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USE OF PERMANENT HAIR DYES AND BLADDER-CANCER RISK

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A population-based case-control study was conducted in Los Angeles, California, which involved 1,514 incident cases of bladder cancer and an equal number of age-, sex- and ethnicity-matched controls. Information on personal use of hair dyes was obtained from 897 cases and their matched controls. After adjustment for cigarette smoking, a major risk factor for bladder cancer, women who used permanent hair dyes at least once a month experienced a 2.1-fold risk of bladder cancer relative to non-users (p for trend = 0.04). Risk increased to 3.3 (95% CI = 1.3–8.4) among regular (at least monthly) users of 15 or more years. Occupational exposure to hair dyes was associated with an increased risk of bladder cancer in this study. Subjects who worked for 10 or more years as hairdressers or barbers experienced a 5-fold (95% CI = 1.3–19.2) increase in risk compared to individuals not exposed.

Key words: *bladder cancer; permanent hair dyes; hairdressers; barbers*; case-control study

Cigarette smoking and occupational exposure to arylamines are the most established etiologic risk factors for bladder cancer, a disease which currently accounts for 6% of all new cancer cases in men and 2% of new cancer cases in women.[1] Many other possible etiologic factors have been extensively explored (*e.g.,* caffeine intake, use of artificial sweetener), but none has been definitively established as a causative agent. Occupational exposure to hair dyes by hairdressers, barbers and beauticians has been previously studied in 7 cohort and 12 case-control studies. The general evidence from cohort studies is in agreement with that from case-control studies and compatible with a moderately increased bladder-cancer risk among hairdressers and barbers.[2] To date, there is little evidence of increased bladder-cancer risk with personal use of hair dyes.

Hair dyes are widely used. It has been estimated that in Europe, North America and Japan, over one-third of women above the age of 18 years and over 10% of men above the age of 40 years use some type of hair dye. Permanent dyes account for about three-quarters of global use. In addition to this widespread personal use, there are about 2 million professional hairdressers, barbers and beauticians in North America and Europe alone, who would be anticipated to have substantial regular exposure to hair dyes.[2]

Aromatic amines in hair dyes are mutagenic *in vitro*[3,4] and carcinogenic in experimental animals.[5] Small amounts of these potentially carcinogenic substances are absorbed percutaneously during normal use.[6–8]

We have identified 2 cohort and 5 case-control studies that provided some information on personal use of hair dyes and bladder-cancer risk,[9–15] and the overall evidence does not support an association. These prior studies were of variable quality and usually did not discriminate between use of the various types of hair dye: permanent, semi-permanent or temporary. This is an important consideration since the different types of hair dye vary in their contents and levels of suspected carcinogenic chemicals.[10]

In 1992, we initiated a case-control study of bladder cancer in Los Angeles County, with one of the aims being the investigation of personal and occupational hair-dye exposure in relation to bladder-cancer risk. We hypothesized that use of hair dyes might be associated with increased bladder-cancer risk. This report describes our findings with respect to permanent, semi-permanent and temporary classes of hair dye and bladder-cancer risk.

MATERIAL AND METHODS

The Los Angeles County Cancer Surveillance Program,[16] the population-based Surveillance, Epidemiology and End Results (SEER) cancer registry of Los Angeles County, identified 2,098 non-Asian patients aged 25–64 years with histologically confirmed bladder cancer between 1 January 1987 and 30 April 1996. Among these, 175 patients died before we could contact them or were too ill to be interviewed. Permission to contact 74 patients was denied by their physicians. Two hundred sixty-seven patients refused to be interviewed. Thus, we interviewed 75% (1,582/2,098) of all eligible patients. Information on use of hair dyes was not included in our original questionnaire but was added to the structured interview instrument beginning in January 1992. A total of 897 case-control pairs answered questions on personal use of hair dyes.

For each interviewed patient, we recruited a control matched by sex, date of birth (within 5 years), ethnicity (non-Hispanic white, Hispanic, African-American) and neighborhood of residence at the time of cancer diagnosis. To search for "neighborhood" controls, we followed a standard procedure that defines a sequence of houses on specified neighborhood blocks. We attempted to identify the sex, age and race of all inhabitants of each housing unit; "not-at-home" units were systematically revisited to complete the census. When we failed to find any resident who met our matching criteria after canvassing 150 housing units, we excluded ethnicity from the matching criteria. If a matched control based on this relaxed criteria could not be found within a maximum of 300 housing units, the case was dropped from the study. Sixty-eight cases were dropped from the study due to lack of a matched control, and 20 controls were not matched by ethnicity to the index case. Therefore, a total of 1,514 case-control pairs were included in the occupational exposure analysis (see below). Of the 1,514 control subjects interviewed, 1,049 (69%) were the first eligible controls and 307 (20%) and 158 (10%) were the second and third eligible controls, respectively.

In-person, structured interviews were conducted in subjects' homes. The questionnaire requested information up to 2 years prior to the diagnosis of cancer for cases and 2 years prior to diagnosis of cancer of the index case for matched controls. The questionnaire included information on demographic characteristics, height, weight, lifetime use of tobacco and alcohol, usual adult dietary habits, lifetime occupational history, prior medical conditions and prior use of medications. Most cases and controls in a given pair were interviewed by the same interviewer. All interviews were conducted by the same team of interviewers throughout the course of data collection.

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In terms of personal hair-dye use, we first asked if the subject had ever used any type of hair dye regularly for 1 year or longer. If the answer was yes, then age started using hair dyes regularly, age stopped using hair dyes regularly, total years of regular use and frequency of use were recorded. In addition, the types of hair dye (permanent, semi-permanent, temporary rinse) usually used by the subject were noted.

In terms of lifetime occupational history, we first asked each subject if he or she had ever held a full- or part-time job for at least 1 year since the age of 16 years. If the answer was yes, then the following information was recorded for each job the subject had held for 1 year or more: job title, usual duties/activities, type of business/industry, name and location of company, starting and ending year at the job and whether the job was full- or part-time.

Data were analyzed by standard matched-pair methods.[17] Associations of bladder cancer with various exposure indices of hair-dye use were measured by odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). Conditional logistic regression models were used to examine the relationship between hair-dye use and bladder-cancer risk, with adjustment for cigarette smoking, a major risk factor for bladder cancer.

RESULTS

Mean age of patients at diagnosis of bladder cancer was 56.2 years. Most patients were non-Hispanic whites (n = 1,413), with the remaining being Hispanic whites (n = 58), African-Americans (n = 42) and Native Americans (n = 1). On average, despite the matching on neighborhood of residence, bladder-cancer patients had a lower level of education than controls. The OR for bladder cancer was 0.6 (95% CI 0.5–0.7) for those who had attended college (13 years or more of schooling) compared with those who had a high school education or lower. Addition of an education variable (high school or less, college or above) as a covariate to all conditional logistic regression models used to examine hair-dye use and bladder-cancer risk did not materially change any of the results. These findings were compatible with the lack of an association between level of education (including husbands' educational levels in women) and use of hair dyes (data not shown). Similarly, addition of another potential confounder [regular use of non-steroidal anti-inflammatory drugs (NSAIDs)][18] effected no appreciable change in the results. Therefore, all ORs presented below are unadjusted for level of education or intake of NSAIDs.

Relative to lifetime non-users of hair dyes, regular users of hair dyes (*i.e.,* used regularly for 1 year or longer) exhibited no increase in risk of bladder cancer (OR = 1.0, 95% CI 0.7–1.4) after adjustment for cigarette smoking (Table I). There were many fewer exposed men than women.

Table I also shows the relationship between hair-dye use and bladder-cancer risk for each of the 3 major classes of hair dye: permanent, semi-permanent and temporary rinse. Risk of bladder cancer was positively associated with any use of permanent hair dyes, and the association was of borderline statistical significance (OR = 1.4, 95% CI 0.96–2.1). An examination by gender revealed that the increased risk associated with use of permanent hair dyes was confined to women (OR = 1.8 in women and 0.9 in men). However, there were only a few male subjects who used permanent hair dyes regularly (14 cases and 16 controls). The permanent hair dye–cancer association in women became stronger and achieved statistical significance (with or without adjustment for cigarette smoking) when exposure was restricted to those who used only permanent dyes (we excluded 10 female cases and 10 female controls who reported use of other types of dye in addition to permanent dyes) (OR = 1.9, 95% CI 1.1–3.2).

Table II shows the dose-response relationships with bladder-cancer risk among subjects who used permanent dyes exclusively. Because there was no indication that semi-permanent and temporary hair dyes had an effect on bladder-cancer risk, users of these types of dye exclusively (*i.e.,* those who never used permanent dyes) were grouped with non-users of hair dyes to form the reference group for relative risk (RR) comparisons. Among women, there was a consistent, monotonic relationship between exposure and risk, regardless of whether exposure was defined by duration of use, frequency of use or cumulative number of times of use over lifetime. A statistically significant trend in risk was found for all 3 indices of exposure (p for trend = 0.01, 0.04 and 0.04, respectively, after adjustment for cigarette smoking). The adjusted ORs for the highest categories of duration, frequency and lifetime use were 3.7 (95% CI 1.2–11.2), 2.1 (95% CI 0.97–4.7) and 2.0 (95% CI 1.04–3.8), respectively. Among the relatively few men who were exclusive users of permanent hair dyes, there was no evidence of an association with any of the 3 exposure indices under examination.

Table III shows the risk of bladder cancer in women by frequency and duration of permanent hair-dye use simultaneously. Risk of bladder cancer increased with duration of use regardless of the frequency of use. Conversely, there is clear evidence of increased risk by frequency of use among long-term users. Highest risk was observed among those with the highest frequency and duration of use of permanent hair dyes (adjusted OR = 3.3, 95% CI 1.3–8.4).

We further examined the relationship between exclusive use of permanent hair dye and bladder-cancer risk separately among lifelong non-smokers and ever-smokers. The OR was much stronger for non-smoking women than for smoking women (OR = 2.7, 95% CI 1.2–5.9, and OR = 1.4, 95% CI 0.8–2.4, respectively). We formally tested for a possible interaction effect between cigarette smoking and permanent hair-dye use; the result was not statistically significant (p = 0.39).

TABLE I – PERSONAL USE OF HAIR DYES AND RISK OF BLADDER CANCER

	Total				Men				Women			
	Number of cases	Number of controls	OR[1]	OR[2] (95% CI)	Number of cases	Number of controls	OR[1]	OR[2] (95% CI)	Number of cases	Number of controls	OR[1]	OR[2] (95% CI)
Regular use of hair dyes												
No	734	735	1.0	1.0	655	643	1.0	1.0	79	92	1.0	1.0
Yes	163	162	1.0	1.0 (0.7–1.4)	39	51	0.8	0.8 (0.5–1.3)	124	111	1.4	1.3 (0.8–2.2)
Any use of												
Permanent dyes[3]	106	82	1.4	1.3 (0.8–2.0)	14	16	0.9	0.8 (0.4–1.9)	92	66	1.8[4]	1.7 (0.9–2.9)
Semi-permanent dyes	24	37	0.6	0.6 (0.3–1.1)	6	10	0.6	0.8 (0.3–2.3)	18	27	0.8	0.6 (0.3–1.4)
Temporary rinse	33	41	0.8	0.9 (0.5–1.5)	11	16	0.7	0.7 (0.3–1.7)	22	25	1.1	1.1 (0.5–2.2)
Exclusive use of permanent dyes	95	71	1.5	1.4 (0.9–2.2)	13	15	0.9	0.8 (0.4–2.0)	82	56	1.9[4]	1.8 (1.01–3.3)

[1]Matched ORs compared to non-users of hair dyes; matching factors were age, sex, ethnicity and neighborhood of residence.–[2]Further adjusted for current smoking status (Yes/No), number of cigarettes smoked/day and number of years of smoking.–[3]Sixteen cases and 19 controls could not recall type of hair dye usually used. Subjects who reported regular use of more than 1 type of hair dye were counted under each of the relevant hair-dye categories.–[4]Two-sided $p < 0.05$, test for OR = 1.0.

TABLE II – USE OF PERMANENT HAIR DYES AND RISK OF BLADDER CANCER

Permanent dyes	Total			Men			Women		
	Ca/Co[1]	OR[2]	OR[3] (95% CI)	Ca/Co[1]	OR[2]	OR[3] (95% CI)	Ca/Co[1]	OR[2]	OR[3] (95% CI)
Non-users	775/796	1.0	1.0	670/667	1.0	1.0	105/129	1.0	1.0
Exclusive users	95/71	1.6[4]	1.5 (0.97–2.3)	13/15	0.9	0.8 (0.3–2.0)	82/56	2.0[5]	1.9 (1.1–3.3)
Number of years of use									
<15	31/35	0.9	0.9 (0.5–1.7)	9/12	0.7	0.7 (0.2–1.9)	22/23	1.2	1.1 (0.5–2.5)
15–<30	40/28	1.6	1.6 (0.8–3.1)	2/3	0.7	1.1 (0.2–7.1)	38/25	1.9	1.7 (0.8–3.6)
30+	24/8	4.5[5]	3.6 (1.2–10.3)	2/0	—	—	22/8	4.3[5]	3.7 (1.2–11.2)
p for trend		0.005	0.02		0.91	0.99		0.002	0.01
Number of times per year									
<12	52/40	1.6	1.5 (0.9–2.6)	7/3	3.0	2.2 (0.4–12.4)	45/37	1.7	1.6 (0.8–2.9)
12+	43/30	1.6	1.4 (0.8–2.6)	6/11	0.5	0.6 (0.2–1.8)	37/19	2.7[5]	2.1 (0.97–4.7)
p for trend		0.04	0.15		0.49	0.56		0.004	0.04
Total number of times over lifetime									
<100	32/31	1.2	1.2 (0.6–2.2)	6/8	0.7	0.8 (0.2–3.0)	26/23	1.5	1.4 (0.6–2.9)
100+	63/39	1.9[4]	1.7 (0.98–2.9)	7/6	1.2	1.0 (0.3–3.3)	56/33	2.3[5]	2.0 (1.04–3.8)
p for trend		0.01	0.06		1.00	0.86		0.005	0.04

[1]Number of cases/number of controls.–[2]Matched ORs compared to non-users of permanent hair dyes; matching factors were age, sex, ethnicity and neighborhood of residence.–[3]Further adjusted for current smoking status (Yes/No), number of cigarettes smoked/day and number of years of smoking.–[4]Two-sided $p < 0.05$.–[5]$p < 0.01$.

TABLE III – RISK OF BLADDER CANCER IN WOMEN ACCORDING TO DURATION AND FREQUENCY OF USE OF PERMANENT HAIR DYES

Frequency of use	Duration of use							
	<15 years				15+ years			
	Number of cases	Number of controls	OR[1]	OR[2] (95% CI)	Number of cases	Number of controls	OR[1]	OR[2] (95% CI)
<12 times/year	14	16	1.3	1.3 (0.5–3.3)	31	21	1.9	1.7 (0.8–3.6)
12+ times/year	8	7	1.1	0.7 (0.2–2.8)	29	12	3.7[3]	3.3 (1.3–8.4)

[1]Matched ORs compared to non-users of permanent hair dyes; matching factors were age, sex, ethnicity and neighborhood of residence.–[2]Further adjusted for current smoking status (Yes/No), number of cigarettes smoked/day and number of years of smoking.–[3]Two-sided $p < 0.01$.

TABLE IV – OCCUPATIONS WITH HIGH LIKELIHOOD OF HAIR-DYE EXPOSURE AND RISK OF BLADDER CANCER

	Total			
	Number of cases	Number of controls	OR[1]	OR[2] (95% CI)
Held job as a hairdresser or barber				
Never	1,494	1,501	1.0	1.0
Ever	20	13	1.5	1.5 (0.7–3.2)
Number of years working				
<10	6	10	0.6	0.5 (0.2–1.6)
10+	14	3	4.7[3]	5.1 (1.3–19.2)

[1]Matched ORs compared to subjects who never held job as a hairdresser or barber; matching factors were age, sex, ethnicity and neighborhood of residence.–[2]Further adjusted for current smoking status (Yes/No), number of cigarettes smoked/day and number of years of smoking.–[3]Two-sided $p < 0.05$.

We examined the relationship between potential occupational exposure to hair dyes and bladder-cancer risk (Table IV). Twenty bladder-cancer patients held jobs as hairdressers (n = 14) or barbers (n = 6), while 13 controls held such jobs (11 and 2, respectively). Compared with those who never held jobs as hairdressers or barbers, these individuals had a 50% increase in risk of bladder cancer, and those who held these jobs for 10 years or more experienced a 5-fold increase in risk (95% CI 1.3–19.2).

We repeated all analyses after excluding the 20 case-control pairs in which controls were not matched by ethnicity. The exclusion did not materially change the hair dye–bladder cancer association. We also repeated analyses in 2 subgroups of case-control pairs: those with first eligible controls and those with subsequent controls. Results were comparable between the 2 subgroups.

DISCUSSION

In our epidemiologic study, we examined personal use of hair dyes as a potential risk factor for bladder cancer according to type of hair dye (permanent, semi-permanent, temporary rinse) usually used. We found no association between use of either semi-permanent or temporary dyes and bladder cancer. However, there was a statistically significant, frequency- and duration-dependent increase in risk with use of permanent dyes. Two other studies have specifically examined the relationship between exposure to permanent dyes and bladder-cancer risk (non-permanent dyes were not investigated in either study). The first was a prospective cohort investigation involving 37 cases of urinary tract cancer.[11] No increase in risk was observed (RR = 0.62, 5 cases of urinary tract cancer *vs.* 7.4 expected). The second study was the American Cancer Society cohort investigation in which the end point was fatal bladder cancer.[15] Again, no increased risk was noted (RR = 0.56, 95% CI 0.32–0.99). In the latter study, although the number of bladder-cancer deaths was not reported, one can infer that the figure is probably no higher than 150. Our study is considerably larger, involving 897 incident bladder cancers.

We are not surprised by the observation that the risk-enhancing effect of permanent hair dyes was confined to women. We believe that the lack of exposure–disease association among our male subjects is likely the result of low exposure rate leading to low study power to detect the anticipated association. In fact, with a hypothesized 2-fold risk in permanent hair-dye users, the present study possesses an expected power of 91% to detect an association in women but only 50% statistical power to observe the same association in men, under the assumption of a 5% significance level.

In our study, occupations with a high likelihood of exposure to hair dyes also were associated with an increased risk of bladder cancer. The strength of the association (OR = 1.5) for hairdressers and barbers was compatible with that (OR = 1.4) based on a combined analysis of prior studies.[2] We found that subjects who had worked in these occupations for 10 or more years experienced a statistically significant, 5.0-fold increase in risk of bladder cancer.

The present study suggests a less than multiplicative effect of exposures to smoking and permanent hair dyes on bladder-cancer risk, though the formal statistical test for interaction was not significant. With a relatively modest sample size, the present study possesses limited statistical power to detect interaction effects between primary risk factors. Nonetheless, our data are compatible with an additive model of bladder-cancer risk from cigarette smoking and permanent hair-dye exposure. In the present study, female smokers experienced a 3-fold bladder-cancer risk (data not shown), and exposure to permanent hair dyes was associated with a 3-fold risk in non-smoking women. These risk parameters would lead one to predict, under the additive model, an RR of 1.7 for permanent hair-dye use among female smokers. Our observed OR among female smokers was 1.4.

There is a possibility that the positive findings in women are due to recall bias. However, there is no evidence that the general public views use of permanent hair dyes as more harmful than use of other types of hair dye. Therefore, the confinement of risk to only 1 type of hair dye (permanent) argues against recall bias playing a role in the association we observed.

As mentioned above, only 2 other epidemiologic studies have examined permanent hair-dye use in relation to bladder cancer. Five other case-control studies have investigated general use of hair dyes (regardless of type) and bladder-cancer risk. The largest case-control study of bladder cancer ever conducted was a multicenter, population-based study coordinated by the U.S. National Cancer Institute.[10] That study did not observe an overall association between hair-dye use and bladder-cancer risk (RR = 0.9 in women and 1.1 in men). The other 4 studies[9,12–14] involved very small numbers of exposed subjects and had relatively low statistical power to detect an association. In 2 of these studies, one from Japan and the other from the United States,[13,14] the overall risk estimates were around 1.5 but not statistically significant. In the Canadian study,[12] no effect was seen in women, with an RR estimate of 0.7 (95% CI 0.3–1.4). Among men, 8 patients and no controls reported use of hair dye (1-sided $p = 0.004$).

There are 5 chemically distinct classes of hair coloring in use (permanent dyes, semi-permanent dyes, vegetable rinses, synthetic chemical rinses and gradual dyes). The 2 main types are the semi-permanent, or direct-color, dyes and the permanent, or oxidative-type, dyes, in which hydrogen peroxide is used to oxidize aromatic diamines, resulting in the production of larger colored molecules which are trapped in the hair shaft. The oxidative-type dyes account for about 75% of the annual hair-dye market;[19] 89% of these commercial oxidative-type hair-dye formulations have been shown to be mutagenic *in vitro*.[3] Except for the 2 cohort studies,[11,15] all other prior studies did not discriminate between permanent, semi-permanent or other categories of hair-dye.

At least 7 cohort and 12 case-control studies have investigated occupational exposure to hair dyes and bladder-cancer risk (reviewed by La Vecchia and Tavani[2]). The 7 cohort studies involved 10 different populations: 4 studies were conducted in Europe, including 1 which targeted 4 Nordic countries (Norway, Sweden, Finland and Denmark); 2 others were from the United States; and the last was from Japan. They typically provided information on bladder-cancer risk among hairdressers, barbers, beauticians and cosmetologists.[20–26] In 7 of the 10 studies, moderately positive associations (RR = 1.3 to 2.1) were found, with a summary RR across all studies of 1.4.[2] The association appears to be stronger in men than women, though not significantly. We similarly found a stronger association in men than women (data not shown). Although these cohort studies in general did not control for smoking, results from case-control studies that included information on smoking also support an association.[2] Seven of 12 case-control studies[12,27–37] found an association between occupations with likely exposure to hair dyes and bladder cancer, though most risk estimates were not statistically significant because of relatively small numbers of exposed individuals. Thus, the association between past occupational exposure to hair dyes and bladder-cancer risk is reasonably consistent based on epidemiologic evidence and plausible on a biologic basis.[2] In 1993, the International Agency for Research on Cancer[4] concluded that "occupation as a hairdresser or barber entails exposures that are probably carcinogenic". In the current study, after adjustment for smoking and other high-risk occupations, working as a hairdresser or barber for more than 10 years was clearly associated with increased bladder-cancer risk.

In summary, this large, population-based case-control study implicates long-term use of permanent hair dyes as a risk factor in bladder-cancer development. We estimate that 19% of bladder cancers in women in Los Angeles County, California, may be attributed to permanent hair-dye use.

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