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

Graham G. Giles, Gianluca Severi, Rod Sinclair, Dallas R. English, Margaret R. E. McCredie, Warren Johnson, Peter Boyle, and John L. Hopper

Cancer Epidemiology Centre, Anti-Cancer Council of Victoria, Melbourne, VIC 3053 Australia [G. G. G., D. R. E.]; Division of Epidemiology and Biostatistics, European Institute of Oncology, 1-20141, Milan, Italy [G. S., P. B.]; Department of Dermatology, St. Vincent’s Hospital, Melbourne, VIC 3065 Australia [R. S.]; Department of Preventive and Social Medicine, Dunedin Medical School, University of Otago, New Zealand 9001 [M. R. E. M.]; Cancer Epidemiology Research Unit, New South Wales Cancer Council, Sydney, 2011 New South Wales, Australia [M. R. E. M.]; Department of Public Health, University of Western Australia, Perth, 6009 Australia [D. R. E.]; Royal Melbourne Hospital, Melbourne, 3052 Australia [W. J.]; and Centre for Genetic Epidemiology, University of Melbourne, Melbourne, 3052 Australia [J. L. H.]

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

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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-

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### Table 1  Demographic characteristics of cases and controls

| Age group | Cases | Controls | OR | 95% CI
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>&lt;55</td>
<td>231</td>
<td>16.0</td>
<td>186</td>
<td>17.1</td>
</tr>
<tr>
<td>55–59</td>
<td>405</td>
<td>28.0</td>
<td>317</td>
<td>29.1</td>
</tr>
<tr>
<td>60–64</td>
<td>359</td>
<td>24.8</td>
<td>261</td>
<td>24.0</td>
</tr>
<tr>
<td>65–69</td>
<td>451</td>
<td>31.2</td>
<td>324</td>
<td>29.8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Alopecia, all ages</th>
<th>All subjects</th>
<th>Moderate grade</th>
<th>High grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>n = 1390</td>
<td>n = 1446</td>
<td>n = 1088</td>
<td>n = 358</td>
</tr>
<tr>
<td>No balding</td>
<td>350</td>
<td>337</td>
<td>1.00</td>
</tr>
<tr>
<td>Frontal</td>
<td>447</td>
<td>438</td>
<td>0.98 (0.79–1.23)</td>
</tr>
<tr>
<td>Vertex</td>
<td>238</td>
<td>310</td>
<td>1.54 (1.19–2.00)</td>
</tr>
<tr>
<td>Frontal and vertex</td>
<td>355</td>
<td>361</td>
<td>1.14 (0.90–1.45)</td>
</tr>
<tr>
<td>Reference age, before 60 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No balding</td>
<td>210</td>
<td>201</td>
<td>1.00</td>
</tr>
<tr>
<td>Frontal</td>
<td>187</td>
<td>184</td>
<td>1.00 (0.73–1.37)</td>
</tr>
<tr>
<td>Vertex</td>
<td>74</td>
<td>118</td>
<td>1.61 (1.08–2.38)</td>
</tr>
<tr>
<td>Frontal and vertex</td>
<td>113</td>
<td>133</td>
<td>1.15 (0.82–1.61)</td>
</tr>
<tr>
<td>Reference age, 60–69 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No balding</td>
<td>140</td>
<td>136</td>
<td>1.00</td>
</tr>
<tr>
<td>Frontal</td>
<td>260</td>
<td>254</td>
<td>1.09 (0.77–1.53)</td>
</tr>
<tr>
<td>Vertex</td>
<td>164</td>
<td>192</td>
<td>1.74 (1.20–2.52)</td>
</tr>
<tr>
<td>Frontal and vertex</td>
<td>242</td>
<td>228</td>
<td>1.24 (0.87–1.76)</td>
</tr>
</tbody>
</table>

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

\( a \) 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 \( \chi^2 \) test with 3 degrees of freedom.  
\( c \) Moderate grade, Gleason scores 5–7; high grade, Gleason scores 8–10.
Baldness and Prostate Cancer

AA and prostate cancer are androgen dependent, differences in and prostate cancer risk is yet to be established. Because both bald at an early age. It is possible that any specificity of the baldness measurement (they were not able
line when 25 cases with the remaining 4421 men examined for AA at base-
trition Examination Survey, comparing 214 prostate cancer
of this cohort study were associated with increased risk of prostate cancer, espe-


Acknowledgments
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References

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 5aR-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 5aR-1 staining within sebaceous glands but not in hair follicles and 5aR-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, 5aR-1, and 5aR-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). Such differences in the biology of the hair follicle are likely to be secondary phenomena because the hair follicle is able to regulate its own response to androgens by enhancing expression of 5aR 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 re-
ceptor), 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.

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 5aR 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