Age dependent associations between androgenetic alopecia and prostate cancer risk

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Title: Age dependent associations between androgenetic alopecia and prostate cancer risk.

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Running Title: Androgenetic alopecia and prostate cancer risk

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Abstract

Background: Both prostate cancer and androgenetic alopecia (AA) are strongly age related conditions that are considered to be androgen dependent, but studies of the relationship between them have yielded inconsistent results. We aimed to assess whether AA at ages 20 and 40 are associated with risk of prostate cancer.

Methods: At a follow up of the Melbourne Collaborative Cohort Study men were asked to assess their hair pattern at ages 20 and 40 years relative to eight categories in showcards. Cases were men notified to the Victorian Cancer Registry with prostate cancer diagnosed between cohort enrolment (1990-1994) and follow up attendance (2003-2009). Flexible parametric survival models were used to estimate age varying hazard ratios and predicted cumulative probabilities of prostate cancer by AA categories.

Results: Of 9,448 men that attended follow-up and provided data on AA we identified 476 prostate cancer cases during a median follow up of 11 years 4 months. Cumulative probability of prostate cancer was greater at all ages up to 76 years for men with vertex versus no AA at age 40. At age 76 the estimated probabilities converged to 0.15. Vertex AA at 40 was also associated with younger age of diagnosis for prostate cancer cases.

Conclusions: Vertex AA at age 40 might be a marker of increased risk of early onset prostate cancer.

Impact: If confirmed, these results suggest that the apparently conflicting findings of previous studies might be explained by failure to adequately model the age-varying nature of the association between AA and prostate cancer.
Introduction

Prostate cancer and androgenetic alopecia (AA), also known as male pattern baldness, are strongly age related conditions that are both considered to be androgen dependent [1-3]. The link between androgens and AA is well established. Progression of AA requires dihydrotestosterone (DHT), the active metabolite of testosterone: previous studies have shown that inhibition of DHT production can stop the progression of AA and even lead to hair regrowth [4], and that DHT levels are higher in hair follicles from balding scalp relative to non-balding scalp [5]. Additionally, high levels of the androgen receptor (AR) have been associated with AA [6], and lower levels of aromatase, which converts testosterone to oestrogen, have been found in balding scalp [7]. Androgens have also been strongly implicated in the carcinogenesis of prostate cancer. Up-regulation and expression of AR activity as well as mutations in the AR gene have been shown to stimulate growth of prostate cancer [1], and alterations in androgen metabolism and inhibition of DHT production appear to influence risk of prostate cancer [8].

Several studies have investigated whether there exists any association between AA and risk of prostate cancer [9-18]. While some studies suggest that AA, especially when it occurs in younger men, might be a marker of increased risk of prostate cancer later in life [12, 13, 18], others have found that AA is in fact associated with lower risk of prostate cancer [16, 17]. We aimed to assess whether retrospectively assessed AA at ages 40 and 20 years are associated with risk of prostate cancer using a subset of men participating in the Melbourne Collaborative Cohort Study (MCCS).

Materials and Methods

Study Sample

The MCCS is a prospective cohort study of 41,514 people (17,045 men) who were aged between 27 and 81 years at baseline (99.3% of whom were aged 40-69). Recruitment occurred between 1990 and 1994 in the Melbourne metropolitan area. Participants were recruited via the Electoral Rolls (enrolment to vote is compulsory for adults in Australia), advertisements and community announcements in local media (e.g., television, radio, and newspapers). All participants provided written informed consent, and the study was approved by the Cancer Council Victoria Human Research Ethics Committee. Full
details of the MCCS baseline phase are published elsewhere [19]. A face-to-face follow-up was conducted between 2003 and 2009 where participants completed an interview which included questions on hair pattern.

Assessment of AA

During the face-to-face follow-up interview, men were asked to assess their AA according to a set of pictures adapted from the Hamilton-Norwood scale (Figure 1) [20, 21]. Men identified which of the 8 images most closely corresponded to their hair patterning at ages 20 and 40 years. At age 40 years we classified men into three groups: no AA (Hamilton-Norwood scale I or II), frontal AA (Hamilton-Norwood scale III), and vertex AA (Hamilton-Norwood scale III vertex, IV, V, VI, VII). At age 20 years, because of the low prevalence of vertex AA, we classified men into two groups: those exhibiting no AA (Hamilton-Norwood scale I or II), and any AA (Hamilton-Norwood scale III – VII).

Cohort follow-up and ascertainment of cancer cases

Cases were men notified to the Victorian Cancer Registry (VCR) with a first diagnosis of adenocarcinoma of the prostate during follow-up from baseline interview to face-to-face follow-up interview (it is a statutory requirement that all cancer diagnoses, excepting those of non-melanoma skin cancer, be reported to the VCR). Cases diagnosed outside Victoria were identified via linkage to the Australian Cancer Database, Australian Institute of Health and Welfare (AIHW). Gleason score or tumour grade were ascertained and used to categorise prostate cancer grade into low (Gleason score 2-4) moderate (Gleason score 5-7), and high (Gleason score 8-10). Classification of cases as aggressive and nonaggressive was made on the basis that only cases with a distant-stage or poorly differentiated tumour have excess mortality compared with the general population [22]. Prostate cancer was therefore defined as “aggressive” if the Gleason score was >7 or if it was classified as poorly differentiated. Cases with stage T4 or N+ (positive lymph nodes) or M+ (distant metastases) were classified as aggressive irrespective of the Gleason score or grade of tumour differentiation. The vital status and, where relevant, cause of death were obtained via linkage to the Victorian death records and the National Death Index, and men whose death was attributed to prostate cancer were also classified as aggressive cases.
**Statistical analysis**

Information on AA was collected retrospectively at follow-up, but we analysed the data prospectively under the assumption that recollection of AA at follow-up is likely to be very similar to that at baseline. The conditions affecting this assumption are discussed below. Follow-up began at baseline and continued until date of attendance at face-to-face follow-up, date of diagnosis of an unknown primary tumour, or date of diagnosis of prostate cancer, whichever occurred first. Overall hazard ratios (HR) and 95% confidence intervals (CI) for each AA category relative to no AA were obtained from Cox regression models with age as the time axis. Models including AA at age 20 years and at age 40 years were fitted separately. Plots of smoothed, scaled Schoenfeld residuals were used to examine whether the assumption of proportional hazards was appropriate. Age-varying HR were estimated by flexible parametric survival models [23]. These models employed restricted cubic splines with 2 knots (placed at the 33rd and 67th percentiles of uncensored log survival times) to model the baseline hazard, and 1 knot (placed at the median of uncensored log survival times) to allow the estimated HR to vary with age. Inclusion of additional knots for the spline basis functions did not materially affect the results of the models. From these models we obtained predicted hazards, HR, cumulative probabilities, and differences in cumulative probabilities for given levels of AA and age. Confidence intervals for these predicted quantities were based on variance estimates calculated using the delta method.

To assess whether associations varied by tumour aggressiveness we fit models in which only non-aggressive tumours were counted as “cases” and aggressive tumours were censored at the date of diagnosis. We also used linear regression models to investigate whether age at diagnosis was associated with AA. All models were adjusted for country of birth. Statistical analyses were performed using Stata 12.0 for Linux (Stata Corporation, College Station, TX, USA).

**Results**

Of the 17,045 men enrolled in the MCCS, 10,869 (64%) attended follow-up and were therefore considered eligible for the present study. Participants who had been diagnosed with non-aggressive prostate cancer between baseline and commencement of follow-up were no less likely to attend follow-up than men with no diagnosis of prostate cancer (63% and 64% attendance respectively), however a substantially smaller proportion of men diagnosed with aggressive prostate cancer attended follow-up (43%). We excluded 30 men who were younger than 40 years at baseline attendance, 45 men who had a pre-baseline diagnosis of prostate cancer, and 1,346 men who completed an early version of the
follow-up questionnaire that did not include hair patterning questions, leaving 9,448 men available for analysis.

From the 9,448 men included in this study we identified 476 incident prostate cancer cases during a total follow-up time of 106,777 person years. The median follow-up per person was 11 years 4 months. Table 1 shows the distribution of age at baseline and follow-up, country of birth, and AA at ages 20 and 40 years by disease status, and Table 2 shows the characteristics of the 476 prostate cancer cases. On average cases were older than non-cases at both baseline and follow-up (difference in median ages of 6 and 7 years respectively). AA was not highly prevalent at age 20 years, with only 7% of men reporting either frontal or vertex balding. At age 40 years, however, 37% of men reported either frontal or vertex balding. AA at age 40 years was most prevalent among men born in Australia, New Zealand, and the United Kingdom (39%), while only 23% of participants born in Greece reported any AA at age 40 years. The proportion of cases and non-cases in each AA category was similar.

Estimates HR from a Cox regression model provided no evidence to suggest that frontal or vertex AA at 40 years is associated with risk of prostate cancer (HR frontal versus no AA 0.88, 95% CI 0.67 - 1.16; HR vertex versus no AA 1.03, 95% CI 0.83 - 1.28). Plots of the scaled Schoenfeld residuals from this model, however, revealed strongly non-proportional hazards for the vertex versus no AA comparison. We therefore fitted flexible parametric time to event models to allow the HR to vary with age. The corresponding predicted hazards for vertex and no AA groups, as well as the age-varying HR are plotted in Figure 2. At younger ages the hazard is greater for those with vertex AA, whereas at older ages those with no AA have a greater hazard of prostate cancer. At age 55 years the hazard of prostate cancer is 1.81 (95% CI 1.13 - 2.90) times higher for those with vertex AA than those with no AA. Between ages 60 and 70 years the HR is not discernible from 1, and at age 75 years the vertex AA group have a 44% (HR 0.56, 95% CI 0.33 - 0.95) lower hazard than those with no AA. The model predicted cumulative probability of prostate cancer for men with vertex and no AA is plotted in Figure 3, along with the difference between these probabilities. The cumulative probability of prostate cancer is greater for men with vertex AA at 40 until approximately age 70 years, when the cumulative probabilities converge to similar values and any difference between them cannot be discerned. At age 76 years the predicted cumulative probability of prostate cancer reaches 0.15 regardless of AA status at age 40 years. To directly assess whether age of diagnosis of prostate cancer differed between men with vertex and no AA at age 40 years we fit a linear regression with age of diagnosis as the outcome and AA as a categorical predictor, adjusting for country of birth. Mean age at diagnosis was 2.77 years younger (95% CI 1.4 - 4.14) for men with vertex AA at age 40 years compared to those with no AA at age 40 years.
We found similar results when considering any frontal or vertex AA versus no AA at age 20 years, with the HR estimated to be 1.43 (95% CI 0.94 - 2.18) at age 65 and 0.70 (95% CI 0.31 - 1.57) at age 75. The pattern of predicted cumulative probabilities was also similar to that we observed for the comparison between no AA and vertex AA at age 40 years (Figure 4). However due to the low prevalence of AA at age 20 our estimates are imprecise and differences in probabilities are not distinguishable from 0 at any age.

Results did not differ substantially when considering only non-aggressive cases. For instance, the HR for vertex versus no AA at age 40 years was 2.05 (95% CI 1.28 - 3.30) at age 55 years, and 0.58 (95% CI 0.31 - 1.07) at age 75 years. The predicted cumulative probability of non-aggressive prostate cancer was also greater at all ages up to 75 years for men with vertex AA at age 40 compared to those with no AA. At age 75 years the predicted cumulative probabilities converged to approximately 0.13 regardless of hair pattern at age 40 years. We did not calculate these quantities for aggressive cases only due to the small number of aggressive cases.

**Discussion**

We found that men with vertex AA at age 40 years had greater hazard of early onset prostate cancer than men with no AA, and had lower hazard of later onset prostate cancer. These age-varying hazard ratios manifest in an increased cumulative probability of prostate cancer for men with vertex AA at 40 relative to men with no AA. This greater cumulative risk is maintained up to approximately age 70 years. At age 76 years the estimated cumulative probability of prostate cancer reaches 0.15 regardless of hair pattern at 40 years. Relatedly, we also found that prostate cancer cases with vertex AA at age 40 years were diagnosed on average almost 3 years earlier than cases with no AA at age 40 years. For AA at age 20 years no definitive conclusions could be reached due to the low prevalence of AA among men at this young age.

Advantages of our study include assessment of AA at specific reference ages (20 and 40 years) using a validated and reliable instrument [21, 24], a study design that enables estimation of cumulative risks in addition to relative risk estimates, and near complete follow-up in terms of cancer diagnosis through routine linkage to the Victorian Cancer Registry and the Australian Cancer Database, AIHW. One limitation of this study is that AA was assessed retrospectively during a face to face follow-up of the MCCS, subsequent to any diagnosis of prostate cancer. Therefore there is a tendency for the study sample to include a smaller proportion of aggressive cases than non-cases and non-aggressive cases. While we found that non-cases were no more likely than non-aggressive cases to attend follow-up, a
substantially smaller proportion of aggressive cases attended. So while our results did not differ substantially when considering only non-aggressive cases, it is important to bear in mind that many men with the most aggressive cancers might have been too unwell to attend follow-up, or might have died prior to commencement of follow-up. Caution should be exercised in generalising our findings to aggressive prostate cancer accordingly.

Several previous studies have investigated whether AA is associated with prostate cancer, with largely conflicting results. A number of studies have found no association between AA and prostate cancer [9-11, 15] or suggestive evidence of an increased risk of prostate cancer [12], others have found AA to be associated with an increased risk of prostate cancer [13, 14, 18], while two recent studies have found AA to be associated with a decreased risk of prostate cancer [16, 17]. While differences in sample size, study design, and exposure assessment might plausibly explain much of the inconsistency between studies, the direction of estimated associations has differed even among those studies that assessed AA at specific reference ages using an adapted Hamilton-Norwood scale [16-18]. One such case-control study found a 2 fold higher relative odds of prostate cancer in men with any AA at age 20 years [18]. Another case-control study which assessed AA at age 30 years found a 29% reduction in the odds of prostate cancer for men with any AA, and a stronger reduction in when considering only men older than 60 years at interview [17]. Another recent case-control study reported similar results, with combined frontal and vertex AA at age 40 years associated with a reduction in odds of prostate cancer of 39% [16]. It has been observed that carriers of a rare allele in the A49T polymorphism of the 5α-reductase type 2 gene are at greater risk of prostate cancer and a reduced risk of AA [25]. While this is consistent with an inverse association between AA and prostate cancer risk, the evidence linking the polymorphism to prostate cancer risk is very weak. Further, the prevalence of the risk allele is low, so even if it were strongly associated with risk of prostate cancer it could not account for an inverse association between AA and prostate cancer risk at the population level.

Our finding that at age 75 years the HR for vertex versus no AA at age 40 was 0.56, yet the cumulative probability of prostate cancer for all ages up to 76 years is estimated to be greater for men with vertex AA at age 40, strongly suggests that AA is associated with increased risk of, and earlier onset of prostate cancer, and that this association might have been masked in previous studies relying on a single estimate of multiplicative relative risk. We therefore argue that much of the inconsistency in the literature might be a result of failure to adequately model the age-varying nature of the association between AA and prostate cancer, and a failure to consider the marginal absolute risk of prostate cancer throughout the lifespan.
We have assessed the extent to which the pattern of results we observed might be due to bias. Retrospective assessment of AA at ages 40 and 20 years might be subject to recall bias, but since onset of AA can influence self perceptions [26], we expect that most men would remember becoming bald, and we have no reason to suspect that cases and controls would systematically differ in remembering or reporting their AA. One possible alternative explanation for the observed association between AA and age at onset of prostate cancer is that men with early onset AA might participate in screening at a higher rate than men with no AA. Whilst this is possible, the earliest reports presenting evidence of an association between AA and prostate cancer were published approximately half way through the follow-up period for the present study. Further, we believe that the limited media attention that these papers received would not have been sufficient to motivate dramatic changes in screening behaviour among men with AA. Another potential source of bias is that an unknown proportion of men might have used finasteride during follow-up.

In summary, we found that vertex AA at age 40 years was associated with earlier age at onset of prostate cancer, and increased cumulative probability of prostate cancer up to age 76 years. Our results also indicate that a single, age invariant estimate of relative risk is insufficient to describe the age dependent association between AA and risk of prostate cancer.

**Acknowledgements**

We would like to acknowledge the work of the many members of the study team past and present who recruited the participants, collected the data, and continue to work on follow-up. We would like to thank the men who participated in this study, and the men and women of Melbourne who continue to participate in the Melbourne Collaborative Cohort Study. This work was supported by the National Health and Medical Research Council (grants #126402, 209057, 170215, 251533, 450104), and infrastructure was provided by the Cancer Council Victoria. Cohort recruitment was funded by VicHealth and Cancer Council Victoria.
References


### Tables

#### Table 1: Characteristics of the study sample by case status.

<table>
<thead>
<tr>
<th></th>
<th>non-cases (n=8,972)</th>
<th>cases (n=476)</th>
<th>total (n=9,448)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median, interquartile range)</td>
<td>54 (47-62)</td>
<td>60 (56-65)</td>
<td>54 (47-62)</td>
</tr>
<tr>
<td><strong>Follow-up age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median, interquartile range)</td>
<td>65 (58-73)</td>
<td>72 (68-77)</td>
<td>66 (58-74)</td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia/New Zealand/United Kingdom</td>
<td>7,480 (83.5)</td>
<td>411 (86.5)</td>
<td>7,891 (83.5)</td>
</tr>
<tr>
<td>Italy</td>
<td>931 (10.5)</td>
<td>45 (9.5)</td>
<td>976 (10.5)</td>
</tr>
<tr>
<td>Greece</td>
<td>561 (6)</td>
<td>20 (4)</td>
<td>581 (6)</td>
</tr>
<tr>
<td><strong>AA category age 20</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>8,347 (93)</td>
<td>441 (92.5)</td>
<td>8,788 (93)</td>
</tr>
<tr>
<td>frontal</td>
<td>393 (4.5)</td>
<td>24 (5)</td>
<td>417 (4.5)</td>
</tr>
<tr>
<td>vertex</td>
<td>228 (2.5)</td>
<td>11 (2.5)</td>
<td>239 (2.5)</td>
</tr>
<tr>
<td><strong>AA category age 40</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>5,624 (62.5)</td>
<td>303 (63.5)</td>
<td>5,927 (63)</td>
</tr>
<tr>
<td>frontal</td>
<td>1,229 (14)</td>
<td>61 (13)</td>
<td>1,290 (13.5)</td>
</tr>
<tr>
<td>vertex</td>
<td>2119 (23.5)</td>
<td>112 (23.5)</td>
<td>2,231 (23.5)</td>
</tr>
</tbody>
</table>

*aFour men were missing AA at age 20.

#### Table 2: Characteristics of the 476 prostate cancer cases.

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-aggressive</strong></td>
<td>364 (76)</td>
</tr>
<tr>
<td><strong>Aggressive</strong></td>
<td>112 (24)</td>
</tr>
<tr>
<td><strong>Gleason score</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>283 (63)</td>
</tr>
<tr>
<td>7</td>
<td>114 (26)</td>
</tr>
<tr>
<td>8-10</td>
<td>50 (11)</td>
</tr>
<tr>
<td><strong>Tumour stage</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>312 (66)</td>
</tr>
<tr>
<td>II</td>
<td>114 (24)</td>
</tr>
<tr>
<td>III</td>
<td>41 (9)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

*a29 men were missing Gleason score

*b5 men were missing Tumour stage*
Figure captions

Figure 1: Pattern of AA according to a modified Hamilton-Norwood scale, used by participants to score AA at ages 20 and 40 years.

Figure 2: Left panel: hazard function for vertex AA at age 40 (dashed line) and no AA at age 40 (solid line) from a flexible parametric survival model adjusted for country of birth. Right panel: age-varying hazard ratio of the hazard functions plotted in the left panel, with 95% CI.

Figure 3: Left panel: predicted cumulative probability of prostate cancer given vertex AA at age 40 (dashed line) and no AA at age 40 (solid line) from a flexible parametric survival model adjusted for country of birth. Right panel: difference between the predicted probabilities plotted in the left panel, with 95% CI.

Figure 4: Left panel: predicted cumulative probability of prostate cancer given any AA at age 20 (dashed line) and no AA at age 20 (solid line) from a flexible parametric survival model adjusted for country of birth. Right panel: difference between the predicted probabilities plotted in the left panel, with 95% CI.
Androgenetic alopecia at age 40 and hazard of prostate cancer

Predicted hazards: no AA (solid), vertex (dashed)

Predicted hazard ratio: vertex versus none

Figure 2
Androgenetic alopecia at age 40 and cumulative risk of prostate cancer

Predicted cumulative probability:
none (solid), vertex (dashed)

Difference in cumulative probability:
vertex versus none

Figure 3

Androgenetic alopecia at age 40 and cumulative risk of prostate cancer

Cumulative probability

0 0.05 0.1 0.15 0.2
50 60 70 80
Age

0.05
0.025
0
-0.025
-0.05
50 60 70 80
Age

Difference in cumulative probability
Androgenetic alopecia at age 20 and cumulative risk of prostate cancer

Figure 4

Androgenetic alopecia at age 20 and cumulative risk of prostate cancer

Predicted cumulative probability:
none (solid), any (dashed)

Difference in cumulative probability:
any versus none
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