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ORIGINAL PAPER

The association between cigarette smoking and non-Hodgkin lymphoid neoplasms in a large US cohort study

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Abstract
Purpose Results from studies of smoking and non-Hodgkin lymphoid neoplasms (NHL) are inconsistent. This study assessed whether this inconsistency might be due to the heterogeneous nature of the disease, to different relationships in subpopulations such as gender, or to chance.
Methods We examined cigarette smoking status, initiation, intensity, and duration in relation to the risk of NHL, and subtypes of NHL in men and women from the American Cancer Society Cancer Prevention Study II Nutrition Cohort. From 1992 to 2007, 1,926 NHL cases were identified among 152,958 subjects. Extended Cox regression was used to compute multivariable rate ratios (RR) and 95 % confidence intervals (95 % CI).
Results The RR (95 % CI) for current smoking associated with NHL incidence in women was 1.37 (1.04–1.81) and in men was 0.88 (0.65–1.19). Among current smokers, there was a positive relationship between years smoked and risk of NHL in women (p-trend < 0.01), but no association in men. In women, the positive associations with current smoking were strongest for follicular lymphoma (RR 2.13, 95 % CI 1.20–3.77) and chronic lymphocytic leukemia/small lymphocyte lymphoma (RR 1.75, 95 % CI 1.03–2.96). In men and women combined, current smoking was associated with an increased risk of T-cell lymphoma and a decreased risk of diffuse large B-cell lymphoma.
Conclusions This study supports an association of current smoking with risk of NHL that varies by gender and subtype. Future studies should focus on differences by gender and disease subtype to better clarify the smoking and NHL relationship.

Keywords Cigarette smoking · Non-Hodgkin lymphoma · Subtypes · Gender · Cohort study

Introduction

Non-Hodgkin lymphoid neoplasms (NHL) are the sixth most commonly diagnosed cancer in the United States [1]. The incidence rate of NHL has nearly doubled since the mid-1970s [2]. Established risk factors for NHL are related to either immunological function or infection such as HIV/AIDS; however, these risk factors explain only a small proportion of NHL cases [3]. Inconsistencies among studies examining associations of other risk factors with NHL have been attributed, at least in part, to the heterogeneous nature of the disease, and potential differences in associations among subpopulations including gender [3].

Cigarette smoking has multiple effects on the immune system that might influence lymphoma risk including direct carcinogenesis, immunosuppression, and increased leukocyte production [4, 5]. However, results of studies of the relationship between cigarette smoking and risk of NHL are inconsistent. A review of 22 studies in 2001 [6] found no overall association between NHL and smoking, although it called for further study of histologic subtypes of NHL, and for stratification by gender. Since then, several large case–control [7–9] and cohort studies [10–14] investigated the association of cigarette smoking with risk of NHL subtypes. In several of those studies, smoking was

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associated with an elevated risk of follicular lymphoma [7, 9, 14]. However, other studies found no associations [8, 11] or even reduced risk [10, 12] with follicular lymphoma. The efforts of some studies to stratify analyses of smoking by both NHL subtype and gender were constrained by sample size [9, 11, 13], while other studies did not present results stratified by subtype and gender [7, 8, 10, 12]. The limited data presented on NHL subtypes stratified by gender make it difficult to discern whether there are no differences by gender, or whether individual studies are simply underpowered. In order to further clarify this relationship, we conducted a prospective cohort analysis of NHL subtypes, gender, and cigarette smoking in a population of older U.S. men and women.

Materials and methods

Study population

Subjects in this analysis were selected from the Cancer Prevention Study II (CPS-II) Nutrition Cohort, a prospective study of cancer incidence and mortality in 184,188 men and women from the United States, described in detail elsewhere [15]. Briefly, the Nutrition Cohort is a subcohort of the approximately 1.2 million subjects in CPS-II, a prospective study of mortality established by the American Cancer Society in 1982 [16]. Participants in the larger study were recruited nationally and completed a four-page questionnaire at enrollment. Subjects between the ages of 50–74 years in 1992 were recruited from 21 states with population-based state cancer registries to participate in the Nutrition Cohort. Participants completed a 10-page mailed questionnaire which included information on demographic, medical, behavioral, environmental, occupational, and dietary factors. Follow-up questionnaires were sent to cohort members in 1997, 1999, 2001, 2003, 2005, and 2007 to ascertain cancer diagnoses. Responses to all surveys were received from at least 89 % of living participants after multiple mailings. The current study encompasses follow-up through the 2007 survey. All aspects of the CPS-II Nutrition Cohort study have been approved by the Emory University Institutional Review Board.

Analytic cohort

These analyses excluded subjects from the CPS-II Nutrition Cohort who were lost to follow-up ($n = 6{,}276$), reported a personal history of cancer other than non-melanoma skin cancer at baseline in 1992 ($n = 22{,}860$), reported a diagnosis of a hematopoietic cancer in the first survey interval that could not be verified ($n = 67$), or were missing smoking status at baseline in 1992 ($n = 2{,}027$). The final analytic cohort includes 152,958 participants including 72,752 men and 80,206 women.

Measures of cigarette smoking

In 1992, never smokers were those participants who answered "No" to the question "Have you smoked at least 100 cigarettes in your entire life?" For participants that answered "Yes" to the previous question, current and former smoking was based on the follow-up question "Do you smoke cigarettes now?" Information on the age began smoking, average number of cigarettes smoked daily, and number of years smoked was collected from both current and former smokers. Additionally, former smokers were asked the age at which they last quit smoking for the calculation of time since quitting. Smoking status was updated on each follow-up questionnaire. For each follow-up questionnaire, it was determined whether a subject was a current smoker. If not, subjects that were never and former smokers on the previous questionnaire maintained their status, and current smokers from the previous questionnaire were converted to former smokers. If the subject reported current smoking, never and former smokers were converted to current smokers, while previous current smokers maintained their status. Current smokers were assigned cigarettes per day based on the most recent questionnaire. Current smokers and former smokers that maintained the same smoking status between intervals accrued additional years of smoking or time since quitting, respectively, equivalent to the length of the interval. Current smokers that quit smoking in the interval were assumed to have quit at the midpoint (except on the 1997 survey where more detailed time since quit was available). Half of the interval was added to the years smoked, the remaining half was considered the time since quitting. Never smokers and former smokers that began smoking between surveys were assumed to have started at the midpoint and those years were added to any previously reported years smoked (for never smokers this was 0 years). Pack years were not calculated, as the above measures of smoking have previously been shown to be better predictors of smoking-related cancers in this cohort [17].

Case ascertainment

This analysis includes 1,926 cases (1,090 men and 836 women) with NHL diagnosed between the date of enrollment and 30 June 2007. The majority of cases were identified by self-report on the follow-up surveys; of these, 1,140 were verified by medical record abstraction, and 402 were verified by linkage with state cancer registries. There were 41 cases identified through the self-report of another cancer that were subsequently verified as NHL during

medical record abstraction or linkage with state cancer registries. An additional 343 cases were identified as deaths through automated linkage of the entire cohort with the National Death Index and subsequently verified by linkage with the state cancer registries.

Histologic subtypes were defined using the Interlymph Pathology Working Group classifications [18], based on the 2001-revised WHO classification of tumors of hematopoietic and lymphoid tissues [19]. Using the International Classification of Disease for Oncology, Second and Third Edition (ICD-O-2 and ICD-O-3), these subtypes include: diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, multiple myeloma, other B-cell lymphomas, and T-cell lymphoma.

Statistical analyses

Smoking was classified in terms of smoking status (never, former, current), age began smoking (>20, 19–20, 17–18, and <=16 years), number of cigarettes smoked per day (<20, 20, and >20), and years smoked (<40, 40−<50, and 50+) in current smokers and years since quit smoking (30+, 20–<30, 10–<20, <10) in former smokers. All smoking variables were updated during follow-up to maintain a clean referent group of lifelong never smokers, update current smoking status, update the number of cigarettes per day smoked, and accumulate additional years of smoking and years since quitting. Descriptive statistics were calculated using distributions of categorical variables and means of continuous variables within strata of smoking status at baseline.

Person-years of follow-up for each participant were calculated as the amount of time from completion of the CPS-II Nutrition Cohort questionnaire in 1992/1993 to date of: (1) diagnosis of NHL; (2) diagnosis of other cancer; (3) death occurring between the last returned survey and next mailed survey; (4) return of last questionnaire (i.e., in 1997, 1999, 2001, 2003, 2005 or 2007); or (5) last questionnaire the participant was known to be cancer free, if they reported a hematopoietic cancer that could not be verified. Extended Cox regression [20] was used to compute multivariable adjusted rate ratios (RR) and 95 % confidence intervals (CI) for the association between time-dependent smoking variables and NHL, and NHL subtype incidence. In all analyses, the reference group was those who reported never smoking. Models were run in men and women separately, as well as combined. All models were stratified on age, and additionally adjusted for gender (in the analyses of men and women combined), education (<high school, high school, some college, college graduate), family history of hematopoietic cancer (no, yes), body mass index (continuous kg/m^2), height (gender-specific quintiles), physical activity (continuous metabolic equivalents of energy in h/week), and alcohol use (continuous drinks/day). Variables for missing status were included for all covariates. Covariates were selected based on the literature and previous work in this cohort. Trend tests were calculated using the median values of each category for the cigarettes per day, and years smoked variables. For variables with no identifiable median in at least 1 category, trends were calculated using a continuous ordinal variable indicating a 1 unit change per category.

Effect modification by gender was assessed by computing p values for multiplicative interactions using likelihood ratio tests comparing Cox multivariable models with and without cross-product terms between each smoking and gender variable. For NHL subtypes with no significant difference by gender, models were run in men and women combined for smoking status, age at initiation, and time since quit in former smokers. All analyses were performed using Statistical Analysis Software (SAS version 9.2; SAS Institute Inc., Cary NC).

Results

Nearly 70 % of male and 45 % of female participants in this study were active cigarette smokers at some point in their lives, although only approximately nine percent in each group continued to smoke at the time of enrollment (Table 1). The smoking habits of former smokers were similar to those of current smokers in men and in women, except that current smokers had smoked on average 17–18 years longer than former smokers. Among former smokers, the average number of years since quitting smoking was 21.9 years (SD 12.31) in men and 20.1 years (SD 12.16) in women. In both men and women, current smokers were less likely to be college educated and physically active, but more likely to report drinking 2 or more drinks of alcohol per day than never and former smokers. A smaller proportion of the currently smoking women were obese when compared to the proportion of obesity in never or former smokers at baseline.

Smoking status was not static during follow-up. Almost 40 % of the current smokers quit smoking over the course of follow-up. On average, they had not been smoking for 7 years by the end of follow-up. Current smokers, who continued to smoke, had smoked for an additional 7 years on average during follow-up. Consequently, 40 % of these moved into a higher category of years of smoking when smoking during follow-up was considered. Only 1 % of the never smokers began smoking. Similarly, only 1 % of the former smokers reverted to smoking during follow-up. On average, the former smokers had not smoked in over 30 years by the end of follow-up. These changes in

Table 1 Characteristics of the CPS-II nutrition cohort by smoking status at baseline and gender

Characteristic	Men			Women		
	Never (n = 23,610) (%)	Former (n = 42,425) (%)	Current (n = 6,717) (%)	Never (n = 44,399) (%)	Former (n = 28,901) (%)	Current (n = 6,906) (%)
Caucasian	97.3	97.6	96.5	97.1	97.6	97
African American	1.2	1.1	2.0	1.5	1.5	2.0
College educated	55.1	43.4	32.4	29.6	35.0	25.8
Obese (body mass index of 30 + kg/m^2)	12.4	15.5	12.5	16.3	15.3	10.5
Non-drinker	41.7	28.7	29.4	55.1	33.7	36.6
>2 drinks of alcohol/day	6.8	15.6	21.8	1.9	7.6	11.1
Family history of hematopoietic cancer	3.3	3.2	2.9	3.6	3.6	3.5
	Mean (SD)			Mean (SD)		
Age (years)	63.8 (6.30)	64.3 (5.99)	62.5 (5.74)	62.4 (6.60)	61.9 (6.49)	60.8 (6.37)
Body mass index (kg/m^2)	26.1 (3.63)	26.7 (3.73)	25.9 (3.76)	25.7 (4.81)	25.6 (4.79)	24.6 (4.44)
Recreational physical activity (METS/week)	13.9 (13.65)	13.2 (13.35)	10.2 (11.60)	11.7 (11.73)	12.8 (12.85)	11.3 (12.48)
Drinks of alcohol/day	0.6 (1.12)	1.0 (1.57)	1.3 (1.97)	0.2 (0.59)	0.6 (1.05)	0.7 (1.24)
Age started smoking (years)	–	18.4 (4.78)	18.2 (6.27)	–	19.7 (5.33)	19.9 (6.48)
Average number of cigarettes smoked/day	–	22.0 (14.53)	19.7 (12.9)	–	14.6 (11.81)	16.3 (10.4)
Age quit smoking (years)	–	42.4 (12.51)	–	–	41.8 (12.82)	–
Years smoked	–	22.6 (12.92)	40.9 (10.63)	–	19.9 (12.74)	36.9 (10.78)
Years since quit smoking	–	21.9 (12.31)	–	–	20.1 (12.16)	–

SD standard deviation, *METS* metabolic equivalents to sitting 1 h

smoking status over time were similar in both men and women.

The relationship between current smoking and NHL differed by gender (p-interaction, 0.02). In men, there was no association between current smoking and risk of NHL, whereas in women, there was a 37 % higher risk of NHL for current smokers compared to never smokers (Table 2). Among current smokers, there was no evidence of a dose–response relationship of number of cigarettes smoked per day with risk of NHL in men or in women. However, there was a statistically significant dose-related association with years smoked and NHL incidence in women but not in men. The association for women culminated in a twofold higher risk for women who smoked 50 years or more compared to never smokers. Among former smokers, there were no clear dose–response relationships of years since quitting smoking with risk of NHL in men or women. Younger age at smoking initiation was associated with a higher risk of NHL in women, but not men. The risk of NHL was 11 % higher among former compared with never smokers in men and women combined.

Gender differences also were observed when evaluating smoking status in relation to NHL subtypes (Fig. 1, Supplemental Table 1). In women, there was a statistically significantly higher risk of follicular lymphoma (RR 2.13, 95 % CI 1.20–3.77), and CLL/SLL (RR 1.75, 95 % CI 1.03–2.96) associated with current smoking compared to never smoking. In men, there was no association with follicular lymphoma or CLL/SLL. The interaction between smoking status and gender for follicular lymphoma was statistically significant (p-interaction, 0.02), but not for CLL/SLL (p-interaction 0.17). However, there was a significant difference by gender for the association between age at initiation and risk of CLL/SLL (p-interaction 0.02). Associations of smoking with risk of other NHL subtypes were not significantly different in men and women; thus, to increase statistical precision, men and women were combined (Table 3). In these analyses, there was a twofold higher risk of T-cell lymphoma associated with current smoking (RR 2.30, 95 % CI 1.18–4.47), and a statistically significant dose–response with time since quitting in former smokers (p-trend 0.03). Conversely, there was a lower risk of DLBCL associated with current smoking in men and women combined (RR 0.32, 95 % CI 0.15–0.69).

Discussion

In the present study, current smoking was associated with an increased risk of NHL in women but not in men. The association between smoking and risk of NHL appeared to differ by histologic subtype of disease. Compared to never

Table 2 Multivariable adjusted rate ratios of Non-Hodgkin lymphoid neoplasms and smoking stratified by gender

	Men (cases = 1,090)			Women (cases = 836)			Men and women combined (cases = 1,926)		
	Person-years	Cases	RR (95 % CI)[a]	Person-years	Cases	RR (95 % CI)[a]	Person-years	Cases	RR (95 % CI)[a]
Smoking status									
Never[b]	269,509	354	1.00	543,379	447	1.00	812,888	801	1.00
Former	477,440	685	1.10 (0.96–1.25)	368,258	330	1.14 (0.98–1.32)	845,698	1,015	1.11 (1.01–1.23)
Current	54,305	51	0.88 (0.65–1.19)	63,395	59	1.37 (1.04–1.81)	117,699	110	1.09 (0.89–1.33)
			p-trend = 0.65			p-trend = 0.01			p-trend = 0.06
Age began smoking									
>20	110,235	168	1.12 (0.93–1.35)	116,182	109	1.13 (0.91–1.39)	226,417	277	1.13 (0.98–1.30)
19–20	89,157	132	1.13 (0.93–1.38)	90,162	72	1.04 (0.81–1.34)	179,318	204	1.10 (0.94–1.29)
17–18	145,956	189	1.01 (0.84–1.21)	128,686	120	1.24 (1.01–1.53)	274,641	309	1.09 (0.95–1.25)
<=16	181,911	242	1.09 (0.92–1.29)	95,919	88	1.26 (0.99–1.59)	277,831	330	1.13 (0.99–1.29)
			p-trend = 0.53			p-trend = 0.02			p-trend = 0.07
Among former smokers only									
Years since quitting									
30+	192,823	328	1.18 (1.01–1.37)	135,069	131	1.12 (0.92–1.36)	327,893	459	1.17 (1.04–1.31)
20–<30	119,683	168	1.12 (0.93–1.35)	87,702	80	1.24 (0.97–1.57)	207,386	248	1.16 (1.00–1.34)
10–<20	93,663	112	0.98 (0.79–1.21)	78,872	63	1.05 (0.80–1.37)	172,535	175	1.00 (0.85–1.19)
<10	67,608	72	0.94 (0.72–1.21)	63,604	54	1.20 (0.90–1.60)	131,212	126	1.04 (0.86–1.26)
			p-trend = 0.68			p-trend = 0.12			p-trend = 0.55
Among current smokers only									
Cigarettes/day									
<20	23,769	22	0.83 (0.54–1.28)	34,424	33	1.40 (0.98–2.00)	58,193	55	1.09 (0.83–1.44)
20	13,940	13	0.86 (0.50–1.51)	17,424	15	1.26 (0.75–2.12)	31,364	28	1.04 (0.71–1.51)
>20	14,624	14	1.00 (0.58–1.71)	9,880	10	1.62 (0.86–3.05)	24,504	24	1.19 (0.79–1.79)
			p-trend = 0.95			p-trend = 0.02			p-trend = 0.18
Years smoked									
<40	14,409	16	1.26 (0.76–2.09)	24,954	13	0.96 (0.55–1.68)	39,363	29	1.10 (0.76–1.61)
40–<50	24,308	19	0.80 (0.50–1.27)	25,496	22	1.27 (0.82–1.95)	49,804	41	1.00 (0.72–1.37)
50+	15,335	16	0.76 (0.46–1.27)	12,639	23	1.91 (1.25–2.92)	27,974	39	1.17 (0.85–1.62)
			p-trend = 0.53			p-trend < 0.01			p-trend = 0.23

[a] Multivariable adjusted rate ratios (RR) and 95 % confidence intervals (95 % CI) are adjusted for age at baseline, gender, family history of hematopoietic cancer, education, METS, BMI, height, and alcohol use

[b] Never smoking is the reference group for all RRs, and included in all trends

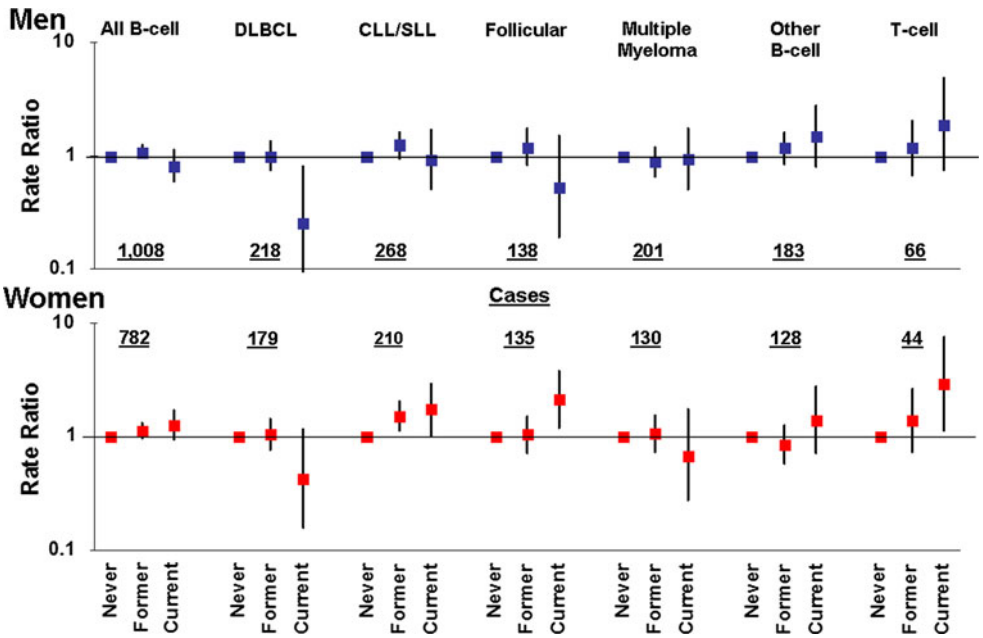

Fig. 1 Plots of multivariable adjusted rate ratios comparing never smokers with former smokers and current smokers in seven different NHL subtypes stratified by gender. The NHL subtypes shown are: all B-cell lymphomas, diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, multiple myeloma, other B-cell lymphomas, and T-cell lymphomas

smoking, current smoking was associated with higher risk of follicular lymphoma and CLL/SLL in women but not men. In analyses of men and women combined, there were positive associations of current smoking and, among former smokers, shorter time since quitting smoking with risk of T-cell lymphoma. Conversely, there was an inverse association between current smoking and risk of DLBCL in men and women combined. There were no associations of smoking habits with risk of other NHL subtypes in men, women, or men and women combined.

A critical review [6] and four recently published prospective cohort studies that examined smoking in relation to NHL risk in both men and women combined were null [10–13]. Few studies published to date have assessed the association between smoking status and risk of NHL in men and women separately. While most show no association in men or women [7–13, 21], results of the California Teachers Study showed an association between smoking intensity and all NHL in women after excluding never smokers that were exposed to the smoke of others [14]. In CPS-II, additional adjustment for passive smoking exposure did not meaningfully alter our findings (data not shown). These results do not preclude passive smoking from having a confounding effect in other studies. In CPS-II, the majority of participants reported exposure to smoke of others and there was no difference in the distribution of passive smoking between never, former, and current smokers. In addition, the heavy smoking of this cohort would outweigh any likely smaller association with passive smoking.

Several studies found that the relationship of smoking with specific NHL subtypes might differ by gender [9, 11, 22–24]. Indeed, our study, like many other studies [7, 9, 11, 21, 24, 25], found a higher risk of follicular lymphoma among current smokers, but in our study this association was limited to women. The large Interlymph consortium of case–control studies identified a significant increased risk of follicular lymphoma associated with current smoking and number of years smoked which did not differ by gender [7]. However, two of the studies included in Interlymph [23, 26] and four additional studies [9, 11, 21, 24] found increased risks only in women. In the Iowa Women's Health Study [21], current smoking was associated with a doubling of risk of follicular lymphoma. In the European Prospective Investigation into Cancer and Nutrition [11], more recent quitting in formerly smoking women was associated with increased risk, and in the California Teachers Study [14], women exposed to over 40 years of passive smoking had a nearly threefold higher risk of follicular lymphoma compared women with no passive smoking exposure. While three other prospective studies reported no gender differences in the association between smoking and follicular lymphoma incidence [10, 12, 25], the overall evidence for an association in women is becoming strong. No other B-cell subtype has been consistently associated with smoking in either men or women [7–12, 14, 21, 24, 25, 27–37].

At least two published studies showed statistically significantly higher risks of T-cell lymphomas associated with current smoking [9, 38], and similar but non-significant associations were observed in two other studies [12, 37]. The Interlymph study [7] identified a significant trend of increasing risk with recent quitting in former smokers and a significant trend of increasing risk with greater number of years smoked for peripheral T-cell lymphoma only. In our

Table 3 Multivariable adjusted rate ratios of selected[a] non-Hodgkin lymphoid neoplasm subtypes and smoking in men and women combined

Variable	Categories	Person-Years	Diffuse large B-cell lymphoma		Multiple myeloma		Other B-cell lymphoma		T-cell lymphoma	
			Cases	RR (95 % CI)[b]	Cases	RR (95 % CI)[b]	Cases	RR (95 % CI)[a]	Cases	RR (95 % CI)[b]
Smoking status	Never[c]	812,888	183	1.00	147	1.00	132	1.00	39	1.00
	Former	845,698	207	1.00 (0.81–1.24)	167	0.94 (0.75–1.19)	156	1.02 (0.80–1.30)	59	1.27 (0.83–1.94)
	Current	117,699	7	0.32 (0.15–0.69)	17	0.86 (0.52–1.44)	23	1.40 (0.89–2.20)	12	2.30 (1.18–4.47)
				p-trend = 0.09		p-trend = 0.50		p-trend = 0.33		p-trend = 0.03
Age began smoking	>20	226,417	60	1.07 (0.80–1.44)	42	0.91 (0.64–1.28)	44	1.09 (0.77–1.54)	15	1.20 (0.66–2.19)
	19–20	179,318	32	0.79 (0.54–1.15)	34	0.96 (0.66–1.40)	39	1.26 (0.88–1.81)	13	1.39 (0.74–2.63)
	17–18	274,641	59	0.93 (0.69–1.26)	52	0.94 (0.68–1.30)	42	0.88 (0.62–1.26)	17	1.21 (0.67–2.16)
	<=16	277,831	62	0.92 (0.68–1.24)	56	0.96 (0.69–1.32)	54	1.09 (0.78–1.52)	26	1.77 (1.04–2.99)
				p-trend = 0.40		p-trend = 0.75		p-trend = 0.87		p-trend = 0.06
Among former smokers only										
Years since quitting										
	30+	327,893	103	1.13 (0.88–1.45)	80	1.06 (0.80–1.40)	77	1.15 (0.86–1.54)	17	0.91 (0.51–1.63)
	20–<30	207,386	47	0.98 (0.71–1.36)	37	0.88 (0.61–1.27)	44	1.24 (0.87–1.76)	13	1.15 (0.60–2.18)
	10–<20	172,535	33	0.85 (0.58–1.23)	26	0.76 (0.50–1.16)	23	0.79 (0.50–1.24)	15	1.63 (0.89–3.00)
	<10	131,212	23	0.89 (0.57–1.38)	23	0.96 (0.61–1.50)	10	0.51 (0.27–0.97)	13	1.92 (1.01–3.66)
				p-trend = 0.36		p-trend = 0.35		p-trend = 0.11		p-trend = 0.03

[a] Selected subtypes were not significantly different by gender at α=0.05

[b] Multivariable adjusted rate ratios (RR) and 95 % confidence intervals (95 % CI) are adjusted for age at baseline, gender, family history of hematopoietic cancer, education, METS, BMI, height, and alcohol use

[c] Never smoking is the reference group for all RRs, and included in all trends

study, there were too few cases of specific T-cell subtypes to examine associations with smoking separately. Studies of T-cell lymphoma and smoking have been small with the largest studies including only 200 cases [7], making it difficult to rule out chance findings. However, even with limited statistical power, several have identified significant associations suggesting continued research on smoking and T-cell lymphomas is warranted.

The biologic mechanism underlying a potential association between smoking and risk of lymphoma subtypes is unclear, but intriguing possibilities exist. A higher prevalence of *t*(14;18) translocations has been shown in peripheral blood of heavy smokers compared with nonsmokers [39]. Consistent with our finding of a positive association between smoking and risk of follicular lymphoma in women, *t*(14;18) translocations are present in a very high proportion of follicular lymphomas(80–90 %) relative to other lymphoma subtypes [40]. However, two recent case–control studies of chromosomal abnormalities found evidence of an increased risk of *t*(14;18)-negative NHL with smoking in women [41, 42]. We can also speculate that smoking is acting on hormone levels, which could explain the gender differences observed in this study. In the past, smoking was thought to have anti-estrogenic effects in women; however, recent evidence suggests positive associations of smoking with circulating levels of estrogens and androgens [43]. Increased estrogen has been shown to reduce pre-cursor B-cell differentiation and proliferation in mice leading to an accumulation of non-cycling cells [44], possibly providing a source of cells for the development of NHL in smoking women. For commonly asymptomatic NHL such as follicular lymphoma and CLL/SLL [45], the observed gender difference in this study could be due to differential healthcare utilization in men and women leading to undiagnosed cases in smoking men, or simply chance. Heavy smoking also impacts T-cell biology including retention of $CD8^+$ T-cells in the lungs, increased clonal expansion of multiple T-cell types and compromised T-cell responsiveness [5]—potentially affecting T-cell lymphoma development. Cigarette smoking could also indirectly lead to an elevated risk of lymphoma by increasing susceptibility to infectious risk factors such as human T-cell leukemia virus-1 and Epstein Barr virus.

The strengths of this study include its large size, prospective design, and availability of detailed lifetime smoking history. With 1,926 verified NHL cases, this is one of the largest prospective cohort studies of incident NHL and smoking to date. The large case numbers enabled us to stratify by gender and examine relationships by subtypes within gender. The long history of smoking in our current smokers allows the identification of associations that may not become apparent until after many decades of smoking. Despite the large sample size, we are still unable to finely examine dose of cigarette smoking in the lymphoma subtypes while stratifying by gender. A pooled analysis of smoking and NHL in prospective studies will likely be necessary to adequately examine the dose relationships by subtype and gender. A second limitation is that there were no measures of infectious or immune-related exposures that could be important confounders in this study, or act in the causal pathway through the weakened immune systems of smokers. However, at this time, only a few rare forms of NHL have been strongly linked to infectious agents [46, 47], making large effects of uncontrolled confounding unlikely.

In conclusion, this large cohort study supports an association with cigarette smoking and increased risk of follicular lymphoma in women. Future analyses should focus on examining the histologic subtypes of NHL in men and women. Large consortia of prospective studies with the ability to pool data on smoking status and histology are required to examine questions of duration, dose, and time since quitting which are essential to establishing a relationship. With over 20 % of adult Americans continuing to smoke in 2009 and no decrease in the previous 5 years [48], it is important to better understand the role of cigarette smoking in NHL etiology.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. American Cancer Society (2010) Cancer Facts & Figures 2010. American Cancer Society, Atlanta
2. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Cronin K, Chen HS, Feuer EJ, Stinchcomb DG, Edwards BK (eds) (2010) SEER Cancer Statistics Review, 1975–2007. National Cancer Institute, Bethesda
3. Alexander DD, Mink PJ, Adami HO, Chang ET, Cole P, Mandel JS, Trichopoulos D (2007) The non-Hodgkin lymphomas: a review of the epidemiologic literature. Int J Cancer 120(Suppl 12):1–39. doi:10.1002/ijc.22719
4. Sopori M (2002) Effects of cigarette smoke on the immune system. Nat Rev Immunol 2(5):372–377. doi:10.1038/nri803
5. Stampfli MR, Anderson GP (2009) How cigarette smoke skews immune responses to promote infection, lung disease and cancer. Nat Rev Immunol 9(5):377–384. doi:10.1038/nri2530
6. Peach HG, Barnett NE (2001) Critical review of epidemiological studies of the association between smoking and non-Hodgkin's lymphoma. Hematol Oncol 19(2):67–80. doi:10.1002/hon.677
7. Morton LM, Hartge P, Holford TR, Holly EA, Chiu BC, Vineis P, Stagnaro E, Willett EV, Franceschi S, La Vecchia C, Hughes AM, Cozen W, Davis S, Severson RK, Bernstein L, Mayne ST,

Dee FR, Cerhan JR, Zheng T (2005) Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (Interlymph). Cancer Epidemiol Biomarkers Prev 14(4):925–933. doi:10.1158/1055-9965.EPI-04-0693

8. Besson H, Brennan P, Becker N, Nieters A, De Sanjose S, Font R, Maynadie M, Foretova L, Cocco PL, Staines A, Vornanen M, Boffetta P (2006) Tobacco smoking, alcohol drinking and non-Hodgkin's lymphoma: a European multicenter case-control study (Epilymph). Int J Cancer 119(4):901–908. doi:10.1002/ijc.21913
9. Schollkopf C, Smedby KE, Hjalgrim H, Rostgaard K, Gadeberg O, Roos G, Porwit-Macdonald A, Glimelius B, Adami HO, Melbye M (2005) Cigarette smoking and risk of non-Hodgkin's lymphoma–a population-based case-control study. Cancer Epidemiol Biomarkers Prev 14(7):1791–1796. doi:10.1158/1055-9965.EPI-05-0077
10. Troy JD, Hartge P, Weissfeld JL, Oken MM, Colditz GA, Mechanic LE, Morton LM (2010) Associations between anthropometry, cigarette smoking, alcohol consumption, and non-Hodgkin lymphoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Epidemiol 171(12):1270–1281. doi:10.1093/aje/kwq085
11. Nieters A, Rohrmann S, Becker N, Linseisen J, Ruediger T, Overvad K, Tjonneland A, Olsen A, Allen NE, Travis RC, Bingham S, Khaw KT, Ardanaz E, Redondo ML, Basterrechea M, Martinez C, Tormo MJ, Rosso S, Tagliabue G, Masala G, Mattiello A, Tumino R, Boeing H, Bergmann M, Kaaks R, Trichopoulou A, Trichopoulos D, Peeters PH, Bueno-de-Mesquita B, Boffetta P, Brennan P, Ferrari P, Neasham D, Lund E, Berglund G, Manjer J, Hallmans G, Johansson I, Vineis P, Riboli E (2008) Smoking and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition. Am J Epidemiol 167(9):1081–1089. doi:10.1093/aje/kwn004
12. Lim U, Morton LM, Subar AF, Baris D, Stolzenberg-Solomon R, Leitzmann M, Kipnis V, Mouw T, Carroll L, Schatzkin A, Hartge P (2007) Alcohol, smoking, and body size in relation to incident Hodgkin's and non-Hodgkin's lymphoma risk. Am J Epidemiol 166(6):697–708. doi:10.1093/aje/kwm122
13. Fernberg P, Odenbro A, Bellocco R, Boffetta P, Pawitan Y, Adami J (2006) Tobacco use, body mass index and the risk of malignant lymphomas–a nationwide cohort study in Sweden. Int J Cancer 118(9):2298–2302. doi:10.1002/ijc.21617
14. Lu Y, Wang SS, Reynolds P, Chang ET, Ma H, Sullivan-Halley J, Clarke CA, Bernstein L (2011) Cigarette smoking, passive smoking, and non-hodgkin lymphoma risk: evidence from the California Teachers Study. Am J Epidemiol 174(5):563–573. doi:10.1093/aje/kwr127
15. Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, Feigelson HS, Thun MJ (2002) The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. Cancer 94(9):2490–2501. doi:10.1002/cncr.101970
16. Garfinkel L (1985) Selection, follow-up, and analysis in the American cancer society prospective studies. Natl Cancer Inst Mongr 67:49–52
17. Thun MJ, Calle EE, Rodriguez C, Wingo PA (2000) Epidemiological research at the American Cancer Society. Cancer Epidemiol Biomarkers Prev 9(9):861–868
18. Morton LM, Turner JJ, Cerhan JR, Linet MS, Treseler PA, Clarke CA, Jack A, Cozen W, Maynadie M, Spinelli JJ, Costantini AS, Rudiger T, Scarpa A, Zheng T, Weisenburger DD (2007) Proposed classification of lymphoid neoplasms for epidemiologic research from the pathology working group of the International Lymphoma Epidemiology Consortium (InterLymph). Blood 110(2):695–708. doi:10.1182/blood-2006-11-051672
19. Jaffe ES, Harris NL, Stein H, Vardiman JW (eds) (2001) Pathology and genetics of tumours of haematopoietic and lymphoid tissues. IARC Press, Lyon
20. Cox D (1972) Regression models and life tables (with discussion). J Roy Stat Soc B 34:187–220
21. Parker AS, Cerhan JR, Dick F, Kemp J, Habermann TM, Wallace RB, Sellers TA, Folsom AR (2000) Smoking and risk of non-Hodgkin lymphoma subtypes in a cohort of older women. Leuk Lymphoma 37(3–4):341–349
22. Besson H, Renaudier P, Merrill RM, Coiffier B, Sebban C, Fabry J, Trepo C, Sasco AJ (2003) Smoking and non-Hodgkin's lymphoma: a case-control study in the Rhone-Alpes region of France. Cancer Causes Control 14(4):381–389
23. Stagnaro E, Ramazzotti V, Crosignani P, Fontana A, Masala G, Miligi L, Nanni O, Neri M, Rodella S, Costantini AS, Tumino R, Vigano C, Vindigni C, Vineis P (2001) Smoking and hematolymphopoietic malignancies. Cancer Causes Control 12(4):325–334
24. Zahm SH, Weisenburger DD, Holmes FF, Cantor KP, Blair A (1997) Tobacco and non-Hodgkin's lymphoma: combined analysis of three case-control studies (United States). Cancer Causes Control 8(2):159–166
25. Herrinton LJ, Friedman GD (1998) Cigarette smoking and risk of non-Hodgkin's lymphoma subtypes. Cancer Epidemiol Biomarkers Prev 7(1):25–28
26. Morton LM, Holford TR, Leaderer B, Boyle P, Zahm SH, Zhang Y, Flynn S, Tallini G, Zhang B, Owens PH, Zheng T (2003) Cigarette smoking and risk of non-Hodgkin lymphoma subtypes among women. Br J Cancer 89(11):2087–2092. doi:10.1038/sj.bjc.6601388
27. Sonoda T, Ishida T, Mori M, Sakai H, Noguchi M, Imai K (2005) A case-control study of multiple myeloma in Japan: association with occupational factors. Asian Pac J Cancer Prev 6(1):33–36
28. Batty GD, Kivimaki M, Gray L, Smith GD, Marmot MG, Shipley MJ (2008) Cigarette smoking and site-specific cancer mortality: testing uncertain associations using extended follow-up of the original Whitehall study. Ann Oncol 19(5):996–1002. doi:10.1093/annonc/mdm578
29. Brown LM, Everett GD, Gibson R, Burmeister LF, Schuman LM, Blair A (1992) Smoking and risk of non-Hodgkin's lymphoma and multiple myeloma. Cancer Causes Control 3(1):49–55
30. Fernberg P, Odenbro A, Bellocco R, Boffetta P, Pawitan Y, Zendehdel K, Adami J (2007) Tobacco use, body mass index, and the risk of leukemia and multiple myeloma: a nationwide cohort study in Sweden. Cancer Res 67(12):5983–5986. doi:10.1158/0008-5472.CAN-07-0274
31. Friedman GD (1993) Cigarette smoking, leukemia, and multiple myeloma. Ann Epidemiol 3(4):425–428
32. Garfinkel L, Boffetta P (1990) Association between smoking and leukemia in two American Cancer Society prospective studies. Cancer 65(10):2356–2360
33. Heineman EF, Zahm SH, McLaughlin JK, Vaught JB, Hrubec Z (1992) A prospective study of tobacco use and multiple myeloma: evidence against an association. Cancer Causes Control 3(1):31–36
34. Linet MS, McLaughlin JK, Hsing AW, Wacholder S, Co Chien HT, Schuman LM, Bjelke E, Blot WJ (1992) Is cigarette smoking a risk factor for non-Hodgkin's lymphoma or multiple myeloma? Results from the Lutheran Brotherhood Cohort Study. Leuk Res 16(6–7):621–624
35. McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr (1995) Smoking and cancer mortality among U.S. veterans: a 26-year follow-up. Int J Cancer 60(2):190–193
36. Monnereau A, Orsi L, Troussard X, Berthou C, Fenaux P, Soubeyran P, Marit G, Huguet F, Milpied N, Leporrier M, Hemon D, Clavel J (2008) Cigarette smoking, alcohol drinking, and risk of lymphoid neoplasms: results of a French case-control study.

Cancer Causes Control 19(10):1147–1160. doi:10.1007/s10552-008-9182-1
37. Nieters A, Deeg E, Becker N (2006) Tobacco and alcohol consumption and risk of lymphoma: results of a population-based case-control study in Germany. Int J Cancer 118(2):422–430. doi:10.1002/ijc.21306
38. Talamini R, Polesel J, Montella M, Maso LD, Crispo A, Spina M, Franceschi S, Crovatto M, La Vecchia C (2005) Smoking and non-Hodgkin lymphoma: case-control study in Italy. Int J Cancer 115(4):606–610. doi:10.1002/ijc.20891
39. Bell DA, Liu Y, Cortopassi GA (1995) Occurrence of bcl-2 oncogene translocation with increased frequency in the peripheral blood of heavy smokers. J Natl Cancer Inst 87(3):223–224
40. Vega F, Medeiros LJ (2003) Chromosomal translocations involved in non-Hodgkin lymphomas. Arch Pathol Lab Med 127(9):1148–1160
41. Chang CM, Schroeder JC, Olshan AF, Dunphy CH, Huang WY, Baric RS, Conway K, Cerhan JR, Lynch CF, Rothman N, Cantor KP, Blair A (2010) A case-control study of tobacco use and other non-occupational risk factors for lymphoma subtypes defined by t(14; 18) translocations and bcl-2 expression. Cancer Causes Control 21:1147–1154. doi:10.1007/s10552-010-9531-8
42. Chiu BC, Dave BJ, Blair A, Gapstur SM, Chmiel JS, Fought AJ, Zahm SH, Weisenburger DD (2007) Cigarette smoking, familial hematopoietic cancer, hair dye use, and risk of t(14;18)-defined subtypes of non-Hodgkin's lymphoma. Am J Epidemiol 165(6):652–659. doi:10.1093/aje/kwk044
43. Endogenous Hormones Breast Cancer Collaborative Group (2011) Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer 105(5):709–722
44. Medina KL, Strasser A, Kincade PW (2000) Estrogen influences the differentiation, proliferation, and survival of early B-lineage precursors. Blood 95(6):2059–2067
45. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds) (2008) WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edn. IARC Press, Lyon
46. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V (2009) A review of human carcinogens–Part B: biological agents. Lancet Oncol 10(4):321–322
47. Engels EA (2007) Infectious agents as causes of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 16(3):401–404. doi:10.1158/1055-9965.EPI-06-1056
48. Centers for Disease Control (CDC) (2010) Vital signs: current cigarette smoking among adults aged > or = 18 years—United States, 2009. MMWR Morb Mortal Wkly Rep 59 (35):1135–1140