



## Hair-coloring Product Use and Risk of Non-Hodgkin's Lymphoma: A Population-based Case-Control Study in Connecticut

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A population-based case-control study was conducted in Connecticut in 1996–2002 to test the hypothesis that lifetime hair-coloring product use increases non-Hodgkin's lymphoma risk. A total of 601 histologically confirmed incident female cases and 717 population-based controls were included in the study. An increased risk of non-Hodgkin's lymphoma was observed among women who reported use of hair-coloring products before 1980 (odds ratio = 1.3, 95% confidence interval (CI): 1.0, 1.8). The odds ratios were 2.1 (95% CI: 1.0, 4.0) for those using darker permanent hair-coloring products for more than 25 years and 1.7 (95% CI: 1.0, 2.8) for those who had more than 200 applications. Follicular type, B-cell, and low-grade lymphoma generally showed an increased risk. On the other hand, the authors found no increased risk of non-Hodgkin's lymphoma overall and by subtype of exposure and disease among women who started using hair-coloring products in 1980 or later. It is currently unknown why an increased risk of non-Hodgkin's lymphoma was found only among women who started using hair-coloring products before 1980. Further studies are warranted to show whether the observed association reflects the change in hair dye formula contents during the past two decades or indicates that recent users are still in their induction and latent periods.

case-control studies; Connecticut; hair dyes; lymphoma, non-Hodgkin; risk factors; women

Abbreviations: CI, confidence interval; OR, odds ratio; RCA, Rapid Case Ascertainment Shared Resource.

There have been consistent reports of increases in incidence and mortality due to non-Hodgkin's lymphoma in many parts of the world, and Connecticut is one of the areas in the world with a confirmed increase in incidence (1). Although considerable efforts have been made, little is known about the etiology and the risk factors responsible for the increasing incidence of the disease. Epidemiologic studies of non-Hodgkin's lymphoma have provided contradictory results with respect to even major suspected risk factors.

Epidemiologic studies have linked hair-coloring product use to non-Hodgkin's lymphoma risk, but the results have been inconclusive. Two population-based case-control studies (2, 3) suggested that the use of hair dye increases the risk of non-Hodgkin's lymphoma. Using these results, Pearce and Bethwaite concluded in 1992 that “the environ-

mental exposure which seems most likely to have contributed to the increase in non-Hodgkin's lymphoma is that of hair dyes” (4, p. 5498s).

Two prospective follow-up studies, however, have reached different conclusions. A study by Grodstein et al. (5) found no overall association between hair dye use and risk of non-Hodgkin's lymphoma among participants in the Nurses' Health Study. Another study by Thun et al. (6) reported that permanent hair dye use in general was not associated with the risk of non-Hodgkin's lymphoma, and while prolonged use of black hair dyes may increase the risk, the proportion of the disease that could be explained by dark dye use is small. A population-based case-control study by Holly et al. (7) in the San Francisco Bay Area also found no association between hair-coloring product use and the risk of non-Hodgkin's lymphoma.

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Earlier epidemiologic studies, however, have suffered several major limitations. In two prospective follow-up studies (5, 6), for example, women were asked only four or five questions related to their lifetime use of permanent hair dye products. Considering the complicated use patterns among hair dye users, hair dye use experience cannot be ascertained by asking only a few questions. As pointed out by Zahm et al. (3), cohort studies that ascertain exposure early in life and observed subjects over time without repeated assessment will underestimate lifetime use, since the history of hair dye use is affected by the age at interview.

Perhaps more importantly, the risk of non-Hodgkin's lymphoma associated with hair-coloring product use may need to be examined by time period of use since the formulations of hair-coloring products have undergone tremendous change over the past 20 years. As recently reviewed by Corbett (8), after the publication in 1975 by Ames et al. (9) of their finding that a number of hair dye ingredients were mutagenic, the experimental studies by the US National Cancer Institute also showed a carcinogenic effect of some hair dye intermediates in rats and mice (10). In 1979, the US Food and Drug Administration, prompted by the positive National Cancer Institute findings, proposed to require a cancer-warning label on hair dyes containing potential carcinogenic material. According to Corbett, "The resulting concern, under the prevailing opinion that there was no safe dose for a carcinogen, caused manufacturers to reformulate all oxidative dye products during 1978–1982" (8, p. 132). This reformulation involved the replacement or elimination of some of the dyes that had been reported to produce tumors in National Cancer Institute bioassays (8). Thus, the significant changes in hair dye formulation have resulted in the discontinuation of some hair-coloring product formulations over the past 20 years (7).

This population-based case-control study conducted among Connecticut women was designed to further investigate the issue of hair-coloring product use and the risk of non-Hodgkin's lymphoma by type of product used, by subtype of the disease, and by time period of use.

## MATERIALS AND METHODS

### Study population

Cases were histologically confirmed, incident, non-Hodgkin's lymphoma patients (*International Classification of Diseases for Oncology*, Second Edition, codes M-9590–9642, 9690–9701, 9740–9750) in Connecticut who were diagnosed between 1995 and 2001. Subjects were restricted to women aged 21–84 years at diagnosis who had had no previous diagnosis of cancer, with the exception of non-melanoma skin cancer, and who were alive at the time of interview. Cases were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA). RCA acts as an agent of the Connecticut Tumor Registry. The Connecticut Public Health Code requires reporting of cancers from licensed hospitals and clinical laboratories to the Connecticut Tumor Registry. RCA field staffs are assigned geographically to survey all of the state's nonpediatric hospitals in order to identify newly diagnosed cases. Information on cases identified in

the field is sent regularly to the RCA data entry staff where the case's demographic data are entered, verified, and screened against the Connecticut Tumor Registry database. The Connecticut Tumor Registry has reciprocal reporting agreements with cancer registries in all adjacent states (and Florida) to identify Connecticut residents with cancer diagnosed and/or treated in these states. A total of 832 incident non-Hodgkin's lymphoma cases were identified during the study period, with 601 of them (72 percent) completing in-person interviews.

To provide accurate and consistent histologic classification of the cases, we obtained pathology slides (or tissue blocks) for all cases from the pathology departments where the case was diagnosed. The specimens were reviewed by two study pathologists (S. F., G. T.) who are experienced in the diagnosis of lymphoma. The non-Hodgkin's lymphoma cases were classified according to the Working Formulation by grade (low, intermediate, or high); by histologic type (diffuse or follicular); or by immunologic type (B cell or T cell).

Population-based controls with Connecticut addresses were recruited using either random digit dialing methods for those below the age of 65 years or Health Care Finance Administration files for those aged 65 years or above. The participation rate for the controls obtained by random digit dialing was 69 percent including the initial telephone screening, and for those obtained from Health Care Finance Administration files, it was 47 percent. Cases and controls were frequency matched by age ( $\pm 5$  years) by adjusting the number of controls randomly selected in each age stratum every few months.

### Interviews

All procedures were performed in accordance with a protocol approved by the Human Investigations Committee at Yale and the Connecticut Department of Public Health. After approval by the hospitals and by each subject's physician (for cases), or following selection through random sampling (for controls), potential participants were approached by letter and then by phone. Those who agreed were interviewed by trained study interviewers at either the subject's home or a convenient location. A standardized, structured questionnaire was used to obtain information on the use of hair-coloring products and other major known or suspected risk factors that might confound the association between hair-coloring product use and risk of non-Hodgkin's lymphoma.

Regarding the use of hair-coloring products, respondents were provided a long list of names of hair-coloring processes and asked whether they had used these products at any time in their lives. If their responses were affirmative, they were asked to provide information related to each period in which they had used a hair-coloring product, with a period defined as the continuous timeframe of use of the same type and color product (without specifying a minimum duration of each period). If either changed, it was considered to be another period. Specifically, for each period of hair dye use, subjects were asked to provide the type and color of the hair-coloring product used, age at first use, age when use stopped, the number of years of use, and the frequency of use per year during those years of reported use. The respondents were also asked their main reason for using a hair-coloring product, such as to cover gray or to change natural hair color.

The study interviewers were trained to use pictures of hair product labels for the interview.

Information on other potential confounding factors, including menstrual and reproductive history, family cancer history, occupation, diet, and demographic factors, was also collected during the interview. Dietary information was collected using a scannable semiquantitative food frequency questionnaire developed and validated by the Fred Hutchinson Cancer Research Center.

### Data analysis

The primary analyses involved comparisons of overall use of hair-coloring products and more specific types (permanent, semipermanent, and temporary) and colors (dark: black, red, and brown, or light: blonde) of hair-coloring product use between cases and controls. As reviewed previously, since the contents of hair-coloring products have changed dramatically since the 1980s (7), we stratified women who started using hair-coloring products before 1980 from women who started in 1980 or later.

Since some subjects reported using a particular type or color of hair dye across different periods of life, with varying frequencies in each period, the average frequency of use for a product was not necessarily representative of the use in any one period. Therefore, instead of calculating an average frequency of lifetime use, we calculated the total number of times that a specific type or color of hair dye product was used, similar to the approach of Koenig et al. (11). We calculated the number of times a specific type was used for each period by taking the product of years of use (duration) and frequency of yearly use and then summed the results over a subject's lifetime.

Unconditional logistic regression was used to estimate the association between hair-coloring product use and risk of non-Hodgkin's lymphoma by histologic type, immunologic type, and tumor grade, and to control for potential confounders. The potential confounding variables included in the final model were age (<50, 50–70, >70 years) and family history of non-Hodgkin's lymphoma in first-degree relatives. Adjustments of other variables, such as race, level of education, tobacco smoking, alcohol consumption, dietary protein or fat intakes, and farming history, did not result in material changes for the observed association and, thus, were not included in the final model reported here. Odds ratios and 95 percent confidence intervals were calculated using PROC LOGISTIC in the SAS statistical software package (SAS Institute, Inc., Cary, North Carolina).

### RESULTS

Table 1 presents the distribution of selected characteristics for cases and controls. More cases than controls reported a family history of non-Hodgkin's lymphoma. Controls, on the other hand, had a slightly higher level of education and alcohol intake. The distribution of other factors (such as race and tobacco smoking) was quite similar between the cases and the controls.

As shown in table 2, there is no significant association between hair-coloring product use and risk of non-

**TABLE 1. Selected baseline characteristics of non-Hodgkin's lymphoma cases and controls, Connecticut, 1996–2002**

	Cases		Controls	
	No.	%	No.	%
Age (years)				
<50	119	19.8	155	21.6
50–70	277	46.1	317	44.2
>70	205	34.1	245	34.2
Race				
White	571	95.0	667	93.0
Black	18	3.0	25	3.5
Others	12	2.0	25	3.5
Family history of NHL*				
No	592	98.5	713	99.4
Yes	9	1.5	4	0.6
Tobacco smoking				
No	270	44.9	323	45.0
Yes	331	55.1	394	55.0
Alcohol drinking				
No	228	37.9	231	32.2
Yes	371	61.8	484	67.5
Missing	2	0.3	2	0.3
Educational level				
High school or less	261	43.4	265	37.0
College or higher	340	56.6	452	63.0

\* NHL, non-Hodgkin's lymphoma.

Hodgkin's lymphoma for ever users or for those who started using the products in 1980 or later. However, women who started using hair-coloring products before 1980 had a slightly increased risk for overall product use (odds ratio (OR) = 1.3, 95 percent confidence interval (CI): 1.0, 1.8), for permanent products (OR = 1.4, 95 percent CI: 1.0, 1.9), and for darker products (OR = 1.4, 95 percent CI: 1.0, 1.9).

Table 3 presents the risk of non-Hodgkin's lymphoma by type, color, and other characteristics of hair-coloring products for women who started using them before 1980. There was a slight increase in risk (OR = 1.5, 95 percent CI: 1.0, 2.1) among women who used dark permanent hair dyes. The increased risk, however, appeared to be limited to those with the longest duration of use and the greatest number of applications. There was no clear evidence of a dose-response with the total number of applications, in duration of use, or in years since first use. A slight increase in risk was also observed for semipermanent dark hair-coloring products, but risk was seen only among those with the shortest duration of use and with the smallest total number of applications. There was no significantly increased risk associated with the use of light-color permanent or semipermanent products.

The risk of non-Hodgkin's lymphoma among women who used hair-coloring products before 1980 by histology, immunologic cell type, and tumor grade is presented in table 4. A significantly increased risk was seen for follicular lymphoma and B-cell non-Hodgkin's lymphoma among

**TABLE 2. Risk of non-Hodgkin's lymphoma by type, color, and time period of hair-coloring product use, Connecticut, 1996–2002**

	Never		Ever		Started before 1980		Started 1980 or later	
	No. of cases/ no. of controls	OR*	No. of cases/ no. of controls	OR† (95% CI)*	No. of cases/ no. of controls	OR† (95% CI)	No. of cases/ no. of controls	OR† (95% CI)
Total	152/198	1.0	449/519	1.1 (0.9, 1.5)	295/295	1.3 (1.0, 1.8)	154/224	0.9 (0.7, 1.2)
Type								
Permanent	152/198	1.0	340/390	1.2 (0.9, 1.5)	176/176	1.4 (1.0, 1.9)	111/161	0.9 (0.7, 1.3)
Semipermanent	152/198	1.0	164/183	1.2 (0.9, 1.6)	70/67	1.4 (0.9, 2.1)	56/90	0.8 (0.5, 1.2)
Temporary	152/198	1.0	31/35	1.2 (0.7, 2.0)	11/17	0.9 (0.4, 1.9)	10/8	1.6 (0.6, 4.3)
Color‡								
Dark color	152/198	1.0	281/321	1.1 (0.9, 1.5)	131/132	1.4 (1.0, 1.9)	107/147	0.9 (0.7, 1.3)
Light color	152/198	1.0	214/250	1.1 (0.8, 1.5)	113/118	1.3 (0.9, 1.8)	58/93	0.8 (0.5, 1.3)

\* OR, odds ratio; CI, confidence interval.

† Adjusted for age and family history of non-Hodgkin's lymphoma in first-degree relatives.

‡ Dark color: black, brown, and red. Light color: blonde.

women who used permanent hair-coloring products. A significantly increased risk was also observed for B-cell lymphoma for women who used dark hair-coloring products and for follicular lymphoma and low-grade non-Hodgkin's lymphoma for women who used light hair-coloring products.

For those subjects who began using these products in 1980 or later, the risk of non-Hodgkin's lymphoma by type and

color of hair-coloring products was also examined. We found no significantly increased risk of non-Hodgkin's lymphoma among these women for any type or color of the products used (data not shown). Further stratification by subtype of non-Hodgkin's lymphoma also showed no significant association with the use of any type of hair-coloring products (table 5).

**TABLE 3. Risk of non-Hodgkin's lymphoma by type, color, and other characteristics of hair-coloring products used before 1980, Connecticut, 1996–2002**

Hair dye use	Permanent				Semipermanent			
	Dark-color products		Light-color products		Dark-color products		Light-color products	
	No. of cases/ no. of controls	OR*,† (95% CI)*	No. of cases/ no. of controls	OR† (95% CI)	No. of cases/ no. of controls	OR (95% CI)	No. of cases/ no. of controls	OR† (95% CI)
Never	152/198	1.0	152/198	1.0	152/198	1.0	152/198	1.0
Ever	84/79	1.5 (1.0, 2.1)	99/105	1.3 (0.9, 1.8)	56/51	1.5 (1.0, 2.3)	14/17	1.1 (0.5, 2.3)
Age at first use (years)								
<25	17/15	1.3 (0.6, 2.7)	36/37	1.1 (0.6, 1.8)	9/10	1.0 (0.4, 2.6)	1/4	0.3 (0.0, 2.5)
≥25	67/64	1.3 (0.9, 1.9)	63/67	1.1 (0.8, 1.6)	47/41	1.4 (0.9, 2.2)	13/13	1.2 (0.5, 2.5)
Duration of use (years)								
<15	22/23	1.2 (0.6, 2.1)	25/21	1.4 (0.7, 2.5)	38/28	1.6 (1.0, 2.7)	5/7	0.8 (0.3, 2.6)
15–25	37/40	1.1 (0.7, 1.8)	38/37	1.0 (0.6, 1.6)	11/13	0.9 (0.4, 1.9)	6/6	1.0 (0.3, 3.0)
>25	25/16	2.1 (1.0, 4.0)	36/46	1.1 (0.6, 1.8)	7/10	1.0 (0.3, 3.1)	3/4	1.2 (0.2, 5.8)
Total no. of applications								
<100	27/28	1.2 (0.7, 2.0)	36/30	1.3 (0.8, 2.1)	37/26	1.7 (1.0, 2.9)	5/8	0.7 (0.2, 2.2)
100–200	17/20	1.1 (0.6, 2.1)	27/30	1.2 (0.7, 2.1)	8/11	0.9 (0.4, 2.2)	3/4	0.9 (0.2, 3.9)
>200	40/30	1.7 (1.0, 2.8)	35/44	0.8 (0.5, 1.4)	11/14	0.9 (0.4, 2.1)	6/5	1.4 (0.4, 4.6)
Years since first use								
<25	24/20	1.4 (0.8, 2.6)	20/17	1.3 (0.7, 2.6)	16/8	2.4 (1.0, 5.7)	3/2	1.8 (0.3, 10.7)
25–35	34/36	1.2 (0.7, 1.9)	47/46	1.2 (0.8, 1.8)	22/24	1.1 (0.6, 2.0)	5/9	0.6 (0.2, 1.9)
>35	26/23	1.4 (0.8, 2.5)	32/41	0.9 (0.6, 1.5)	18/19	1.1 (0.6, 2.2)	6/6	1.1 (0.4, 3.6)

\* OR, odds ratio; CI, confidence interval.

† Adjusted for age and family history of non-Hodgkin's lymphoma in first-degree relatives.

**TABLE 4. Risk of NHL\* associated with hair-coloring product use, by type of NHL and type of hair color products used before 1980, Connecticut, 1996–2002**

NHL subtype	Never users		Type				Color†			
	No. of cases/ no. of controls	OR*	Permanent		Semipermanent		Dark		Light	
			No. of cases/ no. of controls	OR‡ (95% CI)*	No. of cases/ no. of controls	OR‡ (95% CI)	No. of cases/ no. of controls	OR (95% CI)	No. of cases/ no. of controls	OR‡ (95% CI)
By histology										
Follicular	27/198	1.0	43/176	1.9 (1.1, 3.2)	14/67	1.5 (0.8, 3.2)	28/132	1.6 (0.9, 2.8)	34/118	2.2 (1.2, 3.8)
Diffuse	94/198	1.0	98/176	1.3 (0.9, 1.9)	36/67	1.2 (0.7, 2.0)	71/132	1.3 (0.9, 1.9)	56/118	1.1 (0.7, 1.6)
Other	31/198	1.0	35/176	1.3 (0.7, 2.1)	20/67	1.9 (1.0, 3.5)	32/132	1.6 (0.9, 2.7)	23/118	1.2 (0.7, 2.2)
By immunologic cell type										
B cell	110/198	1.0	147/176	1.6 (1.2, 2.3)	52/67	1.5 (1.0, 2.3)	106/132	1.6 (1.1, 2.3)	93/118	1.5 (1.0, 2.2)
T cell	16/198	1.0	6/176	0.4 (0.2, 1.1)	4/67	0.8 (0.2, 2.4)	7/132	0.7 (0.3, 1.6)	1/118	0.1 (0.0, 0.8)
Other	26/198	1.0	23/176	1.0 (0.5, 1.8)	14/67	1.5 (0.7, 3.0)	18/132	1.0 (0.5, 2.0)	19/118	1.2 (0.6, 2.3)
By grade										
Low	42/198	1.0	59/176	1.6 (1.0, 2.5)	21/67	1.4 (0.8, 2.6)	39/132	1.4 (0.8, 2.2)	44/118	1.8 (1.1, 2.9)
Intermediate/ high	73/198	1.0	82/176	1.3 (0.9, 1.9)	29/67	1.2 (0.7, 2.0)	60/132	1.3 (0.8, 1.9)	46/118	1.0 (0.7, 1.6)
Other	30/198	1.0	35/176	1.3 (0.8, 2.2)	20/67	1.9 (1.0, 3.7)	32/132	1.6 (0.9, 2.8)	23/118	1.3 (0.7, 2.3)

\* NHL, non-Hodgkin's lymphoma; OR, odds ratio; CI, confidence interval.

† Dark color: black, brown, and red. Light color: blonde.

‡ Adjusted for age and family history of NHL in first-degree relatives.

**DISCUSSION**

In this population-based case-control study, we found no increased risk of non-Hodgkin's lymphoma among women who started using hair-coloring products in 1980 or later. Among women who started using the products before 1980, however, we did find an increased risk of non-Hodgkin's

lymphoma. The risk was mainly seen among women with the longest duration and the greatest number of applications of dark permanent hair-coloring products. There was, however, no clear evidence of a dose-response with the total number of applications, in the duration of use, or in the years since first use. The risk appears to vary by non-Hodgkin's

**TABLE 5. Risk of NHL\* associated with hair-coloring product use, by type of NHL and type of hair color products used in 1980 or later, Connecticut, 1996–2002**

NHL subtype	Never users		Type				Color†			
	No. of cases/ no. of controls	OR*	Permanent		Semipermanent		Dark		Light	
			No. of cases/ no. of controls	OR‡ (95% CI)*	No. of cases/ no. of controls	OR‡ (95% CI)	No. of cases/ no. of controls	OR‡ (95% CI)	No. of cases/ no. of controls	OR‡ (95% CI)
By histology										
Follicular	27/198	1.0	24/161	1.0 (0.5, 1.9)	13/90	0.9 (0.4, 1.9)	24/147	1.1 (0.6, 2.0)	14/93	1.0 (0.5, 2.1)
Diffuse	94/198	1.0	64/161	0.9 (0.6, 1.4)	35/90	0.9 (0.5, 1.4)	63/147	0.9 (0.6, 1.4)	36/93	0.9 (0.5, 1.4)
Other	31/198	1.0	23/161	1.0 (0.5, 1.8)	8/90	0.6 (0.3, 1.4)	20/147	0.9 (0.5, 1.6)	8/93	0.6 (0.2, 1.4)
By immunologic cell type										
B cell	110/198	1.0	88/161	1.0 (0.7, 1.5)	48/90	0.9 (0.6, 1.5)	89/147	1.1 (0.8, 1.6)	47/93	0.9 (0.6, 1.5)
T cell	16/198	1.0	10/161	0.6 (0.3, 1.5)	5/90	0.6 (0.2, 1.7)	9/147	0.6 (0.3, 1.5)	5/93	0.6 (0.2, 1.7)
Other	26/198	1.0	13/161	0.8 (0.4, 1.6)	3/90	0.3 (0.1, 1.1)	9/147	0.6 (0.2, 1.2)	6/93	0.6 (0.2, 1.7)
By grade										
Low	42/198	1.0	29/161	0.9 (0.5, 1.5)	15/90	0.8 (0.4, 1.5)	27/147	0.8 (0.5, 1.5)	18/93	1.0 (0.5, 1.8)
Intermediate/ high	80/198	1.0	59/161	1.0 (0.6, 1.5)	33/90	0.9 (0.6, 1.5)	60/147	1.0 (0.7, 1.6)	32/93	0.9 (0.5, 1.5)
Other	30/198	1.0	23/161	1.0 (0.5, 1.8)	8/90	0.6 (0.3, 1.4)	20/147	0.9 (0.5, 1.7)	8/93	0.6 (0.3, 1.4)

\* NHL, non-Hodgkin's lymphoma; OR, odds ratio; CI, confidence interval.

† Dark color: black, brown, and red. Light color: blonde.

‡ Adjusted for age and family history of NHL in first-degree relatives.

lymphoma subtypes, with a significantly increased risk observed for follicular and B-cell non-Hodgkin's lymphoma for permanent hair dye users, for B-cell non-Hodgkin's lymphoma for dark dye users, and for follicular and low-grade non-Hodgkin's lymphoma for light dye users.

Hair dyes and other constituents vary according to the type and the color of hair-coloring product (12, 13). Carcinogenic compounds can be found in both permanent and semipermanent products and in most color formulations, but they usually occur in greater concentrations in the dark color products than in the light color products (3). Compounds used in the formulation of permanent dyes may be used in semipermanent dyes, with the addition of an oxidizing agent. Studies show that some hair dye components become strongly mutagenic after oxidization by H<sub>2</sub>O<sub>2</sub> (9). Thus, a higher risk of non-Hodgkin's lymphoma associated with darker permanent hair-coloring products is biologically plausible.

As cited earlier, the formulations of hair-coloring products have changed dramatically over the past 20 years (7, 8). Some carcinogenic compounds have been removed from the components of hair-coloring products. An increased risk of non-Hodgkin's lymphoma found only among women who started using the products before 1980, but not among women who began use after 1980, is consistent with these changes.

It should also be noted that an increased risk of non-Hodgkin's lymphoma among users of permanent darker-color products, who started using the products before 1980, was seen in our study only among women who had used the products for more than 25 years (table 3). This may indicate that a period of at least 25 years of use is needed for hair dye use to increase non-Hodgkin's lymphoma risk. If this were the case, users who started using hair dye products after 1980 in our study would have used the products for less than 25 years, and our study would not be able to find an association because subjects were still in their induction and latency periods. Thus, while it is tempting to conclude that the observed different association for the two time periods appears to be consistent with the change in carcinogen contents in hair dye products during the past two decades, there is still a possibility that women who started using the products after 1980 have not yet reached the minimum induction and latency period. Since the number of subjects who used hair dye after 1980 was in general smaller than that whose use was before 1980, it is possible that this observed difference could be due to chance. Future studies are clearly needed to address the issue.

Several strengths and potential limitations of the study design must be considered in interpreting our findings. First, in this relatively large population-based case-control study, we assessed hair dye use at the time of diagnosis of the disease, not years before the diagnosis when young women may not have begun their hair dye use; second, we asked detailed questions and used a long list of names of hair-coloring processes to capture all hair dye uses; third, we collected detailed information on the duration, frequency, and type and color of hair-coloring products used for each period of use, which allowed us to quantitatively evaluate the risk by the major characteristics of hair-coloring product uses. Information regarding the year of first use allowed

evaluation of the effect of changes in the contents of hair-coloring products during the past 20 years. Finally, the standardized, structured questionnaires used in this study were administered through face-to-face interviews with the subjects; no surrogate interviewing was used, which minimized the potential for misclassification of exposure.

The section of the questionnaire used to collect information on hair-coloring product use in this study was developed by the Johns Hopkins University and Clairol Company; it was specifically designed to assess hair-coloring product use and the risk of non-Hodgkin's lymphoma. Although we have no direct measures of validity in this study, other research relating hair dye use and risk of breast cancer (6, 14–21), non-Hodgkin's lymphoma (3, 5, 7), multiple myeloma (22, 23), leukemia (3), and bladder cancer (24) suggests that women generally are able to report hair-coloring product use characteristics (such as duration, timing, frequency, type, and color).

One limitation for this case-control study is the potential for recall bias resulting from self-report of lifetime hair-coloring product use. In a reliability study, Shore et al. (16) reported a correlation coefficient (*r*) of 0.86 for duration of hair dye use from two interviews 1 year apart, with virtually no difference for cases and controls. The correlation coefficient for frequency of use was 0.92. However, although the results may indicate that the hair-coloring product information collected through self-report was reliable, differential overreporting of hair-coloring product use among non-Hodgkin's lymphoma patients may still occur if patients believe that hair-coloring product use or specific type (or color) of hair-coloring product may increase a person's non-Hodgkin's lymphoma risk. The lack of association between overall hair-coloring product use or hair color products used after 1980 and non-Hodgkin's lymphoma argues against recall bias as having a major role for the results of our study.

Another potential limitation of the study is the relatively low response rate from potentially eligible subjects. Selection bias, however, is unlikely to have played a major role in the observed associations since we found no overall association between hair-coloring product use and non-Hodgkin's lymphoma risk when all cases and controls were considered. The observed association also differs by duration of use and total number of applications and varies by type, color of products used, and period of use.

The role of chance should also be considered when interpreting our findings. Although a sample size of 601 cases and more than 700 age-matched controls gives us sufficient power to examine the overall relation between hair-coloring product use and non-Hodgkin's lymphoma risk, the statistical power to examine the relation by non-Hodgkin's lymphoma subtype, by color and type of hair-coloring products used, and by time period of use may be still limited.

In summary, in this population-based case-control study, we found an increased risk of non-Hodgkin's lymphoma among women who started using darker hair-coloring products before 1980 but not among women who started using the products after that. Future studies designed to collect similar exposure information are needed to determine whether our findings for hair dye use before 1980 are replicated in other populations.

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