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Cancer Epidemiology, Biomarkers & Prevention

Research Article

Age-Dependent Associations between Androgenetic Alopecia and Prostate Cancer Risk

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Abstract

Background: Both prostate cancer and androgenetic alopecia 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 androgenetic alopecia at ages 20 and 40 years 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 enrollment (1990–1994) and follow-up attendance (2003–2009). Flexible parametric survival models were used to estimate age-varying HRs and predicted cumulative probabilities of prostate cancer by androgenetic alopecia categories.

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

Conclusions: Vertex androgenetic alopecia at age of 40 years 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 androgenetic alopecia and prostate cancer. *Cancer Epidemiol Biomarkers Prev; 22(2); 209–15. ©2012 AACR.*

Introduction

Prostate cancer and androgenetic alopecia, 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 androgenetic alopecia is well established. Progression of androgenetic alopecia requires dihydrotestosterone (DHT), the active metabolite of testosterone; previous studies have shown that inhibition of DHT production can stop the progression of androgenetic alopecia and even lead to hair regrowth (4), and that DHT levels are higher in hair follicles from balding scalp relative to nonbalding scalp (5). In addition, high levels of the androgen receptor have been associated with androgenetic alopecia (6), and lower levels of aromatase, which converts testosterone to estrogen, have been found in balding scalp (7). Androgens have also been strongly implicated in the carcinogenesis of prostate cancer. Upregulation and expression of androgen receptor activity as well as mutations in the androgen receptor gene have been shown to stimulate growth of prostate cancer (1), and alterations in androgen metabolism and inhibition of DHT production seem to influence risk of prostate cancer (8).

Several studies have investigated whether there exists any association between androgenetic alopecia and risk of prostate cancer (9–18). While some studies suggest that androgenetic alopecia, 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 androgenetic alopecia is in fact associated with lower risk of prostate cancer (16, 17). We aimed to assess whether retrospectively assessed androgenetic alopecia 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).

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Materials and Methods

Study sample

The MCCS is a prospective cohort study of 41,514 people (17,045 men) who were of ages between 27 and 81 years at baseline (99.3% of whom were of ages 40–69 years). Recruitment occurred between 1990 and 1994 in the Melbourne metropolitan area. Participants were recruited via the Electoral Rolls (enrollment 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 androgenetic alopecia

During the face-to-face follow-up interview, men were asked to assess their androgenetic alopecia according to a set of pictures adapted from the Hamilton–Norwood scale (Fig. 1; refs. 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 3 groups: no androgenetic alopecia (Hamilton–Norwood scale I or II), frontal androgenetic alopecia (Hamilton–Norwood scale III), and vertex androgenetic alopecia (Hamilton–Norwood scale III vertex, IV–VII). At age 20 years, because of the low prevalence of vertex androgenetic alopecia, we classified men into 2 groups: those exhibiting no androgenetic alopecia (Hamilton–Norwood scale I or II), and any androgenetic alopecia (Hamilton–Norwood scale III–VII).

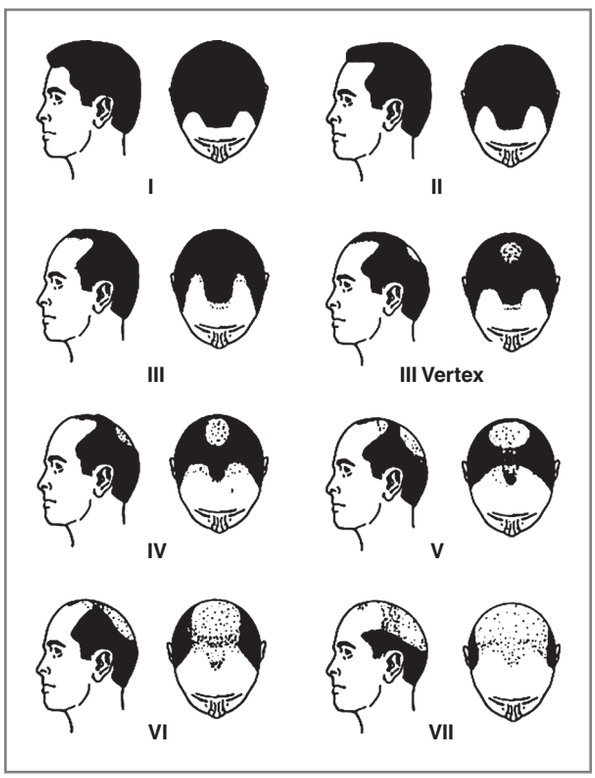

Figure 1. Pattern of androgenetic alopecia according to a modified Hamilton–Norwood scale, used by participants to score androgenetic alopecia at ages 20 and 40 years. Adapted from Norwood (21) with permission of Wolters Kluwer Health.

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 nonmelanoma 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 tumor grade were ascertained and used to categorize 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 tumor have excess mortality compared with the general population (22). Prostate cancer was therefore defined as "aggressive" if the Gleason score was more than 7 or if it was classified as poorly differentiated. Cases with stage T_4 or N+ (positive lymph nodes) or M+ (distant metastases) were classified as aggressive irrespective of the Gleason score or grade of tumor 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 androgenetic alopecia was collected retrospectively at follow-up, but we analyzed the data prospectively under the assumption that recollection of androgenetic alopecia at follow-up is likely to be very similar to that at baseline. The conditions affecting this assumption are discussed later. Follow-up began at baseline and continued until date of attendance at face-to-face follow-up, date of diagnosis of an unknown primary tumor, or date of diagnosis of prostate cancer, whichever occurred first. Overall HR and 95% confidence intervals (CI) for each androgenetic alopecia category relative to no androgenetic alopecia were obtained from Cox regression models with age as the time axis. Models including androgenetic alopecia 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 HRs were estimated by flexible parametric survival models (23). These models used restricted cubic splines

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Table 1. Characteristics of the study sample by case status

	Noncases ($n = 8,972$)	Cases ($n = 476$)	Total ($n = 9,448$)
Baseline age (median, interquartile range)	54 (47–62)	60 (56–65)	54 (47–62)
Follow-up age (median, interquartile range)	65 (58–73)	72 (68–77)	66 (58–74)
Country of birth (*n*, %)			
Australia/New Zealand/United Kingdom	7,480 (83.5)	411 (86.5)	7,891 (83.5)
Italy	931 (10.5)	45 (9.5)	976 (10.5)
Greece	561 (6)	20 (4)	581 (6)
Androgenetic alopecia category age 20[a] (*n*, %)			
None	8,347 (93)	441 (92.5)	8,788 (93)
Frontal	393 (4.5)	24 (5)	417 (4.5)
Vertex	228 (2.5)	11 (2.5)	239 (2.5)
Androgenetic alopecia category age 40 (*n*, %)			
None	5,624 (62.5)	303 (63.5)	5,927 (63)
Frontal	1,229 (14)	61 (13)	1,290 (13.5)
Vertex	2,119 (23.5)	112 (23.5)	2,231 (23.5)

[a]Four men were missing androgenetic alopecia at age of 20 years.

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 androgenetic alopecia and age. CIs for these predicted quantities were based on variance estimates calculated using the delta method.

To assess whether associations varied by tumor aggressiveness, we fit models in which only nonaggressive tumors were counted as "cases" and aggressive tumors were censored at the date of diagnosis. We also used linear regression models to investigate whether age at diagnosis was associated with androgenetic alopecia. All models were adjusted for country of birth. Statistical analyses were conducted using Stata 12.0 for Linux (Stata Corporation).

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 nonaggressive 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 prebaseline 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 androgenetic alopecia 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 noncases at both baseline and follow-up (difference in median ages of 6 and 7 years, respectively). Androgenetic alopecia 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

Table 2. Characteristics of the 476 prostate cancer cases

	N (%)
Nonaggressive	364 (76)
Aggressive	112 (24)
Gleason score[a]	
<7	283 (63)
7	114 (26)
8–10	50 (11)
Tumor stage[b]	
I	312 (66)
II	114 (24)
III	41 (9)
IV	4 (1)

[a]Twenty-nine men were missing Gleason score.
[b]Five men were missing tumor stage.

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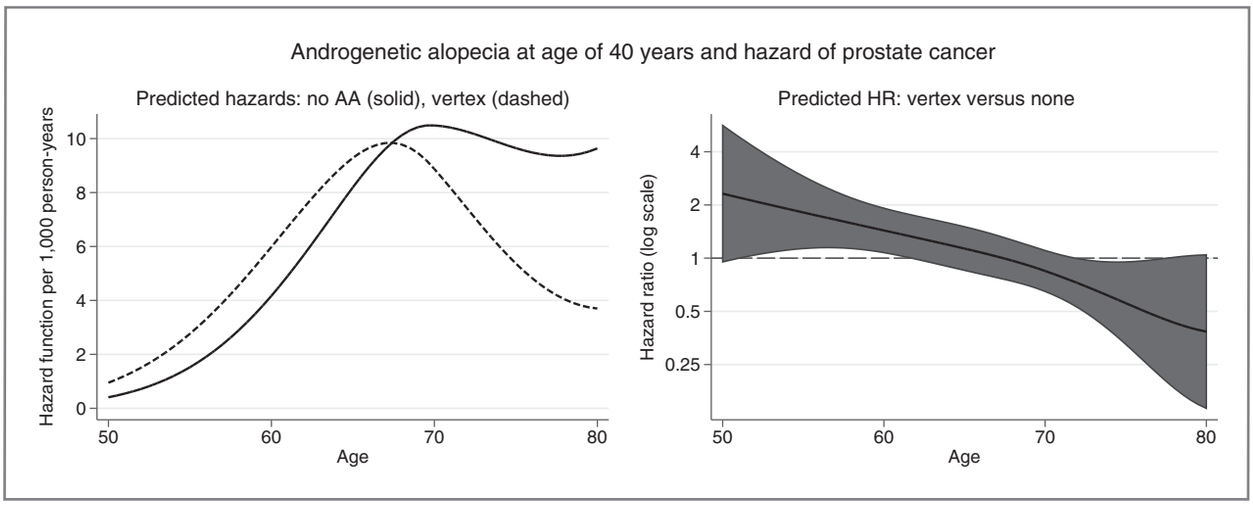

Figure 2. Left, hazard function for vertex androgenetic alopecia at age 40 years (dashed line) and no androgenetic alopecia at age 40 years (solid line) from a flexible parametric survival model adjusted for country of birth. Right, age-varying HR of the hazard functions plotted in the left, with 95%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

either frontal or vertex balding. Androgenetic alopecia at age 40 years was most prevalent among men born in Australia, New Zealand, and the United Kingdom (39%), whereas only 23% of participants born in Greece reported any androgenetic alopecia at age 40 years. The proportion of cases and noncases in each androgenetic alopecia category was similar.

Estimates HR from a Cox regression model provided no evidence to suggest that frontal or vertex androgenetic alopecia at 40 years is associated with risk of prostate cancer (HR frontal vs. no androgenetic alopecia 0.88; 95% CI, 0.67–1.16; HR vertex vs. no androgenetic alopecia 1.03; 95% CI, 0.83–1.28). Plots of the scaled Schoenfeld residuals from this model, however, revealed strongly nonproportional hazards for the vertex versus no androgenetic alopecia 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 androgenetic alopecia groups, as well as the age-varying HR are plotted in Fig. 2. At younger ages, the hazard is greater for those with vertex androgenetic alopecia, whereas at older ages those with no androgenetic alopecia 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 androgenetic alopecia than those with no androgenetic alopecia. Between ages 60 and 70 years, the HR is not discernible from 1, and at age 75 years, the vertex androgenetic alopecia group have a 44% (HR 0.56; 95% CI, 0.33–0.95) lower hazard than those with no androgenetic alopecia. The model predicted cumulative probability of prostate cancer for men with vertex and no androgenetic alopecia is plotted in Fig. 3,

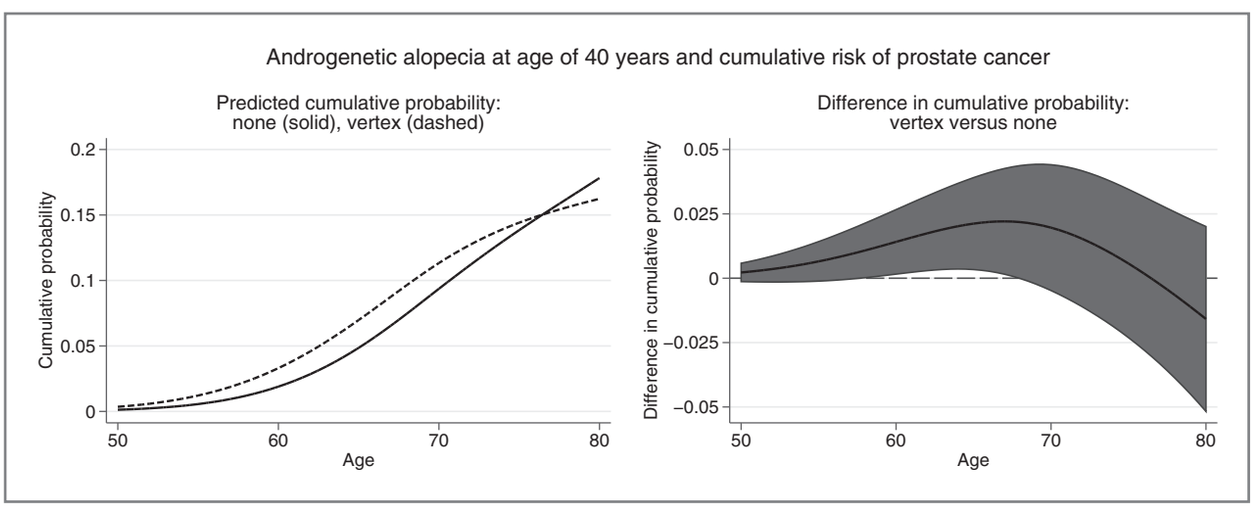

Figure 3. Left, predicted cumulative probability of prostate cancer given vertex androgenetic alopecia at age 40 years (dashed line) and no androgenetic alopecia at age 40 years (solid line) from a flexible parametric survival model adjusted for country of birth. Right, difference between the predicted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

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along with the difference between these probabilities. The cumulative probability of prostate cancer is greater for men with vertex androgenetic alopecia at 40 years 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 androgenetic alopecia status at age 40 years. To directly assess whether age of diagnosis of prostate cancer differed between men with vertex and no androgenetic alopecia at age 40 years, we fit a linear regression with age of diagnosis as the outcome and androgenetic alopecia 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 androgenetic alopecia at age 40 years as compared with those with no androgenetic alopecia at age 40 years.

We found similar results when considering any frontal or vertex androgenetic alopecia versus no androgenetic alopecia at age 20 years, with the HR estimated to be 1.43 (95% CI, 0.94–2.18) at age 65 years and 0.70 (95% CI, 0.31–1.57) at age 75 years. The pattern of predicted cumulative probabilities was also similar to that we observed for the comparison between no androgenetic alopecia and vertex androgenetic alopecia at age 40 years (Fig. 4). However, due to the low prevalence of androgenetic alopecia at age 20 years, our estimates are imprecise and differences in probabilities are not distinguishable from 0 at any age.

Results did not differ substantially when considering only nonaggressive cases. For instance, the HR for vertex versus no androgenetic alopecia 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 nonaggressive prostate cancer was also greater at all ages up to 75 years for men with vertex androgenetic alopecia at age 40 years as compared with those with no androgenetic alopecia. 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 androgenetic alopecia at age 40 years had greater hazard of early-onset prostate cancer than men with no androgenetic alopecia, and had lower hazard of later-onset prostate cancer. These age-varying HRs manifest in an increased cumulative probability of prostate cancer for men with vertex androgenetic alopecia at 40 years relative to men with no androgenetic alopecia. This greater cumulative risk is maintained up to approximately age of 70 years. At age of 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 androgenetic alopecia at age 40 years were diagnosed on average almost 3 years earlier than cases with no androgenetic alopecia at age 40 years. For androgenetic alopecia at age 20 years, no definitive conclusions could be reached because of the low prevalence of androgenetic alopecia among men at this young age.

Advantages of our study include assessment of androgenetic alopecia 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 VCR and the Australian Cancer Database, AIHW. One limitation of this study is that androgenetic alopecia 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

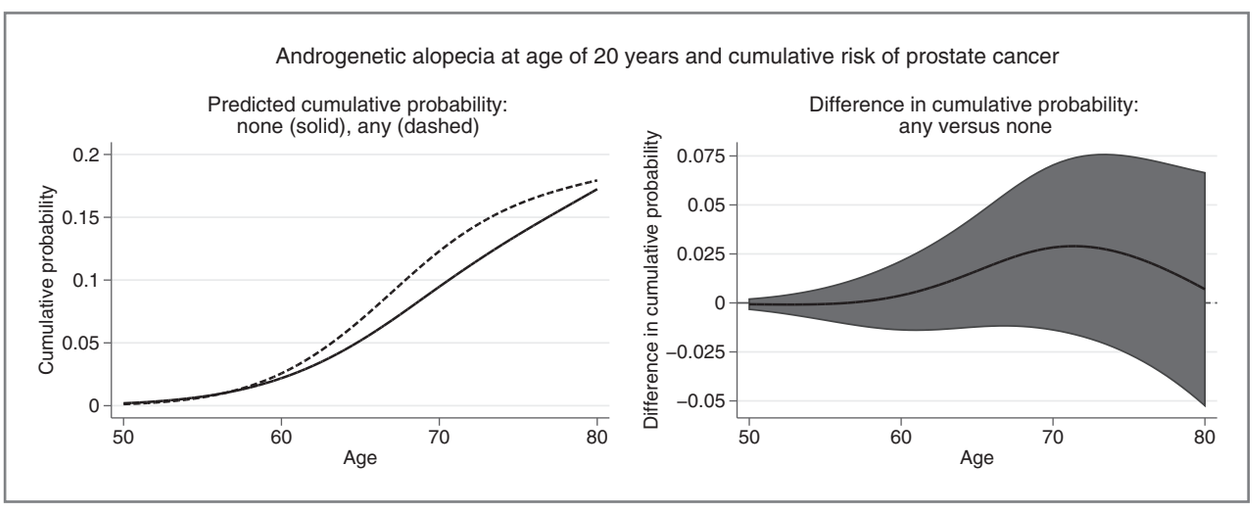

Figure 4. Left, predicted cumulative probability of prostate cancer given any androgenetic alopecia at age 20 years (dashed line) and no androgenetic alopecia at age 20 years (solid line) from a flexible parametric survival model adjusted for country of birth. Right, difference between the predicted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

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study sample to include a smaller proportion of aggressive cases than noncases and nonaggressive cases. While we found that noncases were no more likely than nonaggressive cases to attend follow-up, a substantially smaller proportion of aggressive cases attended. So, while our results did not differ substantially when considering only nonaggressive 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 before commencement of follow-up. Caution should be exercised in generalizing our findings to aggressive prostate cancer accordingly.

Several previous studies have investigated whether androgenetic alopecia is associated with prostate cancer, with largely conflicting results. A number of studies have found no association between androgenetic alopecia and prostate cancer (9–11, 15) or suggestive evidence of an increased risk of prostate cancer (12), others have found androgenetic alopecia to be associated with an increased risk of prostate cancer (13, 14, 18), whereas 2 recent studies have found androgenetic alopecia 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 androgenetic alopecia 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 androgenetic alopecia at age 20 years (18). Another case–control study, which assessed androgenetic alopecia at age 30 years, found a 29% reduction in the odds of prostate cancer for men with any androgenetic alopecia, 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 androgenetic alopecia 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 II gene are at greater risk of prostate cancer and a reduced risk of androgenetic alopecia (25). While this is consistent with an inverse association between androgenetic alopecia and prostate cancer risk, the evidence linking the polymorphism to prostate cancer risk is very weak. Furthermore, 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 androgenetic alopecia and prostate cancer risk at the population level.

Our finding that at age 75 years, the HR for vertex versus no androgenetic alopecia 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 androgenetic alopecia at age 40 years, strongly suggests that androgenetic alopecia 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 androgenetic alopecia 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 androgenetic alopecia at ages 40 and 20 years might be subject to recall bias, but as onset of androgenetic alopecia 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 androgenetic alopecia. One possible alternative explanation for the observed association between androgenetic alopecia and age at onset of prostate cancer is that men with early-onset androgenetic alopecia might participate in screening at a higher rate than men with no androgenetic alopecia. While this is possible, the earliest reports presenting evidence of an association between androgenetic alopecia and prostate cancer were published approximately half way through the follow-up period for the present study. Furthermore, we believe that the limited media attention that these articles received would not have been sufficient to motivate dramatic changes in screening behavior among men with androgenetic alopecia. 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 androgenetic alopecia 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 androgenetic alopecia and risk of prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G.G. Giles, R. Sinclair, J.L. Hopper, D.R. English, G. Severi
Development of methodology: D.C. Muller, G.G. Giles, R. Sinclair, J.L. Hopper, G. Severi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G.G. Giles, R. Sinclair, J.L. Hopper, G. Severi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.C. Muller, R. Sinclair, J.L. Hopper, D.R. English, G. Severi
Writing, review, and/or revision of the manuscript: D.C. Muller, G.G. Giles, R. Sinclair, J.L. Hopper, D.R. English, G. Severi
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G.G. Giles
Study supervision: G.G. Giles, G. Severi

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