Cigarette Smoking and Risk of Non-Hodgkin Lymphoma: A Pooled Analysis from the International Lymphoma Epidemiology Consortium (InterLymph)

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Abstract

Background: **The International Lymphoma Epidemiology Consortium (InterLymph) provides an opportunity to analyze the relationship between cigarette smoking and non-Hodgkin lymphoma with sufficient statistical power to consider non-Hodgkin lymphoma subtype. The results from previous studies of this relationship have been inconsistent, likely due to the small sample sizes that arose from stratification by disease subtype. To clarify the role of cigarette smoking in the etiology of non-Hodgkin lymphoma, we conducted a pooled analysis of original patient data from nine case-control studies of non-Hodgkin lymphoma conducted in the United States, Europe, and Australia.**

Methods: **Original data were obtained from each study and uniformly coded. Risk estimates from fixed-effects and two-stage random-effects models were compared to determine the impact of interstudy heterogeneity. Odds ratios (OR) and 95% confidence intervals (95% CI) were derived from unconditional logistic regression models, controlling for study center, age, sex, and race.**

Results: **In our pooled study population of 6,594 cases and 8,892 controls, smoking was associated with slightly increased risk estimates (OR, 1.07; 95% CI, 1.00-1.15). Stratification by non-Hodgkin lymphoma subtype revealed that the most consistent association between cigarette smoking and non-Hodgkin lymphoma was observed among follicular lymphomas (n = 1452). Compared with nonsmokers, current smokers had a higher OR for follicular lymphoma (1.31; 95% CI, 1.12-1.52) than former smokers (1.06; 95% CI, 0.93-1.22). Current heavy smoking (≥36 pack-years) was associated with a 45% increased OR for follicular lymphoma (1.45; 95% CI, 1.15-1.82) compared with nonsmokers.**

Conclusions: **Cigarette smoking may increase the risk of developing follicular lymphoma but does not seem to affect risk of the other non-Hodgkin lymphoma subtypes we examined. Future research is needed to determine the biological mechanism responsible for our subtype-specific results.** (Cancer Epidemiol Biomarkers Prev 2005;14(4):925–33)

Introduction

Non-Hodgkin lymphomas represent a group of heterogeneous malignancies arising in lymphoid tissue throughout the body (1). With >145,000 cases of non-Hodgkin lymphoma diagnosed in developed regions throughout the world in the year 2000, non-Hodgkin lymphoma is now the sixth most common cancer occurring among men and the eighth among women in these regions (2).

The results from previous epidemiologic studies investigating the role of cigarette smoking in the etiology of non-Hodgkin lymphoma have been inconsistent. Some studies have reported that cigarette smoking is associated with non-Hodgkin lymphoma incidence (3-11) and mortality (12, 13), but others have reported no association between smoking and non-Hodgkin lymphoma (14-31). Several epidemiologic studies have investigated whether the association between non-Hodgkin lymphoma and cigarette smoking varies by subtype of the disease (3, 8-10, 14, 23-27, 29, 32). However, the small sample sizes that result from stratification in individual studies have prevented a thorough exploration of the potential relationship between cigarette smoking and non-Hodgkin lymphoma subtypes.

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The International Lymphoma Epidemiology Consortium (InterLymph) is a voluntary case-control consortium that was established in 2000 to facilitate collaboration among researchers working on epidemiologic case-control studies of lymphoma worldwide (33). We conducted a pooled analysis of original data from nine case-control studies of non-Hodgkin lymphoma identified through InterLymph to clarify the potential role of cigarette smoking in the etiology of non-Hodgkin lymphoma.

Materials and Methods

Study Population. Epidemiologic studies of non-Hodgkin lymphoma were identified through InterLymph. Studies that were completed between January 1, 1990 and January 1, 2004 with available electronic data sets were eligible for inclusion. Based on these criteria, original data from eight population-based case-control studies and one hospital-based case-control study (northern Italy) of non-Hodgkin lymphoma were included in the pooled analysis. Table 1 presents selected characteristics for each study, including information about the location and study population.

Data Collection and Exposure Definitions. This pooled analysis was conducted according to a protocol approved by the Human Investigations Committee at Yale University. Informed consent was obtained in individual studies that were approved by local human investigations committees. In each of the nine participating studies, data on cigarette smoking, demographics, and potential confounding variables were collected during in-person or telephone interviews. Detailed descriptions of the data collection methods for the individual studies (except the Nebraska study) have been published previously (3-5, 8, 17-19, 27, 29, 34). From each study, we requested copies of original questionnaires, descriptions of study methods, and an electronic data set that excluded personal identifiers and included variables on history of cigarette smoking, case/control status, non-Hodgkin

Table 1. Characteristics of case-control studies included in the pooled analysis

Study (reference)	Location	Year	Cases (n = 6,594)			Controls (n = 8,892)			
			Age range (y)	n	Participation rate (%)*	Matching	Source	n	Participation rate (%)*
Connecticut (27)	Connecticut	1995-2001	21-84	601	72	Frequency matched by age	<65 y: RDD; ≥65 y: random selection from CMMS files	718	RDD: 69, CMMS: 47
NCI Surveillance, Epidemiology and End Results Multicenter Study (34)†	Detroit, MI; Iowa; Los Angeles, CA; Seattle, WA	1998-2001	20-74	483	76	Frequency matched by age, sex, and study site	<65 y: RDD; ≥65 y: random selection from CMMS files	412	52
Nebraska‡	Nebraska	1999-2002	20-75	329	74	Frequency matched by age and sex	RDD	444	78
UCSF (17)§	San Francisco, CA	1988-1995	21-74	1,303	72	Frequency matched by age, sex, and county of residence	RDD	2,402	78
USC (5)	Los Angeles, CA	1989-1992	18-75	378	68	Individually matched by age, sex, race, language of interview, and neighborhood of residence	Neighborhood address	378	66
NSW (18)	NSW; Australian Capital Territory	2000-2002	20-74	704	85	Frequency matched by age, sex, and area of residence	Random selection from electoral rolls	694	61
Northern Italy (4, 19)‖	Aviano, Milan	1983-1992	17-79	429	>97	None	Patients admitted for acute, nonneoplastic, nonimmunologic conditions in the hospitals where cases were diagnosed	1,156	>97
United Kingdom (29)	Parts of north and southwest England	1998-2001	18-64	714	75	Individually matched by age, sex, and region (north/south)	Random selection from general practice lists	919	71
Italy (3, 8, 11)†	11 geographic areas throughout Italy¶	1990-1993	20-74	1,653	82	Frequency matched by age, sex, and area of residence (11 areas)	Random selection from demographic or National Health Service files	1,769	74

NOTE: RDD, random digit dialing; CMMS, Centers for Medicare and Medicaid Services.
*Participation rate = number participated/number eligible. The overall participation rate for the pooled data was 76% for cases and 70% for controls.
† Findings on the relationship between smoking and non-Hodgkin's lymphoma have not been reported previously. Reference provides additional information on study methodology.
‡ Information on methodology from the Nebraska study has not been published previously.
§ Known HIV-positive cases were excluded from this analysis.
‖ The northern Italy study was hospital based (cases identified via hospitals); all other studies were population based (cases identified via hospitals and registries).
¶ The geographic centers for the Italy study included Turin, Novara, Vercelli, Varese, Verona, Forlì, Florence, Siena, Latina, Ragusa, and Imperia.

Table 2. Risk estimates for non-Hodgkin's lymphoma associated with cigarette smoking by study

Study	Nonsmoker,* controls/ cases (*n*)	Ever smoker, controls/ cases (*n*)	OR (95% CI)†
Nebraska	226/173	218/156	0.92 (0.69-1.23)
NCI Surveillance, Epidemiology and End Results	186/224	226/259	0.97 (0.74-1.27)‡
USC	181/183	197/195	0.98 (0.73-1.31)
Connecticut	323/270	395/331	1.00 (0.81-1.25)
United Kingdom	367/273	552/441	1.04 (0.85-1.28)‡
NSW	333/329	361/375	1.06 (0.85-1.31)
Northern Italy	469/174	687/255	1.07 (0.82-1.39)‡
UCSF	1,014/527	1,388/776	1.07 (0.92-1.23)
Italy	815/676	954/977	1.21 (1.03-1.41)‡
Pooled data set	3,914/2,829	4,978/3,765	1.07 (1.00-1.15)§

*Reference group is defined as participants who smoked 100 cigarettes in their lifetime or smoked for 6 months.
†ORs and 95% CIs were estimated using unconditional logistic regression models, adjusted for age, sex, and race.
‡Adjusted for study center or geographic region of data collection.
§Joint fixed-effects logistic regression model; also adjusted for study center.

lymphoma subtype (cases only), sex, age, race/ethnicity, body mass index (BMI), family history of non-Hodgkin lymphoma, history of alcohol consumption, and socioeconomic status (SES). Known HIV-positive participants were excluded from these analyses. Individual data sets were uniformly coded and checked for internal consistency and agreement with previously published results. Discrepancies were resolved with individual study investigators.

Study questionnaires were compared to define a uniform set of exposure variables. Participants were classified as ''ever smokers'' if they had ever smoked >100 cigarettes [Connecticut and University of California at San Francisco (UCSF)] or if they had ever smoked regularly for at least 6 months [National Cancer Institute (NCI), Nebraska, University of Southern California (USC), New South Wales (NSW), northern Italy, United Kingdom, and Italy]. Conversely, participants who had never smoked at least 100 cigarettes or who had never smoked regularly for at least 6 months were categorized as ''nonsmokers'' and used as the reference category for all analyses.

Ever smokers were asked to provide additional information about the age they began smoking, current smoking habits, and duration and intensity of smoking. Former smokers were defined as those who stopped smoking at least 1 year before diagnosis (for cases) or interview (for controls), because more recent smoking cessation could be related to disease onset. The cumulative lifetime exposure to cigarette smoking was computed using information on intensity and duration of smoking (pack-years = number of packs smoked per day × number of years smoked). Continuous exposure variables, including age at initiation, years since quitting smoking, and intensity, duration, and pack-years of smoking, were categorized into quartiles *a priori* based on the distribution among controls.

Sex, age, race, BMI, family history of non-Hodgkin lymphoma in a first-degree relative, history of alcohol consumption, and SES were considered as potential confounding factors or effect modifiers in this pooled analysis. Continuous variables (age and BMI) were categorized *a priori* into quartiles based on the distribution among all control participants combined. In the five United States studies and the two Italian studies, the highest level of education attained was used as a measure of SES. In the NSW and United Kingdom studies, a deprivation indicator was computed using census data (18, 29). For this pooled analysis, SES was grouped into three categories (low, medium, and high) in each study based on the distribution among controls.

Case Ascertainment and Non-Hodgkin Lymphoma Subtype Classification. Cases were histologically confirmed, incident cases. The population-based studies identified cases via rapid case ascertainment systems. Data were not obtained for cases who died before they could be interviewed. Case ascertainment varied slightly between studies and included all non-Hodgkin lymphoma (Connecticut, NCI, Nebraska, UCSF, NSW, and northern Italy), intermediate-grade or high-grade non-Hodgkin lymphoma only (USC), non-Hodgkin lymphoma and Hodgkin's lymphoma (United Kingdom), or all hematolymphopoietic malignancies (Italy). This pooled analysis is restricted to cases of non-Hodgkin lymphoma.

The WHO non-Hodgkin lymphoma classification system was used to classify cases by disease subtype for this pooled analysis (1, 35). For the individual studies, cases were classified into non-Hodgkin lymphoma subtypes by study pathologists who reviewed pathology specimens and pathology reports. The Connecticut, NCI, Nebraska, NSW, and United Kingdom studies classified non-Hodgkin lymphoma subtypes according to either the WHO non-Hodgkin lymphoma classification system (1) or the Revised European American lymphoma classification system (36). The UCSF, USC, northern Italy (Aviano), and Italy studies classified non-Hodgkin lymphoma subtypes according to the Working Formulation (37), because the WHO system had not been developed at the time of case recruitment in those studies. Cases were not classified by non-Hodgkin lymphoma subtype in the Milan study center in northern Italy (n = 118).

Because slightly different categories were used in each study to classify non-Hodgkin lymphoma subtypes, the various classification systems were combined based on codes from the *International Classification of Diseases for Oncology, Second Edition* (38) and *Third Edition* (35), previous research on non-Hodgkin lymphoma subtypes and classification systems

Table 3. Risk estimates for non-Hodgkin's lymphoma associated with cigarette smoking in the pooled study population

Smoking exposure	Controls/cases	OR (95% CI)*	*P* for linear trend†
Nonsmoker	3,914/2,829	1.00 (Reference)	
Ever smoker	4,978/3,765	1.07 (1.00-1.15)	
Current	2,100/1,495	1.10 (1.00-1.20)	
Former	2,874/2,262	1.06 (0.98-1.15)	
Years since quit			
1-10	876/610	1.09 (0.97-1.23)	0.07
11-20	739/567	1.07 (0.94-1.21)	
21-30	586/425	0.97 (0.85-1.12)	
≥31	645/623	1.09 (0.95-1.24)	
Age at initiation			
≤15	1,283/971	1.10 (0.99-1.22)	0.45
16-17	1,074/811	1.07 (0.96-1.19)	
18-19	1,080/816	1.03 (0.92-1.14)	
≥20	1,524/1,157	1.08 (0.98-1.19)	
Intensity (cigarettes/d)			
1-10	1,623/1,146	1.02 (0.93-1.12)	0.21
11-20	1,908/1,471	1.12 (1.02-1.22)	
21-30	588/505	1.19 (1.04-1.36)	
≥31	567/442	1.07 (0.93-1.23)	
Duration (y)			
1-10	985/594	0.94 (0.84-1.06)	<0.01
11-20	1,085/717	1.02 (0.91-1.13)	
21-35	1,527/1,233	1.12 (1.02-1.23)	
≥36	1,349/1,197	1.16 (1.05-1.28)	
Pack-years			
1-10	1,607/1,057	0.99 (0.90-1.08)	0.01
11-20	919/653	1.04 (0.93-1.17)	
21-35	945/768	1.14 (1.02-1.27)	
≥36	1,194/1,066	1.21 (1.09-1.34)	

*ORs and 95% CIs were estimated using joint fixed-effects logistic regression models, adjusted for study center, age, sex, and race.
†*P* for linear trend among smokers only (excludes nonsmokers).

Table 4. Risk estimates for non-Hodgkin's lymphoma subtypes associated with cigarette smoking in the pooled study population [OR (95% CI)]

Smoking exposure	Burkitt (n = 117)	Chronic lymphocytic leukemia/small lymphocytic lymphoma (n = 867)	Diffuse (n = 2,211)	Follicular (n = 1,452)
Nonsmoker	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Ever smoker	0.92 (0.63-1.35)	1.01 (0.86-1.18)	1.09 (0.99-1.20)	1.15 (1.02-1.29)
Current	0.88 (0.53-1.49)	1.04 (0.85-1.28)	1.06 (0.93-1.21)	1.31 (1.12-1.52)
Former	0.94 (0.60-1.46)	1.03 (0.86-1.23)	1.11 (0.99-1.24)	1.06 (0.93-1.22)
Years since quit				
1-10	1.20 (0.68-2.12)	0.96 (0.69-1.35)	1.14 (0.96-1.35)	1.16 (0.95-1.41)
11-20	0.46 (0.18-1.16)	1.12 (0.82-1.53)	1.12 (0.94-1.34)	1.12 (0.91-1.38)
21-30	0.65 (0.25-1.67)	0.85 (0.59-1.20)	1.09 (0.90-1.32)	0.90 (0.70-1.15)
≥31	1.36	1.08 (0.85-1.38)	1.04 (0.86-1.27)	0.98 (0.76-1.28)
P for linear trend	0.35	0.68	0.06	0.03
Age at initiation				
≤15	0.88 (0.48-1.60)	1.14 (0.90-1.45)	1.07 (0.92-1.23)	1.12 (0.93-1.33)
16-17	0.92 (0.49-1.73)	0.95 (0.73-1.25)	1.06 (0.91-1.24)	1.19 (1.00-1.43)
18-19	0.99 (0.54-1.79)	1.12 (0.88-1.41)	1.06 (0.91-1.24)	1.04 (0.86-1.25)
≥20	0.92 (0.51-1.65)	0.89 (0.72-1.10)	1.14 (0.99-1.31)	1.24 (1.05-1.46)
P for linear trend	0.90	0.20	0.36	0.14
Intensity (cigarettes/d)				
1-10	0.75 (0.43-1.31)	1.00 (0.81-1.23)	1.02 (0.89-1.17)	1.11 (0.94-1.30)
11-20	1.06 (0.64-1.73)	1.04 (0.85-1.26)	1.12 (0.99-1.28)	1.25 (1.08-1.46)
21-30	0.90 (0.40-2.04)	1.17 (0.87-1.56)	1.27 (1.05-1.53)	1.33 (1.06-1.67)
≥31	1.14 (0.56-2.35)	0.82 (0.59-1.14)	1.13 (0.92-1.38)	0.95 (0.73-1.23)
P for linear trend	0.37	0.35	0.11	0.72
Duration (y)				
1-10	0.93 (0.50-1.75)	0.94 (0.69-1.27)	1.08 (0.91-1.27)	0.91 (0.74-1.12)
11-20	0.80 (0.41-1.55)	0.78 (0.58-1.05)	0.99 (0.85-1.17)	1.15 (0.95-1.38)
21-35	0.74 (0.41-1.34)	0.98 (0.79-1.22)	1.12 (0.97-1.28)	1.21 (1.03-1.42)
≥36	1.23 (0.67-2.26)	1.16 (0.95-1.42)	1.13 (0.97-1.31)	1.28 (1.08-1.53)
P for linear trend	0.54	0.01	0.38	0.01
Pack-years				
1-10	0.80 (0.47-1.37)	0.96 (0.77-1.21)	1.02 (0.88-1.17)	1.09 (0.93-1.29)
11-20	0.59 (0.26-1.32)	1.01 (0.78-1.31)	1.01 (0.85-1.20)	1.15 (0.94-1.41)
21-35	1.31 (0.70-2.43)	0.97 (0.76-1.25)	1.17 (0.99-1.38)	1.20 (0.99-1.47)
≥36	1.00 (0.55-1.84)	1.11 (0.89-1.38)	1.24 (1.06-1.44)	1.30 (1.08-1.56)
P for linear trend	0.56	0.62	0.07	0.60

NOTE: ORs and 95% CIs were estimated using joint fixed-effects logistic regression models, adjusted for study center, age, sex, and race. P for linear trend among smokers only (excludes nonsmokers).

(1, 36, 37, 39-41), and consultation with a pathologist (Dr. Fred Dee) experienced in the diagnosis of lymphomas. This pooled analysis considers risk of six B-cell non-Hodgkin lymphoma subtypes (Burkitt lymphoma/leukemia, chronic lymphocytic leukemia/small lymphocytic lymphoma, diffuse large cell lymphoma, follicular lymphoma, mantle cell lymphoma, and marginal zone lymphoma) and three T-cell non-Hodgkin lymphoma subtypes (Mycosis fungoides/Sézary syndrome, peripheral T-cell lymphoma, and other T-cell non-Hodgkin lymphoma; ref. 1). Cases who could not be classified into these groups were categorized as ''other'' and excluded from subtype-specific analyses.

Statistical Analyses. After the original data from each study were uniformly coded and checked, the distributions of demographic and potential confounding variables were compared among cases and controls within each study center and for the pooled data set. Correlates of smoking behavior among the controls were assessed. Odds ratios (OR) and 95% confidence intervals (95% CI) were derived from unconditional joint fixed-effects dichotomous and polytomous logistic regression models as estimates of the risk of non-Hodgkin lymphoma and non-Hodgkin lymphoma subtypes, respectively (42).

Study center was controlled for in all models of the pooled data set using the 24 centers or geographic regions of data collection for the nine participating studies (Table 1). All models also controlled for sex, age (≤45, 46-55, 56-65, ≥66 years), and race (White, Black, other), because these variables were used as matching variables in most of the original studies. The inclusion of BMI (<22.5, 22.5-24.9, 25.0-27.4, ≥27.5 kg/m^2), family history of non-Hodgkin lymphoma, history of alcohol consumption (beer, wine, liquor, any alcohol; ever/never), and SES (low, medium, high) did not result in a >10% change in the overall non-Hodgkin lymphoma risk estimates for each individual study or for the overall pooled data set; therefore, final risk estimates were adjusted for study center, sex, age, and race. Individuals with missing values for smoking explanatory variables were excluded from that analysis. Variables that might modify the effect of smoking on non-Hodgkin lymphoma risk estimates were chosen *a priori* based on hypotheses proposed in previous epidemiologic studies of cigarette smoking and non-Hodgkin lymphoma (3, 5, 8, 10, 13, 24, 26, 29, 32). Using the multiplicative model (43, 44), effect modification by sex, age (≤45, 46-55, 56-65, ≥66 years), family history of non-Hodgkin lymphoma, and history of alcohol consumption (beer, wine, liquor, any alcohol; ever/never) was determined to have occurred if the interaction term in the logistic regression model was statistically significant at $P < 0.05$. Tests for linear trend among smokers were conducted by including smoking variables as continuous variables in logistic regression models that excluded nonsmokers (43, 44). Nonsmokers were excluded from these models to evaluate a potential dose-response relationship among smokers only.

Heterogeneity in the risk estimates between study centers was assessed using a Wald χ^2 test by including an interaction term in both dichotomous and polytomous logistic regression models under the null hypothesis of no difference in the risk estimates between studies (43, 44). The risk estimates were considered to be heterogeneous among study centers when

Table 4. Risk estimates for non-Hodgkin's lymphoma subtypes associated with cigarette smoking in the pooled study population [OR (95% CI)] (Cont'd)

Mantle cell (n = 185)	Marginal zone (n = 261)	Mycosis fungoides (n = 101)	Peripheral T (n = 89)	Other T-cell non-Hodgkin's lymphoma (n = 163)
1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
0.81 (0.59-1.11)	1.01 (0.78-1.31)	1.00 (0.66-1.50)	0.99 (0.64-1.53)	1.10 (0.79-1.53)
0.79 (0.52-1.20)	0.88 (0.61-1.27)	1.11 (0.66-1.85)	1.06 (0.60-1.84)	0.94 (0.62-1.43)
0.89 (0.62-1.27)	1.08 (0.81-1.44)	0.90 (0.56-1.46)	0.98 (0.59-1.62)	1.22 (0.83-1.80)
1.35 (0.72-2.52)	0.99 (0.61-1.59)	0.62 (0.26-1.49)	1.86 (0.98-3.53)	0.71 (0.33-1.53)
0.78 (0.39-1.54)	1.37 (0.91-2.06)	0.69 (0.29-1.64)	0.74 (0.31-1.78)	1.16 (0.63-2.15)
0.56 (0.26-1.25)	1.34 (0.86-2.09)	0.97 (0.43-2.21)	0.71 (0.27-1.84)	0.83 (0.37-1.84)
0.91 (0.56-1.47)	0.68 (0.38-1.21)	1.41 (0.67-2.94)	0.57 (0.19-1.69)	2.04 (1.14-3.65)
0.05	0.29	0.55	0.05	0.95
0.66 (0.40-1.09)	1.14 (0.78-1.67)	0.83 (0.43-1.61)	1.39 (0.78-2.48)	1.28 (0.81-2.02)
1.00 (0.62-1.60)	0.99 (0.67-1.47)	0.86 (0.44-1.69)	1.10 (0.59-2.06)	1.30 (0.81-2.10)
0.75 (0.45-1.25)	0.98 (0.65-1.47)	1.18 (0.65-2.15)	0.34 (0.12-0.96)	1.20 (0.73-1.97)
0.86 (0.56-1.31)	0.94 (0.63-1.39)	1.10 (0.63-1.93)	1.03 (0.54-1.97)	0.70 (0.41-1.22)
0.21	0.25	0.75	0.49	0.46
0.83 (0.54-1.28)	0.99 (0.68-1.43)	1.13 (0.67-1.92)	0.81 (0.41-1.61)	1.03 (0.66-1.60)
0.63 (0.40-0.98)	1.04 (0.74-1.48)	0.86 (0.50-1.50)	0.97 (0.53-1.78)	1.14 (0.76-1.72)
1.08 (0.62-1.88)	1.15 (0.69-1.91)	0.54 (0.19-1.52)	1.73 (0.83-3.60)	1.14 (0.61-2.12)
0.97 (0.53-1.78)	1.18 (0.68-2.04)	1.45 (0.70-3.00)	0.67 (0.20-2.24)	1.19 (0.59-2.40)
0.58	0.52	0.61	0.61	0.62
0.75 (0.41-1.37)	0.76 (0.46-1.26)	0.71 (0.33-1.54)	0.42 (0.15-1.18)	1.35 (0.84-2.18)
0.71 (0.40-1.25)	1.06 (0.71-1.60)	1.32 (0.73-2.39)	0.79 (0.38-1.67)	1.13 (0.69-1.84)
1.00 (0.67-1.51)	1.15 (0.81-1.62)	0.73 (0.38-1.41)	0.92 (0.50-1.70)	0.93 (0.58-1.51)
0.73 (0.47-1.14)	1.00 (0.68-1.46)	1.27 (0.72-2.25)	1.71 (0.95-3.05)	0.99 (0.56-1.74)
0.79	0.78	0.79	0.01	0.31
0.88 (0.57-1.38)	0.92 (0.63-1.35)	0.90 (0.51-1.60)	0.38 (0.15-0.97)	1.10 (0.72-1.67)
0.45 (0.23-0.89)	1.02 (0.65-1.62)	1.17 (0.62-2.20)	1.27 (0.62-2.62)	1.25 (0.77-2.03)
0.75 (0.44-1.27)	1.18 (0.78-1.80)	0.94 (0.47-1.90)	1.28 (0.64-2.59)	0.86 (0.47-1.55)
1.00 (0.64-1.57)	1.19 (0.79-1.79)	1.01 (0.54-1.87)	1.36 (0.68-2.70)	1.12 (0.64-1.95)
0.91	0.50	0.52	0.16	0.99

the P of the χ^2 statistic was <0.10 (45). A two-stage method for analyzing pooled data was used to compare risk estimates from fixed-effects and random-effects models to determine the impact of interstudy heterogeneity on estimates of risk (42). First, associations between cigarette smoking and non-Hodgkin lymphoma were estimated for each study center using individual unconditional logistic regression models. The USC (5) and United Kingdom (29) studies individually matched cases and controls. Because the results from these studies were similar using conditional and unconditional logistic regression, unconditional logistic regression models were used to compute study-specific risk estimates. Random-effects risk estimates (ORs and 95% CIs) were then computed using a weighted average of the estimates from individual studies, weighting the natural logarithm of the OR from each study by the inverse of the sum of the variance of individual study estimates and an estimate of the random-effects variance (42, 45). The random-effects variance was computed using moment estimation, which yields an unbiased, noniterative estimator (42, 45). Sensitivity analyses were conducted to compare pooled risk estimates after systematically excluding each study to confirm that no single study unduly influenced the pooled estimates. Statistical analyses were done using the SAS System version 8.2 (SAS Institute, Inc., Cary, NC).

Results

Original data were pooled from nine case-control studies recently conducted in the United States, Europe, and Australia, resulting in a data set of 15,486 participants (6,594 cases and 8,892 controls) with information on history of cigarette smoking. The pooled study population had approximately equal numbers of men and women and was predominantly Caucasian (95%). The median age was 55 years. Controls tended to have higher SES and were more likely to drink alcohol than cases, whereas cases tended to have a higher BMI and were more likely to report family history of non-Hodgkin lymphoma in a first-degree relative than controls (data not shown). Compared with controls who did not smoke regularly, controls who were smokers were more likely to be ages >45 years, male, and of medium SES, to have a BMI of <22.5 kg/m^2, and to consume alcohol (data not shown).

The overall association between cigarette smoking and risk of non-Hodgkin lymphoma is presented by study (Table 2). In the pooled data set, smokers had slightly higher ORs for non-Hodgkin lymphoma compared with nonsmokers (1.07; 95% CI, 1.00-1.15). The pooled risk estimates obtained using joint fixed-effects and two-stage random-effects logistic regression models were consistent (data not shown). Sensitivity analyses revealed that the pooled estimates remained stable following the systematic exclusion of each study (data not shown). Differences among study centers in the estimates of non-Hodgkin lymphoma risk associated with cigarette smoking were likely due to chance (χ^2 = 29.9; df = 23; P = 0.15). Non-Hodgkin lymphoma risk estimates modestly increased with increasing duration and pack-years of cigarette smoking (P for linear trend < 0.01 and P = 0.01, respectively; Table 3). Compared with nonsmokers, risk estimates were elevated for the longest duration of smoking (≥36 years; OR, 1.16; 95% CI, 1.05-1.28) and the heaviest smoking (≥36 pack-years; OR, 1.21; 95% CI, 1.09-1.34). We found no significant effect modification between cigarette smoking and age, sex, race, SES, BMI, family history of non-Hodgkin lymphoma, or alcohol consumption

under the multiplicative model for risk of all non-Hodgkin lymphoma (data not shown).

Stratification by non-Hodgkin lymphoma subtype revealed that the association between non-Hodgkin lymphoma and cigarette smoking varied by disease subtype (Table 4). The most consistent increased risk estimates were observed for follicular lymphoma. Compared with nonsmokers, current smokers had a higher estimate of risk for follicular lymphoma (OR, 1.31; 95% CI, 1.12-1.52) than former smokers (OR, 1.06; 95% CI, 0.93-1.22). Heavy smoking (≥36 pack-years) was associated with a 30% increased OR for follicular lymphoma (1.30; 95% CI, 1.08-1.56) compared with nonsmokers. When the population of smokers was limited to current smokers, heavy smoking (≥36 pack-years) was associated with a 45% increased OR for follicular lymphoma (1.45; 95% CI, 1.15-1.82; Table 5). Measures of cigarette smoking also were associated with modestly increased risk estimates for diffuse lymphoma, but few of the estimates reached statistical significance (Table 4). Compared with nonsmokers, heavy smoking (≥36 pack-years) was associated with a 24% increased risk estimate for diffuse lymphoma (OR, 1.24; 95% CI, 1.06-1.44). The association between cigarette smoking and diffuse lymphoma did not depend on whether individuals were current or former smokers (data not shown). Comparing current smokers to nonsmokers, the risk estimates for follicular lymphoma were similar where the original disease classification system was the WHO (n = 557 cases; OR, 1.27; 95% CI, 1.03-1.56) or the Working Formulation (n = 403 cases; OR, 1.37; 95% CI, 1.10-1.71), whereas the risk estimates for diffuse lymphoma varied slightly by the classification system (WHO, n = 612 cases; OR, 0.92; 95% CI, 0.75-1.14; Working Formulation, n = 804 cases; OR, 1.19; 95% CI, 1.00-1.40).

Discussion

In this pooled analysis of 15,486 participants from nine case-control studies, cigarette smoking was associated with slightly increased risk estimates for all non-Hodgkin lymphoma subtypes combined, but the estimates varied by non-Hodgkin lymphoma subtype. The most consistent positive associations were observed for follicular lymphoma, particularly among current smokers compared with former smokers, with slight evidence of a linear trend for cumulative lifetime exposure to cigarette smoking.

Although previous epidemiologic studies have suggested that the association between cigarette smoking and non-Hodgkin lymphoma may vary by subtype of the disease (3, 8-10, 14, 23-27, 29, 32), few of those studies had sufficient power to stratify cases by non-Hodgkin lymphoma subtype. Consistent with the findings from this pooled analysis, follicular lymphoma is the only subtype with a statistically significant association reported consistently (3, 8, 23, 25, 27, 46). However, smoking also has been associated infrequently with significantly increased risk of several other non-Hodgkin lymphoma subtypes, including low grade (10), high grade (9, 10), and other large cell lymphomas (8). The lack of statistically significant subtype-specific results in some studies (24, 26, 29, 32) and the inconsistency of previously published reports reflect the insufficient sample size in individual studies to consider subtype-specific findings, particularly for an exposure, such as cigarette smoking, that seems to have a weak effect on disease risk.

It is biologically plausible that cigarette smoking increases risk of non-Hodgkin lymphoma through direct carcinogenic effects, such as t(14;18) translocation. This somatic mutation joins the immunoglobulin heavy chain gene on chromosome 14 with the *bcl-2* gene on chromosome 18, resulting in increased production of the bcl-2 protein that inhibits apoptosis (47). Direct effects of carcinogenic compounds in cigarettes may increase the percentage of t(14;18) translocation in lymphoma cells, because this mutation occurs more frequently among heavy smokers (48). A recent case-control study of non-Hodgkin lymphoma that classified cases by t(14;18) translocation status reported a nonsignificant 70% increased risk of t(14;18)-positive non-Hodgkin lymphoma, but not t(14;18)-negative non-Hodgkin lymphoma, among cigarette smokers, although the wide 95% CIs reflected the small sample size [n = 30 t(14;18)-positive non-Hodgkin lymphoma,

Table 5. Risk estimates for follicular lymphoma associated with cigarette smoking in the pooled study population by smoking history

Smoking exposure	Current smokers		Former smokers	
	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)
Years since quit				
1-10			876/160	1.16 (0.95-1.41)
11-20			739/144	1.12 (0.91-1.38)
21-30			586/93	0.90 (0.70-1.15)
≥31			645/83	0.98 (0.76-1.28)
P for linear trend				0.03
Intensity				
1-10	639/83	1.16 (0.90-1.50)	982/171	1.10 (0.91-1.33)
11-20	901/156	1.45 (1.18-1.77)	1,006/168	1.13 (0.93-1.36)
21-30	276/53	1.41 (1.02-1.95)	311/64	1.28 (0.96-1.72)
≥31	161/26	1.14 (0.73-1.77)	406/53	0.86 (0.63-1.17)
P for linear trend		0.67		0.30
Duration				
1-10	229/11	0.51 (0.27-0.96)	756/120	0.97 (0.78-1.21)
11-20	370/41	1.11 (0.77-1.59)	715/140	1.16 (0.94-1.43)
21-35	657/137	1.48 (1.18-1.84)	870/154	1.08 (0.88-1.32)
≥36	840/158	1.38 (1.12-1.70)	509/76	1.09 (0.83-1.43)
P for linear trend		0.20		0.34
Pack-years				
1-10	514/59	1.08 (0.80-1.45)	1,093/191	1.10 (0.92-1.32)
11-20	404/57	1.27 (0.94-1.73)	515/89	1.10 (0.85-1.41)
21-35	465/82	1.43 (1.09-1.86)	480/79	1.07 (0.82-1.39)
≥36	591/119	1.45 (1.15-1.82)	603/97	1.13 (0.88-1.44)
P for linear trend		0.85		0.63

NOTE: Reference group = nonsmokers (n = 3,914 controls, n = 612 follicular lymphoma cases). ORs and 95% CIs were estimated using joint fixed-effects logistic regression models, adjusted for study center, age, sex, and race. P for linear trend among smokers only (excludes nonsmokers).

n = 38 t(14;18)-negative non-Hodgkin lymphoma; ref. 14]. That study also reported an association between family history of hemolymphatic cancer and t(14;18)-negative non-Hodgkin lymphoma but not t(14;18)-positive non-Hodgkin lymphoma (14), which is consistent with our finding that family history does not modify the effect of smoking on follicular lymphoma. Although no data on translocation status were available for our analysis, the findings of Schroeder et al. are particularly intriguing, because it is estimated that t(14;18) translocation occurs in ~85% of follicular lymphomas and 30% of diffuse lymphomas (1, 49).

Cigarette smoke–induced immunosuppression is another mechanism by which smoking may affect risk estimates for non-Hodgkin lymphoma. Chronic exposure to cigarette smoke has been associated with decreased immune responsiveness, particularly for T cells, in both human and animal studies (50), potentially leading to decreased immune surveillance. Cigarette smoke also may indirectly cause immunosuppression via a neuroendocrine pathway (50). Immunosuppression is a well-established risk factor for overall non-Hodgkin lymphoma, but disease subtype-specific effects of immunosuppression are not clearly understood. Nevertheless, it is noteworthy that follicular lymphoma is not a non-Hodgkin lymphoma subtype typically associated with severe immune deficiency (1, 51). Future research is needed to clarify the potential biological mechanism responsible for our findings.

This pooled analysis is the largest study ever published on the association between smoking and non-Hodgkin lymphoma, and the resulting sample provided us with greater power than that of individual studies to explore the relationship between smoking and non-Hodgkin lymphoma subtype. Several additional strengths and limitations of this pooled analysis should be taken into account when interpreting our findings. Information bias resulting from exposure misclassification was minimized because data were gathered using standardized, structured questionnaires. Further, self-reported smoking history is reliable and accurate based on comparisons of self-reported data with biochemical markers of tobacco exposure (52). Exposure misclassification also was possible because we were unable to obtain data for all studies on the type of tobacco smoked (blond versus black), although previous research on the importance of this distinction has been inconsistent (7, 8, 10). Although it is possible that the cases overreported their tobacco exposure, the subtype-specific nature of our findings suggests it is unlikely that the associations we observed are due to recall bias. In addition, the hypothesized association between cigarette smoking and non-Hodgkin lymphoma risk is not well known in the general population, so reporting bias is also improbable. Our study may have been biased against finding an association for more aggressive non-Hodgkin lymphoma subtypes, if smokers with non-Hodgkin lymphoma have poorer survival than nonsmokers with non-Hodgkin lymphoma, because we excluded dead cases. However, survival bias was minimized through the use of rapid case reporting systems in most of the individual studies. The similarity of exposure measurement across studies and the use of original data allowed us to uniformly define exposures, one of the major advantages of conducting a pooled analysis with original data rather than a meta-analysis (42, 53).

We examined the results of the eight published case-control studies that were not included in this analysis to determine whether there were systematic differences between the studies included in this pooled analysis and those excluded (7, 9, 10, 16, 22, 24, 26, 28). A risk estimate for the association between smoking and overall non-Hodgkin lymphoma was presented in six of these publications; the ORs ranged from 0.9 to 2.4 and were not statistically significant (7, 9, 10, 16, 22, 24). The Mantel-Haenszel estimate of the common OR from these six studies was 1.06 (95% CI, 1.01-1.05; ref. 43). The similarity of this estimate to the pooled estimate in our analysis suggests that the selection of studies included in this pooling project did not bias our results.

We analyzed our data using both joint fixed-effects and two-stage random-effects unconditional logistic regression models to evaluate the potential effects of interstudy heterogeneity on our pooled risk estimates (42). Risk estimates from joint fixed-effects models and two-stage random-effects models have been shown to be consistent in the presence of homogeneous exposure effects between studies (42). As interstudy heterogeneity increases, the moment estimator of the random-effects variance that we used in this study has been shown to produce less biased risk estimates than other estimators of the random-effects variance (42). The similarity of our results using joint fixed-effects models and two-stage random-effects models suggests that differences between study populations included in this pooled analysis did not substantially affect our risk estimates.

All cases were histologically confirmed, incident cases of non-Hodgkin lymphoma. The slight differences in case ascertainment in the individual studies likely led to an underascertainment of leukemic lymphomas, including chronic lymphocytic leukemia and Burkitt leukemia. In the WHO classification system, these entities are considered equivalent to small lymphocytic lymphoma and Burkitt lymphoma, respectively (1). Because chronic lymphocytic leukemia and Burkitt leukemia were not included in the definition of non-Hodgkin lymphoma before the publication of the WHO in 2001, these cases were excluded from most of the individual studies. Follicular lymphomas were also somewhat underascertained because the USC study included only intermediate-grade and high-grade non-Hodgkin lymphoma, and most follicular lymphomas are low grade. These slight differences in case ascertainment were unlikely to have affected materially our results because it is unlikely that underascertainment was related to cigarette smoking. Further, sensitivity analyses revealed that our pooled estimates remained stable following the systematic exclusion of each study.

Central review of all cases by a study pathologist was not feasible, so it is possible that some disease misclassification occurred for analyses by non-Hodgkin lymphoma subtype if classification rules differed between studies. However, diagnostic accuracy using the WHO classification system has been estimated to be >85% for both diffuse and follicular lymphomas (39). Because WHO non-Hodgkin lymphoma subtypes are thought to be more homogenous than Working Formulation non-Hodgkin lymphoma subtypes, however, it is possible that disease misclassification occurred when we converted the non-Hodgkin lymphoma subtype data between the two classification systems. For example, ~75% of cases classified as ''diffuse large cell lymphoma'' using the Working Formulation are categorized as ''diffuse large B-cell lymphoma'' using the more strict guidelines of the WHO non-Hodgkin lymphoma classification system, whereas the remaining 25% are classified as various other WHO subtypes (41). Nevertheless, the similarity of the follicular lymphoma definition in both classification systems (1, 41), the similarity of the estimated association between smoking and follicular lymphoma when our pooled data were stratified by non-Hodgkin lymphoma classification system, and the consistency of our results with previous epidemiologic studies suggest that our non-Hodgkin lymphoma subtype-specific findings are unlikely to be explained entirely by disease misclassification.

In conclusion, the findings from this pooled analysis suggest that cigarette smoking may be a risk factor for the development of follicular lymphoma. During the period from 1978-1983 to 1990-1995, incidence of follicular lymphoma increased ~22% among Whites in the United States (40). During a

similar period, incidence of all non-Hodgkin lymphoma increased by ~50% throughout the world (54), and evidence suggests that non-Hodgkin lymphoma incidence may have been increasing steadily since the 1930s (55). In contrast, prevalence of cigarette smoking in developed countries has not increased in recent years, and in several countries, smoking prevalence has declined (56). It thus seems unlikely that smoking contributed substantially to the long-term increase in non-Hodgkin lymphoma. Nonetheless, demonstration of a relationship between cigarette smoking and non-Hodgkin lymphoma risk adds to the considerable evidence of the health benefits of smoking prevention and cessation programs.

The current finding of an association specific to follicular lymphoma supports the possibility of etiologic heterogeneity among non-Hodgkin lymphoma subtypes. Epidemiologic investigations of other risk factors should consider disease subtypes as defined by the WHO non-Hodgkin lymphoma classification system. In addition, it may be valuable to consider alternative characterizations of non-Hodgkin lymphoma subtypes by cytogenetic abnormalities. Additional research is needed to determine the biological mechanisms responsible for the subtype-specific findings reported here.

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