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Hair dye use is not associated with risk for bladder cancer: Evidence from a case-control study in Spain

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ABSTRACT

An increased bladder cancer risk has been suggested among users of hair dyes. We evaluated this association among females in a hospital-based case-control study in Spain (152 female incident cases, 166 female controls). The effect of hair dye use was also evaluated among potentially susceptible subgroups defined by *NAT1*, *NAT2*, *CYP1A2*, *GSTM1*, *GSTT1* and *GSTP1* genotypes. Use of any hair dye (OR = 0.8, CI 0.5–1.4) or of permanent hair dyes (OR = 0.8, CI 0.5–1.5) was not associated with increased risk. Small non-significant increases in risks were observed in a lagged analysis that ignores exposures within ten years of diagnosis (OR = 1.3, CI 0.8–2.2). No trend in risk with increasing exposure was seen for duration of use, average use or cumulative use. None of the polymorphisms examined significantly modified the hair dye associated risk. Overall, this study does not support an association between hair dye use and bladder cancer.

1. Introduction

Epidemiological studies have examined risk for cancer of the bladder and for other neoplasms in hairdressers, barbers and users of hair dyes. The International Agency for Research on Cancer[1] evaluated hairdressers and barbers as occupations entailing exposures that are probably carcinogenic to humans; personal use of hair colourants could not be evaluated as to its

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carcinogenicity. *In vitro* and animal studies provide some support on the carcinogenic potential of certain hair dye constituents.[1,2] The prevalence of use of hair dyes is high among women in industrialized countries with more than a third of women above age 18 applying hair dyes in Europe and the USA.[1] Consumers use all major types of hair colourants. These include permanent (oxidative) dyes that may entail exposure to aromatic amines and amino-phenols with hydrogen peroxide; semi-permanent dyes with potential exposure to nitro-substituted aromatic amines, aminophenols, aminoanthraquinones and azo dyes, and temporary dyes that entail exposure to high molecular weight or insoluble complexes and metal salts. A recent exposure study identified small amounts of the bladder carcinogen 4-aminobiphenyl (4-ABP) an aromatic amine, in 8 out of the 11 hair dyes tested.[3]

An excess bladder cancer risk has been detected in two recent case-control studies that included information on personal use of permanent hair dyes[4] or in subgroups of women using dyes,[5] but the overall results are not consistent.[6–14] Large studies, including the American Cancer Society cohort study[15,16] and the National Bladder Cancer Study in the USA[17] indicated no overall increased risk of bladder cancer among hair dye users. This latter study[17] did not evaluate bladder cancer risk specifically among users of permanent hair dyes. Two recent meta-analyses both yielded a pooled relative risk of 1.01.[18,19] In the only study to evaluate genetic polymorphisms in relation to hair dye use and bladder cancer, risk was higher among subjects with a *NAT2* and *CYP1A2* 'slow' phenotype who were exclusive permanent hair dye users.[20]

We examined bladder cancer risk in relation to hair dye use among women in a case-control study in Spain and evaluated the effects of polymorphisms in *NAT*, *GST* and *CYP1A2* genes as modifiers of the effect of hair dye use.

2. Patients and methods

2.1. Study population

The Spanish Bladder Cancer (SBC) study is a hospital-based case-control study conducted from June, 1998, to June, 2001, in five areas in Spain (Asturias, Barcelona metropolitan area, Vallès/Bages, Alicante, and Tenerife). Cases were patients newly diagnosed with histologically confirmed bladder cancer in 18 participating hospitals. Controls were selected from patients hospitalized with diagnoses believed to be unrelated to the exposures of interest, matched to the cases on age (±5 yrs), gender, ethnicity and study hospital. Controls included subjects who were mainly hospitalized for trauma or minor surgery (Table 1). Information on exposure was obtained using computer-aided personal interviews (CAPI) administered at the hospital. The CAPI interview elicited detailed information on black and blond tobacco use, lifetime occupational history using job modules, residential history, environmental exposures, and other potential bladder carcinogens. Eighty-four percent of the cases and 88 percent of the controls responded to the CAPI interview.

Female case and controls were re-contacted in December 2001 to March 2002 and information on lifetime and recent hair dye use was requested through a computer assisted telephone interview. To secure comparability with previous studies, the hair dyes questionnaire used in Spain was a modification of a questionnaire that had been used in a study in California.[4] Of the 152 female cases originally recruited, 128 responded the hair dye questionnaire (participation rate 84%), while 24 had died, declined participation or could not be traced. Among controls, 131 out of 166 originally recruited responded the hair dye questionnaire (participation rate 79%), while 35 had died, refused to participate or could not be traced. Information was requested on types of hair dyes, colour, mode of application and time period and frequency of application. Similar to other studies, detailed information on hair dye use was requested only among women who reported having used hair dyes more than ten times in their lifetime and the 8 cases and 3 controls who reported lifetime use less than 10 times were excluded from most analyses. Inclusion of these 11 subjects did not substantially modify results on ever/never use of hair dyes (not shown). Women who reported positively to the question "Have you ever used any coloring product, either at home or in the hairdresser (including hair or eyebrows)?" were classified as ever users. Occupational exposure to hair dyes was not examined since the study population included only 7 female hairdressers (4 cases, 3 controls).

Initial histological classification at participating hospitals was reviewed by a panel of expert pathologists to confirm diagnosis and ensure uniformity of diagnostic criteria across all cases. The WHO-ISUP classification was used.[21] Demographic and risk factor characteristics for subjects are shown in Table 1. The mean (±SD) age of subjects was 67 (±10) years old.

Among controls, ever users of hair dyes tended to have a slightly higher income, with 39% in the lowest income category (less than 300 Euros per month) as compared to 44% among never users. The distribution by education was similar among users and non-users, while the percentage of ever users that was married (52%) was lower compared to never

Table 1 – Description of the study population

	Cases (128)	Controls (131)
Age mean(SD)	67 (10.1)	67 (9.3)
Region		
Barcelona	22 (17%)	26 (20%)
Vallès/Bajes	23 (18%)	22 (17%)
Alicante	10 (8%)	10 (8%)
Tenerife	19 (15%)	15 (11%)
Asturias	54 (42%)	58 (44%)
Smoking Status		
Non-smoker	107 (84%)	122 (93%)
Former	5 (4%)	5 (4%)
Current	16 (12%)	4 (3%)
Education		
Less than primary	71 (55%)	81 (62%)
Primary complete	41 (32%)	43 (33%)
Higher than primary	15 (12%)	7 (5%)
Other	1 (1%)	0 (0%)
Reason for control's admission to hospital		
Fractures		(36%)
Hernia		(23%)
Other orthopedics		(14%)
Other abdominal surgery		(12%)
Vascular diseases		(8%)
Other diagnoses		(7%)

users (59%). Ever users were slightly younger (mean 66.4 years) than never users (69.7 years) and tended to smoke more (9% smokers among hair dye users compared to 2% smokers among non-users).

2.2. Genotype assays

Among subjects from whom hair dye information was available, DNA was obtained for 127 cases (99%) and 125 controls (95%). Genotype assays were performed at the core genotype facility (CGF) of the Division of Cancer Epidemiology and Genetics, National Cancer Institute. Description of genotype assays for *NAT1* (215bp 3′STP, 222bp 3′STP, V149I, R187Q, R187, R33, D251V, R64W), *NAT2* (K268E, G286E, R64Q, Y94, I114T, L161, R197Q), *GSTM1* deletion, *GSTT1* deletion, *GSTP1* (I105V), *GSTM3* (V224I, IVS8 -30G > T) and *CYP1A2*1F* can be found at http://snp500cancer.nci.nih.gov. All genotypes under study were in Hardy-Weinberg equilibrium among the control population. Details on assay reproducibility and accuracy as well as the main effects of the genes are described in Garcia-Closas (2005).[22]

For *NAT2*, individuals homozygous for rapid acetylator alleles (*NAT2*4*, *NAT2*11A*, *NAT2*12A*, *NAT2*12B*, *NAT2*12C*, *NAT2*13*) were classified as rapid acetylator phenotype; individuals homozygous for slow acetylator alleles were classified as slow acetylator phenotype, and individuals heterozygous (one rapid and one slow NAT2 allele) were classified as intermediate acetylator phenotype.

2.3. Statistical analysis

Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated using unconditional logistic regression models, adjusting for age (continuous), region and smoking status (never, former, current smokers). Adjustment for socioeconomic status did not modify results (not shown). The reference date was defined as the date of diagnosis for cases and the date of the CAPI interview for controls. In a lagged analysis applying an *a priori* defined 10-year lag, we ignored exposures occurring within ten years of diagnosis. In this analysis the never exposed included those who had only recent (less than 10 years since diagnosis or interview) exposure.

Multiplicative interactions between genotypes and hair dye use were evaluated using conventional logistic models in STATA v.8.0.

3. Results

Women who used hair dyes more than 10 times in their lifetime did not have an increased risk of bladder cancer

Table 2 – Odds ratios (OR) and 95% confidence intervals (95%CI) for the effect of hair dye use on bladder cancer risk, adjusted by age, region and smoking status

Characteristics of hair dye use	No. Cases/ Controls[a]	OR	(95%CI)
Never used hair dyes	42/41	1.0	–
Used hair dyes at least ten times	78/87	0.8	(0.5–1.4)
10 year lagged analysis[b]			
Never used hair dyes or used only 10 years prior to diagnosis or interview	54/67	1.0	–
Used hair dyes at least ten times	66/61	1.3	(0.8–2.2)
Type of hair dye			
Never used hair dyes	42/41	1.0	–
Only permanent hair dye use, at least ten times	60/66	0.8	(0.5–1.5)
Other hair dye use at least ten times[c]	18/21	0.6	(0.3–1.5)
Type of hair dye, 10 year lagged analysis			
Never used hair dyes or used only 10 years prior to diagnosis or interview[b]	54/67	1.0	–
Only Permanent hair dye use, at least ten times	50/48	1.3	(0.8–2.3)
Other hair dye use at least ten times	16/13	1.3	(0.6–3.1)
Year of first use			
Never used hair dyes	42/41	1.0	–
Before 1970	22/20	1.2	(0.5–2.7)
After 1970	48/65	0.6	(0.3–1.2)
Colour			
Never used hair dyes	42/41	1.0	–
Only Light (light brown, blond)	50/66	0.7	(0.4–1.2)
Only Dark (dark brown, black, red)	23/19	1.1	(0.5–2.5)
Person applying			
Never used hair dyes	42/41	1.0	–
Hairdresser	49/61	0.7	(0.4–1.3)
Self	29/25	1.1	(0.5–2.2)
Self, no gloves	4/3	1.2	(0.2–6.1)

a Numbers do not always add up because of missing values.
b Lagged analysis ignores exposures occurring within ten year of diagnosis.
c Includes subjects who used non-permanent dyes ($n = 20$) and those using more than one type ($n = 19$).

(OR = 0.8, 95%CI 0.5–1.4) compared with women who never used hair dyes (Table 2). Most women (76%) had used permanent hair dyes exclusively and the overall OR reflected mainly exposure to permanent dyes (OR = 0.8, 0.5–1.5). Those who used non-permanent dyes or used more than one type of dye had an OR = 0.6 (0.3–1.5). Analyses for those who used "only" permanent hair dyes and those who used "ever" permanent hair dyes were very similar results. A higher OR (1.3, 0.8–2.2) was observed when applying an *a priori* defined 10-year lag that ignored exposures occurring within ten years of diagnosis. The OR for permanent dye use, when applying the lagged analysis, was similar (1.3, 0.8–2.3). ORs did not differ depending on diagnoses of controls (detailed results not shown). The ORs for permanent dye use based on mostly minor surgery controls was 0.82 while that based on mainly trauma controls was 0.87.

Women who used hair dyes for the first time before 1970 had slightly elevated OR (1.2, 0.5–2.7) whereas those who began using hair dyes after 1970 had no increased risk (0.6, 0.3–1.2) (Table 2). For most women, hair dye was mainly applied by a hairdresser and these women had a lower risk than 'never' users (OR = 0.7, 0.4–1.3). Whereas, the OR for women who applied on their own was 1.1 (0.5–2.2) and those who did not use gloves had an OR of 1.2 (0.2–6.1, Table 2). There were small differences in risk by type of colour applied with users of dark hair dyes having an OR of 1.1 (0.5–2.5) and those using light hair dyes an OR of 0.7(0.4–1.3). No differences were observed using an alternative classification of colour classifying hair dyes into those of brown colour (light or dark) and other colours (Table 2).

No trend in risk by duration of hair dye use was apparent; women at the highest quartile (use for more than 32 years) had an OR of 1.2 (0.5–2.7). There was no gradient in risk with frequency of use of hair dyes or with cumulative exposure calculated through the combination of frequency of use and duration of use (Table 3). Women who started using hair dyes at a young age (youngest quartile less than 34 years of age) had higher ORs compared to those who started using them

Table 3 – Odds ratios (OR) and 95% confidence intervals (95%CI) for women exposed to hair dyes by duration of use, average frequency of use, cumulative exposure and age at first use

	No. Cases/ Controls[a]	OR	(95%CI)
Duration of use (quartiles)			
Never users	42/41	1.0	–
⩽10 yrs	15/29	0.4	(0.2–0.9)
11–24 yrs	20/16	1.0	(0.4–2.4)
25–32 yrs	15/23	0.5	(0.2–1.2)
>32 yrs	20/17	1.2	(0.5–2.7)
Average frequency of use			
Never users	42/41	1.0	
Less than once every 3 months	2/8	0.1	(0.02–0.8)
Once every 2 or 3 months	30/24	1.2	(0.6–2.5)
One or more times per month	37/53	0.6	(0.3–1.1)
Cumulative exposure in time[a] years (quartiles)			
Never users	42/41	1.0	–
⩽90	16/25	0.6	(0.2–1.3)
91–210	16/17	0.8	(0.3–1.9)
211–504	18/20	0.7	(0.3–1.6)
>504	14/21	0.6	(0.3–1.4)
Age of first use (quartiles)			
Never users	42/41	1.0	–
<34 yrs	20/15	1.2	(0.5–3.0)
34–44 yrs	18/24	0.7	(0.3–1.6)
45–52 yrs	18/19	0.8	(0.3–1.8)
>52 yrs	14/27	0.5	(0.2–1.1)

a Numbers do not always add up because of missing values.

Table 4 – Genotype-specific odds ratios (OR) and 95% confidence intervals for hair dye exposure, with the reference category being women unexposed to hair dyes within each genotype category

Genotypes		Non-exposed Cases/controls (reference)	Exposed Cases/ Controls	OR* (95%CI)	P-value for interaction
NAT1	NAT1*4/ NAT1*4/	16/15	20/29	0.6 (0.2–1.6)	0.07
	NAT1*4/NAT1*10 or NAT1*10/NAT1*10	10/9	19/8	2.9 (0.7–11.6)	
NAT2	Slow	22/21	32/41	0.6 (0.3–1.4)	0.5
	Rapid/Intermediate	19/12	24/16	0.9 (0.3–2.6)	
GSTM1	+/+ or +/–	15/17	14/32	0.4 (0.1–1.1)	0.1
	–/–	25/17	43/24	1.3 (0.6–3.0)	
GSTM3 V224I	Val/Val	25/12	23/20	0.5 (0.2–1.3)	0.3
	Val/Ile or Ile/Ile	16/21	34/36	1.2 (0.5–2.9)	
GSTP1 I105V	Ile/Ile	25/14	29/21	0.9 (0.3–2.2)	0.9
	Ile/Val or Val/Val	16/20	29/36	0.8 (0.3–1.8)	
GSTT1	+/+ or +/–	33/28	42/46	0.7 (0.3–1.3)	0.4
	–/–	8/6	16/11	1.4 (0.3–6.9)	
*CYP1A2*1F (-164A > C)*	AA	17/13	23/15	1.4 (0.5–4.2)	0.4
	AC or CC	24/15	29/36	0.4 (0.2–1.1)	

ORs are adjusted for age, region and smoking status.

at a later age (Table 3), but this increase was small and not statistically significant. Subgroups of women defined *a priori* by a combination of several exposures or time related variables had a higher risk but these were based on small numbers (data not shown). For example, women who used dark coloured permanent hair dyes and applied them on their own had an OR of 6.0 (0.7–54) but this estimate was based on only 6 exposed cases and 1 control.

Genotype-specific odds ratios for permanent hair dye exposure, with the reference category being women unexposed to hair dyes within each genotype category are shown in Table 4. Similar to previous analyses only women having used hair dyes more than 10 times during their lifetime were considered as exposed. Among carriers of the *NAT1*10* allele, use of permanent hair dyes was associated with a higher OR (2.9, 0.7–11.6) compared to non-users (Table 4). Conventional logistic regression analyses did not show a significant multiplicative interaction between any of the genotypes examined and use of any hair dye (data not shown) or permanent hair dye use (Table 4). The test for interaction between the *NAT1*10* genotype and use of permanent hair dyes was not significant (*P*-value = 0.07) overall. This interaction was marginally significant in the lagged analysis (P-value = 0.057). In the lagged analysis, among carriers of the *NAT1*10* allele the OR for users of permanent dyes was 3.6 (1.0–13.0) compared to non-users.

4. Discussion

Overall, we found little evidence that use of hair dyes in Spanish women was associated with an increased bladder cancer risk or that genetic predisposition modified this risk. Similar to other studies, small excess risks were found in certain subgroups such as genetically defined subgroups, but these observations were based on small numbers. Similarly, decreased risks in specific strata by duration or frequency of use were based on small numbers and there was no consistent trend of a decreasing risk by either of these variables. Hair dyes used in the past[1] and in recent years[3] have been shown to contain bladder carcinogens and consequently the occurrence of an increased bladder cancer risk is biologically plausible. The main difficulties in the evaluation of hair dye use and bladder cancer risk in our study, as well as an in other epidemiological studies, is exposure assessment, potential confounding by lifestyle factors and small sample size. The latter is particularly important when analyzing gene-environment interactions.

Results from cohort and case control studies examining the association between personal use of hair dyes and bladder cancer risk are not consistent.[4–17,14] An excess bladder cancer risk among women but not among men was detected in a recent case-control study in California that included information on personal use of permanent hair dyes.[4] A second recent study in the United States did not find an overall excess risk but found increased risks in subgroups of women using hair dyes and a decreased risk among men.[5] Other studies in the USA including a large cohort study[15,16] did not find any increase in risk. The questionnaires used in the Spanish study and the Californian study[4] are similar and differences in the way information on use of hair dyes was collected can not explain discrepancies in results. Information on differences in the composition of hair dyes in Europe and the United States is not publicly available.

Evaluation of hair dye exposure in epidemiologic studies may be one of the main problems in assessing risks of chronic diseases with long latent periods such as bladder cancer. Most previous bladder cancer studies did not collect detailed information on use of hair dyes such as colour or type of hair dyes.[7] The use of permanent hair dyes is, however, predominant in industrialized countries[1] so an overall effect probably would have been observed if permanent hair dyes were associated with an increased risk. Although we collected detailed information on hair dye use, we did not observe differences in risk among subgroups with distinct exposure patterns such as use of different colours, types of hair dyes or duration of use. P-phenylenediamine (PPD), a synthetic organic compound classified as a coal-tar derivative and other potential carcinogens such as 4-ABP, have been detected in hair dyes. Results from *in vitro* or *in vivo* studies are not consistent.[1] The evaluation of the carcinogenicity of hair dye use is mainly complicated by the lack of information on exposure to specific chemicals present in hair dyes that could be related to bladder cancer risk such as PPD or 4-ABP, and the changes in composition of hair dyes over time. The most likely direction of bias in the presence of such exposure misclassification is the null which reduces the possibility of detecting an effect.

Use of hair dyes could be associated with several lifestyle factors such as smoking status, marital status, age or employment. In our study differences in use of hair dyes between major socio-demographic groups existed but were small and adjustment for these factors did not modify results.

Our analysis was limited to women and was based on small numbers. The Spanish Bladder Cancer Study is one of the largest case-control studies on bladder cancer with a total of 1219 cases and 1271 controls but the high male-to-female ratio typical of southern European countries,[23] resulted in a relatively small number of female subjects. In a pilot study, we evaluated use of hair dyes among 100 men, but the prevalence of exposure was low (around 5%) and was not investigated further. Of the four studies that evaluated hair dye use in men two did not find an excess risk,[4,17] one found weak positive association[11] and one found a statistically significant decreased risk.[5] The small number of subjects included in our and other studies is particularly important when evaluating gene-environment interactions because of the documented high probability of false positive findings in such studies.[24,25] The difficulty in evaluating gene-environment interactions in relation to hair dye use is accentuated because the environmental exposure (hair dyes) cannot be well defined since it is a mixture rather than a compound and the active agents producing any effect may differ between countries and time periods.

We examined a limited number of genes involved in the metabolism of aromatic amines, PAHs and other carcinogens that had also been evaluated in the study by Gago and colleagues.[20] The *NAT1* gene encodes an enzyme involved in the activation of aromatic amines through *O*-acetylation.[26] Although *NAT1* polymorphisms have not been consistently associated with bladder cancer risk,[22,27,28] it was of particular interest in relation to hair dye use since it is ex-

pressed in the skin and keratinocytes where hair dye exposure occurs.[2] Our data were consistent with an increase risk of permanent hair dyes among *NAT1*10* carriers but this observation was based on small numbers. An interaction with hair dye use was not found in the study by Gago and colleagues.[20] In that study, the association between hair dye use and bladder cancer was stronger among *NAT2* slow acetylators and subjects with the *CYP1A2* slow phenotype. Although we did not measure the *CYP1A2* phenotype, we did not observe any interaction between polymorphisms in *NAT2* or *CYP1A2*.

In conclusion, results of our study do not support an association between hair dye use and bladder cancer risk. Pooling of epidemiological studies on hair dye use would be advantageous but might not resolve the problem of heterogeneous findings among studies in women with high exposures.[18] Use of intermediate markers coupled with a detailed evaluation of exposure may provide an important aid in the evaluation of the potential genotoxic effects of hair dye use.

Conflict of interest statement

None

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