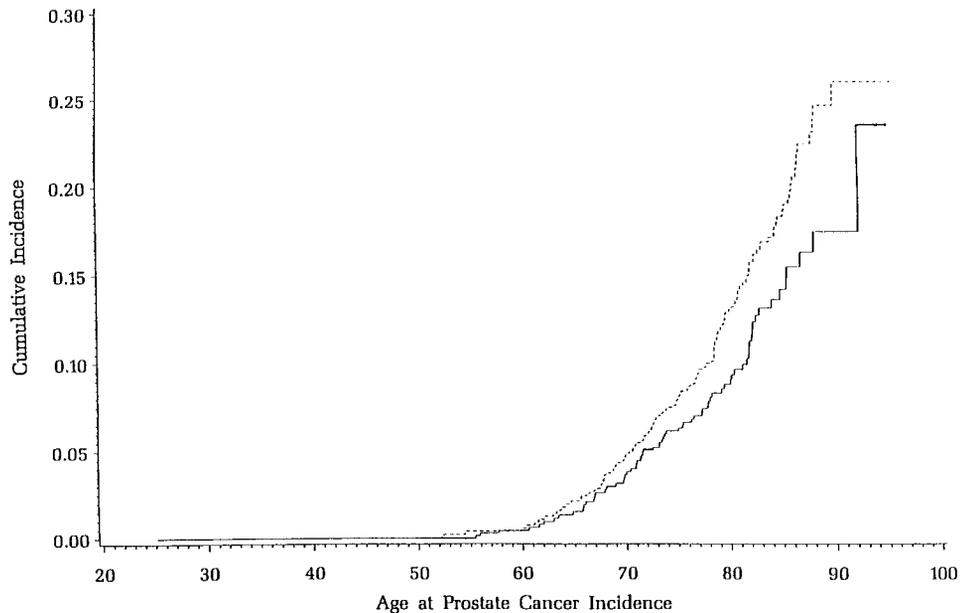
^b Age-standardized incidence of prostate cancer per 10,000 person-years.

^c Adjusted for age at baseline and design variables (unchanged by inclusion of education, race, region, and family history of prostate cancer).

^d Referent category.

^e $P < 0.01$.

Fig. 1. Cumulative incidence of prostate cancer by baldness in the Epidemiologic Follow-up Study of the First National Health and Nutrition Examination Survey, 1971–1974 through 1992. —, no baldness;, any baldness.



(9%), which suggests that this variable is underreported in this cohort (21).

Table 2 shows the age-standardized prostate cancer incidence from baseline (1971–74) to 1992, and the RR for prostate cancer from a Cox regression model adjusting for age at baseline and design variables. The incidence of clinical prostate cancer was comparatively higher for men with MPB at baseline compared with those without (17.5 versus 12.5 per 10,000 person-years), although no detectable trend across the three ordered levels of baldness was observed. The cumulative incidence curves in Fig. 1 demonstrate differences in the cumulative incidence of prostate cancer between men with any MPB on the baseline exam versus those without. Men with MPB had a consistently higher incidence of prostate cancer compared with those without MPB ($P = 0.02$), beginning at approximately 60 years of age. The adjusted RR for prostate cancer was significantly elevated for men with any degree of MPB compared with those without MPB (RR, 1.50; $P = 0.01$). The results of these adjusted RRs were not substantially altered by the inclusion of additional covariates (e.g., educational status, region, race, family history of prostate cancer) to the Cox model. The RRs for prostate cancer by the ordinal level of MPB at baseline were 1.40, 1.60, and 1.40 for mild, moderate, and severe MPB, respectively, when compared with no MPB. The RRs were statistically significant only for the largest subset of men, those with moderate MPB ($P = 0.01$).

Additional analyses of the RR of prostate cancer in men with MPB were conducted separately within baseline age groups of <55, 55–64, and 65–74, and within racial groups of nonblack and black. Men with MPB were at greater risk for prostate cancer within all of the age subsets compared with those without MPB [<55 years old: RR, 1.56 (CI, 0.77–3.17); 55–64 years old: RR, 1.16 (CI, 0.64–2.07); 65–74 years old: RR, 1.69 (CI, 1.14–2.46)], although statistically significant RRs were noted only in the oldest subset of men 65–74 years old at entry ($P = 0.01$), in whom prostate cancer diagnoses were most frequent (132 cases). Interaction between these age groups and baldness was not statistically significant ($P = 0.20$). MPB was significantly associated with prostate cancer in both blacks [RR, 2.10 (95%CI, 1.04–4.25)] and nonblacks [RR, 1.42 (95%CI, 1.01–1.98)]. Although the risk in blacks was greater than in nonblacks, this difference was not statistically significant ($P = 0.22$).

Discussion

Men with MPB had an approximate 50% excess risk for clinical prostate cancer. The positive association between MPB and clinical prostate cancer was similar regardless of the degree of MPB and was independent of several known risk factors, including age, race, and family history of prostate cancer. The association was strongest in elderly men and blacks.

Although five prior case-control studies did not identify a significant association between MPB and prostate cancer (22–26), they may have been limited by: (a) small sample sizes (most did not power their studies to specifically investigate the relationship between baldness and prostate cancer; Refs. 22, 24–26); (b) photographic rather than clinical assessments of baldness (23); (c) incomplete case ascertainment because of the use of death records alone (23); (d) limited statistical analyses (23); or (e) difficulties in control group selection. Strengths of our study include its prospective design, large sample size, extended follow-up, and generalizability attributable to nationally representative sampling. In addition, classification of exposure and outcome variables were improved by the use of dermatological physician exams for MPB and cancer diagnoses derived from a variety of sources, with medical or pathological confirmation in the majority of instances. Any residual misclassification in clinical prostate cancer diagnoses should be nondifferential, tending to bias risk estimates toward the null.

Limitations of our study include our inability to obtain detailed information on the patterns of baldness (*i.e.*, frontal, vertex, and so forth) and the incidence or rate of progression of MPB in men over time. Both the specific pattern of MPB and its rate of progression have been identified as risk determinants for other chronic conditions, including several cardiovascular outcomes (27, 28). Another limitation was the age composition of our cohort. Approximately 33% of our cohort had not yet reached the advanced age range in which clinical prostate cancer is typically manifest (6), thus limiting the effective power of our study. The analyses conducted separately for age groups demonstrate this, inasmuch as those in the 64+ years-of-age group were the only subset with a statistically significant increased risk for clinical prostate cancer (see “Results”).

We did not find a dose-response relationship between the extent of MPB and the risk of prostate cancer. This is not particularly surprising. Whereas the extent of MPB offered a biologically plausible and testable hypothesis related to the issue of “dose,” other measures (*e.g.*, time of MPB onset, rate of MPB progression) may provide better estimates of the dose of the presumed common mechanistic factor(s) underlying these conditions. In addition, our ability to measure the extent of MPB was crude; therefore, measurement errors may account for our failure to identify a dose-response relationship. Finally, we are using the concept of dose in a nontraditional way here because the measure of exposure is physically remote from the response of interest. Indeed, it would not be unusual for a common mechanistic factor to contribute to each condition in a different manner—determinative in one yielding a threshold relationship, and merely permissive in the other resulting in a more continuous association.

A link between MPB and prostate cancer may be explained by aging, heritable genetic factors, or androgen metabolism; all of these are presumed to play substantial roles in both conditions (8, 29, 30). MPB may represent a biological measure of aging that transcends chronological measures. If this is the case, MPB may predict aging-related pathological processes [such as carcinogenesis or atherogenesis, which tend to remain clinically silent until advanced stages of disease] better than calendar time.

Genetic susceptibility to MPB and prostate cancer are well-described, although the specific genetic lesions responsible have not been identified. Consideration should be given to the possibility that heritable genetic factors may reside in the specific tissues themselves, at least in the case of MPB, because the bilaterality and regional variation of baldness in the scalps of men with MPB would argue in favor of region-specific

molecular factor(s) determined early in life, rather than for a systemic factor, such as serum androgens, alone.

Finally, androgens seem to be necessary, although not solely causative, in the pathogenesis and clinical expression of MPB and prostate carcinogenesis. In both the scalp and prostate, 5 α -dihydrotestosterone (DHT) is considered to be the primary physiological androgen and is the result of the action of 5 α -reductase on testosterone (7, 30). Recently, two isoforms of 5 α -reductase have been identified with differing pHs, activities, inhibitor sensitivities, and tissue distributions—although each isoform seems to be present in scalp and prostatic tissues (31–33). Tissue from affected scalps of men with MPB and from prostates harboring cancer demonstrate enhanced 5 α -reductase activities (34–36). Finasteride, a relatively specific inhibitor of the type II isoenzyme, is now an approved treatment for benign prostatic hypertrophy and MPB (37–40) and is under investigation as a preventive agent for prostate cancer (41).

In summary, we found a significantly increased risk for prostate cancer among men with MPB, independent of established risk factors including aging and race. Although remote from the prostate, MPB may represent an early, clinically obvious marker of susceptibility and may provide clues to the pathogenesis of prostate cancer.

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