

# Use of Hair Coloring Products and the Risk of Lymphoma, Multiple Myeloma, and Chronic Lymphocytic Leukemia

## ABSTRACT

**Objectives.** Hair coloring products are widely used and contain components that are mutagenic and carcinogenic. An association between occupational exposure to hair coloring products and hematopoietic cancers has been reported, but the risk for these cancers among users has not been carefully evaluated.

**Methods.** We conducted a population-based, case-control study with telephone interviews from 385 non-Hodgkin's lymphoma cases, 70 Hodgkin's disease cases, 72 multiple myeloma cases, 56 chronic lymphocytic leukemia cases, and 1432 controls.

**Results.** Among women, use was associated with odds ratios of 1.5 for non-Hodgkin's lymphoma, 1.7 for Hodgkin's disease, 1.8 for multiple myeloma, and 1.0 for chronic lymphocytic leukemia. Risk was higher for permanent hair coloring products than for semi- or nonpermanent products, particularly for dark colors. Long duration and early age of first use tended to increase risk, but the patterns were inconsistent. Use was much less common in men and did not significantly increase risk.

**Conclusions.** The use of hair coloring products appears to increase the risk of non-Hodgkin's lymphoma. Multiple myeloma and Hodgkin's disease were also associated, although based on far fewer subjects. If these results represent a causal association, use of hair coloring products would account for 35% of non-Hodgkin's lymphoma cases in exposed women and 20% in all women. (*Am J Public Health.* 1992; 82:990-997)

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### Introduction

Hair coloring products are widely used and are known to contain components that are mutagenic and carcinogenic in animals.<sup>1-4</sup> Associations between occupational exposure to hair coloring products and hematopoietic cancer have been reported,<sup>5-9</sup> but little is known about the risks for hematopoietic cancers among users of such products. Two case-control studies have suggested that use of hair coloring products may increase the risk of leukemia and non-Hodgkin's lymphoma.<sup>10,11</sup> We evaluated risks associated with the use of hair coloring products in a population-based, case-control study of incident lymphoma, multiple myeloma, and chronic lymphocytic leukemia conducted in eastern Nebraska. Our report includes both sexes and involves more detailed data on personal use of hair coloring products than earlier studies.

### Methods

Cases of non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia among White men and women, aged 21 years or older, residing in the 66 counties of eastern Nebraska, and diagnosed between July 1, 1983, and June 30, 1986, were identified through the Nebraska Lymphoma Study Group and area hospitals. Details concerning completeness of reporting and other study methods have been published elsewhere.<sup>12</sup> There were 426 non-Hodgkin's lymphoma, 73 Hodgkin's disease, 82 multiple myeloma, and 69 chronic lymphocytic leukemia cases histologically confirmed. Non-Hodgkin's lymphoma cases were reviewed and classified according to the Working Formulation<sup>13</sup> and

underwent immunologic typing.<sup>14,15</sup> The various histologic types of non-Hodgkin's lymphoma were grouped as follicular (29%), diffuse (68%), or not otherwise specified (3%). The cases were also categorized histologically into follicular center cell (Working Formulation categories B through G and J: 71%) and nonfollicular center cell (categories A, H, I, and K: 29%) groups.<sup>16</sup> Composite lymphomas with follicular and diffuse components of the same cell type were assigned to the follicular category. Composite lymphomas with different cell types were assigned to the more indolent cell type. B-cell lymphomas accounted for 81% of the non-Hodgkin's lymphoma cases, whereas 8% of the cases were T-cell lymphomas. The remaining cases could not be classified: 5% were of indeterminant immunologic type and 5% had no specimens available for study.

The controls were selected from residents of the same 66-county area by 3:1 frequency matching by race, sex, vital status, and age ( $\pm 2$  years) to the combined age distribution of the four cancer case series (non-Hodgkin's lymphoma, Hodg-

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TABLE 1—Number of Cases and Controls and Odds Ratios for Non-Hodgkin's Lymphoma, Hodgkin's Disease, Multiple Myeloma, and Chronic Lymphocytic Leukemia, by Sex and Hair Coloring Product Use

	No. of Controls	Non-Hodgkin's Lymphoma		Hodgkin's Disease		Multiple Myeloma		Chronic Lymphocytic Leukemia		
		No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)	
<i>Women</i>										
Never used any hair coloring product	373	74	1.0 ...	19	1.0 ...	14	1.0 ...	10	1.0 ...	
Ever used any hair coloring product <sup>b</sup>	322	106	1.5 (1.1, 2.2)	16	1.7 (0.7, 4.0)	24	1.8 (0.9, 3.7)	9	1.0 (0.3, 2.6)	
Semi- or nonpermanent hair coloring products	250	78	1.4 (1.0, 2.1)	8	1.2 (0.4, 3.2)	18	1.7 (0.8, 3.6)	7	0.9 (0.3, 2.8)	
Permanent hair coloring products	109	41	1.7 (1.1, 2.8)	12	3.0 (1.1, 7.9)	11	2.8 (1.1, 7.1)	2	0.8 (0.1, 4.0)	
Products that gradually change hair color	17	5	1.4 (0.4, 4.3)	0	... ...	2	3.1 (0.4, 17.0)	0	... ...	
<i>Men</i>										
Never used any hair coloring product	675	190	1.0 ...	32	1.0 ...	27	1.0 ...	34	1.0 ...	
Ever used any hair coloring product <sup>b</sup>	48	11	0.8 (0.4, 1.6)	3	1.7 (0.4, 6.3)	4	1.8 (0.5, 5.7)	3	1.0 (0.2, 3.8)	
Semi- or nonpermanent hair coloring products	7	2	1.0 (0.1, 5.1)	0	... ...	1	3.6 (0.2, 33.8)	1	3.2 (0.1, 28.6)	
Permanent hair coloring products	1	0	... ...	1	8.2 (0.2, 363.0)	1	29.1 (0.7, 1207.7)	0	... ...	
Products that gradually change hair color	45	11	0.8 (0.4, 1.7)	2	1.3 (0.2, 5.9)	2	0.9 (0.1, 4.1)	2	0.7 (0.1, 3.2)	

<sup>a</sup>Age adjusted.  
<sup>b</sup>Subjects could have used more than one type of hair coloring product and therefore may contribute to more than one category.

kin's disease, multiple myeloma, and chronic lymphocytic leukemia). For living cases under age 65, 472 controls were selected by two-stage random-digit dialing.<sup>17</sup> For living cases aged 65 or older, 603 controls were selected from Health Care Financing Administration (Medicare) records. For deceased cases, 580 controls were selected from the Nebraska state mortality files using the additional matching factor of year of death. Persons with an underlying cause of death of non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, leukemia, malignancy of unknown site, aplastic anemia, suicide, homicide, or legal intervention were excluded as controls. A total of 1655 controls was selected.

Telephone interviews were conducted with 385 (201 men, 184 women) non-Hodgkin's lymphoma cases, 70 (35 men, 35 women) Hodgkin's disease cases, 72 (32 men, 40 women) multiple myeloma cases, 56 (37 men, 19 women) chronic lymphocytic leukemia cases, and 1432 (725 men, 707 women) controls, or their next of kin. The interview response rates were 90%, 96%, 88%, 81%, and 87%, respectively. The overall control response rate was 84% (a weighted average accounting for the 91% response rate in the

household census phase of the random-digit dialing procedure, the 94% response rate of the randomly selected eligible random-digit dialing controls, the 84% response rate of the Health Care Financing Administration controls, and the 83% response rate of next of kin of deceased controls).

The interview questions included the ages of first and last use of products that gradually change hair color, of nonpermanent or semipermanent hair coloring products (defined as products that rinse out after a few shampoos), and of permanent hair coloring products (defined as products that last until the hair grows out). Users of non- or semipermanent products and permanent products were also asked the usual frequency of use and the basic color used most often. Because being diagnosed with cancer could affect use of hair coloring products, exposure histories for all cases and controls were truncated as of December 31, 1982, which precedes the earliest diagnosis date for all cases. Other known and suspected risk factors for the cancers under study, such as family history of cancer and pesticide exposures, were also included in the interview.

The measure of association was the odds ratio (OR). All risk estimates were

adjusted for the effects of age by stratification (21 through 39, 40 through 59, 60 through 69, 70 through 79, and greater than 79 years). Maximum likelihood estimates of the overall risk and 95% confidence intervals (CIs) were computed by Gart's method.<sup>18</sup> For duration-response and frequency-response relationships, significance was assessed by means of Mantel's one-tailed linear trend test.<sup>19</sup> Logistic regression analyses were conducted using an SAS procedure for polychotomous outcomes, a method that accounts for the use of a single control group for the four case groups in its estimation of variance.<sup>20</sup> Attributable risks and CIs were calculated using the method proposed by Whittemore.<sup>21</sup>

## Results

Table 1 presents the number of cases and controls and the ORs by sex and hair coloring product type. Among women, use of any hair coloring product was associated with non-Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma. Non-Hodgkin's lymphoma was significantly associated with the use of both semi- and nonpermanent hair coloring products (OR = 1.4) and permanent

TABLE 2—Number of Cases and Controls and Odds Ratios for Non-Hodgkin's Lymphoma, Hodgkin's Disease, Multiple Myeloma, and Chronic Lymphocytic Leukemia among Women by the Most Frequently Used Hair Coloring Product Color

	No. of Controls	Non-Hodgkin's Lymphoma		Hodgkin's Disease		Multiple Myeloma		Chronic Lymphocytic Leukemia	
		No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)
Never used any hair coloring product	373	74		19		14		10	
Semi- or nonpermanent hair coloring product users <sup>b</sup>									
Blonde	41	10	1.1 (0.5, 2.5)	3	1.8 (0.4, 8.1)	2	1.3 (0.2, 6.8)	1	1.1 (0.05, 9.1)
Brown/brunette	138	44	1.4 (0.9, 2.2)	4	1.0 (0.3, 3.7)	9	1.6 (0.6, 4.1)	4	1.0 (0.3, 3.6)
Black	11	5	2.1 (0.6, 6.9)	0	...	2	3.9 (0.5, 22.1)	0	...
Red	6	4	2.5 (0.6, 10.5)	0	...	2	7.4 (0.9, 52.0)	0	...
Other	51	9	0.8 (0.3, 1.8)	1	1.7 (0.1, 17.6)	3	1.3 (0.3, 5.2)	2	1.1 (0.2, 5.9)
Unknown	3	6	...	0	...	0	...	0	...
Permanent hair coloring product users <sup>b</sup>									
Blonde	44	8	0.9 (0.4, 2.2)	6	2.5 (0.7, 8.5)	2	1.4 (0.2, 7.6)	0	...
Brown/brunette	43	20	2.0 (1.0, 3.8)	3	2.6 (0.5, 12.3)	6	3.8 (1.2, 11.6)	2	1.8 (0.3, 9.9)
Black	5	4	4.1 (0.9, 18.8)	0	...	0	...	0	...
Red	4	3	3.0 (0.5, 16.8)	0	...	1	5.4 (0.2, 68.5)	0	...
Other	12	6	2.4 (0.8, 7.5)	3	8.6 (1.1, 62.8)	2	4.1 (0.5, 23.9)	0	...
Unknown	1	0	...	0	...	0	...	0	...

<sup>a</sup>Age adjusted.

<sup>b</sup>Subjects could have used semi- or nonpermanent and permanent hair coloring products, and, therefore, may appear in the table twice.

hair coloring products (OR = 1.7). Women who used permanent hair coloring products only had an OR for non-Hodgkin's lymphoma of 1.9 (95% CI = 1.1, 3.4). Hodgkin's disease and multiple myeloma showed significant associations with the use of permanent hair coloring products. Women who had used permanent hair coloring products only had an OR of 3.4 (95% CI = 1.1, 10.7) for Hodgkin's disease, while users of semi- or nonpermanent products had an OR of 0.8. Chronic lymphocytic leukemia was not associated with the use of any hair coloring products. For all cancer types among women, except chronic lymphocytic leukemia, the risks associated with permanent hair coloring products were higher than those for semi- or nonpermanent hair coloring products, although CIs overlap.

Among men, the ORs for hair coloring product use were 0.8 for non-Hodgkin's lymphoma, 1.7 for Hodgkin's disease, 1.8 for multiple myeloma, and 1.0 for chronic lymphocytic leukemia. Non-Hodgkin's lymphoma was elevated among men who were long-term users of products that gradually changed hair color (1 year: OR = 1.0; 2 through 5 years: OR = 0.2; 6+ years: OR = 1.6; 95% CI = 0.5, 5.0), but neither their risk nor the duration trend ( $P = .362$ ) was significant. The number of men using other hair coloring products was much less than the

number of women and precluded meaningful analysis. The remaining results presented are for women only.

Risk varied by the most frequently used hair coloring product color (Table 2). For non-Hodgkin's lymphoma and multiple myeloma, the risks were higher among women who most often used brown or brunette, black, or red hair coloring products. In general, the risks associated with these darker color products were higher among users of permanent hair coloring products than semi- or nonpermanent products.

The risk of non-Hodgkin's lymphoma increased significantly with the duration of use and younger age at first use of semi- or nonpermanent products, although the risks dropped off in the highest category of both variables (Table 3). Risk also increased significantly with duration of use of dark permanent hair coloring products and younger age at first use of permanent hair coloring products, but did not show consistent exposure-response gradients (Table 4). Risk did not increase with frequency of use. The same patterns, with higher levels of risk, were seen when the analyses were restricted to black, brown/brunette, and red hair coloring products only. In general, users of permanent hair coloring products had a higher risk of non-Hodgkin's lymphoma relative to women who never used any hair col-

oring products and relative to women who used semi- or nonpermanent hair coloring products at most levels of duration, age, and frequency of use. Women who began using hair coloring products prior to 1970 had slightly lower risks (semi- or nonpermanent: OR = 1.3; permanent: OR = 1.6) than women who began using hair coloring products after that date (semi- or nonpermanent: OR = 1.5; permanent: OR = 2.2).

Because many of the age and time characteristics were interrelated, we performed polychotomous logistic regression entering all the variables presented in Tables 1 through 4. The results of the regression analyses were similar to the analyses already presented. Color of hair coloring products used, duration of semi- or nonpermanent hair coloring product use, decreasing age of first use of permanent hair coloring products, and age at diagnosis significantly increased the risk of non-Hodgkin's lymphoma. The other age, duration, and frequency variables were not significantly associated with non-Hodgkin's lymphoma.

Women who had ever used semi- or nonpermanent hair coloring products had a higher risk of follicular center cell lymphoma (OR = 1.6; 95% CI = 1.0, 2.5) than those who developed nonfollicular center cell lymphoma (OR = 1.1; 95% CI = 0.6, 2.0). Users of permanent hair coloring

TABLE 3—Number of Cases and Controls and Odds Ratios for Non-Hodgkin's Lymphoma, Hodgkin's Disease, and Multiple Myeloma among Women, by Characteristics of Semipermanent or Nonpermanent Hair Coloring Product Use

	Non-Hodgkin's Lymphoma						Hodgkin's Disease						Multiple Myeloma							
	All Colors			Black, Brown/Brunette, Red Only			All Colors			Black, Brown/Brunette, Red			All Colors			Black, Brown/Brunette, Red				
	No.	No. of Controls	Odds Ratio <sup>a</sup> (95% CI)	No.	No. of Controls	Odds Ratio <sup>a</sup> (95% CI)	No.	No. of Controls	Odds Ratio <sup>a</sup> (95% CI)	No.	No. of Controls	Odds Ratio <sup>a</sup> (95% CI)	No.	No. of Controls	Odds Ratio <sup>a</sup> (95% CI)	No.	No. of Controls	Odds Ratio <sup>a</sup> (95% CI)		
Never used any hair coloring product	74	373	1.0	74	373	1.0	19	19	1.0	19	1.0	19	1.0	14	14	1.0	14	14	1.0	
Duration of use, y																				
1-10	29	113	1.1 (0.7, 1.9)	19	75	1.1 (0.6, 2.0)	5	5	1.1 (0.3, 3.6)	2	2	0.7 (0.1, 3.7)	2	10	2.2 (0.9, 5.8)	6	6	2.1 (0.7, 6.4)	6	
11-20	27	57	2.0 (1.2, 3.6)	18	36	2.1 (1.1, 4.2)	1	1	0.8 (0.04, 7.1)	1	1	1.5 (0.1, 13.9)	3	3	1.3 (0.3, 4.9)	3	3	2.0 (0.4, 8.0)	3	
21+	11	40	1.2 (0.6, 2.7)	9	19	2.2 (0.9, 5.6)	2	2	5.0 (0.5, 40.2)	1	1	4.6 (0.2, 54.0)	2	2	1.0 (0.1, 5.0)	1	1	1.1 (0.1, 8.8)	1	
Unknown	9	32	...	6	20	...	0	0	...	0	0	...	2	2	...	2	2	...	2	
P value for trend			.024			.004			.154			.239			.320			...	.174	
Age at first use, y																				
61+	9	46	0.9 (0.4, 2.0)	4	31	0.6 (0.2, 1.8)	1	1	1.6 (0.1, 18.0)	1	1	2.4 (0.1, 27.4)	1	1	0.4 (0.02, 3.4)	1	1	0.7 (0.03, 5.2)	1	
51-60	18	50	1.4 (0.7, 2.7)	15	31	1.9 (0.9, 4.0)	1	1	1.6 (0.1, 15.6)	0	0	...	4	4	1.8 (0.5, 6.2)	3	3	2.2 (0.5, 9.1)	3	
41-50	20	52	1.6 (0.9, 3.0)	15	31	2.1 (1.0, 4.3)	0	0	...	0	0	...	5	5	2.2 (0.7, 7.3)	3	3	2.4 (0.5, 10.0)	3	
≤40	20	67	1.4 (0.7, 2.6)	12	39	1.5 (0.7, 3.2)	6	6	1.5 (0.5, 4.7)	3	3	1.3 (0.3, 5.8)	6	6	3.1 (1.0, 9.5)	4	4	3.9 (1.0, 14.6)	4	
Unknown	11	35	...	7	23	...	0	0	...	0	0	...	2	2	...	2	2	...	2	
P value for trend			.030			.012			.300			.475			.010			...	.006	
Frequency of use per year																				
1-11	33	80	1.9 (1.1, 3.2)	25	54	2.1 (1.2, 3.7)	5	5	1.6 (0.4, 5.6)	2	2	1.1 (0.2, 6.3)	8	8	2.8 (1.0, 7.7)	6	6	3.1 (1.0, 9.5)	6	
12-23	16	76	1.0 (0.5, 1.8)	11	50	1.0 (0.5, 2.2)	2	2	1.0 (0.1, 5.4)	1	1	0.7 (0.03, 6.2)	3	3	0.9 (0.2, 3.5)	2	2	0.9 (0.1, 4.6)	2	
24-51	7	28	1.2 (0.4, 3.0)	4	16	1.2 (0.3, 4.0)	0	0	...	0	0	...	2	2	1.6 (0.2, 8.2)	2	2	2.9 (0.4, 15.4)	2	
52+	16	48	1.4 (0.7, 2.7)	10	22	1.8 (0.7, 4.2)	1	1	1.5 (0.1, 16.9)	1	1	3.4 (0.1, 41.4)	2	2	0.9 (0.1, 4.4)	1	1	0.9 (0.04, 7.6)	1	
Unknown	6	18	...	3	13	...	0	0	...	0	0	...	3	3	...	2	2	...	2	
P value for trend			.177			.083			.493			.429			.497			...	.268	

<sup>a</sup>Age adjusted.

**TABLE 4—Number of Cases and Controls and Odds Ratios for Non-Hodgkin's Lymphoma, Hodgkin's Disease, and Multiple Myeloma among Women, by Characteristics of Permanent Hair Coloring Product Use**

	Non-Hodgkin's Lymphoma				Hodgkin's Disease				Multiple Myeloma			
	All Colors		Black, Brown/Brunette, Red Only		All Colors		Black, Brown/Brunette, Red		All Colors		Black, Brown/Brunette, Red	
	No. Controls	Odds Ratio <sup>a</sup> (95% CI)	No. Controls	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)	No.	Odds Ratio <sup>a</sup> (95% CI)
Never used any hair coloring product	74	1.0	74	1.0	19	1.0	19	1.0	14	1.0	14	1.0
Duration of use, y												
1-10	23	2.4 (1.3, 4.6)	15	2.8 (1.3, 6.0)	9	3.6 (1.2, 11.1)	2	2.5 (0.3, 15.7)	3	1.9 (0.4, 8.2)	2	2.2 (0.3, 11.7)
11-20	11	2.2 (0.9, 5.0)	7	2.2 (0.8, 6.2)	2	2.8 (0.4, 17.9)	1	3.6 (0.1, 36.8)	5	5.6 (1.5, 19.6)	3	5.4 (1.1, 24.4)
21+	4	0.7 (0.2, 2.3)	4	2.3 (0.6, 9.4)	1	2.0 (0.1, 20.5)	0	...	2	2.3 (0.3, 12.1)	1	3.4 (0.1, 33.1)
Unknown	3	...	1	...	0	...	0	...	1	...	1	...
P value for trend		.102		.003		.018		.145		.008		.005
Age at first use, y <sup>b</sup>												
51+	9	1.4 (0.6, 3.3)	9	1.9 (0.7, 4.8)	0	...	0	...	2	1.7 (0.2, 8.6)	2	2.3 (0.3, 12.1)
41-50	11	3.3 (1.3, 8.5)	8	5.0 (1.5, 16.9)	0	...	0	...	7	13.4 (3.7, 49.5)	4	18.0 (3.3, 99.3)
31-40	10	1.4 (0.6, 3.2)	6	1.8 (0.6, 5.2)	3	4.1 (0.7, 22.4)	2	5.9 (0.7, 39.4)	0	...	0	...
≤30	8	2.1 (0.7, 5.6)	3	3.7 (0.6, 23.3)	9	4.1 (1.3, 12.9)	1	2.3 (0.1, 37.6)	1	2.0 (0.1, 23.6)	0	...
Unknown	3	...	1	...	0	...	0	...	1	...	1	...
P value for trend		.013		.001		.001		.045		.042		.040
Frequency of use per year												
1-3	20	3.6 (1.8, 7.4)	10	4.6 (1.7, 12.6)	4	3.5 (0.8, 15.0)	2	10.5 (1.2, 76.3)	1	1.0 (0.05, 8.8)	0	...
4-6	9	2.0 (0.8, 5.0)	6	2.9 (0.9, 9.6)	7	7.5 (2.0, 29.1)	1	1.8 (0.1, 23.9)	3	4.2 (0.8, 19.4)	2	6.5 (0.8, 44.3)
7+	8	0.7 (0.3, 1.7)	7	1.1 (0.4, 2.8)	1	0.6 (0.03, 5.7)	0	...	4	2.4 (0.6, 9.0)	4	3.7 (0.9, 14.1)
Unknown	4	...	4	...	0	...	0	...	3	...	1	...
P value for trend		.339		.107		.052		.423		.030		.004

<sup>a</sup>Age adjusted.

<sup>b</sup>The age categories for first use of permanent hair coloring products differ from the categories used for semi- or nonpermanent hair coloring products because use patterns differ. For both analyses, the categories were selected to achieve as equal a distribution of the control subjects as possible.

products also had a higher risk of follicular center cell lymphoma (OR = 2.0; 95% CI = 1.1, 3.5) than those who developed nonfollicular center cell lymphoma (OR = 1.3; 95% CI = 0.6, 2.8). Women using dark permanent products also had the highest risk for follicular center cell lymphoma (OR = 2.5; 95% CI = 1.3, 4.9) and had an almost threefold increased risk (OR = 2.8; 95% CI = 1.2, 6.5) of developing large cell lymphoma of follicular center cell origin (categories D, G, and J).

Users of semi- or nonpermanent hair coloring products had similar risks for B-cell lymphoma (OR = 1.5; 95% CI = 1.0, 2.2) and for T-cell lymphoma (OR = 1.5; 95% CI = 0.3, 7.7), whereas users of permanent hair coloring products had a higher risk for T-cell lymphoma (OR = 3.5; 95% CI = 0.6, 19.3) than for B-cell lymphoma (OR = 1.7; 95% CI = 1.0, 2.9). However, the ORs were not significantly different from each other.

Adjustments for family history of cancer, cigarette smoking, herbicide use, and insecticide use did not change the risk estimates for non-Hodgkin's lymphoma and hair coloring product use.

Risk estimates for non-Hodgkin's lymphoma based on data from self-respondents or proxy respondents were similar for use of any hair coloring products (self: OR = 1.5; proxy: OR = 1.6), semi- or nonpermanent products (self: OR = 1.4; proxy: OR = 1.4), permanent products (self: OR = 1.7; proxy: OR = 1.9), and products that changed hair color gradually (men, self: OR = 0.8; proxy: OR = 0.9). Risks and trends associated with age at first use and duration of semi- or nonpermanent hair coloring products and age at first use of permanent products were slightly stronger among self-respondents than among subjects whose data were supplied by proxies. No meaningful differences were seen between self-respondents and proxies for frequency and color of semi- or nonpermanent hair coloring products. Conversely, risks by duration, frequency, and color of permanent hair coloring products were slightly higher among subjects whose data were supplied by proxies than among self-respondents.

There were far fewer cases of the other three cancers than of non-Hodgkin's lymphoma, which limited our ability to investigate risks by use characteristics. Nevertheless, significant trends in risk for multiple myeloma were observed for decreasing age at first use of semi- or nonpermanent hair coloring products (Table 3) and duration, decreasing age at first use,

and frequency of use of permanent hair coloring products (Table 4); however, at least in part because of small numbers, most risk patterns were inconsistent. Polychotomous logistic regression analyses, based on all variables in Tables 1 through 4, revealed only color to be significantly associated with risk of multiple myeloma. Nonsignificant associations were observed with decreasing age at first use of semi- or nonpermanent or permanent hair coloring products and frequency of use of permanent hair coloring products.

A significant trend was seen for Hodgkin's disease and decreasing age at first use of permanent hair coloring products (Table 4), but the significant trend was primarily due to the lack of Hodgkin's disease cases in the older age at first use categories. The Hodgkin's disease cases were younger on average than the controls, who were frequency matched to the combined group of four cancer types; thus, the difference observed by age at first use may not have etiologic significance. The logistic regression analyses showed age at diagnosis and decreasing age at first use of permanent hair coloring products to be significantly associated with development of Hodgkin's disease. Nonsignificant associations were seen with duration and younger age at first use of semi- or nonpermanent hair coloring products.

## Discussion

Experimental studies have shown that hair coloring products contain mutagenic and carcinogenic compounds, which vary by hair coloring product type and color.<sup>1-4</sup> Although some of these components have been removed from use over the last two decades, many carcinogenic aromatic, nitroso, and amino compounds remain and are found in both semipermanent and permanent hair coloring products. Permanent hair coloring products also contain oxidizing agents that allow the dye to irreversibly bind to the hair shaft. This generally lowers absorption by the skin of specific aromatic amines, but the oxidation process also results in the formation of some products, such as the three-ringed "Bandrowski-base," that are absorbed.<sup>1</sup> Many different chemical dyes can be found in most color formulations, but they usually occur in greater concentrations in the black, brown, and red dyes than in blond and silver bleach toner formulations. It is interesting that, in the present epidemiologic study, the variation in cancer risks by product type and color is somewhat consistent with what

would be expected based on the concentration of the constituents and biochemical action of the product formulations. Hair coloring products that gradually change hair color have been shown to be absorbed by the users.<sup>22</sup> For example, gradual products contain lead acetate<sup>23,24</sup> and result in absorption of lead by the users.<sup>22</sup> Although the target sites for carcinogenic hair coloring components in feeding studies of rats and mice have generally been the urinary tract, liver, mammary gland, skin, forestomach, and thyroid gland,<sup>25</sup> there have been reports of increased lymphoma in mice in two skin painting studies of hair dyes.<sup>26,27</sup>

In the present study, significant risks were observed for overall use of hair coloring products, darker colors, and trends of some use characteristics, but the patterns of risk by some use characteristics were inconsistent. These inconsistencies could arise because the association is non-causal, because of chance (numbers of exposed cases were small), or because of misclassification of self- and proxy-reported exposure data for some of the use characteristics. There is little information in the scientific literature on the quality of self- or proxy-reported histories of hair coloring product use. In a small reliability study of 32 women (16 cases and 16 controls), the correlation between reported duration of hair dye use from two interviews 1 year apart was .86 and was similar for cases and controls.<sup>28</sup> The correlation for frequency of use (.92) was slightly higher. We have no such data on our subjects, and no information on recall over longer time periods or by surrogate respondents. It seems reasonable, however, to assume that the quality of reporting on type and color of hair coloring product used would be more accurate than reporting on age of first use or annual frequency of use. Recall worsens with the degree of detail required.<sup>29</sup> The type of misclassification of the use characteristics likely to occur would tend to reduce ORs and dampen or disrupt trends.<sup>30,31</sup> In the present study, there was little difference between self-respondents and proxy respondents for risk estimates of non-Hodgkin's lymphoma for the overall "ever" use of hair coloring products. Although the number of subjects in each category was small and risk estimates were highly variable, we did examine use characteristics by respondent type. Slightly greater risks and trends were seen among self-respondents than among proxies for the age at first use of any hair coloring product and duration of semipermanent hair coloring products.

These data suggest that inclusion of proxies, with their potentially less accurate data, may have resulted in underestimates of true risks and dampened trends for the detailed use characteristics. However, proxies yielded slightly higher risk estimates for duration, frequency, and color of permanent hair coloring products than self-respondents. Similar results for subjects and proxies for semipermanent frequency variables suggest that the data from the two groups may be equally poor.

Case response bias needs to be considered as a possible explanation for the associations observed in this study. With several cancers showing an association, one cannot easily dismiss case response bias completely. Shore et al.,<sup>28</sup> however, found little evidence for case response bias for hair dye use in breast cancer patients in 1979. More recent data on potential for case response bias with respect to hair coloring product use are not available. Awareness of potential health risks associated with hair coloring products may have increased. It seems unlikely, however, that case response bias would operate in a manner so as to yield risks by type and color of product that are consistent with what might be expected based on the concentration of oxidizers and dyes in the formulations, facts not likely to be known by study subjects.

We were able to adjust for the influence of several known or suspected risk factors for non-Hodgkin's lymphoma and the other cancers and found no evidence of confounding. It has been hypothesized that the hair graying or other conditions that lead to the use of hair coloring products are a reflection of hormonal status or other factors that themselves are responsible for increased cancer risk.<sup>32</sup> While this may be relevant for breast cancer, there is no evidence that hormonal factors play a role in the development of non-Hodgkin's lymphoma,<sup>33</sup> Hodgkin's disease,<sup>34</sup> or multiple myeloma.<sup>35</sup> A single report links the use of hair dyes to connective tissue disorders, such as systemic lupus erythematosus and scleroderma.<sup>36</sup> These acquired disorders of immunity have also been associated with an increased risk of non-Hodgkin's lymphoma<sup>33</sup> and multiple myeloma, although the association with multiple myeloma was observed in clinical series<sup>37</sup> but not case-control studies.<sup>38-40</sup> These findings suggest that hair coloring products may act by affecting the immune system. Freni-Titulaer et al.<sup>36</sup> hypothesized that the association between connective tissue disease and hair coloring products may be

affected by acetylator phenotype. Slow acetylators would be at greater risk than fast acetylators. The aromatic amines in hair coloring products, which are absorbed through the scalp, are metabolized through acetylation. Genetically determined metabolic phenotypes could affect risk, dampening apparent associations in populations that are heterogeneous for the metabolic phenotype.

Most epidemiologic studies of hair coloring products and hematopoietic cancers have focused on people who were occupationally exposed (i.e., cosmetologists). The relative exposure levels of professional compared with personal use are unknown. If cosmetologists use protective gloves, their dermal exposures may, in fact, be less than those of persons whose hair is being colored. Two reports of significant excesses of multiple myeloma,<sup>7,9</sup> one report of a significant excess of leukemia,<sup>9</sup> and several reports of non-significant excesses of all hematopoietic cancers combined<sup>5,8,41-43</sup> have been reported among cosmetologists.

Far fewer data are available on the risk of hematopoietic cancers among users of hair coloring products. A study of registered nurses had fewer than expected lymphoma cases (10 vs 15.7) among women who had used permanent hair dyes.<sup>44</sup> Another study, which combined lymphoma and leukemia, reported an excess risk in London but a deficit risk in Toronto associated with use of permanent or semipermanent dyes.<sup>45</sup> The study by Cantor et al.<sup>11</sup> of non-Hodgkin's lymphoma and leukemia is by far the largest case-control study to address the risk for these tumors in hair coloring product users. Both cancer types were associated with hair dye use, but the study was restricted to men. The present study included only 21 male cases (11 non-Hodgkin's lymphoma, 3 Hodgkin's disease, 4 multiple myeloma, and 3 chronic lymphocytic leukemia) who reported use of hair coloring products; therefore, we were unable to thoroughly evaluate their risk or the consistency of the results for men between the two studies. Our data suggest that men are more likely to use products that gradually change hair color (6% of controls) than other types of hair coloring products (1% of controls). More research is needed on the risk of these gradual hair coloring products. There were only 12 cases of chronic lymphocytic leukemia (9 women, 3 men) exposed to hair coloring products in the present study, too few to assess risk with any confidence. The study of Cantor

et al.<sup>11</sup> found at least a twofold excess risk of leukemia associated with hair coloring product use in men for a number of different leukemia subtypes, but not chronic lymphocytic leukemia and acute nonlymphocytic leukemia. A case-control study of acute nonlymphocytic leukemia conducted in Baltimore, however, found an association with use of hair dyes among both men and women.<sup>10</sup> To our knowledge, there are no reports on the risk of multiple myeloma associated with the use of hair coloring products, although there are several reports of excesses of multiple myeloma in persons occupationally exposed to hair dyes.<sup>35</sup>

With the widespread use of hair coloring products among women (46% of the controls), the question of cancer risk is an important public health issue. Using the Whittemore method<sup>21</sup> for calculating attributable risks and CIs, based on a relative risk of 1.53 for non-Hodgkin's lymphoma for ever having used any hair coloring product, these exposures would account for 35% (95% CI = 9%, 52%) of the non-Hodgkin's lymphoma occurring in exposed women and 20% (95% CI = 3%, 35%) in all women. Non-Hodgkin's lymphoma is one of the most rapidly increasing cancers in developed countries,<sup>46,47</sup> second in the United States only to melanoma and female lung cancer.<sup>48</sup> Between 1973 and 1987, the incidence of non-Hodgkin's lymphoma in the United States increased by more than 50%.<sup>48</sup> Some, but not the majority, of this increase is due to lymphomas arising in patients with the acquired immunodeficiency syndrome. Historical data on trends in hair coloring product use, which would help assess its role in the changing occurrence of non-Hodgkin's lymphoma, are not available. In the United States, however, current estimates of the percentage of women who have used or are using hair coloring products range from 20% (G. N. McEwen, Jr, personal communication, February 1991) to 40%.<sup>49</sup> The excess of non-Hodgkin's lymphoma in the present study is consistent with findings from the largest case-control study of this tumor and non-occupational hair dye exposure.<sup>11</sup> If it is causal, hair coloring product use would explain a larger percentage of non-Hodgkin's lymphoma cases among women than any other currently known or suspected risk factor. □

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