The association of male pattern baldness and risk of cancer and high-grade disease among men presenting for prostate biopsy

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Abstract

Introduction: Androgens have been implicated in both male pattern baldness (MPB) and prostate cancer (PCa). We set out to prospectively determine if men with independently assessed MPB are at higher risk for PCa at biopsy and determine if any grade associations exist.

Methods: We prospectively enrolled 394 eligible patients presenting for prostate biopsy and independently determined their MPB pattern using the validated modified Norwood classification system (0: no balding; 1: frontal balding; 2: mild vertex balding; 3: moderate vertex balding; 4: sever vertex balding). Univariate and multivariable models, including Norwood score, age, prostate-specific antigen, and digital rectal examination abnormalities, were calculated for the outcomes of cancer and high-grade disease (Gleason >6). C-statistics analyses of our models were then compared with and without MPB pattern for marginal utility.

Results: Norwood patterns were increasingly associated with cancer and high-grade disease with a dose-effect (p for trend <0.001 on univariate and multivariable analyses for cancer and p=0.001 and p=0.0036 for high-grade disease on univariate and multivariable analyses, respectively). On multivariable analyses, trends still held, with all patients exhibiting Norwood scale 3 and 4 at increased risk for cancer. In predicting risk of high-grade disease, only patients with Norwood pattern 4 exhibited an increased risk.

Conclusions: MPB appears to be a strong and independent risk factor for both cancer and high-grade disease for men presenting for prostate biopsy. Ours could be superior to marketed costly genetic tests. Further research is needed to understand the biology behind this observation and to incorporate these findings into clinical decision-making.

Introduction

Globally, prostate cancer (PCa) is the second most common type of cancer and the fifth leading cause of cancer-related death in men.[1] It was the most common cancer in males in 84 countries, occurring more commonly in the developed world.[2] Only four risk factors for PCa have been established — advancing age, black race, family history of the malignancy, and certain genetic polymorphisms.[3,4] PCa is the most commonly diagnosed cancer among Canadian men; in 2014, an estimated 23 600 Canadian men were diagnosed with PCa and 4000 died from the disease.[5]

PCa is a hormone-dependent disease, while the most common form of hair loss in men is androgenic alopecia. Aging and androgens are known risk factors for both PCa and male-pattern baldness (MPB), with androgens implicated in the development of both conditions.[6,7] With regard to endogenous hormones, both hair follicles and the prostate gland are androgen-responsive. Men with baldness seem to have higher circulating androgens than those without.[8,9]

Testosterone is an important androgenic hormone and its effect on the hair follicle is via its metabolite dihydrotestosterone (DHT). 5-alpha reductase enzyme is the converter of testosterone to the potent androgen, DHT.[10] This enzyme has two forms in the skin: type I is in the sebaceous glands and type II in the hair follicle, prostate, and epididymis. DHT binds to the androgenic receptor on the hair follicle, transforms the terminal hairs to vellus hairs in the human scalp hair of androgenic alopecia patients, and shortens the anagen phase.[11]

Methods

For this study, we prospectively enrolled 394 men with negative history of PCa who presented for prostate biopsy at Princess Margaret Cancer Centre. After informed consent, men were asked to rate their degree of hair loss at two time points (age of 30 and present day) after looking at a validated Norwood score calcification. Scoring is as follows: 0: no balding; 1: frontal balding; 2: mild vertex balding; 3: moderate vertex balding; 4: severe vertex balding. The study coordinator confirmed the self-reporting score for present day.

In addition to hair loss rating, the following variables were collected: age, prostate-specific antigen (PSA) (pre-biopsy), weight, height, ethnicity, family history, digital rectal exam

(DRE) results, International Prognostic Scoring System (IPSS) score, use of 5-alpha reductase inhibitors, transrectal ultrasound (TRUS) biopsy results (including prostate volume, areas of suspicion), and Gleason score if cancer was found (including tumour volume and number of cores involved with the tumour).

Univariate and multivariable models, including Norwood score, age, PSA, and DRE abnormalities, were calculated for the outcomes of cancer and high-grade disease (Gleason >6). C-statistics analyses of our models were then compared with and without MPB pattern for marginal utility.

Results

Three hundred ninety-four (394) eligible men presenting for prostate biopsy with no past history of PCa independently determined their MPB pattern (univariate and multivariable models) (Table 1). C-statistics analyses of our models were then compared with and without MPB pattern for marginal utility. One hundred ninety-four (194) men (49.2%) had cancer and 110 (27.9%) had Gleason 7 disease or higher at biopsy. Total cohort median PSA was 5.87 ng/ml (4.3–8.51), mean age was 62.7 years, 108 patients (27.4%) had abnormal DRE, and median prostate volume was 43 cc. Fifty-eight (58) patients had a prior biopsy and a total of 78 patients had positive family history for PCa.

On univariate and multivariable analyses, Norwood patterns were increasingly associated with cancer and high-grade disease with a dose effect (p for trend <0.001 on univariate and multivariable analyses for cancer and p=0.001 and p=0.0036 for high-grade disease on univariate and multivariable analyses, respectively) (Tables 1, 2).

On multivariable analysis, trends still held, with all patients exhibiting Norwood scale 3 and 4 at increased risk for cancer (Norwood 3 odds ratio [OR] 2.86; p=0.008 and Norwood 4 OR 3.11; p<0.007) (Table 3). In predicting risk of high-grade disease, only patients with Norwood pattern 4 (Norwood 4 OR 3.07; p=0.003 on univariate analysis and OR 2.79; p=0.023 on multivariable analysis) exhibited an increased risk (Table 4). Age and DRE abnormalities were also associated with cancer and high-grade disease. There was no association between MPB and prostate volume. In comparing the C-statistics of our models, significant improvement was noted in both cancer and high-grade models (Tables 1, 2).

Discussion

The aim of the study was to prospectively determine if men with independently assessed MPB are at higher risk for PCa at biopsy and determine if any grade associations exist.

The prevalence of baldness, especially vertex and frontal with vertex baldness, increases with age.[12] Baldness affects about 50–70% of men.[13] Some studies suggested a relationship between PCa and baldness in a positive[13] or inverse[14] relationship, although some suggested no relation at all.[15] Aging and androgens are known risk factors for both PCa and MPB, with androgens implicated in the development of both conditions.[6,7]

Our data analyses showed that with MPB measured by a modified Norwood scale, the higher the grade, the higher the risk of developing PCa. We also found that higher-grade PCa is associated with higher grade of baldness, but not with milder forms of baldness. We believe these results may be explained by the shared risk factors for both MPB and PCa, including aging, heritable genetic factors, and androgen metabolism.

The association between MPB and PCa may actually represent a shared pathogenesis. Androgens, insulin-like growth factor 1 (IGF-1), and microRNAs are some of the proposed underlying etiologies behind both PCa and MPB. The role of androgens in the development of PCa has been investigated and although some studies found no association between androgen serum levels and PCa, other studies

Table 1. Univariate and multivariable logistic regression analysis for cancer detection

Parameter	Univariate		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Norwood scale (per 1-unit increase)	1.38 (1.19–1.60)	<0.001	1.42 (1.19–1.71)	<0.001
Age (per 5-year increase)	1.28 (1.13–1.46)	<0.001	1.52 (1.285–1.80)	<0.001
Ethnicity				
Caucasian	Ref	Ref	Ref	Ref
African	2.79 (1.20–6.49)	0.018	2.71 (1.04–7.09)	0.042
Southeast Asian	1.00 (0.49–2.05)	0.99	0.99 (0.39–2.51)	0.98
Other	0.58 (0.27–1.26)	0.17	0.74 (0.30–1.84)	0.52
Family history	1.30 (0.84–2.01)	0.23	1.81 (1.06–3.09)	0.030
Previous biopsy	0.51 (0.31–0.84)	0.008	0.59 (0.32–1.11)	0.10
Abnormal DRE	2.16 (1.37–3.40)	<0.001	2.11 (1.21–3.67)	0.008
PSA (per 1 ng/ml)	1.04 (1.01–1.08)	0.020	1.08 (1.03–1.14)	0.002

CI: confidence interval; DRE: digital rectal exam; OR: odds ratio; PSA: prostate-specific antigen.

Table 2. Univariate and multivariable logistic regression analysis for clinically significant cancer detection

Parameter	Univariate		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Norwood scale (per 1-unit increase)	1.32 (1.12–1.55)	<0.001	1.35 (1.11–1.65)	0.003
Age (per 5 years)	1.31 (1.14–1.51)	<0.001	1.44 (1.20–1.73)	<0.001
Ethnicity				
Caucasian	Ref	Ref	Ref	Ref
African	2.24 (1.03–4.87)	0.041	2.25 (0.90–5.64)	0.083
Southeast Asian	1.58 (0.74–3.36)	0.24	1.43 (0.54–3.79)	0.47
Other	0.53 (0.20–1.43)	0.21	0.53 (0.16–1.75)	0.30
Family history	1.06 (0.65–1.71)	0.83	1.51 (0.85–2.68)	0.16
Previous biopsy	0.81 (0.47–1.41)	0.46	0.93 (0.46–1.88)	0.83
Abnormal DRE	2.89 (1.80–4.64)	<0.001	2.94 (1.65–5.23)	<0.001
PSA (per 1 ng/ml)	1.10 (1.05–1.15)	<0.001	1.14 (1.08–1.21)	<0.001
Prostate volume (per 5 cc)	0.89 (0.84–0.95)	<0.001	0.81 (.74–0.89)	<0.001
5-ARI use	1.19 (0.62–2.28)	0.61	1.05 (0.39–2.87)	0.92
IPSS (per 1 unit)	0.97 (0.94–1.01)	0.14	0.97 (0.93–1.02)	0.21

ARI: alpha reductase inhibitor; CI: confidence interval; DRE: Digital rectal exam; IPSS: International Prognostic Scoring System ; OR: odds ratio; PSA: prostate-specific antigen.

found higher free testosterone levels in patients with PCa. Men with vertex baldness were also significantly associated with higher serum testosterone, DHT, and DHT/testosterone ratio.[8,9] High levels of IGF-1 has been linked to MPB by stimulating androgen receptors or increasing 5-alpha reductase activity.[16] Males with high levels of IGF-1 have been shown to have an increased risk of developing PCa when compared with those with low IGF-1.[17] MicroRNA changes have been found to be associated with both MPB[18] and prostate cancer.[19] And still other undiscovered mechanisms of association may exist.

Our study also showed that age and DRE abnormalities were also associated with cancer and high-grade disease. There was no association between MPB and prostate volume.

Further research needs to be done to confirm our results and whether MPB can be considered an independent risk factor for PCa.

The limitations of this study were its prospective nature, although specimens were procured at the time of prostate biopsy. In addition, the cohort is isolated to patients presenting for prostate biopsy; weather this association holds in the general population needs further investigation.

Conclusion

MPB appears to be a strong and independent risk factor for cancer and high-grade disease for men presenting for prostate biopsy. A link between MPB and PCa may be explained by aging, heritable genetic factors, or androgen metabolism. To validate these findings, we plan to enroll an additional 175 patients, following the same inclusion criteria, intervention, and data analyses plan, with the aim to better understand the biology behind this observation and incorporate these findings into clinical decision-making. Additionally, we will measure total testosterone and DHT levels in this new cohort to assess androgenic effect. If testosterone levels are found to be significant, we will measure them in the original cohort, using banked serum samples from the Genito-Urinary (GU) BioBank at The Princess Margaret and University Health Network (UHN).

Competing interests: Dr. Zlotta has been an advisor for Amgen, Astellas, Ferring, Paladin Labs, and Sanofi; has received educational grants from Red Leaf Medical and Sanofi; and has participated in clinical trials for Sanofi. Dr. Fleshner has been an advisor for and received honoraria from Amgen, Astellas, Eli Lilly, and Janssen; and has participated in clinical trials for Amgen, Janssen, Medivation, OICR, and Prostate Cancer Canada. The remaining authors report no competing personal or financial interests.

Table 3. Odds by Norwood scale for cancer detection

Parameter	Univariate		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Norwood scale				
0	Ref	Ref	Ref	Ref
1	1.30 (0.72–2.36)	0.39	0.86 (0.43–1.74)	0.68
2	2.33 (1.20–4.54)	0.012	1.38 (0.63–3.00)	0.42
3	2.87 (1.49–5.53)	0.002	2.86 (1.31–6.24)	0.008
4	3.23 (1.64–6.39)	<0.001	3.11 (1.36–7.09)	0.007

CI: confidence interval; OR: odds ratio.

Table 4. Odds ratio by Norwood scale for high-grade cancer detection

Parameter	Univariate		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Norwood scale				
0	Ref	Ref	Ref	Ref
1	1.16 (0.57–2.36)	0.68	0.74 (032–1.71)	0.48
2	1.61 (0.75–3.45)	0.22	0.84 (0.34–2.10)	0.71
3	1.67 (0.89–3.90)	0.096	1.54 (0.64–3.72)	0.34
4	3.07 (1.47–6.41)	0.003	2.79 (1.15–6.74)	0.023

CI: confidence interval; OR: odds ratio.

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