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Original Contribution

Personal Use of Hair Dye and the Risk of Certain Subtypes of Non-Hodgkin Lymphoma

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Personal use of hair dye has been inconsistently linked to risk of non-Hodgkin lymphoma (NHL), perhaps because of small samples or a lack of detailed information on personal hair-dye use in previous studies. This study included 4,461 NHL cases and 5,799 controls from the International Lymphoma Epidemiology Consortium 1988–2003. Increased risk of NHL (odds ratio (OR) = 1.3, 95% confidence interval (CI): 1.1, 1.4) associated with hair-dye use was observed among women who began using hair dye before 1980. Analyses by NHL subtype showed increased risk for follicular lymphoma (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) but not for other NHL subtypes. The increased risks of FL (OR = 1.4, 95% CI: 1.1, 1.9) and CLL/SLL (OR = 1.5, 95% CI: 1.1, 2.0) were mainly observed among women who started using hair dyes before 1980. For women who began using hair dye in 1980 or afterward, increased FL risk was limited to users of dark-colored dyes (OR = 1.5, 95% CI: 1.1, 2.0). These results indicate that personal hair-dye use may play a role in risks of FL and CLL/SLL in women who started use before 1980 and that increased risk of FL among women who started use during or after 1980 cannot be excluded.

case-control studies; hair dyes; lymphoma, non-Hodgkin

Abbreviations: CI, confidence interval; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; InterLymph, International Lymphoma Epidemiology Consortium; NHL, non-Hodgkin lymphoma; OR, odds ratio; PPD, paraphenylenediamine.

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The incidence of non-Hodgkin lymphoma (NHL) has been increasing worldwide during the past several decades (1, 2). A recent study showed continuing increases in several major subtypes of NHL, including diffuse large B-cell lymphoma and follicular lymphoma, especially among older persons (3). Although severe immunosuppression resulting from acquired or congenital conditions, organ transplants, medical treatments, or viral infections is an established risk factor for NHL (4), it explains only a small proportion of NHL cases. Thus, the etiology of NHL is largely unknown, and presently there are few specific interventions to reduce risk of the disease.

Personal use of hair dye has been suggested as a risk factor for NHL. As a modifiable exposure, the role of hair dye in NHL is of particular interest because of the potential opportunity for prevention. It is estimated that sales of hair-color products worldwide total approximately $12 billion per year and that up to 50 percent of the adult population of high-resource countries uses hair colorants (5). Hair-coloring products include permanent, semipermanent, and temporary dyes that vary by chemical formulation and are distinguished mainly by how long they last and whether they penetrate the hair shaft. Permanent dyes represent approximately 80 percent of the hair-color market (5). Some compounds in hair dyes have been reported to be mutagenic or carcinogenic in bioassay systems (6). Many oxidative dye products were reformulated in the early 1980s to eliminate ingredients that produced tumors in experimental bioassay studies. Although it is unclear whether the current compounds have carcinogenic effects or can affect overall immune response, paraphenylenediamine (PPD), a major arylamine currently used in most hair dyes, has been suggested as a putative carcinogen (7). In addition, it has been found that many permanent hair dyes are contaminated with 4-aminobiphenyl, a recognized human carcinogen (8).

During the past two decades, the general public and the scientific community have shown great interest in the potential health impact of personal hair dyes. Epidemiologic studies have been conducted to investigate the relation between hair-dye use and human cancer risk, including risk of NHL (9–19). The reported results have been inconsistent, perhaps because of methodological limitations, including recall bias, limited detailed information about lifetime hair-dye use, and small samples. Three recent studies from the United States and one from Europe suggested that it might be necessary to investigate the relation between hair-dye use and NHL risk by dye color and time period of use, separating persons who started using hair dyes before 1980 from those who started using them later, when hair-dye formulations underwent significant modification (14, 17, 19, 20).

In this analysis, we pooled original data from four previously published case-control studies (14, 17, 19, 20) that are part of the International Lymphoma Epidemiology Consortium (InterLymph) to investigate the relation between personal hair-dye use and risk of NHL in detail. Each study collected detailed information on hair-dye use (including duration of use, total number of applications, dates of use, and type and color of dye used). In addition, NHL was classified by histologic subtype. With a total of 10,260 study participants (4,461 NHL cases and 5,799 controls), this InterLymph-based study had greater statistical power than previous studies to evaluate the relation between personal use of hair dyes and NHL risk, particularly for analyses by NHL subtype.

MATERIALS AND METHODS

Study population

A total of 4,461 patients with incident NHL (*International Classification of Diseases for Oncology* codes M-9590–9591, M-9595, M-9670–9673, M-9675–9676, M-9680–9688, M-9690–9691, M-9695–9698, M-9700, M-9702–9703, M-9705–9711, M-9713–9715, M-9823, and M-9827) and 5,799 controls from four case-control studies (14, 17, 19, 20) that collected detailed information on personal hair-dye use were included in this pooled analysis. The characteristics of each study are presented in table 1. All study protocols were approved by local institutional review boards, and written informed consent was obtained from all participants.

Within each study, NHL diagnoses and subtypes were confirmed by pathologists, and NHL cases were categorized by histologic type. For this pooled analysis, NHL cases were classified according to the World Health Organization classification system and as proposed by the InterLymph Pathology Working Group (21). Five major subtypes of NHL were included for subtype analyses: diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal-zone lymphoma, and T-cell lymphoma.

Information on hair-dye use and other potential risk factors was collected by trained interviewers using standardized, structured questionnaires. The Connecticut Women's NHL Study (from Yale University), the NCI/SEER (National Cancer Institute/Surveillance, Epidemiology, and End Results) Multi-Center Case-Control Study, and the International Case-Control Study of Lymphomas from Europe (EpiLymph) used very similar questionnaires pertaining to history of hair-dye use. For example, subjects in these studies were first asked whether they had ever used any hair-coloring products. If they had, these subjects were asked: 1) at what age they used each product for the first time; 2) how often they used each product (weekly, monthly, yearly, or other); 3) at what age they used each product for the last time; and 4) what type (permanent or nonpermanent, including semipermanent and temporary) and color (dark color, including black, brown, and red, or light color, including blond) of product they used. In the Epidemiology of NHL Study (from the University of California, San Francisco), participants were first asked whether they had ever used hair-coloring products on their own hair more than five times up to 1 year before the diagnosis or interview. If they had, they were asked about their ages at first and last use of each product and the frequency, duration (in years), type, and color of each product used. For analyses that included time period of use, the participants were categorized on the basis of whether they had started using hair dyes before 1980 or during 1980 or later (i.e., no use of any type prior to 1980).

TABLE 1. Characteristics of case-control studies included in a pooled analysis of hair-dye use and non-Hodgkin lymphoma, 1988–2003

Study	Published article	Location(s)	Years of study	Age (years) of participants	Cases ($n = 4,461$)			Controls ($n = 5,799$)			
					Source	No.	Participation rate (%)	Matching criteria	Source	No.	Participation rate (%)
Connecticut Women's NHL* Study (Yale University)	Zhang et al., 2004 (17)	Connecticut	1996–2000	21–84	Population-based	601	72	Frequency-matched by age within 5-year groups	Age <65 years: RDD*; age ≥65 years: random selection from CMS* files	717	RDD: 69, CMS: 47
NCI/SEER* Multi-Center Case-Control Study	Morton et al., 2007 (20)	Detroit, Michigan; Los Angeles, California; Seattle, Washington; and Iowa	1998–2001	20–74	Population-based	1,319	76	Frequency-matched by age within 5-year groups, sex, and study site	Age <65 years: RDD; age ≥65 years: random selection from CMS files	1,056	52
Epidemiology of NHL Study (University of California, San Francisco)	Holly et al., 1998 (14)	San Francisco Bay Area, California	1988–1993	21–74	Population-based	837	72	Frequency-matched by 5-year age group, sex, and county of residence within 5 years	RDD and random selection from CMS files for persons aged ≥65 years	1,609	78
International Case-Control Study of Lymphomas from Europe (EpiLymph)	de Sanjosé et al., 2006 (19)	Italy, Spain, Germany, France, Finland, Ireland, and the Czech Republic	1998–2003	≥18	Population-based (Italy and Germany) or hospital-based (Spain, France, Finland, Ireland, and Czech Republic)	1,704	87	Age, sex, and geographic area	Population-based (Italy and Germany) or hospital-based (Spain, France, Finland, Ireland, and Czech Republic)	2,417	75

* NHL, non-Hodgkin lymphoma; RDD, random digit dialing; CMS, Centers for Medicare and Medicaid Services; NCI/SEER, National Cancer Institute/Surveillance, Epidemiology, and End Results.

TABLE 2. Characteristics of cases and controls in a pooled analysis of hair-dye use and non-Hodgkin lymphoma, 1988–2003

Characteristic	Cases ($n = 4,461$)		Controls ($n = 5,799$)	
	No.	%	No.	%
Study				
Connecticut Women's NHL* Study (Yale University)	601	13.5	717	12.4
NCI/SEER* Multi-Center Case-Control Study	1,319	29.5	1,056	18.2
Epidemiology of NHL Study (University of California, San Francisco)	837	18.8	1,609	27.7
International Case-Control Study of Lymphomas from Europe (EpiLymph)	1,704	38.2	2,417	41.7
Sex				
Male	2,123	47.6	2,837	48.9
Female	2,338	52.4	2,962	51.1
Race				
White	4,108	92.1	5,347	92.2
Black	175	3.9	248	4.3
Other	178	4.0	204	3.5
Age group (years)				
<30	147	3.3	309	5.3
30–39	362	8.1	599	10.3
40–49	644	14.4	798	13.8
50–59	971	21.8	1,183	20.4
60–69	1,330	29.8	1,631	28.1
70–79	912	20.5	1,159	20.0
≥80	95	2.1	120	2.1
NHL subtype				
Diffuse large B-cell lymphoma	1,543	34.6		
Follicular lymphoma	908	20.3		
CLL/SLL*	736	16.5		
Marginal zone lymphoma	146	3.3		
T-cell lymphoma	298	6.7		
Other	830	18.6		

* NHL, non-Hodgkin lymphoma; NCI/SEER, National Cancer Institute/Surveillance, Epidemiology, and End Results; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

Data analysis

From each study, we obtained original data for this pooled analysis in order to investigate the relation between personal hair-dye use and risk of NHL. The likelihood ratio test was used to test heterogeneity across studies by comparing the logistic regression models with and without the cross-product terms of hair-dye use (i.e., ever use of dark-colored dyes or ever use of permanent dyes) and study. A random-effects model was used to compute the pooled risk estimates and 95 percent confidence intervals, weighted by the inverse

TABLE 3. Risk of non-Hodgkin lymphoma associated with use of hair dye, by sex and year of starting hair-dye use, 1988–2003

	Total					Women					Men				
	No. of controls	No. of cases	OR*,†	95% CI*	*p* value	No. of controls	No. of cases	OR†	95% CI	*p* value	No. of controls	No. of cases	OR†	95% CI	*p* value
Any use of hair dye															
Never use	3,432	2,433				874	576				2,558	1,857			
Ever use	2,365	1,915	1.0	0.9, 1.2	0.38	2,087	1,711	1.1	1.0, 1.3	0.04	278	204	0.9	0.7, 1.1	0.38
Type of dye															
Permanent	1,561	1,217	1.0	0.9, 1.2	0.60	1,433	1,131	1.1	1.0, 1.3	0.09	128	86	0.9	0.6, 1.2	0.33
Nonpermanent	997	854	1.1	1.0, 1.3	0.11	884	765	1.2	1.0, 1.4	0.02	113	89	1.1	0.8, 1.4	0.72
Color of dye															
Dark color (including black, brown, and red)	1,405	1,158	1.0	0.9, 1.1	0.82	1,252	1,033	1.1	1.0, 1.3	0.12	153	125	0.9	0.7, 1.1	0.27
Light color (including blond)	939	763	1.0	0.9, 1.2	0.54	879	734	1.1	1.0, 1.3	0.07	60	29	0.7	0.4, 1.1	0.15
Both type and color															
Permanent dark	898	697	1.0	0.9, 1.1	0.95	813	637	1.1	0.9, 1.3	0.22	85	60	0.8	0.6, 1.2	0.27
Permanent light	715	551	1.1	0.9, 1.2	0.35	671	530	1.2	1.0, 1.4	0.07	44	21	0.8	0.5, 1.4	0.48
Nonpermanent dark	580	565	1.1	1.0, 1.3	0.17	525	507	1.2	1.0, 1.5	0.02	55	58	1.0	0.7, 1.5	0.87
Nonpermanent light	158	144	1.0	0.8, 1.3	0.74	153	142	1.2	0.9, 1.5	0.20	5	2	0.5	0.1, 2.6	0.42
Use of hair dye starting before 1980															
Never use	3,432	2,433				874	576				2,558	1,857			
Ever use	1,169	1,053	1.2	1.0, 1.3	0.01	1,102	997	1.3	1.1, 1.4	<0.01	67	56	1.0	0.7, 1.5	0.90
Type of dye															
Permanent	778	678	1.2	1.0, 1.4	0.02	746	658	1.3	1.1, 1.5	<0.01	32	20	0.8	0.4, 1.4	0.45
Nonpermanent	444	392	1.2	1.0, 1.4	0.06	413	365	1.2	1.0, 1.5	0.02	31	27	1.3	0.7, 2.2	0.41
Color of dye															
Dark color (including black, brown, and red)	644	579	1.1	1.0, 1.3	0.07	607	547	1.2	1.1, 1.5	0.01	37	32	0.9	0.6, 1.5	0.69
Light color (including blond)	479	462	1.2	1.1, 1.5	<0.01	469	457	1.3	1.1, 1.6	<0.01	10	5	0.7	0.2, 2.2	0.58
Both type and color															
Permanent dark	435	372	1.2	1.0, 1.4	0.05	413	356	1.3	1.0, 1.5	0.01	22	16	0.9	0.4, 1.7	0.67
Permanent light	363	328	1.3	1.1, 1.5	<0.01	354	326	1.3	1.1, 1.6	<0.01	9	2	0.4	0.1, 2.0	0.28
Nonpermanent dark	226	232	1.1	0.9, 1.4	0.28	213	217	1.2	1.0, 1.6	0.06	13	15	1.1	0.5, 2.3	0.89
Nonpermanent light	72	76	1.2	0.8, 1.7	0.32	72	76	1.3	0.9, 1.9	0.12	0	0			
Use of hair dye starting in 1980 or later															
Never use	3,432	2,433				874	576				2,558	1,857			
Ever use	1,157	844	1.0	0.9, 1.1	0.67	966	703	1.1	0.9, 1.2	0.40	191	141	0.9	0.7, 1.1	0.32
Type of dye															
Permanent	709	480	0.9	0.8, 1.1	0.35	616	415	1.0	0.9, 1.2	0.86	93	65	0.9	0.6, 1.3	0.51

Nonpermanent	486	401	1.1	0.9, 1.3	0.23	406	342	1.2	1.0, 1.5	0.05	80	59	1.0	0.7, 1.4	0.85			
Color of dye																		
Dark color (including black, brown, and red)	716	548	1.0	0.8, 1.1	0.76	604	459	1.1	0.9, 1.3	0.32	112	89	0.8	0.6, 1.1	0.24			
Light color (including blond)	390	262	0.9	0.8, 1.1	0.35	341	238	1.0	0.8, 1.3	0.83	49	24	0.7	0.4, 1.2	0.20			
Both type and color																		
Permanent dark	421	288	0.9	0.8, 1.1	0.29	362	246	1.0	0.8, 1.2	0.97	59	42	0.8	0.5, 1.2	0.32			
Permanent light	288	185	0.9	0.8, 1.2	0.58	254	166	1.0	0.8, 1.3	0.88	34	19	0.9	0.5, 1.7	0.84			
Nonpermanent dark	314	294	1.2	1.0, 1.4	0.13	272	254	1.3	1.0, 1.6	0.02	42	40	1.0	0.6, 1.5	0.84			
Nonpermanent light	71	52	0.9	0.6, 1.3	0.65	66	50	1.1	0.7, 1.6	0.77	5	2	0.5	0.1, 2.6	0.42			

* OR, odds ratio; CI, confidence interval.
† Adjusted for age (continuous), sex (male/female), race (White, Black, or other), and study site.

marginal variance (the sum of the study-specific variance and the variance of the exposure effect across studies or random study effects) (22). Risk estimates from the random-effects models were consistent with the results from dichotomous and polytomous unconditional logistic regression models. Therefore, we present odds ratios and 95 percent confidence intervals derived from dichotomous and polytomous unconditional logistic regression models. Continuous variables, including duration of hair-dye use, frequency of hair-dye use, and total number of applications of hair dye, were categorized into tertiles based on the distribution of any hair-dye use among controls. The final model was adjusted for age (continuous), sex (male/female), race (White, Black, or other), and study center. Adjustments for other variables, such as family history of hematopoietic cancer in first-degree relatives, tobacco smoking, alcohol consumption, and highest level of education, did not produce material changes in the risk estimates (<10 percent change in risk estimates) and thus were not included in the final model.

Formal testing between NHL and the linear trends for duration, frequency, and total number of applications of hair-dye was performed by assigning values of 0, 1, 2, or 3 for exposure groups. More specifically, restricted cubic splines were compared with the linear models and evaluated by likelihood ratio test and by visual inspection of the restricted cubic spline graphs (23). Evidence from the cubic spline analyses did not support a departure from linear trend of a dose-response relation. Sensitivity analyses were performed by comparing the risk estimates obtained from models that systematically excluded each study population to determine whether any one population had a disproportionate influence on the summary estimated risk. All analyses were performed using SAS 9.1 (SAS Institute, Inc., Cary, North Carolina) and Stata 8.0 (Stata Corporation, College Station, Texas). All statistical tests were two-sided with a significance level of 0.05.

RESULTS

Table 2 provides demographic and subtype data for the pooled study population by case ($n = 4{,}461$) or control ($n = 5{,}799$) status. Both the case population and the control population were predominantly White (≥92 percent), and they had similar age and sex distributions.

Table 3 presents the results for personal hair-dye use and NHL risk, overall and by sex and time period of hair-dye use. Among women, 75 percent of the cases and 70 percent of the controls reported ever having used hair dyes. Stratification by time period of use showed an increased risk of NHL among women who started using hair dyes before 1980 as compared with nonusers (odds ratio (OR) = 1.3, 95 percent confidence interval (CI): 1.1, 1.4). The increased risk among women did not show a clear pattern by product type or color. For women who started using hair dyes in 1980 or later, an increased risk was associated with use of nonpermanent dark-colored dye (OR = 1.3, 95 percent CI: 1.0, 1.6). Among men, approximately 10 percent of cases and 10 percent of controls had ever used hair dyes. Risk of NHL was not associated with hair-dye use before or after

TABLE 4. Risk of non-Hodgkin lymphoma associated with use of hair dye among women, by subtype and year of starting hair-dye use, 1988–2003

	Diffuse large B-cell lymphoma				Follicular lymphoma				CLL/SLL*				Marginal-zone lymphoma				T-cell lymphoma			
	No. of cases	OR*,†	95% CI*	*p* value	No. of cases	OR†	95% CI	*p* value	No. of cases	OR†	95% CI	*p* value	No. of cases	OR†	95% CI	*p* value	No. of cases	OR†	95% CI	*p* value
Any use of hair dye																				
Never use	224				117				80				20				40			
Ever use	564	1.0	0.9, 1.2	0.69	400	1.3	1.0, 1.6	0.02	244	1.3	1.0, 1.6	0.10	74	1.1	0.7, 1.9	0.69	109	1.0	0.7, 1.5)	0.91
Type of dye																				
Permanent	351	1.0	0.8, 1.2	0.64	274	1.3	1.1, 1.7	0.02	163	1.2	0.9, 1.6	0.15	52	1.2	0.7, 2.1	0.42	65	0.9	0.6, 1.4	0.61
Nonpermanent	261	1.1	0.9, 1.4	0.36	180	1.3	1.0, 1.7	0.03	101	1.3	0.9, 1.7	0.14	32	1.0	0.6, 1.8	0.97	58	1.3	0.8, 2.0	0.24
Color of dye																				
Dark color (including black, brown, and red)	314	0.9	0.8, 1.2	0.61	249	1.3	1.0, 1.7	0.02	148	1.2	0.9, 1.7	0.14	53	1.2	0.7, 2.0	0.57	65	1.0	0.6, 1.4	0.83
Light color (including blond)	251	1.1	0.9, 1.3	0.4	173	1.3	1.0, 1.7	0.06	104	1.3	0.9, 1.8	0.12	29	1.0	0.6, 1.8	0.96	40	0.9	0.6, 1.4	0.58
Both type and color																				
Permanent dark	185	0.9	0.7, 1.1	0.24	164	1.4	1.1, 1.8	0.01	96	1.3	0.9, 1.7	0.14	35	1.4	0.8, 2.4	0.3	38	0.9	0.6, 1.4	0.68
Permanent light	175	1.0	0.8, 1.3	0.76	124	1.3	1.0, 1.7	0.05	75	1.3	0.9, 1.8	0.18	22	1.3	0.7, 2.5	0.4	30	0.9	0.6, 1.5	0.69
Nonpermanent dark	155	1.1	0.9, 1.4	0.43	118	1.4	1.0, 1.8	0.03	64	1.3	0.9, 1.8	0.18	24	1.0	0.5, 1.8	0.96	35	1.1	0.7, 1.8	0.61
Nonpermanent light	45	1.1	0.8, 1.6	0.57	31	1.2	0.8, 1.9	0.34	27	1.7	1.0, 2.7	0.04	7	1.1	0.4, 2.6	0.86	11	1.3	0.7, 2.7	0.44
Use of hair dye starting before 1980																				
Never use	224				117				80				20				40			
Ever use	311	1.1	0.9, 1.3	0.47	236	1.4	1.1, 1.9	<0.01	159	1.5	1.1, 2.0	<0.01	47	1.1	0.7, 2.0	0.64	55	1.0	0.6, 1.5	0.93
Type of dye																				
Permanent	204	1.1	0.9, 1.3	0.57	151	1.4	1.1, 1.9	<0.01	105	1.5	1.1, 2.0	0.01	33	1.4	0.8, 2.4	0.3	36	1.0	0.6, 1.5	0.9
Nonpermanent	114	1.0	0.8, 1.3	0.78	84	1.4	1.0, 1.9	0.05	56	1.5	1.0, 2.1	0.04	18	1.1	0.6, 2.1	0.79	23	1.1	0.7, 2.0	0.62
Color of dye																				
Dark color (including black, brown, and red)	161	1.0	0.8, 1.3	0.94	124	1.4	1.0, 1.8	0.02	90	1.5	1.1, 2.1	0.01	31	1.3	0.7, 2.3	0.4	33	1.0	0.6, 1.7	0.86
Light color (including blond)	145	1.2	0.9, 1.5	0.17	115	1.6	1.2, 2.1	<0.01	73	1.6	1.1, 2.2	<0.01	21	1.2	0.6, 2.3	0.59	19	0.8	0.4, 1.4	0.38
Both type and color																				
Permanent dark	111	1.0	0.8, 1.3	0.77	80	1.4	1.0, 1.9	0.03	58	1.5	1.0, 2.2	0.03	21	1.6	0.8, 3.0	0.15	23	1.2	0.7, 2.0	0.58
Permanent light	102	1.1	0.9, 1.5	0.32	80	1.6	1.2, 2.2	<0.01	51	1.5	1.0, 2.2	0.03	15	1.5	0.8, 3.1	0.23	14	0.8	0.4, 1.5	0.5
Nonpermanent dark	58	1.0	0.7, 1.4	0.99	44	1.2	0.8, 1.8	0.34	36	1.6	1.0, 2.5	0.03	12	1.0	0.5, 2.1	0.94	13	1.0	0.5, 1.9	1
Nonpermanent light	19	1.0	0.6, 1.7	1	20	1.7	1.0, 3.0	0.05	15	1.9	1.1, 3.6	0.03	4	1.1	0.4, 3.3	0.9	5	1.2	0.4, 3.2	0.72
Use of hair dye starting in 1980 or later																				
Never use	224				117				80				20				40			
Ever use	246	1.0	0.8, 1.2	0.89	163	1.3	1.0, 1.7	0.07	84	1.1	0.8, 1.5	0.63	27	1.0	0.6, 1.9	0.93	52	1.0	0.7, 1.6	0.93

Type of dye																							
Permanent	128	0.8	0.6, 1.1	0.12	104	1.3	1.0, 1.8	0.06	50	1.1	0.7, 1.6	0.8	18	1.2	0.6, 2.5	0.52	29	0.9	0.5, 1.5	0.66			
Nonpermanent	124	1.1	0.9, 1.5	0.3	80	1.4	1.0, 2.0	0.03	41	1.3	0.8, 1.9	0.24	12	0.9	0.4, 2.0	0.85	33	1.5	0.9, 2.6	0.09			
Color of dye																							
Dark color (including black, brown, and red)	149	0.9	0.7, 1.2	0.65	114	1.5	1.1, 2.0	0.02	54	1.1	0.8, 1.6	0.6	22	1.2	0.6, 2.2	0.66	31	0.9	0.6, 1.6	0.82			
Light color (including blond)	88	1.0	0.7, 1.3	0.98	51	1.1	0.8, 1.6	0.58	28	1.1	0.7, 1.7	0.75	5	0.6	0.2, 1.6	0.28	20	1.1	0.6, 1.9	0.8			
Both type and color																							
Permanent dark	69	0.7	0.5, 1.0	0.05	69	1.5	1.1, 2.1	0.02	32	1.1	0.7, 1.8	0.62	14	1.4	0.7, 2.9	0.36	14	0.7	0.4, 1.4	0.35			
Permanent light	60	1.0	0.7, 1.3	0.77	38	1.2	0.8, 1.8	0.35	17	0.9	0.5, 1.7	0.82	3	0.6	0.2, 2.2	0.45	16	1.2	0.6, 2.2	0.62			
Nonpermanent dark	85	1.2	0.9, 1.6	0.28	61	1.7	1.1, 2.4	<0.01	27	1.3	0.8, 2.1	0.35	11	1.0	0.5, 2.3	0.9	22	1.4	0.8, 2.5	0.23			
Nonpermanent light	19	1.1	0.6, 1.9	0.75	9	1.0	0.5, 2.1	0.98	11	1.8	0.9, 3.7	0.09	1	0.5	0.1, 4.0	0.52	5	1.4	0.5, 3.8	0.48			

* CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; OR, odds ratio; CI, confidence interval.
† Adjusted for age (continuous), race (White, Black, or other), and study site.

1980 among men. Thus, the results presented below are restricted to women.

Use of hair dye was associated with increased risks of follicular lymphoma and CLL/SLL but not of other NHL subtypes (table 4). The increased risk of follicular lymphoma was not modified or confounded by time period of use. However, for women who started using hair dyes in 1980 or later, risk of follicular lymphoma was increased among those who had used dark-colored dyes (for permanent dark-colored dyes, OR = 1.5, 95 percent CI: 1.1, 2.1; for nonpermanent dark-colored dyes, OR = 1.7, 95 percent CI: 1.1, 2.4). An increased risk of CLL/SLL was limited to women who started using hair dyes before 1980 (OR = 1.5, 95 percent CI: 1.1, 2.0). The risk did not vary by product type or color. Risk of other B-cell or T-cell lymphomas was not associated with hair-dye use. Risk estimates from random-effects models were consistent with the results from dichotomous or polytomous unconditional logistic regression models (figure 1). However, risk estimates from random-effects models were less precise.

Results from further detailed analyses of the associations of hair-dye use with follicular lymphoma and CLL/SLL among women are presented in table 5. Overall, a longer duration of hair-dye use was associated with a greater risk of follicular lymphoma (p-trend = 0.01), and the significant trend was mainly seen in women who started using the products before 1980 (p-trend < 0.01). For women who started using hair dyes in 1980 or afterward, significant trends for duration of use were observed only for permanent (p-trend = 0.02) and dark-colored (p-trend = 0.04) dyes. An increased risk of CLL/SLL was mainly observed among women who started using hair dyes before 1980. The risk was increased with greater duration, frequency, and total number of applications (p values for trend were 0.02, <0.01, and <0.01, respectively). However, no significant trends were observed among hair-dye users only. No major differences in risk patterns were observed for different types and colors of hair dye by frequency of application or total number of applications (data not shown).

Stratification by continent among persons who started using hair dyes before 1980 showed an increased risk of CLL/SLL associated with hair-dye use for European women (OR = 2.2, 95 percent CI: 1.4, 3.4) but not for US women (OR = 1.1, 95 percent CI: 0.8, 1.7). The association with follicular lymphoma, however, was apparent for both European women (OR = 1.4, 95 percent CI: 1.0, 1.8) and US women (OR = 1.6, 95 percent CI: 1.0, 2.7).

DISCUSSION

Results from this large, pooled, InterLymph-based case-control study indicate that personal use of hair dyes may play a role in the risk of NHL mainly for women who started using these products before 1980, particularly for follicular lymphoma and CLL/SLL.

The underlying mechanisms that may explain an association between NHL and hair-dye use, particularly for follicular lymphoma and CLL/SLL, are unknown. Many ingredients used in hair dyes before 1980 were shown to be mutagenic or carcinogenic in bacteria and rodents (6,

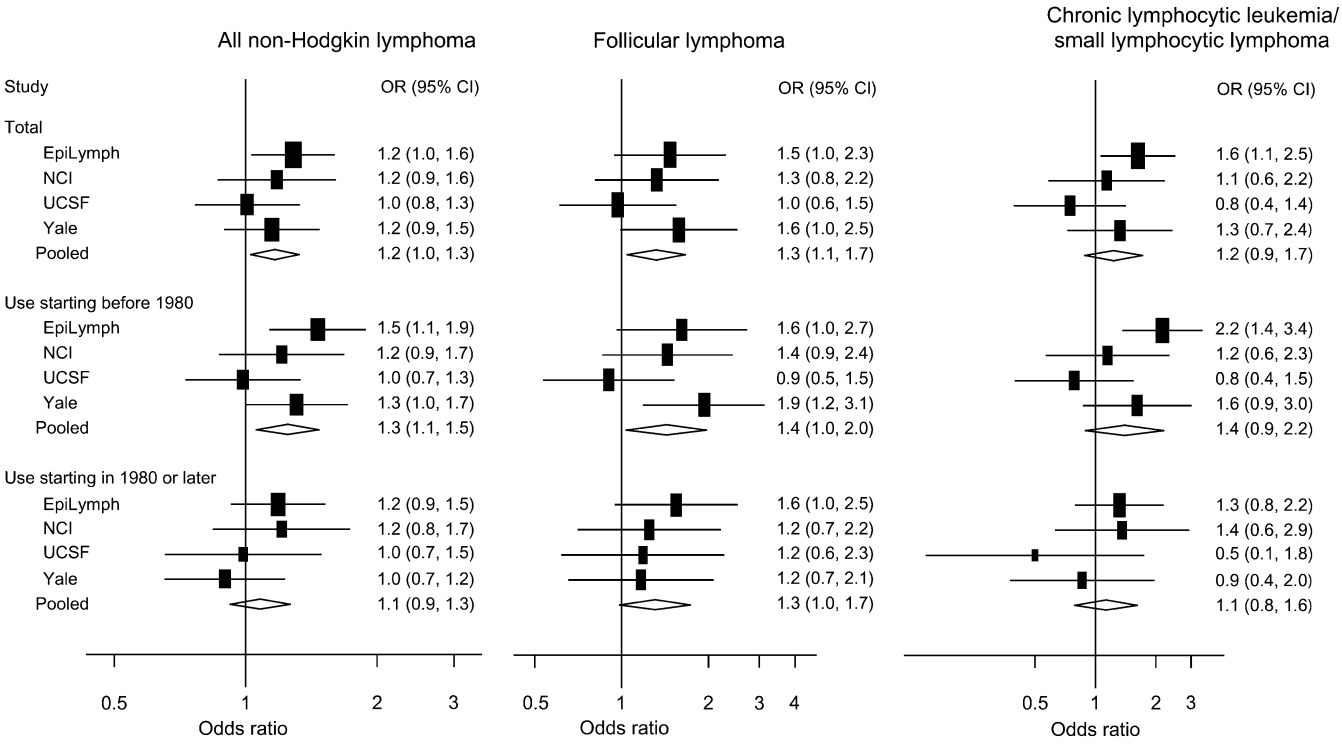

FIGURE 1. Odds ratios (ORs) for non-Hodgkin lymphoma (NHL) among women, by study center, in a pooled analysis of hair-dye use and NHL, 1988–2003. Boxes show results from individual studies; diamonds indicate pooled data. Bars, 95% confidence interval (CI). EpiLymph, International Case-Control Study of Lymphomas from Europe; NCI, NCI/SEER (National Cancer Institute/Surveillance, Epidemiology, and End Results) Multi-Center Case-Control Study; UCSF, Epidemiology of NHL Study (University of California, San Francisco); Yale, Connecticut Women's NHL Study (Yale University).

24). This may partly explain the observed association with NHL. Chromosome translocations are a hallmark of some lymphoma subtypes. Among follicular lymphomas, more than 75 percent of patients carry t(14:18)(q32;21) translocations, and 50–60 percent of CLL/SLL patients carry chromosomal changes, most frequently a numerical change of chromosome 12 and del(13q) (25). Chromosome alterations produced by chemical carcinogens have been reported in both in vitro and in vivo studies (26, 27). Thus, it is biologically plausible that personal use of hair dye may result in increased risks of follicular lymphoma and CLL/SLL.

Our results also showed that the risk associated with personal hair-dye use was present mainly among women who started using hair dyes before 1980. However, the increased risk was not limited to these women. Although the use of some carcinogenic compounds in hair dyes (such as 2,4-diaminoanisole and several yellow nitro dyes) (28) was discontinued after 1980, NHL risk may be associated with current formulations and with compounds created during the oxidization process. For example, PPD, a major arylamine currently used in hair dyes, is a putative carcinogen and a known agent for allergic contact dermatitis (7). When oxidized, PPD in bioassays can form a compound called Bandrowski's base, which has been reported to be mutagenic (29). In addition, an in vitro study showed that PPD can activate dendritic cell function, resulting in increased expression of CD40 protein and major histocompatibility complex class II, as well as stimulation of allogeneic lymphocyte proliferation (30). Among follicular lymphoma patients, an association between survival and gene expression signatures of nonmalignant tumor-infiltrating immune cells, including T cells, macrophages, and dendritic cells, was reported in a recent study (31). This suggests that PPD-induced overexpression of CD40 protein and major histocompatibility complex class II molecules may be associated with risk of this NHL subtype.

Whereas a biologically plausible explanation for the association between hair-dye use and NHL risk exists, studies of hair-dye use and NHL risk have provided inconsistent results, with some studies showing an increased risk (9–11, 15, 17–19) and others showing no association (12–14, 16). Several factors may explain these conflicting findings. First, not all studies obtained detailed information on lifetime use of hair dye. As Zahm and Fraumeni (32) emphasized, detailed information on lifetime exposure to hair-dye products, such as duration of use, dates of use, and type and color, is needed to establish a relation between hair-dye use and risk of NHL. The results from this analysis support the importance of these measures in providing additional evidence of a dose-response effect and thus strengthening the plausibility of an association with hair-dye use. Second, as demonstrated in this study, it is necessary to examine the

TABLE 5. Risk of two subtypes of non-Hodgkin lymphoma (follicular lymphoma and CLL/SLL*) associated with use (versus never use) of hair dye among women, by duration, frequency, and total number of applications, 1988–2003

	Follicular lymphoma									CLL/SLL								
	Any use of hair dye			Use starting before 1980			Use starting in 1980 or later			Any use of hair dye			Use starting before 1980			Use starting in 1980 or later		
	OR*,†	95% CI*	*p* value	OR†	95% CI	*p* value	OR†	95% CI	*p* value	OR†	95% CI	*p* value	OR†	95% CI	*p* value	OR†	95% CI	*p* value
Duration of use (years)																		
<8	1.2	0.9, 1.6	0.23	1.4	0.9, 2.1	0.11	1.2	0.9, 1.7	0.21	1.2	0.8, 1.6	0.40	1.5	1.0, 2.4	0.08	1.1	0.7, 1.7	0.61
8–19	1.3	1.0, 1.7	0.09	1.3	0.9, 1.9	0.11	1.4	1.0, 1.9	0.08	1.3	0.9, 1.8	0.16	1.6	1.0, 2.4	0.03	1.2	0.8, 1.8	0.46
≥20	1.5	1.1, 1.9	0.01	1.5	1.1, 2.0	<0.01	1.5	0.6, 4.0	0.41	1.3	1.0, 1.8	0.08	1.5	1.1, 2.0	0.02	0.3	0.0, 2.0	0.20
p for trend		0.01			<0.01			0.06			0.07			0.02			0.90	
Type of dye																		
Permanent																		
<8	1.3	0.9, 1.7	0.13	1.6	1.0, 2.5	0.03	1.2	0.8, 1.7	0.35	1.0	0.7, 1.5	0.96	1.2	0.7, 2.2	0.53	1.0	0.6, 1.6	0.95
8–19	1.3	1.0, 1.8	0.08	1.2	0.8, 1.8	0.44	1.5	1.0, 2.2	0.03	1.3	0.9, 1.9	0.17	1.5	0.9, 2.5	0.09	1.2	0.7, 2.0	0.43
≥20	1.4	1.1, 1.9	0.02	1.5	1.1, 2.0	0.01	1.9	0.6, 5.6	0.26	1.4	1.0, 2.0	0.05	1.5	1.1, 2.2	0.02	0.4	0.1, 3.3	0.42
p for trend		0.02			0.02			0.02			0.03			0.01			0.75	
Nonpermanent																		
<8	1.3	0.9, 1.9	0.14	1.2	0.7, 1.9	0.54	1.5	0.9, 2.4	0.09	1.0	0.6, 1.7	0.94	1.1	0.6, 2.1	0.81	1.1	0.6, 2.3	0.71
8–19	1.3	0.8, 2.1	0.31	1.5	0.7, 3.2	0.28	1.3	0.7, 2.4	0.49	2.0	1.1, 3.4	0.02	2.3	1.0, 5.2	0.04	1.9	0.9, 3.9	0.08
≥20	1.3	0.9, 1.7	0.12	1.3	0.9, 2.0	0.13	1.4	0.9, 2.2	0.13	1.2	0.8, 1.8	0.34	1.6	1.0, 2.5	0.03	0.9	0.5, 1.7	0.84
p for trend		0.11			0.13			0.10			0.15			0.02			0.90	
Color of dye																		
Dark color (including black, brown, and red)																		
<8	1.3	1.0, 1.8	0.05	1.3	0.8, 2.0	0.27	1.4	1.0, 2.1	0.05	1.2	0.8, 1.7	0.43	1.3	0.8, 2.3	0.29	1.1	0.7, 1.8	0.59
8–19	1.2	0.9, 1.7	0.22	1.0	0.6, 1.7	0.87	1.6	1.1, 2.3	0.02	1.2	0.8, 1.8	0.28	1.6	0.9, 2.7	0.08	1.2	0.7, 2.0	0.46
≥20	1.5	1.1, 2.2	0.01	1.6	1.1, 2.3	0.01	1.5	0.4, 5.2	0.53	1.4	1.0, 2.1	0.08	1.6	1.1, 2.4	0.02	0.4	0.1, 3.3	0.42
p for trend		0.02			0.01			0.04			0.08			0.01			0.74	
Light color (including blond)																		
<8	1.2	0.9, 1.7	0.22	1.6	1.1, 2.6	0.03	1.2	0.8, 1.9	0.41	1.0	0.7, 1.7	0.84	1.2	0.6, 2.2	0.66	1.1	0.6, 2.0	0.82
8–19	1.1	0.8, 1.6	0.56	1.7	1.1, 2.8	0.03	0.9	0.5, 1.6	0.69	1.2	0.7, 1.8	0.50	1.7	0.9, 3.1	0.08	1.2	0.7, 2.2	0.55
≥20	1.5	1.1, 2.1	0.02	1.5	1.1, 2.1	0.02	2.7	0.7, 10.1	0.13	1.6	1.1, 2.4	0.01	1.7	1.2, 2.6	0.01			
p for trend		0.02			0.01			0.60			0.02			<0.01			0.91	
Frequency of use (no. of applications per year)																		
<5	1.3	1.0, 1.7	0.09	1.4	1.0, 2.0	0.05	1.3	0.9, 1.8	0.21	1.1	0.7, 1.5	0.78	1.2	0.8, 1.9	0.42	1.0	0.6, 1.7	0.86
5–8	1.2	0.9, 1.6	0.17	1.4	1.0, 2.0	0.05	1.1	0.8, 1.7	0.49	1.2	0.8, 1.7	0.30	1.7	1.2, 2.5	0.01	0.7	0.4, 1.3	0.27
≥9	1.3	1.0, 1.8	0.03	1.4	1.0, 1.9	0.04	1.5	1.0, 2.2	0.04	1.6	1.1, 2.1	0.01	1.7	1.2, 2.4	<0.01	1.6	1.0, 2.5	0.04
p for trend		0.05			0.03			0.06			<0.01			<0.01			0.19	
Total no. of applications																		
<31	1.2	0.9, 1.6	0.20	1.4	0.9, 2.0	0.10	1.2	0.9, 1.7	0.25	1.1	0.8, 1.6	0.58	1.3	0.8, 2.1	0.22	1.1	0.7, 1.7	0.77
31–138	1.2	0.9, 1.6	0.15	1.2	0.9, 1.8	0.24	1.4	1.0, 1.9	0.08	1.2	0.8, 1.7	0.31	1.6	1.1, 2.5	0.02	0.9	0.6, 1.5	0.75
≥139	1.4	1.1, 1.9	0.01	1.5	1.1, 2.0	0.01	1.3	0.8, 2.3	0.33	1.5	1.1, 2.1	0.01	1.6	1.1, 2.2	0.01	1.8	1.0, 3.2	0.04
p for trend		0.02			0.01			0.07			0.01			<0.01			0.24	

* CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; OR, odds ratio; CI, confidence interval.
† Adjusted for age (continuous), race (White, Black, or other), and study site.

relation between personal hair-dye use and NHL by time period of use. The risk pattern by time period observed in this study is consistent with changes in hair-dye formulations during the past two decades that may have affected the magnitude of the underlying association. Holly et al. (14) first suggested the need to examine the relation between hair-dye use and NHL risk by time period of use, and this is supported by results from Zhang et al. (17), Morton et al. (20), and the current pooled analysis. Third, few earlier studies investigated the association between NHL risk and hair-dye use by histologic subtype. As the results from our analyses indicate, risk is likely to differ by subtype and may account for some of the inconsistencies in reported results. Fourth, statistical power was limited in most of the earlier studies, especially for analyses by type of hair dye and by NHL subtype. Fifth, Morton et al. (20) recently reported that genetic polymorphisms may affect the risk of NHL associated with hair-dye exposure. One putative carcinogen, PPD, may lose its reactivity through *N*-acetylation (33). An in vitro study showed that acetylated PPD, monoacetyl-PPD, and *N*,*N*′-diacetyl-PPD cannot be transformed to the mutagenic Bandrowski's base (33). Thus, the genetic predisposition for *N*-acetylation of PPD may alter susceptibility to PPD carcinogenicity among PPD-exposed persons. Population differences in genetic susceptibility to putative carcinogens in hair dyes may partly explain the variation in reported results linking hair-dye use and NHL risk. It also may explain the observed difference in risk of NHL associated with hair-dye use between men and women. Animal studies have shown higher activity of *N*-acetyltransferase 1, an enzyme responsible for biotransformation of carcinogens, including many arylamine and hydroxylamine xenobiotics, in males than in females (34), although results from human studies have been inconsistent (35). Finally, it also is possible that differences in product formulations across countries may have contributed to variation in the reported results.

Results from our analyses showed that risk of CLL/SLL was increased mainly for European women who used hair dyes, not US women, whereas the association with follicular lymphoma was seen in both geographic regions. Although the duration and frequency of hair-dye use in the control group were similar between European women and US women, duration of use among European women with CLL/SLL was greater than that for US women (p values ranged from 0.006 to 0.06 for various hair-dye products). Other factors, such as differences in hair-dye formulations, classification of rare NHL subtypes, or chance variations, also may have contributed to the observed difference in risk pattern between the European and US populations.

Note that although statistical power was adequate to test the overall association, power was reduced for analyses conducted by exposure and NHL subtype, especially for men, in whom the prevalence of hair-dye use was low, and racial minorities, who comprised less than 10 percent of the pooled population.

Information about hair-dye use in these analyses was obtained through participants' recall during in-person interviews. If NHL patients overreported their lifetime use of hair dye in comparison with controls, the observed results could have overestimated the association between hair-dye use and risk of NHL. However, the lack of an association with diffuse large B-cell lymphoma, a major subtype of NHL in Western populations, suggests that recall bias does not play a major role in the observed association between hair-dye use and risk of follicular lymphoma and CLL/SLL. Nondifferential misclassification of exposure status also may exist and would have resulted in underestimation of the association between hair-dye use and NHL risk. Central review of all cases by a study pathologist was not feasible, so it is possible that some disease misclassification occurred for analyses by NHL subtype if classification rules differed between studies. However, it is likely that any disease misclassification was nondifferential, thus biasing the results toward the null hypothesis. Finally, multiple comparisons were made in these analyses, and therefore some of the observed associations may be due to chance.

In summary, the results from this large InterLymph-based pooled analysis indicate that personal use of hair dye may play a role in the risk of NHL, particularly for follicular lymphoma and CLL/SLL. Our study also indicates that although the risk associated with personal hair-dye use was observed mainly among women who started using hair dyes before 1980, the risk was not limited to those women. Future studies are needed to examine the risk of NHL by time period of hair-dye use and by genetic susceptibility.

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Conflict of interest: none declared.

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