

### Short Communication

## Early Onset Baldness and Prostate Cancer Risk<sup>1</sup>

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#### Abstract

**Prostatic carcinoma is the leading cancer among American men, yet few risk factors have been established. Although increased androgen levels have long been associated with both prostatic carcinoma and baldness, to date no studies have shown an association between hair patterning and prostate cancer risk. A lack of standardized instruments to assess baldness or the assessment of hair patterning during uninformative periods of time may have precluded the ability of previous studies to detect an association. We hypothesized that baldness, specifically vertex baldness, should be assessed using standardized instruments and during early adulthood if an association with prostate cancer risk is to be found. To test this hypothesis, we included identical items related to hair patterning in surveys that were administered in two distinct prostate cancer case-control studies (Duke-based study,  $n = 149$ ; 78 cases; 71 controls and community-based study,  $n = 130$ ; 56 cases; 74 controls). In each, participants were provided with an illustration of the Hamilton Scale of Baldness and asked to select the diagrams that best represented their hair patterning at age 30 and again at age 40. From these data, the following five categories were created and compared: not bald (referent group); vertex bald early onset (by age 30); vertex bald later onset (by age 40); frontal bald early onset (by age 30); frontal bald later onset (by age 40); and frontal (at age 30) to vertex bald (at age 40). Separate analyses of the two studies are consistent and suggest an association between vertex baldness and prostate cancer {vertex bald early onset odds ratios, 2.44 [confidence interval (CI), 0.57–10.46] and 2.11 (CI, 0.66–6.73), respectively; vertex bald later**

**onset odds ratios, 2.10 (CI, 0.63–7.00) and 1.37 (CI, 0.47–4.06), respectively}. Although statistical significance was not achieved in either one of these studies, the concordance between the data suggests a need for future studies to determine whether early onset vertex baldness serves as a novel biomarker for prostate cancer and whether androgen production, metabolism, or receptor status differs among these men when compared to those who exhibit other types of hair patterning.**

#### Introduction

One of five American men will develop prostate cancer during their lifetime (1). Despite the high incidence of prostatic carcinoma, few risk factors other than increasing age, family history, and black race are established (2). A long-standing hypothesis is that prostatic neoplasia is stimulated by testosterone, and therefore, increased androgen levels represent a risk factor for this disease (2, 3). Evidence in support of the role of androgens is provided by the fact that eunuchs rarely develop prostate cancer, that castration has a palliative effect on prostate cancer, and that testosterone alone can produce prostatic adenocarcinoma in rats (2, 4, 5). Likewise, eunuchs will not develop baldness if castrated before age 25, and if supplemented with testosterone, eunuchs will assume age-appropriate hair patterns characteristic of their pedigree (6, 7). Despite these apparent similarities, only a few studies have explored whether hair patterning is associated with prostate cancer, and no associations have been found (8–11). In the most recent of these studies, Demark-Wahnefried *et al.* (8) found that men who displayed vertex (crown) baldness had significantly higher levels of free testosterone, as did prostate cancer cases when compared to controls. However, despite strong associations between testosterone levels and disease and between testosterone levels and vertex baldness, no association between present hair patterning and prostate cancer risk was found within the sample of 50–70-year-old men (8). Given the strategy of targeting patients with early disease onset commonly used in studies of genetic susceptibility, we speculated on the emergence of early onset phenotypes that may be associated with disease and hypothesized that vertex baldness may indeed portend risk if assessed during an informative period of time (*i.e.*, early adulthood). To explore this issue further, retrospective data related to hair patterning at age 30 and age 40 were gathered from men participating in two discrete prostate cancer case-control investigations and are reported herein.

#### Materials and Methods

Data were generated from two prostate cancer case-control studies conducted by investigators at Duke University Medical Center during April 1993 to March 1998. For both studies, subjects were limited to mentally competent black or white men who had no prior cancer histories other than nonmelanoma skin cancer. In addition, the items and procedures used to assess and collect hair patterning data were identical for both studies, *i.e.*,

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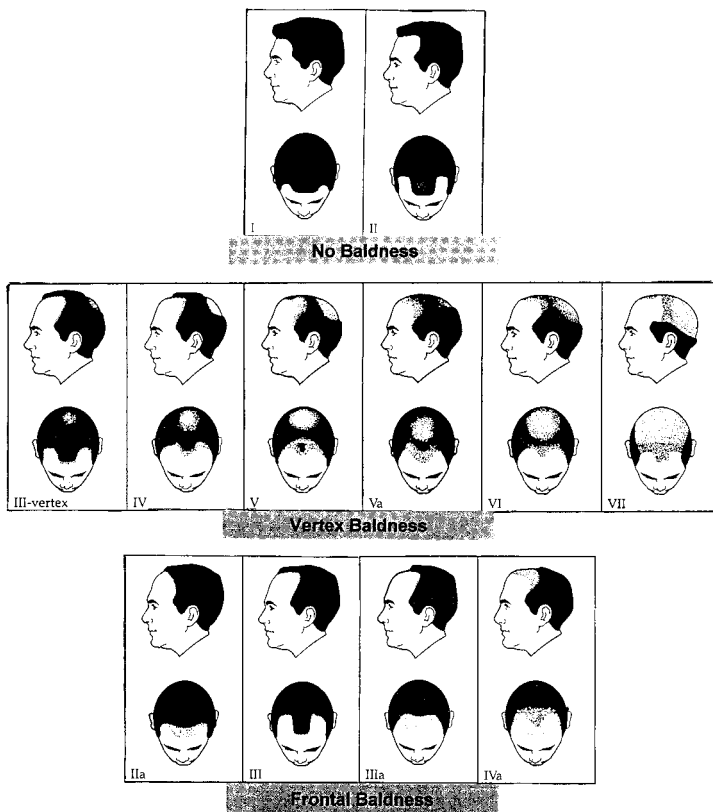


Fig. 1. HS of Baldness hair patterns. Hair patterns have been rearranged from the original  $4 \times 3$  block (organized by Roman numerals) as proposed by Norwood (12) and arranged according to "not bald," "vertex bald," and "frontal bald" status.

subjects were provided with a diagram of the HS<sup>3</sup> of Baldness as modified by Norwood (12) and asked to select the view pair that best represented their hair patterning at age 30 and again at age 40 (6). Although assessment using the HS requires no special training and concordance between lay and expert scores or repeated ratings have been reported as 98 and 99%, respectively (6), no validation studies have been performed to determine the validity and reliability of hair patterning data that are gathered retrospectively and by self-report. There, however, is no reason to believe that case-control status would influence the patterns, which were reported.

The first study was a prostate cancer case-control investigation that was aimed at determining anthropometric (body fat distribution, skeletal structure, and body musculature) and hormonal (total and free testosterone, dihydrotestosterone, and sex hormone binding globulin) risk factors for prostate cancer. The sample was recruited exclusively from the urology clinics at Duke University Medical Center and was further delimited to men who had been weight stable within 1 year of recruitment (no weight loss or gain >10% of body weight), between the ages of 50 and 70, and who had not received any hormonal treatment (including orchiectomy). Only cases with localized prostate cancer who were within 3 months of diagnosis were included. Controls were patients who came to the clinic expressly for prostate cancer screening (19%) or to be evaluated for benign prostatic hypertrophy (26%), prostatitis (19%), hematuria (6%), dysuria (6%), impotence (5%), nephrolithiasis (5%), nocturia (3%), epididymitis (3%), spermatocele (3%), urinary tract infections (2%), inguinal hernia (1%), renal or seminal vesicle cysts (1%), or retroperitoneal fibrosis (1%). Cases and controls were frequency-matched on age (50% between ages

Characteristics	Duke-based study		Community-based study	
	Cases (N = 78)	Controls (N = 71)	Cases (N = 56)	Controls (N = 74)
Racial distribution (%)				
White	92.3 (72)	91.6 (65)	60.7 (34)	54.1 (40)
Black	7.7 (6)	8.5 (6)	39.3 (22)	46.0 (34)
Age (yr)				
Mean $\pm$ SD	61.5 $\pm$ 5.3	61.8 $\pm$ 6.1	58.1 $\pm$ 6.7	57.8 $\pm$ 6.6
Range	50–70	50–70	45–67	45–67
Stage at diagnosis (%)				
Localized	100 (78)	N/A <sup>a</sup>	53.6 (30)	N/A
Regional	0	N/A	35.7 (20)	N/A
Distant	0	N/A	7.1 (4)	N/A
Unstaged	0	N/A	3.6 (2)	N/A

<sup>a</sup> N/A, not applicable.

50 and 60; 50% between ages 60 and 70) and race (80% white; 20% black). Recruitment for this study was conducted in person from April 1993 to January 1995. The refusal rate was 5%, with "lack of time" cited as the primary reason for nonparticipation, which was slightly higher among blacks as well as control subjects (total,  $n = 315$ ). In November 1997, all surviving patients (per the Duke patient database,  $n = 287$ ) were sent reprints of resulting papers along with a copy of the baldness scale, questions regarding their hair patterning at ages 30 and 40, and a preaddressed stamped postcard to record and return their response. Control participants also were asked whether they had been diagnosed with prostate cancer in the interval between their initial participation and the time at which they received the mailing (four controls were diag-

<sup>3</sup> The abbreviations used are: HS, Hamilton Scale; OR, odds ratio.

Table 2 Hair patterning at ages 30 and 40 as reported by prostate cancer cases and controls

Case-control status	Duke-based study (N = 149)			Community-based study (N = 130)		
	Not bald % (N)	Vertex bald % (N)	Frontal bald % (N)	Not bald % (N)	Vertex bald % (N)	Frontal bald % (N)
At age 30						
Cases	79 (62)	13 (10)	8 (6)	84 (47)	11 (6)	5 (3)
Controls	82 (58)	7 (5)	11 (8)	84 (62)	4 (3)	12 (9)
At age 40						
Cases	53 (41)	29 (23)	18 (14)	68 (38)	27 (15)	5 (3)
Controls	61 (43)	24 (17)	15 (11)	64 (48)	18 (13)	18 (13)

Table 3 Hair patterns and race and age-adjusted ORs with 95% confidence intervals

Baldness categories	Duke-based study (N = 149) <sup>a</sup>		Community-based study (N = 130)		Combined (N = 279)	
	OR	95% CI	OR	95% CI	OR	95% CI
Not bald	1.00		1.00		1.00	
DB Cases, N = 41; DB Controls, N = 43						
CB Cases, N = 38; CB Controls, N = 48						
Vertex bald earlier onset (by age 30)	2.11	0.66–6.73	2.44	0.57–10.46	2.20	0.89–5.43
DB Cases, N = 10; DB Controls, N = 5						
CB Cases, N = 6; CB Controls, N = 3						
Vertex bald later onset (by age 40)	1.37	0.47–4.06	2.10	0.63–7.00	1.67	0.75–3.72
DB Cases, N = 9; DB Controls, N = 7						
CB Cases, N = 8; CB Controls, N = 5						
Frontal bald earlier onset (by age 30)	0.71	0.11–4.71	0.58	0.10–3.39	0.66	0.19–2.35
DB Cases, N = 2; DB Controls, N = 3						
CB Cases, N = 2; CB Controls, N = 4						
Frontal bald later onset (by age 40)	1.58	0.58–4.28	0.14	0.02–1.17	0.88	0.40–1.94
DB Cases, N = 12; DB Controls, N = 8						
CB Cases, N = 1; CB Controls, N = 9						
Frontal (age 30) to vertex bald (age 40)	0.85	0.21–3.39	0.24	0.03–2.19	0.55	0.18–1.68
DB Cases, N = 4; DB Controls, N = 5						
CB Cases, N = 1; CB Controls, N = 5						

<sup>a</sup> CI, confidence interval; DB, Duke-based; CB, Community-based.

nosed with prostate cancer and were recorded and analyzed as cases). Response cards from 150 men and 42 unopened letters with no forwarding address were received, thus yielding a second tier response rate of 61%. Response rates did not differ between cases and controls; however, they did differ between blacks (34%) and whites (63%).

The second study was a community-based prostate cancer case-control investigation that was conducted within a 63 contiguous county region of North Carolina. The primary aim of the study was to ascertain the effect of environmental and occupational exposures on prostate cancer risk. Cases were identified from 16 hospitals that contributed 75% of cases within the geographic region; community-based controls frequency-matched on age (the age criteria for both cases and controls was  $\leq 67$  years of age), race, and county of residence were identified from Department of Motor Vehicle tapes. Recruitment was conducted via a mailed letter, which instructed interested participants to mail back a preaddressed stamped postcard. Given the limited funding that precluded active follow-up, a reliance on active consent was necessary and resulted in an overall acceptance rate of 9.7%. Rates of acceptance varied with regard to race (6.9% among blacks versus 13.6% among whites) and case-control status (6.4% among controls versus 22.3% among cases). Cases and controls, however, did not differ with regard to income and educational status. Cases were interviewed within 1 year of diagnosis, and data for this study were collected via an in person interview. Nurse interviewers showed each participant the HS of Baldness and asked men to indicate the

view pair that best “fit” their hair patterning at age 30 and also at age 40; their responses to each question were recorded.

Data from both studies were reviewed and double-key entered (responses from four subjects, one from the Duke-based study and three from the community-based study, were excluded due to failed logic checks and inconsistency). For data analyses, HS scores of baldness at each age were collapsed into three categories: not bald (I/II); frontal bald (IIa/III/IIIa/IVa), and vertex bald (III-vertex, IV/V/Va/VI, and VII; see Fig. 1). To better classify balding individuals with regard to the directionality of their hair loss, *i.e.*, balding beginning at the hairline versus balding beginning at the crown, and also to discriminate between early versus later onset balding, the following five categories were created and compared: not bald at 30/not bald at 40 (not bald: referent group); not bald at 30/vertex bald at 40 (vertex bald later onset); vertex bald at 30/vertex bald at 40 (vertex bald early onset); not bald at 30/frontal bald at 40 (frontal bald later onset); frontal bald at 30/frontal bald at 40 (frontal bald early onset); and frontal bald at 30/vertex bald at 40 (frontal to vertex bald). Given the centrality of vertex balding to our hypothesis, men reporting any vertex baldness were classified as being “vertex bald,” thus excluding the possibility of vertex to frontal hair loss pattern.

Given the differences in study design and proportionate accrual, as well as sample characteristics (*e.g.*, racial composition and stage distribution) that are associated with prostate cancer and could confound androgen-related effects, a decision was made to

conduct separate analyses on data from each study.  $\chi^2$  analyses were conducted to determine whether differences in hair patterning existed between cases and controls. Additional analyses using unconditional logistic regression models and adjusting for age and race also were conducted. Age was modeled as a continuous variable in the logistic regression analysis, with age set at age of diagnosis for cases and age at interview for controls.

## Results

There were significant differences between the studies with regard to race and stage. The community-based study had proportionately more blacks and more men with later-staged disease than the Duke-based study (Table 1).

Hair patterning data for prostate cancer cases and controls are presented in Table 2, and baldness categories with race and age-adjusted ORs are presented in Table 3 (unadjusted ORs are not presented because of their similarity to these data). Data suggest that vertex baldness is associated with an increased risk for prostate cancer, with an ~2-fold increase in risk noted among men who develop vertex baldness by age 30. In contrast, data related to frontal baldness suggest that it might be protective or modify the risk associated with vertex baldness; however, data are too inconsistent to draw firm conclusions. For all analyses, the magnitude of the ORs was consistently greater in the community-based study, with effects that approached significance (at the 5% level), as compared to the Duke-based study where weaker trends were observed.

## Discussion and Conclusion

Of the studies that have explored the association between hair patterning and prostate cancer risk, this is the first to suggest differences between cases and controls. Wynder *et al.* (11), Oishi *et al.* (10), and Greenwald *et al.* (9) were all unable to detect differences between prostate cancer cases and controls with regard to body hair, hair thickness, and/or baldness (8). These investigations used different discriminators, such as body hair, and also did not employ standardized tools, such as the HS of Baldness, to assess hair patterning. In addition, some of these prior studies used techniques, such as the use of reunion photographs, which were incapable of capturing hair loss at the crown. However, even using standardized scales and techniques to capture vertex baldness, Demark-Wahnefried *et al.* (8) also were unable to detect case-control differences in hair patterning when assessed in men over the age of 50. Given the prevalence of hair loss with increasing age and evidence that eunuchs will only demonstrate baldness if castrated after age 25 or if supplemented with testosterone (6), it may be important to capture hair patterning at critical periods of time if its utility as a risk factor is to be adequately tested. This study is unique because: (a) head hair patterning was assessed using a standardized scale; and (b) data were collected on hair patterning during earlier adulthood.

Although the limitations of this investigation included its reliance on self-reported, retrospective data that may be subject to respondent and recall bias and a lack of power to achieve statistical significance, the ORs for vertex baldness were of similar direction and magnitude. The concordance between these results lends strength to our conclusion that early onset vertex baldness may place men at "moderate risk" for prostate cancer (13), with ORs that suggest a >2-fold increased risk among men who develop vertex baldness by age 30.

In summary, given the consistency of our findings, as well as the growing body of research that indicates that there are common biological factors and pathways that are associated with both

prostate cancer and baldness [*i.e.*, variations in the A2 allele in CYP17 (cytochrome P450c17 $\alpha$  gene on 10q24.3 encoding for 17 $\alpha$ -hydroxylase and 17/20-lyase; key enzymes in the androgen steroidogenesis pathway; Refs. 14–16), expressed levels of androgens and insulin-like growth factor-1 (3, 8, 17, 18), conversion of testosterone to dihydrotestosterone (2, 19), and androgen receptor status (19–21)], we encourage further study of early vertex baldness as a potential risk factor for prostate cancer.

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## References

- Landis, S. H., Murray, T., Bolden, S., and Wingo, P. A. Cancer statistics, 1999. *CA Cancer J. Clin.*, 49: 8–31, 1999.
- Nomera, A., and Kolonel, L. Prostate cancer: a current prospective. *Am. J. Epidemiol.*, 13: 200–227, 1991.
- Gann, P., Hennekens, C., Ma, J., Longcope, C., and Stampfer, M. Prospective study of sex hormone levels and risk of prostate cancer. *J. Natl. Cancer Inst.*, 88: 1118–1122, 1996.
- Bagatell, C. J., and Bremner, W. J. Androgens in men—uses and abuses. *N. Engl. J. Med.*, 334: 707–714, 1996.
- Isaacs, J. T. Role of androgens in prostatic cancer. *Vitam. Horm.*, 49: 433–504, 1994.
- Hamilton, J. B. Male hormone stimulation is prerequisite and an incitant in common baldness. *Am. J. Anat.*, 71: 451–480, 1942.
- Randall, V. A. Androgens and human hair growth. *Clin. Endocrinol.*, 40: 439–457, 1994.
- Demark-Wahnefried, W., Lesko, S. M., Conaway, M. R., Clark, R. V., Lobaugh, B., Mathias, B. J., Strigo, T. S., Robertson, C. N., and Paulson, D. F. Serum androgens: associations with prostate cancer risk and hair patterning. *J. Androl.*, 18: 495–500, 1997.
- Greenwald, P., Damon, A., Kirmss, V., and Polan, A. K. Physical and demographic features of men before developing cancer of the prostate. *J. Natl. Cancer Inst.*, 53: 341–346, 1974.
- Oishi, K., Okada, K., Yoshida, O., Yamabe, H., Ohno, Y., Hayes, R. B., and Schroeder, F. H. Case-control study of prostatic cancer in Kyoto, Japan: demographic and some lifestyle risk factors. *Prostate*, 14: 117–122, 1989.
- Wynder, E. L., Mabuchi, K., and Whitmore, W. F., Jr. Epidemiology of the prostate. *Cancer (Phila.)*, 28: 344–360, 1971.
- Norwood, O. T. Male pattern baldness: classification and incidence. *South Med. J.*, 68: 1359–1365, 1975.
- World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, and Prevention of Cancer. A Global Perspective. Washington, DC: American Institute for Cancer Research, 1997.
- Carey, A. H., Waterworth, D., Patel, K., White, D., Little, J., Novelli, P., Franks, S., and Willamson, R. Polycystic ovaries and premature male pattern baldness are associated with one allele of the steroid metabolism gene CYP17. *Hum. Mol. Genet.*, 3: 1873–1876, 1994.
- Dufau, M. L., Miyagawa, Y., Takada, S., Khanum, A., Miyagawa, H., and Buczko, E. Regulation of androgen synthesis: the late steroidogenic pathway. *Steroids*, 62: 128–132, 1997.
- Techatrasak, K., Conway, G. S., and Rumsby, G. Frequency of a polymorphism in the regulatory region of the 17 $\alpha$ -hydroxylase-17,20 lyase (CYP17) gene in hyperandrogenic states. *Clin. Endocrinol.*, 46: 131–134, 1997.
- Chan, J. M., Stampfer, M. J., Giovannuci, E., Gann, P. H., Ma, J., Wilkinson, P., Hennekens, C. H., and Pollak, M. Plasma insulin-like growth factor 1 and prostate cancer risk: A prospective study. *Science (Washington DC)*, 279: 563–567, 1998.
- Signorello, L. B., Wu, J., Hsieh, C.-C., Tzonou, A., Trichopoulos, D., and Mantzoros, C. S. Hormones and hair patterning in men: a role for insulin-like growth factor 1? *J. Am. Acad. Dermatol.*, 40: 200–203, 1999.
- Sawaya, M. E. Biochemical mechanisms regulating human hair growth. *Skin Pharmacol.*, 7: 5–7, 1994.
- Giovannuci, E., Stampfer, M., Krithivas, K., Brown, M., Brufsky, A., Talcott, J., Hennekens, C., and Kantoff, P. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. *Proc. Natl. Acad. Sci. USA*, 94: 3320–3323, 1997.
- Hibberts, N. A., Howell, A. E., and Randall, V. A. Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from non-balding scalp. *J. Endocrinol.*, 156: 59–65, 1998.