Androgenetic Alopecia and Prostate Cancer: Findings from an Australian Case-Control Study[1]

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Abstract

The purpose of this study was to examine the relationship between androgenetic alopecia (AA) and prostate cancer with particular emphasis on early age at diagnosis and higher grade tumors. We conducted an age-stratified, population-based case-control study in Australia of men who were diagnosed before 70 years of age during 1994–1997 with histopathology-confirmed adenocarcinoma of the prostate, excluding well-differentiated tumors. Controls were selected from the electoral rolls, and the frequency was matched on age. After excluding subjects with missing values, the analysis was based on 1446 cases and 1390 controls of whom direct observations were made of their pattern of AA during face-to-face interviews. Our data suggest an association between prostate cancer and vertex baldness; compared with men who had no balding, the adjusted odds ratio (OR) was 1.54 (1.19–2.00). No associations were found between prostate cancer and frontal baldness or when frontal baldness was present concurrently with vertex baldness. The ORs were 0.98 (0.79–1.23) and 1.14 (0.90–1.45), respectively. The highest ORs were for high-grade disease in men 60–69 years of age: 1.80 (1.02–3.16) for frontal baldness; 2.91 (1.59–5.32) for vertex baldness; and 1.95 (1.10–3.45) for frontal and vertex baldness. This association between the pattern of AA and prostate cancer points to shared androgen pathways that are worthy of additional investigation.

Introduction

One important characteristic of prostate cancer is its rapid increase with age. Male pattern baldness, AA,[3] is also strongly age dependent and, similar to prostate cancer, is considered to be androgen dependent (1, 2).

Androgens exert their effects by binding to a single cytoplasmic AR, and their potency is determined by the binding affinity to the AR, with DHT binding five times more strongly than T (2). The enzyme 5αR converts T to its active form, DHT. DHT is implicated not only in the development of benign prostatic hypertrophy but also in the pathogenesis of prostate cancer (3, 4). Isozymes of 5αR are differentially expressed in tissues; 5αR-1 is expressed in the skin, sebaceous glands, liver, adrenal, and kidney, whereas 5αR-2 is expressed in the prostate, testes, seminal vesicles, liver, and hair follicles (5, 6). Inherited deficiency of 5αR-2 leads to absence of AA and a small prostate (7). Finasteride, a 5αR-2 inhibitor with little 5αR-1 activity, has been useful in the treatment of AA and benign prostatic hypertrophy (8, 9). Finasteride down-regulates expression and secretion of PSA (10), but its short-term use in the chemoprevention of prostate cancer, benign prostatic hypertrophy, and elevated PSA has not been successful (11), and long-term use is still subject to trial (12). Studies that have specifically addressed the question of whether AA is associated with prostate cancer are few and have produced inconsistent findings (13–17). We examined associations of AA with early-onset, moderate- to high-grade prostate cancer in a large case-control study (18). The main thrust of the case-control study was to examine lifestyle associations with the diagnosis of "clinically important" prostate cancer. To this end, we excluded tumors that were well differentiated (low grade or Gleason score <5). We also focused on early-onset cancers because we were interested in finding factors relevant to the prevention of prostate cancer in men before the age of 70.

Materials and Methods

We carried out an age-stratified, population-based case-control study of prostate cancer in Melbourne, Sydney, and Perth, Australia (18). The subjects were residents of the three cities' metropolitan areas. Prior approval of the study protocol was obtained from all relevant hospital and cancer registry human research ethics committees in Victoria, New South Wales, and Western Australia.

Eligible cases comprised all male residents of Melbourne,

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[3] The abbreviations used are: AA, androgenetic alopecia; T, testosterone; IGF, insulin-like growth factor; AR, androgen receptor; DHT, dihydrotestosterone; 5αR, 5-α reductase; PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval; VDR, vitamin D receptor.

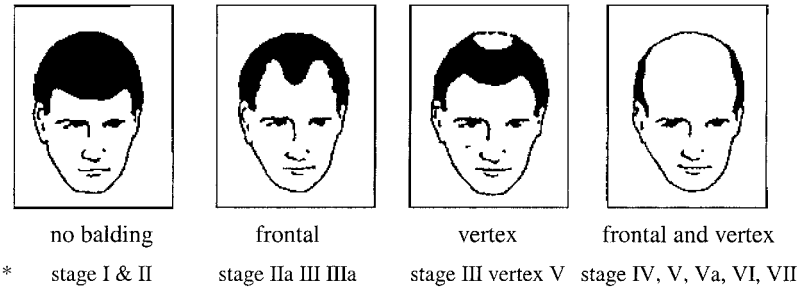

Fig. 1. Androgenetic alopecia patterns in men. *, adapted from the Hamilton-Norwood scale (19).

Sydney, and Perth diagnosed from 1994 to 1997 and recorded in the population-based cancer registries with a histopathology-confirmed diagnosis of adenocarcinoma of the prostate (International Classification of Diseases, 9th revision, rubric 185), excluding well-differentiated tumors (defined as low grade, *i.e.*, those with Gleason scores <5). Cases had to be <70 years of age at diagnosis and also had to be registered to vote on the state electoral rolls (adult registration to vote is compulsory in Australia). Meeting this criteria, all cases diagnosed before the age of 60 years were included, and random samples of 50% of cases diagnosed at 60–64 years of age and 25% of cases diagnosed at 65–69 years of age were selected, with the proportions varying over time to fit interview quotas.

Controls were randomly selected from men on the current state electoral rolls and were frequency matched to the predicted age distribution of the cases in a ratio of one control per case. Potential controls were matched against the cancer registries at the time of recruitment to exclude men with a known history of prostate cancer. Controls were identified and interviewed contemporaneously with the cases over the period 1994 to 1997. During the course of this study, 3 controls were subsequently diagnosed with prostate cancer and were selected as eligible cases. These subjects are included as cases and as controls.

After seeking advice from the case subjects' urologists, from whom some clinical details were sought, we wrote to each subject inviting him to participate. We wrote to the control subjects directly. Face-to-face interviews were arranged, usually at the man's home. A structured interview schedule was used to obtain information on lifestyle exposures and personal attributes. While the subject was completing a sexual history questionnaire in private, the interviewer scored the subject's AA according to a set of four pictures (Fig. 1) adapted from the Hamilton-Norwood scale (19). The first picture shows essentially no balding (Hamilton-Norwood stages I and II), the second shows frontal balding (Hamilton-Norwood stages II, III, IIIa, and IVa), the third shows vertex balding (Hamilton-Norwood stage III vertex-V), and the fourth shows frontal baldness concurrent with vertex baldness (Hamilton-Norwood stage IV, V, Va, VI, and VII).

Case-control analyses were conducted using unconditional logistic regression, adjusting for reference age (at diagnosis for cases and at date of selection from electoral roll for controls), study center (Sydney, Melbourne, and Perth), calendar year, family history (none *versus* any first-degree relative diagnosed with prostate cancer), and country of birth (Australia *versus* other). Study center and calendar year were included because the zeal for prostate cancer screening using PSA tests varied among centers and over time (20). The ORs and CIs of each category of AA relative to no balding were estimated. The effect of including AA in the model was assessed by a likelihood ratio test with 3 degrees of freedom.

Given that smoking and educational status may be predictors of response, we assessed the association of these factors with AA (no balding *versus* other) by logistic regression. To investigate whether effects differed by potential disease aggressiveness, we analyzed men with moderate-grade (Gleason scores 5–7) and high-grade (Gleason scores 8–10) tumors separately. We also examined the effects in two age groups (*i.e.*, reference age <60 *versus* 60–69). Tests for heterogeneity in the ORs between high- and moderate-grade prostate cancer were performed using polytomous logistic regression models (21).

Results

Of the 2328 cases and 3125 controls that were considered eligible at the time of selection, 1497 cases (65%) and 1434 controls (46%) were interviewed. Doctors could not be identified for, or refused access to, 16% of cases. Controls were more likely to refuse (38% *versus* 17%), to be unable to speak sufficient English to be interviewed (7% *versus* 1%), or to have moved (8% *versus* 2%).

Because the electoral roll is never completely up to date, we considered that a more appropriate response rate in controls excluded those who had moved or died, which was 50%. After excluding subjects with missing data on AA and the variables to be controlled for in the analysis, there were 1446 cases (1088 with moderate-grade and 358 with high-grade tumors) and 1390 controls available.

The distributions of demographic variables are shown in Table 1. The cases were more likely than the controls to be Australian born (OR, 1.38; 95% CI, 1.17–1.63) and to have at least one first-degree relative affected with prostate cancer (OR, 3.21; 95% CI, 2.45–4.23). There was no association between AA and educational status, smoking status, or migrant status in either cases or controls (all $P > 0.1$). Models that excluded those born overseas produced very similar findings (data not shown).

Table 2 shows that, compared with no balding, vertex balding was associated with a 50% increase in risk of prostate cancer in all subjects. No increased risk was seen for frontal balding or frontal concurrent with vertex balding. The effect of vertex balding appeared stronger in the subgroup of high-grade tumors (2-fold increased risk), but the differences in ORs between moderate- and high-grade tumors were not significant ($P = 0.6$).

The ORs for all cases in each of the two age groups were similar to those for the whole group (Table 2). In the younger subjects, the ORs were also similar for moderate- and high-grade disease (Table 2). In the older subjects, the ORs for moderate-grade disease were again similar. For high-grade disease, the ORs for all types of AA were elevated, nearly 3-fold for vertex balding and close to 2-fold for frontal balding and frontal concurrent with vertex balding, and all CIs excluded unity. However, as in the analysis in which the age groups were

Table 1 Demographic characteristics of cases and controls

	Cases						Controls[c]	
	Total[a]		Moderate grade[b]		High grade[b]			
	n	%	*n*	%	*n*	%	*n*	%
Age group								
<55	231	16.0	186	17.1	45	12.6	273	19.6
55–59	405	28.0	317	29.1	88	24.6	311	22.4
60–64	359	24.8	261	24.0	98	27.4	401	28.8
65–69	451	31.2	324	29.8	127	35.5	405	29.1
Country of birth								
Australia	1001	69.2	766	70.4	235	65.6	840	60.4
Not Australia	445	30.8	322	29.6	123	34.4	550	39.6
Educational level								
Primary only (5–11)	105	7.3	75	6.9	30	8.4	143	10.3
Secondary only (11–16)	452	31.3	351	32.3	101	28.2	445	32.0
Post secondary training	640	44.3	468	43.0	172	48.0	587	42.2
Tertiary	249	17.2	194	17.8	55	15.4	213	15.3
Family history								
No first-degree relative affected	1215	84.0	903	83.0	312	87.2	1306	94.0
Any first-degree relative affected	231	16.0	185	17.0	46	12.8	84	6.0
Smoking								
Never	530	36.7	419	38.5	111	31.0	478	34.4
Current	197	13.6	147	13.5	50	14.0	268	19.3
Former	719	49.7	522	48.0	197	55.0	643	46.3

[a] Total, 1446.
[b] Moderate grade, Gleason scores 5–7 (total, 1088); high grade, Gleason scores 8–10 (total, 358).
[c] Total, 1390.

Table 2 The association between androgenetic alopecia and prostate cancer by tumor grade and reference age

	Controls $n = 1390$	All subjects			P^b	Moderate grade[c]			P^b	High grade[c]			P^b
		Cases $n = 1446$	OR[a]	95% CI[c]		Cases $n = 1088$	OR	95% CI		Cases $n = 358$	OR	95% CI	
Alopecia, all ages													
No balding	350	337	1.00		*<0.01*	273	1.00		*0.01*	64	1.00		*0.01*
Frontal	447	438	0.98	(0.79–1.23)		326	0.96	(0.75–1.21)		112	1.24	(0.85–1.79)	
Vertex	238	310	1.54	(1.19–2.00)		223	1.45	(1.10–1.92)		87	2.04	(1.35–3.08)	
Frontal and vertex	355	361	1.14	(0.90–1.45)		266	1.11	(0.86–1.43)		95	1.39	(0.94–2.05)	
Reference age, before 60 years													
No balding	210	201	1.00		*0.07*	164	1.00		*0.14*	37	1.00		*0.24*
Frontal	187	184	1.00	(0.73–1.37)		142	1.00	(0.71–1.39)		42	0.96	(0.57–1.62)	
Vertex	74	118	1.61	(1.08–2.38)		88	1.56	(1.03–2.37)		30	1.69	(0.93–3.09)	
Frontal and vertex	113	133	1.15	(0.82–1.61)		109	1.16	(0.81–1.66)		24	1.01	(0.56–1.83)	
Reference age, 60–69 years													
No balding	140	136	1.00		*0.01*	109	1.00		*0.06*	27	1.00		*0.01*
Frontal	260	254	1.09	(0.77–1.53)		184	1.01	(0.70–1.45)		70	1.80	(1.02–3.16)	
Vertex	164	192	1.74	(1.20–2.52)		135	1.56	(1.04–2.32)		57	2.91	(1.59–5.32)	
Frontal and vertex	242	228	1.24	(0.87–1.76)		157	1.15	(0.79–1.66)		71	1.95	(1.10–3.45)	

[a] All ORs are adjusted for reference age, study center, calendar year, family history, and country of birth.
[b] P from likelihood ratio test to remove variable from model based on a χ^2 test with 3 degrees of freedom.
[c] Moderate grade, Gleason scores 5–7; high grade, Gleason scores 8–10.

combined, the difference between the ORs for high-grade and moderate-grade tumors was not significant ($P = 0.31$).

Discussion

Our analysis suggests a positive association between prostate cancer and vertex baldness that appeared to be more evident for high-grade prostate cancer, especially when diagnosed in men 60–69 years of age. We have considered the extent to which this finding might be attributable to bias or confounding, given the response rates, and the fact that subjects were ascertained during a period of intense PSA testing in the population (20). With respect to response, in neither cases nor controls could we find an association between either educational status or smoking status (as surrogates for response) with AA (data not shown). The association between prostate cancer and AA was at least as strong for high-grade prostate cancer as for moderate-grade prostate cancer, suggesting that PSA testing, which identifies large numbers of moderate-grade tumors (20), cannot explain the difference. Furthermore, we believe it is implausible that vertex balding would be associated with PSA testing, and although the interviewers were often not blind to the case-control status of subjects, they were not informed of any hy-

pothesis concerning AA. Having controlled for the strongest established risk factors (age and family history) and given the lack of other known risk factors, we consider that confounding is unlikely to have influenced our findings.

Our observation of an increased risk of prostate cancer associated with vertex baldness is consistent with two small case-control studies (13) and one cohort study (14) but not with another cohort study (15) and two hospital-based case-control studies (16, 17). Of those studies not in agreement with ours, the cohort study of Harvard alumni (15) assessed men's baldness from photographs taken from college yearbooks published 25 years after graduation when former students were in their mid-forties and compared the men who had died from prostate cancer with those who had not. No attempt was made to assess vertex baldness. A hospital-based case-control study (17) conducted in Athens, Greece, on 320 prostate cancer patients and a mix of 246 patients without prostate cancer excluded men with benign prostatic hypertrophy from the controls. This could be problematic, given that AA may be associated with benign prostatic hypertrophy (22) and both are related to 5αR activity (23, 24).

Of the case-control studies in agreement with ours (13), one was a hospital-based study of 78 cases and 71 controls and the other was a community-based study of 56 cases and 74 controls (13). The Hamilton-Norwood scale was used to measure AA (19); subjects were asked to choose pictures that best described their hair pattern at 30 and 40 years of age. The analysis produced consistent but statistically not significant results: an OR for vertex baldness of 2.44 (95% CI, 0.57–10.46); an OR for baldness by age 30 of 2.11 (95% CI, 0.66–6.73); and an OR for baldness by age 40 of 1.37 (95% CI, 0.47–4.06). A follow-up of the first National Health and Nutrition Examination Survey, comparing 214 prostate cancer cases with the remaining 4421 men examined for AA at baseline when 25–75 years of age, found an OR of 1.5 (95% CI, 1.12–2.00) for any form of baldness (14). This estimate has been considered to be possibly attenuated, not only by the lack of specificity of the baldness measurement (they were not able to distinguish vertex baldness) but also by the wide range of ages at which baldness was assessed (25). It is possible that any association with baldness may be stronger in men who become bald at an early age.

A mechanism for the putative relationship between AA and prostate cancer risk is yet to be established. Because both AA and prostate cancer are androgen dependent, differences in androgen metabolism, coactivators of the AR, *AR* gene mutations and polymorphisms of the *AR*, and *5αR* genes are all obvious candidates for investigation (26–28). Other candidates for investigation include physiological pathways important to prostate cell differentiation and proliferation, *e.g.*, IGF-1 and the VDR. IGF-1 can lead to aberrant activation of the AR and mediates the perpetuating effects of growth hormone on AA (29). Vitamin D (as 1α,25-hydroxyvitamin D) inhibits prostate cell growth (30), and polymorphic variation in the *VDR* has been linked to prostate cancer risk (31). 1α,25-Hydroxyvitamin D resistance has been linked to alopecia in humans (32), and VDR knockout mice also develop alopecia (33).

A case-control study of 159 cases and 156 controls found a positive association between free T levels in serum from men with frontal or vertex baldness, compared with men who had only minimal hair loss (16). The association between T (and IGF-1) and AA was also found in a cross-sectional study (34). Associations between prostate cancer and elevated T have been reported in a case-control (35) and a prospective (36) study. In the latter, elevated T levels in blood sampled before diagnosis were associated with increased risk of prostate cancer, especially advanced disease. Other analyses of this cohort study have shown positive associations between IGF-1 and prostate cancer (37) and also between IGF-1 and vertex baldness (38).

It is considered that premature AA is related to high levels of androgens generally and to high DHT levels specifically in the frontal scalp (39), with 5αR-2 playing a central role in the intrafollicular conversion of T to DHT (2). This is supported by the immunohistochemical localization, in cryosections of scalp from men with AA, of 5αR-1 staining within sebaceous glands but not in hair follicles and 5αR-2 staining in the root sheath and the infundibular region of the follicle but not within the dermal papilla or sebaceous glands (40). Others have shown that the outer root sheaths of frontal hair follicles have higher levels of AR, 5αR-1, and 5αR-2 and less aromatase than in occipital follicles (41), and a higher level of AR has been demonstrated in hair follicles from balding skin compared with nonbalding skin (42). Aberrant activation of the AR has been demonstrated *in vitro* with IGF-1, keratinocyte growth factor, and epidermal growth factor. These agents can directly activate the AR in the absence of androgens and may contribute to the progression of prostate cancer and AA (43, 44). Some consider that prostate cancer risk might be associated with the CAG repeat polymorphism in the *AR* (11, 27, 28), although we have been unable to detect such an association in our study (data not shown). However, shorter CAG repeat lengths in the *AR* may affect androgen-mediated gene expression in hair follicles and sebaceous glands (45). Platz *et al.* (38) and Ellis *et al.* (46), in comparing men with early-onset AA and older nonbald men, failed to detect any variation in allele, genotype, or haplotype frequencies in the genes encoding 5αR-1, 5αR-2, and insulin, suggesting that these were not associated with early-onset AA. This is not altogether surprising because whole follicle transplantation experiments have demonstrated that each hair follicle is genetically programmed not only to respond, or not respond, to androgens but also in what manner to respond (47). Although the geographical patterning of the hair loss in AA is associated with quantitative differences in androgens and numbers of ARs, these are likely to be secondary phenomena because the hair follicle is able to regulate its own response to androgens by enhancing expression of 5αR and ARs *in vitro* (48). Genetic control of AA may reside with differentiation/morphogen genes, *e.g.*, genes that code for developmental regulator proteins implicated in the *sonic hedgehog* signaling pathway or its cognate receptor *patched* (49). Notably, these genes also play an important role in oncogenic transformation (50).

The extent to which different androgens interact with each other, and with the molecules that produce, transport, activate, receive, and remove them from circulation, is far from completely understood. It is possible that common polymorphisms in genes that encode steroid hormones and their reductases and other relevant molecules, *e.g.*, the genes for IGF (and its receptor), the AR, and aromatase, might influence the etiology of all these conditions. To better understand this complexity, there is an obvious need for larger studies of prostate cancer and AA that include measures of polymorphic variation in an increasing number of candidate genes.

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