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Use of Hair Dyes and Risk of Bladder Cancer[1]

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ABSTRACT

The relation between use of hair dyes and risk of bladder cancer was assessed using data from a case-control study of bladder cancer. Incident cases (2982) and general population controls (5782) were interviewed. The overall estimate of relative risk of bladder cancer for users of hair dyes was 1.0 (95% confidence interval, 0.9 to 1.2) compared to nonusers. No consistent pattern of association was detected between bladder cancer risk and various indices of timing or intensity of exposure to hair dyes. Various explanations of the lack of association are discussed.

INTRODUCTION

Many of the compounds in hair dyes and rinses cause mutations, as measured by a variety of assays (1, 2, 15). Furthermore, some of the compounds induce bladder tumors when fed to rats or mice (12–14). Since people who dye their hair have been found to excrete dye compounds in their urine (10), the possibility that hair dyes cause human bladder tumors warrants investigation. One epidemiological study reported a positive association between hair dye use and bladder cancer in men but not in women (7), another reported no association (9), and a third reported a negative association (5).

METHODS

We interviewed 2,982 cases and 5,782 controls as part of a collaborative population-based case-control study of bladder cancer conducted in 10 geographic areas of the United States (6). The eligible cases were all residents of the areas aged 21 to 84 who were diagnosed with histologically confirmed bladder cancer in a 1-year period (beginning in late 1977 or early 1978). We identified the cases from cancer registries, 9 of which were part of the National Cancer Institute Surveillance Epidemiology and End Results Program. The control group was randomly selected from the general population of the study areas stratified according to the age, sex, and geographic distribution of the cases. Controls aged 65 to 84 were selected from Health Care Financing Administration rosters, and controls aged 21 to 64 were selected from 22,633 households chosen by telephone sampling using random-digit dialing (17). The 22,633 households that cooperated by reporting the age and sex of household members were 88% of the total of 25,826 nonbusiness, working telephone numbers dialed.

We identified 4086 eligible cases in total, of whom 2982 (73%) were interviewed. The remaining 1104 were not interviewed because of death (282), illness (288), patient refusal (252), physician refusal (128), being identified after the study period (65), not being found (81), and other reasons (8). We interviewed 3313 (82%) of the 4057 eligible older controls. The remaining 744 were not interviewed because of death (94), illness (174), refusal (348), not being found (105), and other reasons (23). We interviewed 2469 (84%) of the 2928 controls younger than 65. The remaining 459 were not interviewed because of death (7), illness (23), refusals (335), not being found (87), and other reasons (7). About 75% of the interviewed subjects were male, and the median age was 67.

Using a questionnaire that included questions about the use of artificial sweeteners, coffee, and tobacco products, occupational history, and residential history, trained interviewers questioned all subjects in their homes. Interviewers also asked respondents a brief series of questions about hair dyes: whether they had ever used hair-coloring products; at what age they had first used such products; at what age they had last used such products; what color they had used most often; and how many times per year they had colored their hair.

The effect of hair dyes on bladder cancer risk was measured by the maximum likelihood estimate of the relative risk, adjusted for potentially confounding variables by stratification into multiple-contingency tables (4). Trends in relative risk were evaluated by the Mantel extension of the Mantel-Haenszel test (11).

RESULTS

Overall, subjects who had ever dyed their hair showed approximately the same risk of bladder cancer as those who had not (Table 1). Among men, the relative risk was estimated as 1.1 and among women as 0.9. The estimates shown in Table 1 and in subsequent tables were adjusted by stratification by sex, race (2 groups), age (3 groups), and cigarette smoking (3 groups). The estimates were unaffected by adjustment for other measures of cigarette exposure, coffee consumption, urinary infections or stones, job exposure, or use of artificial sweeteners. (We adjusted for each of these factors, in turn, in combination with age, sex, and race.)

We estimated relative risk according to the frequency of hair dyeing, dividing annual frequency into 6 categories (1 to 2, 3 to 9, 10 to 12, 13 to 22, 23 to 48, 49+). These categories corresponded approximately to occasional use, semiannual use, monthly use (probably typical of permanent hair dyes), use between monthly and semimonthly (probably of permanent or semipermanent dyes), semimonthly use (probably typical of semipermanent dyes), and weekly use (probably typical of rinses), respectively (Table 2). The estimates of relative risk did not vary consistently with frequency of dyeing. (The 2-tailed p values of the tests for trend were 0.75, 0.93, and 0.82 for males, females, and both sexes, respectively.) For monthly

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Table 1

Relative risks of bladder cancer according to history of hair dyeing, by sex

Sex	History	Cases	Controls	Relative risk[a]	95% CI
Males	Never dyed hair	2065 (92)[b]	3978 (93)	1.0	
	Ever dyed hair	172 (8)	292 (7)	1.1	0.9–1.4
	Unknown	12 (0.5)	12 (0.3)		
	Total	2249 (100)	4282 (100)		
Females	Never dyed hair	288 (39)	626 (42)	1.0	
	Ever dyed hair	443 (60)	872 (58)	0.9	0.8–1.1
	Unknown	2 (0.2)	2 (0.1)		
	Total	733 (100)	1500 (100)		
Both sexes	Never dyed hair	2353 (79)	4604 (80)	1.0	
	Ever dyed hair	615 (21)	1164 (20)	1.0	0.9–1.2
	Unknown	14 (0.5)	14 (0.2)		
	Total	2982 (100)	5782 (100)		

[a] Adjusted for age, sex, race, and cigarette smoking.
[b] Numbers in parentheses, percentage.

Table 2

Relative risks of bladder cancer according to frequency of hair dyeing, by sex

Sex	Frequency	Cases	Controls	Relative risk[a]
Males	Never dyed hair	2065 (92)[b]	3978 (93)	1.0
	<3 times/yr	47 (2)	64 (1)	1.4
	3–9 times/yr	33 (1)	61 (1)	1.1
	10–12 times/yr	22 (1)	42 (1)	1.0
	13–22 times/yr	7 (0.3)	6 (0.1)	2.1
	23–48 times/yr	15 (1)	28 (1)	0.9
	≥49 times/yr	41 (2)	83 (2)	1.0
	Unknown	19 (1)	20 (0.5)	
	Total	2249 (100)	4282 (100)	
Females	Never dyed hair	288 (39)	626 (42)	1.0
	<3 times/yr	89 (12)	193 (13)	0.9
	3–9 times/yr	186 (25)	331 (22)	1.0
	10–12 times/yr	82 (11)	177 (12)	0.9
	13–22 times/yr	15 (2)	19 (1)	1.6
	23–48 times/yr	32 (4)	63 (4)	0.9
	≥49 times/yr	31 (4)	68 (5)	0.9
	Unknown	10 (1)	24 (2)	
	Total	733 (100)	1500 (100)	
Both sexes	Never dyed hair	2353 (79)	4604 (80)	1.0
	<3 times/yr	136 (5)	257 (4)	1.0
	3–9 times/yr	219 (7)	392 (7)	1.0
	10–12 times/yr	104 (3)	219 (4)	0.9
	13–22 times/yr	22 (1)	24 (0.4)	1.7
	23–48 times/yr	47 (2)	91 (2)	0.9
	≥49 times/yr	72 (2)	151 (3)	1.0
	Unknown	29 (1)	44 (1)	
	Total	2982 (100)	5782 (100)	

[a] Adjusted for sex, age, race, and cigarette smoking.
[b] Numbers in parentheses, percentage.

Table 3

Relative risks of bladder cancer according to duration of hair dyeing, by sex

Sex	Durations	Cases	Controls	Relative risk[a]
Males	Never dyed hair	2065 (92)[b]	3978 (93)	1.0
	<5 yr	115 (5)	159 (4)	1.4
	5–10 yr	27 (1)	64 (1)	0.8
	10–19 yr	23 (1)	43 (1)	1.1
	≥20 yr	6 (0.3)	19 (0.4)	0.7
	Unknown	13 (1)	19 (0.4)	
	Total	2249 (100)	4282 (100)	
Females	Never dyed hair	288 (39)	626 (42)	1.0
	<5 yr	109 (15)	188 (13)	1.1
	5–10 yr	68 (9)	146 (10)	0.9
	10–19 yr	149 (21)	256 (17)	1.1
	≥20 yr	104 (14)	244 (16)	0.8
	Unknown	15 (2)	40 (3)	
	Total	733 (100)	1500 (100)	
Both sexes	Never dyed hair	2353 (79)	4604 (80)	1.0
	<5 yr	224 (8)	347 (6)	1.3
	5–9 yr	95 (3)	210 (4)	0.8
	10–19 yr	172 (6)	299 (5)	1.1
	≥20 yr	110 (4)	263 (5)	0.8
	Unknown	28 (1)	59 (1)	
	Total	2982 (100)	5782 (100)	

[a] Adjusted for sex, age, race, cigarette smoking.
[b] Numbers in parentheses, percentage.

users, the estimated relative risk was 0.9 (95% CI,[3] 0.7 to 1.3). We also examined frequency of hair dyeing as a risk factor among subjects who had used dyes for 10 years or more; we found no consistent association between frequency and risk.

We also categorized subjects according to duration of use (Table 3). For men who had used hair dyes for less than 5 years, the estimated relative risk was 1.4 (95% CI, 1.1 to 1.8), while men who had used them longer had estimates near or below 1.0. Among women, there was virtually no variation in relative risk according to duration.

Because the chemical formulations of hair dyes vary according to color, we calculated relative risk according to the usual color of the dye used (Table 4). Among men, users of red or black dyes had estimated relative risks slightly above 1.0, while users of blonde or silver had estimates slightly below 1.0. Among women, users of black dye had estimates above 1.0, while users of brown or uncolored (metallic or gradual) dyes had estimates below 1.0. The excess risk seen for male or female users of black dyes was limited to users younger than 65, and no consistent relation was seen between frequency or duration of black dye use and estimated relative risk. Although black and brown dyes contain many of the same compounds, no excess risk was seen for users of brown dyes.

Estimated relative risk according to the age at which the subject first dyed his hair is shown in Table 5. Subjects who began dyeing their hair at early ages showed no excess risk. We also considered the calendar period of the first exposure of a subject as a risk factor because some carcinogens exert a detectable effect only after a long induction period. Subjects who had begun dyeing their hair 20 or more years ago were not at excess risk (relative risk, 0.8; 95% CI, 0.6 to 1.0). We also examined relative risk assuming 3 possible induction periods (<10 years, 10 to 19 years, 20+ years), requiring that 5 years of use have been completed before a subject was classified as exposed (16). We found no appreciable elevation

[3] The abbreviation used is: CI, confidence interval.

Table 4

Relative risks of bladder cancer according to usual color of hair dye, by sex

Sex	Color	Cases	Controls	Relative risk[a]	95% CI
Males	Never dyed hair	2065 (92)[b]	3978 (93)	1.0	
	Red/auburn	5 (0.2)	6 (0.1)	1.6	0.4–5.9
	Black	36 (2)	55 (1)	1.5	0.9–2.3
	Blonde	4 (0.2)	14 (0.3)	0.5	0.2–1.6
	Brown	45 2	82 (2)	1.0	0.7–1.5
	Silver/gray	4 (0.2)	11 (0.3)	0.7	0.2–2.2
	Frosted	0 (0)	0 (0)		
	Uncolored[c]	66 (3)	107 (2)	1.2	0.8–1.6
	Unknown/other	24 (1)	29 (1)		
	Total	2249 (100)	4282 (100)		
Females	Never dyed hair	288 (39)	626 (42)	1.0	
	Red/auburn	44 (6)	74 (5)	1.1	0.7–1.7
	Black	32 (5)	64 (4)	1.3	0.8–2.1
	Blonde	111 (15)	197 (13)	1.0	0.7–1.3
	Brown	165 (23)	384 (26)	0.8	0.6–1.1
	Silver/gray	49 (7)	80 (5)	1.2	0.8–1.9
	Frosted	9 (1)	19 (1)	1.0	0.4–2.1
	Uncolored[c]	2 (0.3)	9 (0.6)	0.5	0.1–2.2
	Unknown/other	33 (5)	47 (3)		
	Total	733 (100)	1500 (100)		
Both sexes	Never dyed hair	2353 (79)	4604 (80)	1.0	
	Red/auburn	49 (2)	80 (1)	1.1	0.7–1.7
	Black	68 (2)	119 (2)	1.4	1.0–1.9
	Blonde	115 (4)	211 (4)	0.9	0.7–1.2
	Brown	210 (7)	466 (8)	0.9	0.7–1.1
	Silver/gray	53 (2)	91 (2)	1.2	0.8–1.7
	Frosted	9 (0.3)	19 (0.3)	0.9	0.4–2.1
	Uncolored[c]	68 (2)	116 (2)	1.1	0.8–1.5
	Unknown/other	57 (2)	76 (1)		
	Total	2982 (100)	5782 (100)		

[a] Adjusted for age, sex, race, cigarette smoking.
[b] Numbers in parentheses, percentage.
[c] Gradual (metallic) dyes.

Table 5

Relative risks of bladder cancer according to age at first hair dyeing, by sex

Sex	First exposure	Cases	Controls	Relative risk[a]
Males	Never dyed hair	2065 (92)[b]	3978 (93)	1.0
	Age ≥60	48 (2)	98 (2)	1.0
	Age 40–59	104 (5)	152 (3)	1.3
	Age 20–39	15 (1)	25 (1)	1.2
	Age <20	4 (0.2)	10 (0.2)	0.9
	Unknown	13 (1)	19 (0.4)	
	Total	2249 (100)	4282 (100)	
Females	Never dyed hair	288 (39)	626 (42)	1.0
	Age ≥60	80 (11)	169 (11)	1.0
	Age 40–59	204 (28)	383 (26)	0.9
	Age 20–39	116 (16)	225 (15)	0.9
	Age <20	31 (4)	61 (4)	1.0
	Unknown	14 (2)	36	
	Total	733 (100)	1500 (100)	
Both sexes	Never dyed hair	2353 (79)	4604 (80)	1.0
	Age ≥60	128 (4)	267 (5)	1.0
	Age 40–59	308 (10)	535 (9)	1.1
	Age 20–39	131 (4)	250 (4)	0.9
	Age <20	35 (1)	71 (1)	1.0
	Unknown	27 (1)	55 (1)	
	Total	2982 (100)	5782 (100)	

[a] Adjusted for sex, age, race, cigarette smoking.
[b] Numbers in parentheses, percentage.

of risk under any of these 3 models. We also examined the number of years since the last use of hair dyes of the subject. Current users showed essentially the same relative risk as former users or those who never used dyes at all.

We examined relative risk of bladder cancer according to history of hair dyeing in combination with other risk factors including age, race, tobacco use, coffee drinking, occupational hazards, use of artificial sweeteners, and history of urinary stones or infections. Hair dye users were at elevated risk among men younger than 45 (relative risk, 2.2; 95% CI, 0.9 to 5.4) but not among women younger than 45. Hair dye users had elevated risks among men with a history of urinary stones or infections (relative risk, 1.8; 95% CI, 1.3 to 2.7) but not among women with such a history (relative risk, 1.1; 95% CI, 0.8 to 1.5). No apparent patterns emerged when we calculated relative risks for hair dyeing in combination with the other risk factors.

DISCUSSION

Concern about the possible carcinogenicity of hair dyes arose when over one-half of 190 hair dye compounds were found to be mutagenic to bacteria (1). At least 9 of the mutagenic compounds have shown some tumorigenicity in male or female rats or mice but not necessarily in both sexes or both species. Some of the experimentally induced tumors have occurred in the urinary bladder. In addition, many of the mutagenic hair dye compounds have chemical structures similar to the aromatic amines used as industrial dyes that cause bladder tumors. It is therefore useful to evaluate the potential effects of hair dyes on human bladder cancer risk.

Three studies of human risk of bladder cancer and hair dyes have been reported. A study of 107 cases with cancer of the bladder and 107 controls with benign prostatic hypertrophy (male controls) or stress incontinence (female) yielded an estimate of the relative risk to hair dye users of 1.1 (95% CI, 0.4 to 3.0), adjusted for sex and age (9). A study of 632 incident

bladder cancer cases and 632 neighborhood controls gave an estimate of 0.7 for females and indeterminately large for males (8 cases: 0 controls; estimated lower 95% confidence limit, 2.3), adjusted for age and residence (7). The authors noted that 7 of the 8 exposed men had begun dyeing their hair fewer than 6 years before diagnosis. A follow-up study of female nurses yielded an estimate of the relative risk of bladder cancer to users of hair dyes of 0.6 (95% CI, 0.2 to 1.4, estimated from data of the authors) (5). The CIs from all 3 studies indicate a wide range of values that could be consistent with all 3 studies.

We estimated the relative risk of bladder cancer to people who had ever used dyes as 1.0 (95% CI, 0.9 to 1.2). Even though we saw no overall elevation of risk, we examined users of hair dyes in a variety of ways to determine whether some of the users might be at elevated risk by virtue of the timing or frequency of their exposure to hair dyes. Annual frequency of dyeing, a measure of dose rate, did not appear to be related to relative risk. The total number of years of hair dyeing, an indication of lifetime dose, also was unrelated to relative risk. Subjects who began dyeing their hair at an early age showed no apparent excess, nor did subjects who began using hair dyes many years ago. The associations seen among men with urinary stones or infections and among users of black dyes can probably be ascribed to chance.

Although these data show no association between hair dyes and bladder cancer, chance or bias could have masked a true association. The narrow CIs indicate that it is unlikely that the study failed to detect a substantial hazard because of chance. One strength of the study was its size. For example, it included 373 subjects who had dyed their hair for more than 20 years.

Bias in selecting cases or controls was absent since eligibility for study was unrelated to hair dye use but willingness to participate could have been related to dye use. The fairly high and similar response rates in cases and controls mitigated the likely effect of such bias.

Bias in data collection was probably negligible because interviewers (and probably respondents) were unaware of the hypothesis; the questions asked about hair dyes were simple; the cases and controls were interviewed in the same setting by the same interviewers for the same length of time, on average; and the questionnaire, materials, and training were standardized to minimize the opportunity for differential recall or interpretation.

Bias in estimation could have occurred because of confounding, but the estimates reported were not confounded by sex, race, age, cigarette smoking, occupational exposure to chemicals, coffee drinking, artificial sweetener use, or urinary infections or stones.

A more likely source of distortion was random misclassification of the exposure status of the subject. Faulty, but probably nondifferential, recollection or reporting almost certainly led to some misclassification, which produces bias in estimation toward the null value (3). Likewise, an effect limited to some particular brand or formulation of dyes could have been obscured by our choice of the particular exposure variables included in the analysis (*i.e.*, misspecification of the model).

Misclassification and misspecification are particularly troublesome in an analysis of hair dyes because of the heterogeneity of the exposure. Five chemically distinct classes of hair colorings are in use (permanent dyes, semipermanent dyes, vegetable rinses, synthetic chemical rinses, and gradual dyes). Although many compounds used in permanent dyes, semipermanent dyes, and synthetic rinses (principally phenylenediamines) are mutagenic to bacteria, many other dye compounds are not. Thus, exposure to hair dyes, as defined in this study, includes many people who were not exposed to the suspect chemicals. We attempted to gauge the likely effects of misclassification following the methods suggested by Copeland *et al.* (3). If 90% of the controls were actually unexposed, not 80% as measured, then only 89% of the unexposed controls were correctly classified. We applied the same 89% specificity to the numbers of cases that would be exposed under various hypothetical values of the true relative risk. A true relative risk of 1.4 would be estimated as 1.2, which was the upper bound of the 95% CI. That is, 1.4 is the maximum relative risk that would have been obscured by a combination of substantial misclassification and chance.

In sum, these data and those from other studies suggest that hair dye users are not at increased risk of bladder cancer. The data from this study do not rule out a very small increase (or decrease) in risk, but the potential effect of the most likely biases and the narrow confidence intervals provide evidence that if any increase in risk exists, it is small.

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