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Androgenic alopecia is not useful as an indicator of men at high risk of prostate cancer

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ABSTRACT

Background: Androgens are assumed to play a central role in the pathophysiology of both prostate cancer (PC) and androgenic alopecia (AA). A correlation between the two phenotypes may be relevant for identification of men at high risk of PC. We evaluated the association between AA at different ages and PC in a large case-control study.

Methods: The case group comprised 938 PC patients recruited from a population-based cancer registry. The controls (n = 2160) were a random sample of the male general population. All subjects completed a questionnaire on risk factors for cancer, including questions on hair pattern at different ages using an adapted version of the Hamilton-Norwood scale, race and family history of PC. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression.

Results: Baldness at early age appeared to be associated with a lower risk of PC (baldness at age 20: OR = 0.86; 95% CI 0.69–1.07 and baldness at age 40: OR = 0.81; 95% CI 0.70–0.96). Baldness at completion of the questionnaire was not associated with PC: OR = 1.10; 95% CI 0.89–1.34. An isolated 'frontal baldness' or 'vertex baldness' pattern was not significantly associated with PC at any age. Presence of a combined 'frontal and vertex' baldness pattern at age 40 was associated with a decreased risk of PC (OR = 0.62; 95% CI 0.45–0.86). There were no significant associations between AA and aggressive PC.

Conclusions: We did not find consistent positive associations between AA at different ages and PC. Surprisingly, if anything, baldness at early age is inversely related to PC in this study. Androgenic alopecia is not useful as an indicator of men at high risk of PC.

1. Introduction

Prostate cancer (PC) and androgenic alopecia (AA), also known as male-pattern baldness, are two common conditions in ageing males. AA produces patterned hair loss beginning with bi-temporal recession of the frontal hair line, followed by diffuse thinning over the vertex. Over time there is complete hair loss centrally on the vertex, producing a bald patch. The patch enlarges and joins the receding frontal hair line, leaving behind an island of hair on the frontal scalp. In some

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men the loss over the vertex occurs more rapidly than the frontal loss; in others the entire frontal hairline marches back before a bald patch on the vertex develops. Androgens are assumed to play a central role in the pathophysiology of both AA and PC. The link between androgens and AA is well established, with reports of lack of balding in eunuchs and androgen-insensitive or 5-alpha-reductase deficient individuals, while high levels of the androgen receptor (AR) and low levels of aromatase, which converts testosterone to oestrogen, have been associated with male-pattern balding.[1–3]

PC growth is stimulated by androgens via expression and up-regulation of AR activity, ligand-independent activation of the AR and mutations in the AR gene.[4] In the Prostate Cancer Prevention Trial, the use of finasteride, a 5-alpha-reductase inhibitor (5ARI) which is FDA approved in the USA to treat male-pattern hair loss (marketed as Propecia®), has shown to reduce prostate cancer prevalence by 25% in men who participate in an annual PSA screening protocol with prostate biopsies at the end of the study.[5] Also, in the REduction by DUtasteride of prostate Cancer Events trial (REDUCE), dutasteride, another 5ARI, decreased the risk of prostate cancer over 4 years by 23% among men at increased risk of prostate cancer, i.e. men who have a PSA of 2.5–10 ng/ml with negative prostate biopsies.[6]

In the last 3 years several genome-wide association studies (GWAS) have identified more than 30 susceptibility loci for prostate cancer.[7] These loci do not overlap with the two susceptibility loci that have been found in a GWAS of AA, located in the *AR* region at Xq11-12 and in the region between *PAX1* and *FOXA2* on chromosome 20p11.22, but a linkage study in hereditary prostate cancer did find evidence for a potential role of the *AR* gene for prostate cancer.[8–11] Other attempts to find evidence for a common pathophysiology between AA and PC have yielded inconsistent and inconclusive results.[12–14]

A proven underlying common cause of PC and AA may be very important for the development of decision aids whether or not to screen for prostate cancer. Recently, the European Randomized Study of Screening for Prostate Cancer reported a reduction in prostate cancer mortality as a consequence of programmed screening with prostate-specific antigen (PSA), but at the cost of significant over-diagnosis.[15] Identification of men who are at increased risk of PC on the basis of simple phenotypes such as AA might lead to screening policies with a better balance between intended and unintended effects. In this paper, we describe a large case-control study on the association between AA and prostate cancer.

2. Methods

The study population and study design have been described in detail before.[16,17] In brief, the case group was recruited for the so-called POLYGENE study and consists of all patients diagnosed with prostate cancer in the period 2003–2006 and registered by the regional cancer registry held by the Comprehensive Cancer Centre East (CCCE) in Nijmegen, The Netherlands. Eligibility criteria included: age at diagnosis of 75 years or younger, alive at the date of invitation to the study and living in the catchment area of the CCCE. Eligible patients were contacted between September 2006 and June 2007. Overall, 1330 patients fulfilled the inclusion criteria and were invited for the study. In total 1020 patients were willing to participate (77%). Participation included the donation of a blood sample and the completion of a questionnaire. Finally, 956 patients (72%) actually filled out the questionnaire. The registration staff of the CCCE had already collected clinical and pathology data of all patients in the cancer registry. These standard cancer registry data were supplemented with more detailed data by extraction from the medical files in the hospitals where the patients were treated.

The control individuals were recruited for the Nijmegen Biomedical Study (NBS), a population-based survey conducted in 2002 by the Department of Epidemiology and Biostatistics and the Department of Clinical Chemistry of the RUNMC. Twenty-two thousand four hundred and fifty-one (49% of whom were males) age- and sex-stratified randomly selected inhabitants of Nijmegen, The Netherlands, were invited to participate in a study on gene-environment interactions in multifactorial diseases such as cancer. Between August 2002 and December 2003, all subjects who were still alive and whose addresses were known (n = 21,756) were invited to fill out the same questionnaire as was sent in the pilot phase (NBS1) and to donate two tubes of blood. Forty-three percent (9350) of the invited persons returned a completed questionnaire, 46% of whom were males. The NBS participants who filled out the NBS questionnaire, had given consent for further research, were still alive and had known addresses were again contacted in 2008 and invited to fill out an additional questionnaire containing, among others, questions on hair pattern. In total, 8109 people were approached (3691 males) of whom 7950 received the questionnaire (3625 males) (159 were deceased or had moved). In total, 5613 completed questionnaires (response 71%) were returned, 2552 of which were returned by males. Participants who had a history of prostate cancer at the time of recruitment were excluded from analysis.

All the cases and controls in the POLYGENE and NBS studies were fully informed about the goals and procedures of the study. The study protocols were approved by the Institutional Review Board of Radboud University Nijmegen Medical Centre and all study subjects gave written informed consent.

The questionnaires that were completed by cases and controls included questions on their balding pattern at the ages of 20 years, 40 years and at the time of completion of the questionnaire. For evaluation of the subject's baldness pattern, a set of four pictures was used, adapted from the Hamilton–Norwood scale (Fig. 1).[14,18] Non-Caucasian subjects were excluded from the analysis, as the balding patterns and the risk of PC differ between different races. We also excluded controls younger than 40 years (none of the cases was younger than 40 years) in order to prevent missing values on the balding questions and to improve comparability of age distributions between cases and controls.

2.1. Statistical analysis

The associations between PC and AA at the ages 20 years, 40 years and at the time of completion of the questionnaire were

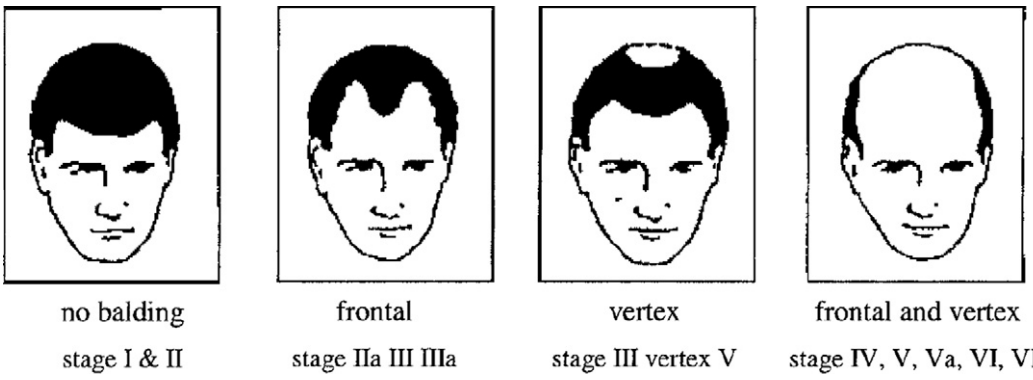

Fig. 1 – Adjusted Hamilton–Norwood scale of baldness. (a) No baldness; (b) frontal baldness; (c) vertex baldness; and (d) frontal and vertex baldness.

evaluated by cross-tabulation. No baldness (Fig. 1a) was used as reference for the other baldness patterns (Fig. 1b–d). Odds ratios (ORs) and corresponding 95% confidence intervals (CI) were calculated for specific baldness patterns as well as for the presence of any type of baldness in order to quantify the strength of any association. Multivariable logistic regression modelling was used to calculate the independent association between balding and PC, in addition to positive family history (i.e. $\geqslant$1 first-degree relative with PC, included in the model as a nominal variable) and age at the time of completing the questionnaire (continuous linear variable). Baldness pattern was included in the model as a categorical variable with four strata, with 'no baldness' as the reference category, except for the overall comparison of 'any baldness' versus 'no baldness', for which a dichotomous variable was created for the presence of any form of baldness (nominal variable).

Subgroup analyses were performed by PC aggressiveness, based on TNM-stage of disease, Gleason grade and serum PSA. Aggressive PC was defined as either growth within both prostate lobes or extending the capsule (T-stage $\geqslant$T2c and/or N+ and/or M+), a Gleason score of eight or higher or a prediagnostic serum PSA higher than 20 ng/ml.[19] cTNM was used for stage of disease if pTNM was not available, i.e. if surgery was not performed. Likewise, Gleason grade of biopsies was used if Gleason grade of a prostatectomy specimen was not available. SPSS version 16.0.01 was used for statistical analysis.

3. Results

3.1. Study population

The total number of men with PC in this study was 956. Fourteen men were non-Caucasian and were therefore excluded from analyses. Four additional patients were excluded because their age at the time of completion of the questionnaire was unknown.

Of the 2552 male controls who completed the additional questionnaire, 2492 were of Caucasian origin. Of these Caucasian controls, 332 were under 40 years of age at the time of completion of the questionnaire and were excluded from the analyses. Demographic characteristics of the remaining 938 cases and 2160 controls with respect to age and family history of PC as well as the patient and tumour characteristics of the cases are listed in Table 1. The mean age at diagnosis of the cases was 5 years higher than the mean age at recruitment of the controls. The difference in mean age between the groups at completion of the questionnaire was 2 years.

3.2. Association between androgenic alopecia and prostate cancer

The presence of any baldness at the time of completion of the questionnaire showed a non-significant association with PC with an OR of 1.11 (95% CI 0.90–1.35) (Table 2). The separate baldness patterns at the time of completion of the questionnaire all showed a trend towards a higher risk of PC, but the ORs were not statistically significant. Vertex baldness showed the strongest association with PC with an OR of 1.19 (95% CI 0.94–1.52).

Baldness at age 40 years was significantly associated with a lower risk of PC with an OR of 0.83 (95% CI 0.71–0.98). Only the combination 'frontal and vertex' baldness at this age was significantly associated with a lower risk of PC with an OR of 0.61 (95% CI 0.44–0.86). The other baldness patterns at this age showed a trend towards a lower risk of PC, but the ORs were not statistically significant. Androgenic alopecia at age 20 years was not significantly associated with PC, but the numbers of men with 'vertex' or with 'frontal and vertex' balding at this early age were very small.

3.3. Association between baldness pattern and prostate cancer aggressiveness

Of the 938 cases in the study, 609 met the criteria for aggressive PC while 329 patients had PC without any aggressive features. The presence of baldness at the time of completion of the questionnaire was non-significantly associated with aggressive PC with an OR of 1.19 (95% CI 0.94–1.53). Evaluation of specific baldness patterns at the time of completion of the questionnaire identified 'vertex' baldness as the pattern with the strongest, again non-significant, association with aggressive PC with an OR of 1.31 (95% CI 0.98–1.74). Also, none of the baldness patterns at ages 40 and 20 years was significantly associated with aggressive PC.

For non-aggressive PC, the presence of any baldness at 40 years of age was significantly associated with a lower

Table 1 – Characteristics of prostate cancer patients and controls.

	Patients						Controls	
	All patients (*n* = 938)		Aggressive[a] cancer (*n* = 609)		Non-aggressive[a] cancer (*n* = 329)		All controls (*n* = 2160)	
	n	%	*n*	%	*n*	%	*n*	%
Age at completion of the questionnaire in years								
<55	27	2.9	19	3.1	8	2.4	542	25.1
55–59	99	10.6	68	11.2	31	9.4	231	10.7
60–64	191	20.4	128	20.9	64	19.5	264	12.2
65–69	229	24.4	159	26.1	70	21.3	242	11.2
70>	392	41.8	236	38.8	156	47.4	881	40.8
Age at diagnosis in years								
<55	49	5.2	36	5.9	13	4.0		
55–59	157	16.7	98	16.1	59	17.9		
60–64	217	23.1	149	24.5	68	20.7		
65–69	263	28.0	185	30.4	78	23.7		
70>	252	26.9	141	23.2	111	33.7		
Family history of prostate cancer								
No first-degree relative affected	729	77.7	473	77.7	256	77.8	1808	83.7
Any first-degree relative affected	209	22.3	136	22.3	73	22.2	120	5.6
Missing	0		0		0		232	10.7
Clinical T-stage								
cT1	381	40.6						
cT2	361	38.5						
cT3	170	18.1						
cT4	16	1.7						
cT0/x	10	1.1						
Clinical N-stage								
cN0	374	39.9						
cN1	65	6.9						
cNx	499	53.2						
Clinical M-stage								
cM0	586	62.5						
cM1	41	4.3						
cMx	311	33.2						
Gleason score								
2–6	567	60.4						
7	237	25.3						
8–10	100	10.7						
Unknown	34	3.6						
PSA in ng/ml								
<4	93	9.9						
4–10	413	44.0						
10–20	204	21.7						
>20	219	23.3						
Unknown	9	1.0						

Abbreviations: PSA: prostate-specific antigen.

[a] *Aggressive cancer*: T-stage ⩾T2c and/or N+ and/or M+ and/or Gleason score 8–10 and/or PSA > 20 ng/ml. *Non-aggressive cancer*: prostate cancer with none of the aggressive characteristics.

risk of non-aggressive PC, with an OR of 0.67 (95% CI 0.53–0.85). Evaluation of specific baldness patterns at this age showed 'vertex' and 'frontal and vertex' baldness to be significantly associated with non-aggressive PC with ORs of 0.58 (95% CI 0.39–0.86) and 0.38 (95% CI 0.21–0.70), respectively. At age 20 years, no significant association between baldness (pattern) and non-aggressive PC was found.

4. Discussion

We found that baldness at age 40 years showed some indication of an inverse association with PC, mainly non-aggressive PC, whereas baldness at the time of completing the questionnaire seemed to occur more frequently among men with PC, especially men with aggressive PC. Most of the associations were, however, not statistically significant

Table 2 – Association between androgenic alopecia at different ages and prostate cancer.

	Controls (n = 2160)	All subjects			Aggressive cancer[b]			Non-aggressive cancer[b]		
		Cases (n = 938)	OR[a]	95% CI	Cases (n = 609)	OR[a]	95% CI	Cases (n = 329)	OR[a]	95% CI
Alopecia at completion of questionnaire										
No balding	421	183	1.00		112	1.00		71	1.00	
Frontal balding	563	270	1.08	(0.86–1.37)	168	1.09	(0.83–1.45)	102	1.03	(0.73–1.44)
Vertex balding	454	252	1.19	(0.94–1.52)	165	1.31	(0.98–1.74)	87	1.02	(0.72–1.45)
Frontal and vertex balding	473	233	1.05	(0.82–1.34)	164	1.23	(0.92–1.64)	69	0.75	(0.52–1.09)
Any balding versus no balding at completion of questionnaire			1.11	(0.90–1.35)		1.19	(0.94–1.53)		0.94	(0.70–1.26)
Alopecia at age 40										
No balding	829	453	1.00		276	1.00		176	1.00	
Frontal balding	632	293	0.86	(0.71–1.03)	189	0.91	(0.73–1.13)	104	0.78	(0.59–1.02)
Vertex balding	285	137	0.89	(0.70–1.13)	102	1.09	(0.83–1.44)	36	0.58	(0.39–0.86)
Frontal and vertex balding	163	55	0.61	(0.44–0.86)	42	0.77	(0.53–1.12)	13	0.38	(0.21–0.70)
Any balding versus no balding at age 40			0.83	(0.71–0.98)		0.94	(0.78–1.13)		0.67	(0.53–0.85)
Alopecia at age 20										
No balding	1593	796	1.00		508	1.00		288	1.00	
Frontal balding	262	123	0.96	(0.75–1.22)	88	1.08	(0.83–1.42)	35	0.79	(0.54–1.15)
Vertex balding	45	17	0.81	(0.45–1.43)	12	0.89	(0.46–1.71)	5	0.65	(0.25–1.66)
Frontal and vertex balding	12	2	0.31	(0.07–1.46)	1	0.24	(0.03–1.90)	1	0.42	(0.05–3.36)
Any balding versus no balding at age 20			0.91	(0.73–1.14)		1.02	(0.79–1.32)		0.75	(0.53–1.07)

Abbreviations: OR: odds ratio; CI: confidence interval; and PSA: prostate-specific antigen.

[a] All ORs were adjusted for age at the time of completion of the questionnaire and family history.

[b] *Aggressive cancer*: T-stage ⩾T2c and/or N+ and/or M+ and/or Gleason score 8–10 and/or PSA > 20 ng/ml. *Non-aggressive cancer*: prostate cancer with none of the aggressive characteristics.

and the associations between AA at the time of completion of the questionnaire and PC were fairly weak. The strongest associations for PC in general were found for 'frontal and vertex' baldness at ages 20 and 40 years with ORs of 0.31 and 0.61, respectively. On the other hand, as 'frontal and vertex' baldness has a very low prevalence at the ages of 20 and 40 years, the 95% confidence intervals were wide. The ORs for aggressive PC, which included 609 cases, were even weaker than this. The strongest (non-significant) association was found for any baldness at the time of completion of the questionnaire with an OR of 1.19 (strongest association of between 'vertex' baldness and aggressive PC with an OR of 1.31).

Potential biases in our study include recall bias, particularly for AA at age 20 years. On the other hand, we do not have any reason to believe that men who have been diagnosed with PC have a different recollection of their baldness pattern at young age as compared to healthy individuals. Differential misclassification is therefore not likely, but non-differential misclassification may have led to some underestimation of the real strength of the association. Because of the nature of this study, selection bias is also unlikely to have played a role. The patients and controls were selected for this study regardless of their observed hair pattern and the questions on baldness pattern were only part of a broader investigation into risk factors for PC where an extensive risk factor questionnaire was taken along with blood samples for DNA. Therefore, we consider it very unlikely that a person's hair pattern has had any influence on whether to participate in this study.

In the mid-1990s, a large population-based case-control study was performed in Australia to investigate the relationship between AA and PC with emphasis on early age at diagnosis and higher grade PC.[14] In this study 1446 cases and 1390 controls were interviewed. A significant association between vertex baldness at the time of the interview and PC was reported with an OR of 1.54 (95% CI 1.19–2.00). No associations were found between PC and frontal baldness or with frontal baldness concurrent with vertex baldness. The highest ORs were found for patients aged 60–69 years with high-grade disease (Gleason score 8–10): 1.80 (95% CI 1.02–3.16) for frontal baldness and 1.95 (95% CI 1.10–3.45) for frontal and vertex baldness. Another smaller case-control study, investigating a possible relation between early-onset vertex baldness at ages 30 and 40 years and PC, produced consistent but statistically non-significant associations between vertex baldness at ages 30 or 40 years and PC: OR = 2.20 (95% CI 0.89–5.43) for vertex baldness at age 30 years and OR = 1.67 (95% CI 0.75–3.72) for vertex baldness at age 40 years.[20] However, early frontal baldness was associated with a decreased risk of PC with ORs of 0.66 (95% CI 0.19–2.35) for frontal baldness at age 30 years and 0.88 (0.40–1.94). Possibly the small number of subjects with baldness in this study caused the reversed association for vertex baldness as compared to our results.

To our knowledge, we are the first to assess AA patterns for subjects at both younger age and after diagnosis of PC. We showed that AA at the time of completion of the questionnaire was associated with a higher risk of (aggressive) PC, but that baldness at earlier age would be indicating men at

lower risk rather than men at higher risk of (non-aggressive) PC. These results may suggest a different effect of androgens on AA and PC at different ages. However, the associations were relatively weak and, even in this large study, mostly non-significant. Therefore, combined with the results from earlier studies, we conclude that the association between AA and PC, especially with respect to early-onset baldness, is too inconsistent and weak to have any predictive value for prostate cancer. Male-pattern baldness should not influence the decision whether or not to test a man for PC.

5. Conclusion

Although a common cause for androgenic alopecia and prostate cancer is intuitive, androgenic alopecia is not useful as an indicator of men at high risk for prostate cancer.

Conflict of interest statement

None declared.

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