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Pigmentation-related phenotypes and risk of prostate cancer

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Background: Solar ultraviolet radiation exposure has been inversely related to prostate cancer incidence and mortality, possibly mediated through vitamin D status. Pigmentation-related traits influence endogenous vitamin D synthesis and may alter risk of prostate cancer.

Methods: We examined prostate cancer in relation to hair and eye colour, and skin phototype in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort. Incident cancer was diagnosed in 1982 out of 20 863 men. Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from Cox proportional hazards models.

Results: Prostate cancer risk did not differ by eye colour or skin phototype. Men with naturally red hair were significantly less likely to develop prostate cancer (HR = 0.46, 95% CI 0.24–0.89) than men with light brown hair (reference).

Conclusion: The red hair phenotype, which results from polymorphisms in the melanocortin-1-receptor (*MC1R*) gene, is associated with lower risk of prostate cancer. This pigmentation-related trait may influence prostate cancer development either directly, through genetic effects or regulatory mechanisms related to *MC1R*, another nearby gene, or other pigmentation genes, or indirectly, through associations with other exposures such as sunlight or vitamin D status.

Exposure to solar ultraviolet (UV) radiation is an established causal factor for skin cancer (Rouzaud *et al*, 2005), but may be associated inversely with prostate cancer (Freedman *et al*, 2002; Moon *et al*, 2005). This latter association is hypothesised to be mediated through improved vitamin D status resulting from sunlight-induced epidermal vitamin D synthesis (Bodiwala *et al*, 2003; Moon *et al*, 2005). However, meta-analyses have not demonstrated a vitamin D–prostate cancer association (Yin *et al*, 2009; Gandini *et al*, 2011). We sought to test the hypothesis through an alternative approach by examining the pigmentation-related traits of hair colour, eye colour, and skin phototype, which influence vitamin D synthesis (Moon *et al*, 2005), in relation to prostate cancer incidence.

Finland (latitude of study area 60–64°N) (The ATBC Cancer Prevention Study Group, 1994).

The original randomised trial tested the effects of daily supplementation with α -tocopherol (50 mg per day), β -carotene (20 mg per day), both, or placebo on cancer incidence. Study supplementation continued for 5–8 years until death or trial closure (30 April 1993), after which participants were followed as a longitudinal cohort. At study entry, participants completed detailed questionnaires including data on education, physical activity, medical history, and smoking and dietary habits. A follow-up questionnaire that queried hair colour at age 20, eye colour, and skin phototype (patterned after the Fitzpatrick (1988) classification) was administered between 1989 and 1993 to the 20 863 active study participants (among these men, 1105 had fasting serum 25-hydroxyvitamin D (25(OH)D) subsequently measured as controls in other substudies (Weinstein *et al*, 2011)). The ATBC study was approved by the institutional review boards of the US National Cancer Institute and the National Public Health Institute of Finland, with written informed consent obtained from each participant.

MATERIALS AND METHODS

Study population. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study included 29 133 male smokers, aged 50–69 years, recruited between 1985 and 1988 from southwestern

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Prostate cancer ascertainment. A total of 1982 incident prostate cancers were identified through the Finnish Cancer Registry from among all 20 863 subjects who completed the follow-up questionnaire (including all trial arms). The Registry has been shown to identify and correctly classify nearly all cancers occurring in the ATBC cohort (Korhonen *et al*, 2002).

Statistical analysis. Follow-up time for each participant was calculated from the date of randomisation through the date of prostate cancer diagnosis, death or end of follow-up (31 December 2009), with up to 25 years of individual follow-up. Calculating follow-up time from the date of the follow-up questionnaire did not alter the findings. Baseline descriptive statistics, contrasting participants with and without self-reported red hair, were compared using Wilcoxon rank sum tests (continuous variables) or χ^2 -tests (categorical variables). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression, with the most common hair colour, eye colour, and skin phototype categories as reference. Multivariate-adjustment (see Table 2 for adjustment factors) did not alter the risk estimates substantially. The hazard proportionality assumption was met. Statistical analyses were performed using SAS software version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Only 188 men (0.9%), including 9 who developed prostate cancer, reported their natural hair colour as red, whereas 12%, 40%, 35%, and 12% reported it being blonde, light brown, dark brown, or

black/almost black, respectively. Men with red hair were more educated, more likely to use vitamin D or calcium supplements, and more likely to report that their skin burns easily and does not tan upon prolonged exposure to direct sunlight, compared with men of other hair colour (Table 1). Serum vitamin D did not differ by hair colour.

Men with red hair had a significantly lower prostate cancer risk compared with men with light brown hair, the most common hair colour in the cohort (HR = 0.46, 95% CI 0.24–0.89, Table 2). The risk for red hair compared with all other hair colours combined was similar (multivariate HR = 0.48, 95% CI 0.25–0.92). There was no evidence of confounding. We were unable to examine the association in subgroups defined by disease stage, the trial vitamin supplementation, vitamin D status, or other potential effect modifiers because of the small number of prostate cancer cases with red hair. Risk did not differ by eye colour or skin phototype, although lower risk was suggested for men with brown eyes.

DISCUSSION

In this large cohort, men with naturally red hair experienced approximately half the risk of prostate cancer compared with men with light brown hair. Eye colour and skin phototype were not associated with risk.

The melanocortin-1-receptor (*MC1R*) gene is among several loci regulating pigmentation in humans, and the first to be identified (Chhajlani and Wikberg, 1992; Mountjoy *et al*, 1992). Over 80 allelic variants in the gene have been reported (Gerstenblith *et al*, 2007; Raimondi *et al*, 2008), which are

Table 1. Selected baseline characteristics – median (interquartile range) or number (%) for the ATBC cohort by hair colour at age 20

Characteristic	Men with hair colour other than red, N = 20 675	Men with red hair, N = 188	P-value ^a
Age (y)	56 (53–60)	57 (53–61)	0.71
Height (cm)	174 (170–178)	174 (170–178)	0.68
Body mass index (kg m ⁻²)	26.0 (23.8–28.5)	26.7 (24.1–29.2)	0.02
Cigarettes smoked per day	20 (15–25)	20 (15–25)	0.95
Years smoked	36 (30–41)	37 (32–42)	0.27
Education (> elementary)	4583 (22.2%)	58 (30.9%)	0.004
Leisure physical activity (moderate and heavy)	12 526 (60.6%)	110 (58.5%)	0.52
Eye colour			0.09
Blue	13 603 (65.9%)	121 (64.7%)	
Brown	2246 (10.9%)	12 (6.4%)	
Green	1390 (6.7%)	18 (9.6%)	
Grey	3409 (16.5%)	36 (19.3%)	
Skin type ^b			0.0001
Will not burn and gets tanned	7357 (35.7%)	11 (5.9%)	
Burns slightly and gets tanned slowly and evenly	5727 (27.8%)	18 (9.6%)	
Burns easily, but gets tanned	6031 (29.2%)	64 (34.0%)	
Burns easily and will not get tanned	1512 (7.3%)	95 (50.5%)	
Family history of prostate cancer	612 (3.0%)	8 (4.3%)	0.25
History of benign prostatic hyperplasia	796 (3.8%)	8 (4.3%)	0.75
Vitamin D supplement use (yes%) ^c	1435 (6.9%)	20 (10.6%)	0.05
Calcium supplement use (yes%) ^c	2299 (11.1%)	34 (18.1%)	0.003
Serum 25(OH)D (nmol l ⁻¹) ^d	33.5 (21.4–48.5)	33.6 (17.7–41.3)	0.65

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention; 25(OH)D = 25-hydroxyvitamin D; y = year.

^aP-value based on χ^2 -tests (for categorical variables) and Wilcoxon rank sum tests (for continuous variables).

^bThe skin type questions were patterned after the Fitzpatrick classification, and the responses are generally equivalent to skin types IV, III, II, and I, respectively.

^cOnly 21.2% of subjects reported any supplement use.

^dOn the basis of 1105 men (9 with red hair) who were included as controls in other substudies that measured 25(OH)D.

Table 2. HRs and 95% CIs for the association between pigmentation-related phenotypes (hair colour, eye colour, and skin phototype) and risk of prostate cancer

Pigmentation-related phenotypes	Cases/non-cases ^a , N	Age-adjusted	Multivariate adjusted ^b
Hair colour			
Light brown (reference)	818/7416	1.00	1.00
Dark brown	702/6609	0.96 (0.87–1.06)	0.97 (0.88–1.08)
Black	225/2354	0.89 (0.77–1.04)	0.93 (0.80–1.08)
Blonde	228/2323	0.90 (0.77–1.04)	0.89 (0.77–1.03)
Red	9/179	0.47 (0.25–0.91)	0.46 (0.24–0.89)
Eye colour			
Blue (reference)	1307/12422	1.00	1.00
Grey	344/3101	1.03 (0.91–1.16)	1.02 (0.90–1.15)
Brown	190/2068	0.88 (0.75–1.02)	0.87 (0.74–1.02)
Green	137/1271	1.02 (0.85–1.22)	1.00 (0.84–1.20)
Skin phototype^c			
Will not burn and gets tanned (reference)	690/6680	1.00	1.00
Burns slightly and gets tanned slowly and evenly	573/5172	1.03 (0.92–1.15)	1.01 (0.90–1.13)
Burns easily, but gets tanned	576/5520	1.01 (0.90–1.13)	1.01 (0.90–1.13)
Burns easily and will not get tanned	141/1468	0.98 (0.82–1.17)	1.01 (0.84–1.22)
Abbreviations: CI = confidence interval; HR = hazard ratio.			
^a Non-cases are cohort members without prostate cancer.			
^b Adjusted for age, body mass index, education, number of cigarettes smoked per day, family history of prostate cancer, use of vitamin D and calcium supplements, trial supplementation group, and mutually adjusted for hair colour, eye colour, and skin phototype.			
^c The skin type questions were patterned after the Fitzpatrick classification, and the responses are generally equivalent to skin types IV, III, II, and I, respectively.			

associated with red hair, fair skin, increased susceptibility to epidermal injury from exposure to UV radiation, and higher risks of melanoma and non-melanoma skin cancer (Schaffer and Bologna, 2001; Raimondi *et al*, 2008; Randerson-Moor *et al*, 2009; Kanetsky *et al*, 2010; Rees, 2010; Williams *et al*, 2011). The MC1R protein determines the relative synthesis and secretion by melanocytes of black/brown eumelanin and red/yellow pheomelanin, with many allelic variants expressing a red hair trait. Recent genome-wide association studies have identified other genetic variants associated with hair colour, eye colour, and skin pigmentation in European populations (Sulem *et al*, 2007; Han *et al*, 2008) and have associated MC1R with risk of cutaneous melanoma, but not with prostate cancer or other cancers (Ioannidis *et al*, 2010).

Melanocortin-1-receptor may also influence cell cycle control, apoptosis, and DNA damage and repair in melanocytes and keratinocytes (Rees, 2010); however, whether such functions are expressed by MC1R in other cells is unknown. In addition, MC1R, along with α -MSH, which has anti-inflammatory properties and both immunostimulatory and immunosuppressive effects, may have a role in inflammation (Schaffer and Bologna, 2001; Rouzaud *et al*, 2005; Raimondi *et al*, 2008) and may consequently influence cancer development (Vendramini-Costa and Carvalho, 2012).

The wild-type allele of the MC1R variant Arg160Trp has been associated with increased prostate cancer risk in a case-control study, and the authors speculated that this variant may mediate the UV/sunlight-prostate cancer association (Luscombe *et al*, 2001).

Others have also hypothesised that the association between geographic latitude, sun exposure, and prostate cancer risk is through a vitamin D mechanism (Bodiwala *et al*, 2003; Moon *et al*, 2005); however, prospective studies of circulating 25(OH)D and prostate cancer have generally been null (Gandini *et al*, 2011), with some studies (Yin *et al*, 2009), including our own (Albanes *et al*, 2011), suggesting an adverse association for higher vitamin D status. Although 25(OH)D concentrations in our study did not differ by hair colour, they were lower among individuals with red hair in another study and postulated to reflect avoidance of sun exposure (Randerson-Moor *et al*, 2009). Whether the lower prostate cancer risk in men with red hair relates to vitamin D, some aspect of melanogenesis, or another mechanism is unclear and will require investigation. A genetic association between hair colour or pigmentation-related traits and family history of prostate cancer can also be studied. Although skin phototype appeared associated with hair colour, mutual adjustment for these factors and eye colour did not influence the hazard estimates. Why red hair colour, but not eye colour or skin phototype was associated with prostate cancer risk is unclear.

Strengths of our study include the prospective design and complete endpoint ascertainment. Men who dropped out of the ATBC study before the clinic visit during which hair and eye colour and skin phototype information would have been collected could not be included in the present analysis, and, as a result, we do not have data to examine the red hair-prostate cancer association in that initial post-baseline period. In addition, as the trial excluded men who were not 50–69 years of age at baseline, our study does not include prostate cancers occurring at younger ages. Natural hair colour at age 20 was self-reported, but misclassification due to recall bias seems unlikely for such a physical characteristic. The ATBC study cohort included only smokers and may not be generalisable to non-smokers; however, smoking intensity and duration were not related to hair colour or prostate cancer. Because the red hair trait was uncommon, our finding is based on a relatively small number of men (and cases) with red hair.

In conclusion, in the present study we found that men with naturally red hair experienced significantly lower prostate cancer incidence than men with other hair colours. Although the novelty of our findings warrant reexamination in other study populations, they support the idea that some pigmentation-related traits may influence the development of prostate cancer, either directly through genetic effects or regulatory mechanisms related to MC1R, another nearby gene, or other pigmentation genes or indirectly through associations with other exposures that may have an impact on risk (e.g., effects of UV-B or vitamin D status).

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