Hair dye use and prostate cancer risk: A prospective analysis in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort

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Abstract

Background: According to the International Agency for Research on Cancer (IARC), some hair dye chemicals are considered mutagenic and carcinogenic in humans. One hospital-based study reported a positive association between hair dye use and prostate cancer risk, but no prospective analyses have been conducted.

Methods: We investigated the association between hair dye use and prostate cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort, a large, well-characterized cohort of 29,133 male Finnish smokers. Participants completed questionnaires regarding lifestyle, medical, and risk factor information, including use of hair dye which was available for 98.8% of the cohort (28,795 men). Prostate cancer cases were identified through linkage with the Finnish Cancer Registry and the Finnish mortality register. Hazard ratios (HRs) and confidence intervals (CIs) were estimated using multivariable Cox proportional hazards regression.

Results: During a 28-year period of observation, 2,703 incident prostate cancer cases were diagnosed. As reported at baseline, 75 men used hair dye among whom 13 were subsequently diagnosed with prostate cancer. After adjusting for potential confounders, men who used hair dyes experienced substantially higher prostate cancer risk as compared men who did not (HR=1.77, 95% CI, 1.03–3.05).

Conclusions: This first prospective investigation of hair dye use and prostate cancer suggests that personal hair dye use may be related to increased risk. Our findings warrant re-examination in

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other prospective cohorts along with studies evaluating specific hair dyes and possible underlying biological mechanisms.

Keywords

Hair dye; prostate cancer risk; prospective study; ATBC Study

Introduction

Prostate cancer was the second most common malignancy in men globally in 2018.[1] Well-established risk factors for the disease are older age, African ancestry, prostate cancer family history, and specific inherited genetic polymorphisms and conditions including *BRCA1* and *BRCA2* mutations and the Lynch syndrome.[2] Smoking, physical activity, diabetes, obesity, and some chemical exposures are modifiable factors having less clear prostate cancer etiologic associations.[2] Higher serum concentrations of vitamins A and D, total cholesterol, insulin and IGF-1, vertex-pattern androgenetic alopecia, and male-pattern baldness also have been suggested as possible risk factors.[3–10]

At the same time, the potential effects of environmental microcontaminant exposures such as organochlorine pesticides, polychlorinated biphenyls, and other xenobiotics on the development of prostate cancer have attracted the attention of toxicologists and epidemiologists.[11,12] According to the International Agency for Research on Cancer (IARC), some chemicals in hair dyes are considered mutagenic and carcinogenic as shown by *in vitro* assays and exposed human populations.[13,14] Oxidative hair dye ingredients belong to the large chemical family of arylamines, which includes the known human carcinogens benzidine, 4-aminobiphenyl and 2-naphthylamine.[15] *In vitro* genotoxicity testing of such compounds has demonstrated deleterious effects, while *in vivo* carcinogenicity for the oxidative hair dye chemical class of aromatic amines is uncertain.[16,17] Epidemiological investigations of hair dye use have for the most part focused on risk of breast and bladder cancer and leukemia, with inconsistent findings, and no prospective analysis has been conducted for the prostate cancer risk.[18–22] Previous meta-analyses of cancer risk among hairdressers showed that they are at higher risk of cancer overall as compared with the general population,[23] and at an increased risk of bladder cancer.[24] In addition, significantly increased incidence of prostate cancer was also observed in a cohort of hairdressers,[25] which is supported by a hospital-based case-control study reported a positive association between hair dye use and prostate cancer (odds ratio=2.2, 95% CI, 1.3–3.6).[26]

To test the hypothesis based on prospective data, we investigated the association between use of hair dye and prostate cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort.

Methods

Study population

The ATBC Study was a randomized, double-blinded, placebo-controlled primary prevention trial conducted to evaluate the effects of supplementation with vitamin E and beta-carotene on the incidence of lung and other cancers.[27] The trial recruited 50–69 years old male smokers (n=29,133) from 1985 to 1988 in southwestern Finland who were randomly assigned to receive one of four supplements daily: (i) alpha-tocopherol (50 IU), (ii) beta-carotene (20 mg), (iii) both vitamins, or (iv) placebo for 5–8 years (a median of 6.1 years).

The ATBC Study was approved by institutional review boards at both the US National Cancer Institute and the Finnish National Public Health Institute, and written informed consent was obtained from all participants.

Exposure and risk factor data

At enrollment, participants completed questionnaires regarding behavioral and lifestyle information, including hair greyness and hair dye use, smoking, alcohol consumption and medical history. Height and weight were measured and body mass index (BMI) calculated as weight in kilograms divided by height in meters (squared). Hair dye use was ascertained in one question that also asked about hair greyness and balding, with response categories being: no grey hair; less than 25%, about 25%, about 50%, about 75%, almost all grey, or all grey hair; bald; or dyed hair. Family history of prostate cancer and natural hair color were ascertained in another questionnaire that was administered between 1989 and 1993 to the 20,863 active study participants.

Fasting serum was collected and stored at −70°C for all trial participants at baseline. Total and high-density lipoprotein cholesterol concentrations were measured using an enzymatic assay.[28] Serum alpha-tocopherol, beta-carotene, and retinol were assayed using high-performance liquid chromatography in one laboratory.[29]

Identification of prostate cancer cases

Prostate cancer cases were identified by linkage of the cohort with the Finnish Cancer Registry, which provides nearly 100% complete incident cancer ascertainment in Finland.[30] Medical records for cases diagnosed before September 2001 were reviewed by one or two study oncologists to confirm diagnoses and stage, and where available, tissue specimens were reviewed by a pathologist. For cases diagnosed after September 2001, cancer information was derived from the Finnish Cancer Registry and the Finnish mortality register, Statistics Finland. Prostate cancer cases with stage 3 or 4 disease or with a Gleason score of 8 or higher were defined as advanced disease.

Statistical analysis

Among the 29,133 study participants, 338 men with missing data on hair greyness and hair dye use were excluded, resulting in 28,795 participants in the analysis. We collapsed the responses into the categories of "no grey hair", "less grey hair" (25% or less), and "more grey hair" (>25% to 100%), bald, and uses hair dye. Hazard ratios (HRs) and confidence

intervals (CIs) for associations between hair dye use and prostate cancer risk (all cases combined, non-advanced cases, and advanced cases) were estimated using multivariable-adjusted Cox proportional hazards regression models with the no grey hair category serving as the reference group. A secondary analysis used all categories other than hair dye users as an alternative reference group. Potential confounders included in the models were baseline age (continuous), number of cigarettes smoked per day (continuous), years of smoking (continuous), and family history of prostate cancer (yes, no or missing).

Subgroup analyses were conducted based on factors including the trial beta-carotene and alpha-tocopherol supplementation assignments, age (<57 or 57 years), number of cigarettes smoked per day (<20 or 20), years of cigarette smoking (<36 or 36 years), BMI (<26 or 26 kg/m^2), alcohol consumption (<11 or 11 g), serum alpha-tocopherol (<11.5 or 11.5 μg/L), serum beta-carotene (<170 or 170 μg/L), serum retinol (<576 or 576 μg/L), serum total cholesterol (6.15 or 6.15 mmol/L), years of follow-up (<14 or 14 years), cancer stage (non-advanced or advanced) and natural hair color [light (red, fair or light brown) or dark (dark brown or black)]. Interactions were assessed through likelihood ratio tests by comparing regression models with and without the cross-product of each factor and hair dye use, or through a multinomial logistic regression model (for non-cases and advanced versus non-advanced disease).

All the analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC). All reported P values were two-sided. The null hypothesis of no difference was rejected if p-values were less than 0.05.

Results

During a 28-year period, 2,703 incident prostate cancer cases were diagnosed in the 28,795 ATBC Study participants included in this analysis. The incidence rate of prostate cancer was 11.18 per 1,000 person years in hair dye users and 5.68 per 1,000 person years in hair dye non-users. At the baseline, 75 men used hair dye, and among them 13 prostate cancer cases were diagnosed. Table 1 presents baseline characteristics for the analytic cohort and compares men using hair dye to those with varying degrees of grey hair but with no reported hair dye use, as well as bald men. Hair dye users were generally similar to other men with the exception of being older; e.g., mean age of 58.95 years as compared with 57.19 years for all other men combined.

Based on the multivariable proportional hazards model, men who used hair dyes experienced substantially higher prostate cancer risk during the 28-year observation period as compared with men with no grey hair (HR 1.81; 95% CI, 1.04–3.14) (Table 2). When we excluded the first year of follow-up, the risk estimate remained unchanged (HR 1.82; 95% CI, 1.05–3.16), and we observed similar though attenuated associations when we excluded two, three or five years of initial cases (data not shown). Comparing hair dye users to all the other men combined (i.e., no hair dye use) gave nearly identical findings (HR 1.77; 95% CI, 1.03–3.05). Baldness and varying degrees of grey hair were not associated with risk of prostate cancer (Table 2).

We explored the hair dye-prostate cancer risk association in several risk factor subgroups (Table 3). Although we found no formal evidence of effect modification, the positive risk association for hair dye use appeared more prominent among men not receiving the trial alpha-tocopherol supplement (P-value for interaction = 0.09), those with fewer years of smoking, higher BMI, shorter follow-up time, and lighter natural hair color. The association also appeared slightly stronger for non-advanced disease (HR 2.79; 95% CI, 1.36–5.69) as compared with advanced disease (HR 1.66; 95% CI, 0.81–3.38). These subgroup findings were essentially unchanged when combining all non-hair dye categories into one reference group.

Discussion

This study is the first prospective analysis of hair dye use and prostate cancer incidence. Based on a large trial-based cohort of male Finnish smokers, we found that men who used hair dye experienced a nearly doubling of prostate cancer risk during a 28-year observation period as compared with men who did not use hair dye. We found no prostate cancer association with specific degrees of hair greyness or with baldness.

Consistent with our overall findings, a hospital-based, retrospective case-control study of 296 men with prostate cancer also showed a positive hair dye-risk association (HR 2.15; 95% CI, 1.32–3.57) and indicated dose-response associations with duration and frequency of exposure.[26] Excess risk of prostate cancer was also seen among 703 male hairdressers in a Swiss cohort analysis based on 12 incident cases between 1970 and 1980.[25] Epidemiological investigations of hair dye use have for the most part focused on risk of breast cancer, bladder cancer, and leukemia, with inconsistent findings, including one meta-analysis of cancer risk that did not include any studies of prostate cancer.[18–22] Overall, the weight of evidence regarding the role of hair dye exposure and human cancer risk suggests no association.[17] Compared with the prostate, the urinary bladder is in greater contact with urine for more extended periods, so a stronger association might be expected for that organ site. However, because of the endocrine disrupting chemical properties of some hair dye chemicals, the risk of hormone-sensitive cancers such as breast and prostate cancer could be more sensitive to hair dye exposure than that of other cancers.[31] Supporting this is the Sister study that recently reported higher breast cancer risk associated with any straightener use and personal use of permanent dye,[31] as well as a recently published meta-analysis which suggested a significant association between the use of hair dyes and breast cancer occurrence.[32] Experimental data also indicate that hair dyes may have specific carcinogenic properties for the prostate gland, which is supported by the present findings and the previous case-control study.[26,33–35] Our recent metabolic profiling analysis of the hair dye use in this study supports the present findings in that we found several top metabolites including cysteinylglycine disulfide and cysteine-glutathione disulfide, compounds directly relevant to the antioxidation/ROS pathways (unpublished data). Importantly, these and related metabolites have been previously associated with prostate cancer risk.[36]

N-acetylation is a major route of biotransformation of aromatic amine compounds, including those found in hair dyes.[19] Two such enzymes, N-acetyltransferase (NAT)-1 and NAT2, have been well-characterized with respect to metabolism of aromatic amines including

p-phenylenediamine (PPD), which is one of the key components of permanent hair dyes.[14,37,38] In animal models, for example, NAT expression in the hamster prostate catalyzes the metabolic activation of the N-hydroxy metabolites which can lead to DNA adduct formation,[34] consistent with the observed NAT-catalyzed metabolic activation of N-hydroxy-heterocyclic amine carcinogens in human prostate epithelium.[39] In addition, the *NAT2* slow acetylator genotype has been associated with prostate cancer risk in Japanese men, with locally advanced, high-grade and metastatic disease, and with increased risk in smokers specifically.[33] Given that the ATBC Study comprises male smokers and that 35% of cases were diagnosed with stage 3 or 4 disease or with Gleason score of 8 or higher (based in part on little or no population-based prostate specific antigen (PSA) screening), examination of the *NAT2* genotype for interaction with the hair dye exposure and prostate cancer will be of interest. Further targeted biological studies are needed to understand specific mechanisms of how hair dyes and their component chemicals may influence prostate cancer risk.

We found no association between baldness and prostate cancer, consistent with an analysis in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial that observed no overall association, while indicating frontal plus moderate vertex baldness at age 45 years was related to greater risk of aggressive disease.[10] A recent meta-analysis of male pattern baldness showed an association with prostate cancer for vertex baldness (RR 1.24, 95% CI 1.05–1.46) but not for other types.[40] Although baldness pattern may have relevance to the prostate cancer association, our questionnaire did not distinguish between baldness types.

Strengths and limitations should be mentioned. Our study is the first prospective investigation of hair dye use and prostate cancer risk and was possible because of the (uncommon) collection of hair dye exposure data and sufficient follow-up time. It was conducted in a large, well-characterized cohort, and, importantly, ascertainment of prostate cancer diagnoses was based on national registries and therefore complete. Study limitations include the relatively small number of hair dye users and lack of information regarding duration and frequency of use as well as specific hair dye chemical compositions. A multicenter survey of such applications has indicated, however, that hair dyes used in Finland in the 1990's did contain 4-amino phenol and toluene-2,5-diamine or toluene-2,5-diamine sulfate.[41] Some misclassification of hair dye exposure may have occurred in that it was assessed only during study enrollment and hair dye use could have changed over time (e.g., baseline non-users beginning use years later, or some baseline users deciding to stop hair coloration), both of which would have biased our findings toward the null. Also, our hypothesis-generating subgroup analyses had very small numbers of exposed cases which resulted in low statistical power, and unmeasured confounders could have affected the observed association even though we adjusted for a large number of available risk factors. Lastly, the relatively homogeneous nature of the cohort (i.e., smokers of European ancestry) limits generalization of our findings to other more diverse populations.

In conclusion, we found personal hair dye use was related to increased prostate cancer risk during a 28-year period in male Finnish smokers. Examination in other cohorts of various racial and ethnic groups, including those with data for use of specific hair dyes, along with

genetic and metabolomic characterizations, should help us better understand the underlying association and responsible biological mechanisms.

Acknowledgements

Data availability

The data that support the findings of our study are available from the corresponding author upon reasonable request.

Abbreviations:

ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention
BMI	body mass index
CI	confidence interval
HR	Hazard ratio
IARC	International Agency for Research on Cancer
NAT	N-acetyltransferase

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Table 1:

Selected baseline characteristics [medians (25th–75th percentile) or proportions (N, %)] by categories of hair greyness and hair dye use in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (1985–2012)

Characteristics	No grey hair (N=5,163)	Less grey hair (≤25%) (N=13,841)	More grey hair (>25%–100%) (N=9,150)	Bald (N=566)	Dyed hair (N=75)	Non-hair dye users[a] (N=28,720)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	54.99 ± 4.37	56.59 ± 4.79	59.20 ± 5.08	59.13 ± 5.29	58.95 ± 4.90	57.19 ± 5.06
Height (cm)	173.6 ± 6.4	173.7 ± 6.1	173.5 ± 6.2	172.4 ± 6.0	174.3 ± 5.8	173.6 ± 6.2
Weight (kg)	78.3 ± 13.2	79.4 ± 12.8	79.9 ± 12.9	78.2 ± 12.3	79.7 ± 11.4	79.3 ± 12.9
Body mass index (kg/m²)[b]	25.9 ± 3.9	26.3 ± 3.8	26.5 ± 3.8	26.3 ± 3.7	26.2 ± 3.1	26.3 ± 3.8
Cigarettes smoked per day	21.4 ± 9.0	20.6 ± 8.9	19.7 ± 8.6	20.3 ± 8.4	18.6 ± 8.2	20.4 ± 8.8
Years of smoking	34.0 ± 7.8	35.3 ± 8.4	37.8 ± 8.5	37.5 ± 9.1	36.4 ± 10.2	35.9 ± 8.5
Serum biomarkers						
Total cholesterol (mmol/L)	6.24 ± 1.18	6.25 ± 1.16	6.21 ± 1.17	6.21 ± 1.20	6.11 ± 1.20	6.23 ± 1.17
HDL cholesterol (mmol/L)	1.22 ± 0.33	1.20 ± 0.32	1.18 ± 0.31	1.19 ± 0.33	1.20 ± 0.38	1.20 ± 0.32
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Trial α-tocopherol supplementation	2,569 (49.8)	6,885 (49.7)	4,628 (50.6)	281 (49.7)	35 (46.7)	14,363 (50.0)
Trial β-carotene supplementation	2,544 (49.3)	6,911 (49.9)	4,608 (50.4)	285 (50.4)	37 (49.3)	14,348 (50.0)
Education/training above 8th grade	3445 (66.8)	9198 (66.5)	6016 (65.8)	322 (56.9)	56 (74.7)	18,984 (66.1)
Physically active	1,329 (25.8)	3,061 (22.1)	1,521 (16.6)	81 (14.3)	12 (16.0)	5,992 (20.9)
Family history of prostate cancer	99 (3.0)	291 (3.2)	207 (3.6)	13 (3.7)	2 (4.6)	610 (3.3)

[a]This column combines 'no grey hair', 'Less grey hair', 'More grey hair' and 'bald'.

[b]Weight (kg)/height (m)²

Abbreviations: SD: standard deviation; HDL: high-density lipoprotein

Table 2.

Association between hair dye use and prostate cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (1985–2012)[a]

Hair category	No. of cases / No. of participants	HR (95% CI)	P-value
No grey hair	466 / 5,163	1.0 (reference)	
Some grey hair	1,378 / 13,841	1.09 (0.98–1.21)	0.11
More grey hair	792 / 9,150	0.94 (0.83–1.06)	0.29
Bald	52 / 566	1.06 (0.80–1.41)	0.68
Dyed hair	13 / 75	1.81 (1.04–3.14)	0.04

[a] Adjusted for age, number of cigarettes smoked per day, years of smoking, and family history of prostate cancer

Abbreviations: CI: confidence interval; HR: hazard ratio

Table 3.

Association between hair dye use and prostate cancer risk stratified by potential effect modifiers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (1985–2012)

Sub-groups[a]	No. of cases in the subgroups	No. of cases/non-cases in men using hair dye[b]	No. of cases/non-cases in the non-exposed men[c]	HR[d,e]	95% CI	P for interaction
Trial supplementation arm						
β-Carotene						0.89
Yes	1,372	6/31	231/2,313	2.14	0.95–4.84	
No	1,331	7/31	235/2,384	1.58	0.75–3.36	
α-Tocopherol						0.09
Yes	1,305	3/32	225/2,344	0.96	0.31–3.00	
No	1,398	10/30	241/2,353	2.39	1.27–4.50	
Age (years)						0.85
<57	1,360	10/39	320/3,184	1.42	0.45–4.41	
57	1,343	3/23	146/1,513	2.30	1.21–4.36	
Number of cigarettes smoked per day						0.54
<20	1,113	7/31	175/1,445	1.67	0.78–3.56	
20	1,590	6/31	291/3,252	1.93	0.86–4.33	
Years of smoking						0.15
<36	1,347	7/21	276/2,774	2.98	1.41–6.30	
36	1,356	6/41	190/1,923	1.21	0.54–2.73	
BMI (kg/m²)[f]						
<26	1,349	3/31	248/2,561	0.94	0.30–2.94	0.40
26	1,354	10/31	218/2,136	2.47	1.31–4.66	
Alcohol consumption (g/day)						0.33
<11	1,458	8/27	223/2,326	2.36	1.17–4.79	
11	1,245	5/35	243/2,371	1.31	0.54–3.17	
Serum α-tocopherol (μg/L)						0.32
<11.5	1,308	5/23	233/2,440	2.56	1.05–6.21	
11.5	1,395	8/39	233/2,257	1.53	0.75–3.09	
Serum β-carotene (μg/L)						0.97

Sub-groups [a]	No. of cases in the subgroups	No. of cases/non-cases in men using hair dye [b]	No. of cases/non-cases in the non-exposed men [c]	HR [d,e]	95% CI	P for interaction
<170	1,183	5/29	202/2,365	1.77	0.73–4.30	
170	1,520	8/33	264/2,332	1.81	0.90–3.66	
Serum total cholesterol (mmol/L)						0.26
<6.15	1,310	9/30	211/2,341	2.58	1.32–5.04	
6.15	1,393	4/32	255/2,356	1.08	0.40–2.90	
Serum retinol (µg/L)						0.77
<576	1,253	5/31	204/2,291	1.62	0.67–3.94	
576	1,450	8/31	262/2,406	1.90	0.94–3.85	
Follow-up time (years)						0.19
<14	1,180	8/23	179/1,508	3.57	1.75–7.26	
14	1,523	5/39	287/3,189	1.36	0.56–3.29	
Cancer stage						0.41
Non-advanced	1,342 [g]	9/1,333 [h]	62/26,030 [i]	2.79	1.36–5.69	
Advanced	722 [j]	3/719 [k]	62/26,030 [i]	1.59	0.49–5.13	
Natural hair color						0.31
Light (red, fair or light brown)	1,164	4/8	228/2,087	4.58	1.70–12.29	
Dark (dark brown or black)	1,029	8/29	150/1,239	1.66	0.81–3.38	

[a] Subgroups are based on median values unless otherwise noted

[b] Dyed hair category

[c] No grey hair category

[d] HR of dyed hair category is presented, with the no grey hair category serving as reference

[e] Adjusted for age

[f] Weight (kg)/height (m)^2

[g] Number of nonadvanced prostate cancer cases

[h] Number of hair dye users in non-advanced prostate cancer group/Number of non-hair dye users in non-advanced prostate cancer group

[i] Number of hair dye users in non-case group/Number of non-hair dye users in non-case group

[j]Number of advanced cancer cases

[k]Number of hair dye users in advanced prostate cancer group/Number of non-hair dye users in advanced prostate cancer group

Abbreviations: CI: confidence interval; HR: hazard ratio