Smoking and Lymphoma Risk in the European Prospective Investigation into Cancer and Nutrition

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Lymphomas are one of the few cancers that have been increasing in incidence over the past decades. So far, only a few established risk factors have been identified, including immunosuppression and viral infections. Recent evidence suggests etiologic heterogeneity of different lymphoma subtypes. Smoking may affect risk differently, depending on the lymphoma entity. The European Prospective Investigation into Cancer and Nutrition was used to study the role of smoking in the etiology of lymphomas and individual subtypes within a prospective study. Information on baseline and lifetime tobacco smoking by 478,590 participants was collected between 1992 and 2000. Cox proportional hazards regression was used to calculate multivariate-adjusted hazard ratios and 95% confidence intervals. During 3,567,410 person-years of follow-up, 1,371 lymphoma cases (1,304 non-Hodgkin's lymphomas and 67 Hodgkin's lymphomas) were identified. Relative risk for smokers at recruitment was more than twofold higher for Hodgkin's lymphoma (hazard ratio = 2.14, 95% confidence interval: 1.18, 3.87) but was not elevated for non-Hodgkin's lymphoma (hazard ratio = 1.06, 95% confidence interval: 0.94, 1.19) and individual B-cell non-Hodgkin's lymphoma subtypes. In this prospective study, smoking appeared to increase Hodgkin's lymphoma risk consistently in both genders, whereas B-cell non–Hodgkin's lymphoma risk was not associated. Future analysis should involve viral biomarkers and genetic susceptibility markers to elucidate potential mechanisms of smoking-induced carcinogenesis, particularly for Hodgkin's lymphoma.

lymphoma; prospective studies; risk factors; smoking

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; ICD-O-2, *International Classification of Diseases for Oncology*, second edition.

Lymphomas involve a group of heterogeneous malignancies that originate from lymphocytes. They are interpreted as the malignant representation of cells arrested at a specific stage of normal lymphocyte differentiation. Lymphomas have traditionally been classified as either Hodgkin's lymphoma or non-Hodgkin's lymphoma. The current World Health Organization classification of hematopoietic and lymphoid tumors (1) differentiates between Hodgkin's lymphoma, B-cell neoplasm, and T/natural killer cell tumors based on distinct morphologic, immunophenotypic, and genetic features. In Europe, 121,200 cases were newly diagnosed with a lymphoma in 2004, and an estimated 65,200 persons died from this disease (2). Over the past decades, incidence rates of non-Hodgkin's lymphoma have increased in many parts of the world (3), although a plateau has recently been reported in several countries (4). Incidence rates of Hodgkin's lymphoma were relatively stable, but some countries reported an increase (5).

Knowledge of etiologic factors in non-Hodgkin's lymphoma and Hodgkin's lymphoma is scarce. The strongest risk factor for non-Hodgkin's lymphoma is acquired or inherited immunodeficiency. Patients undergoing immunosuppressive therapy after organ or tissue transplantation are at a 20- to more than 100-fold increased risk of non-Hodgkin's lymphoma (6). Prior to the availability of highly active antiretroviral therapy, the incidence of lymphoma among persons infected with human immunodeficiency virus was about 1–6 percent (7). An infectious etiology has been established for Hodgkin's lymphoma and some non-Hodgkin's lymphoma subtypes (7). In general, all currently known risk factors are expected to account for only a small proportion of the overall incidence of lymphoma.

A large number of case-control studies (earlier studies reviewed by Peach and Barnett (8–16)), but only eight cohort studies (reviewed by Peach and Barnett (8, 17)), have explored the association between smoking and non-Hodgkin's lymphoma risk, with inconsistent results (8). A recent pooled analysis involving 6,594 cases and 8,892 controls from case-control studies in the United States, Europe, and Australia (10) found a slightly elevated risk of non-Hodgkin's lymphoma associated with smoking (odds ratio = 1.07, 95 percent confidence interval (CI) = 1.00, 1.15). Compared with nonsmokers, current smokers had a higher risk specifically for follicular lymphoma (odds ratio = 1.31, 95 percent CI: 1.12, 1.52), an association also found in other studies (9, 11, 13, 18–20). A large European study of 1,742 non-Hodgkin's lymphoma cases and 2,465 controls did not support a role of smoking in the etiology of non-Hodgkin's lymphoma or non-Hodgkin's lymphoma subtypes (12). Several reports linked smoking with Hodgkin's lymphoma (14, 21–27), whereas other studies failed to find an association (17, 28–30).

The aim of this study was to examine the association of tobacco smoking with the risk of lymphoma and various lymphoma subtypes within a prospective European study.

MATERIALS AND METHODS

Population

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a large, prospective cohort study involving 521,448 participants and was conducted in 23 centers in 10 European countries (France, Italy, Spain, the Netherlands, United Kingdom, Greece, Germany, Sweden, Norway, Denmark). The participants were usually recruited from the general population, with some exceptions; for details, refer to Riboli et al. (31). The cohorts in France, Norway, Utrecht (the Netherlands), and Naples (Italy) were restricted to women (31).

Of the 521,448 participants, prevalent cancer cases and subjects for whom nondietary or follow-up information was incomplete (n = 27,080) were excluded. For this analysis,

we also excluded the French cohort ($n = 69,427$) because lymphomas have not been part of the outcome assessment, 6,445 subjects for whom smoking information was missing, and 14 cases with an uncertain lymphoma diagnosis. Accordingly, the current analysis was based on 418,482 EPIC participants, including 1,371 incident lymphoma cases.

This study was approved by the ethical review board of the International Agency for Research on Cancer (Lyon, France) and those of all EPIC centers. All EPIC participants provided written consent for the use of all data.

Exposure assessment

Lifestyle questionnaires were used to collect information on tobacco use, education, medical history, and physical activity. Lifetime history of use of tobacco products was assessed by asking about smoking status (current, past, or never smoker), type of tobacco products used (cigarettes, cigars, or pipe), number of cigarettes smoked at different ages, and age at which participants started and, if applicable, quit smoking. Current smoking refers to smoking at baseline. Diet over the previous 12 months, including alcohol consumption, was assessed by using dietary questionnaires specifically developed for each participating country based on a common core protocol (31). Baseline ethanol and energy intakes were calculated from the dietary instruments applied in each center. Height and weight were measured at the baseline examination except in Norway and Oxford (United Kingdom), where self-reported height and weight were assessed via questionnaire (31).

Outcome assessment

Cancer diagnoses were based on population registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. In France, Germany, and Greece, a combination of sources and methods was used, including health insurance records, cancer and pathology registries, active follow-up of study subjects, and next-of-kin information. Mortality data were collected from either the cancer or the mortality registries at the regional or national level. Cancer cases were identified by the end of the censoring periods, which were December 2002–December 2005 in the EPIC centers; in Germany and Greece, the end of follow-up was considered the last known contact, date of diagnosis, or date of death, whichever occurred first.

Following the core protocol of 1992, the diagnosis of lymphoma cases included in the central EPIC database was based on the *International Classification of Diseases for Oncology*, second edition (ICD-O-2). All cases of lymphoma were subsequently reclassified according to the recently published World Health Organization document on classification of tumors of the hematopoietic and lymphoid tissues (1) by applying a conversion program available on the Surveillance, Epidemiology, and End Results Web page (http://seer.cancer.gov/tools/conversion/ICDO2-3manual.pdf). ICD-O-2 diagnoses that could not be translated into the World Health Organization classification were left unclassified (''NOS'') on the level at which further detailed specification failed.

The current analysis considered the following groups of disease: Hodgkin's lymphoma and non-Hodgkin's lymphoma; within non-Hodgkin's lymphoma, B-cell lymphoma and T-cell lymphoma; and within B-cell non-Hodgkin's lymphoma, the entities of diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, B-cell chronic lymphocytic leukemia, and multiple myeloma/plasmacytoma. Other rare entities were not considered (refer to the Appendix).

Statistical analysis

Cox proportional hazards regression was used to examine the association of smoking with lymphoma and individual lymphoma subtypes. Never smokers were considered the reference category. Various smoking variables were considered in separate analyses: current smoking status (never smokers, current cigarette smokers, former smokers, cigar and pipe smokers, other cigarette smokers who were occasional smokers or for whom information on smoking amount or duration was missing), average intensity of smoking (0–<10, 10–<20, ≥20 cigarettes per day), smoking duration (0–<10, 10–<20, ≥20 years), pack-years (0.075–15, >15–30, >30), age at onset of smoking (≤16 years, >16 years), and number of years to the date of enrollment in the cohort since smoking cessation (0–<10, 10–<20, ≥20). Time at study entry was age at recruitment; exit time was age at which participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever occurred first. The analyses were stratified by sex to control for differences in smoking behavior between men and women and by centers to account for center effects such as follow-up procedures and questionnaire design. We further stratified by age at recruitment (in 1-year categories) because our Cox regression models assumed that the hazard function did not change during follow-up, which was probably not true because of calendar effects. Trend tests for duration, intensity of cigarette smoking, pack-years of smoking, age at onset of smoking, and years since smoking cessation were conducted by using the continuous variables.

All models were adjusted for educational level (low (none, primary school, technical/professional school), high (secondary school, university degree)). Additional adjustment for alcohol consumption at baseline (g/day), total fruit consumption (g/day), total vegetable consumption (g/day), and body mass index (kg/m^2) did not alter the results appreciably and was therefore not included in the final models. Subanalyses were performed separately by sex for the main lymphoma categories (Hodgkin's lymphoma, non-Hodgkin's lymphoma, B-cell non-Hodgkin's lymphoma, T-cell non-Hodgkin's lymphoma) and by age (<50 years, ≥50 years) for Hodgkin's lymphoma. In this paper, hazard ratio estimates are presented for only those cells with more than two counts. All analyses were conducted by using SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

This analysis was based on 1,371 lymphoma cases (666 men, 705 women) and 417,111 noncases (145,570 men,

271,541 women). Median follow-up time was 8.5 years (interquartile range, 7.3–9.8 years). The great majority (n = 1,304) were non-Hodgkin's lymphoma cases (1,156 B-cell non-Hodgkin's lymphoma, 47 T-cell non-Hodgkin's lymphoma), and 67 were diagnosed with Hodgkin's lymphoma (table 1). The most frequent subtypes were multiple myeloma (n = 305), B-cell chronic lymphocytic leukemia (n = 238), DLBCL (n = 163), and follicular lymphoma (n = 143). A total of 101 cases of non-Hodgkin's lymphoma and 184 cases of B-cell lymphoma could not be further specified. The baseline characteristics of the study population are depicted in table 1.

For Hodgkin's lymphoma, we observed a higher risk for ever smokers (hazard ratio (HR) = 2.14, 95 percent CI: 1.18, 3.87), current smokers (HR = 2.54, 95 percent CI: 1.30, 4.96), and former smokers (HR = 1.94, 95 percent CI: 0.99, 3.82) compared with never smokers (table 2). The increased risk for ever smoking was slightly higher for men (HR = 2.49, 95 percent CI: 1.01, 6.13) than for women (HR = 1.87, 95 percent CI: 0.83, 4.18). Early onset of smoking, long-term smoking, intense smoking, and short time since smoking cessation were all associated with increased Hodgkin's lymphoma risk (table 2). When mutually adjusting for smoking intensity and duration of smoking, the effect for smoking intensity was attenuated, whereas the positive association for long-term smoking was not (HR = 3.28, 95 percent CI: 1.23, 8.74). When we stratified by age, current smoking was a strong risk factor for Hodgkin's lymphoma in participants aged 50 years or older (HR = 3.55, 95 percent CI: 1.62, 7.76), but not for young-adult-onset cases (HR = 1.29, 95 percent CI: 0.41, 4.10).

Ever smoking and the categories of intensity and duration of smoking lacked a statistically significant association with risk of non-Hodgkin's lymphoma and B-cell non-Hodgkin's lymphoma (table 2). Ever smokers had no elevated risk of any of the B-cell lymphoma subtypes studied (table 3). However, heavy smoking was positively related to the risk of DLBCL (HR = 2.00; table 3), which was stronger for women (HR = 2.88, 95 percent CI: 1.40, 5.93) than for men (HR = 1.84, 95 percent CI: 0.85, 3.97). Smoking cessation soon before study entry was also related to an increased risk of DLBCL (HR = 1.72; table 3). However, the effect was found for only men (HR = 2.38, 95 percent CI: 1.14, 5.00), not women (HR = 1.32, 95 percent CI: 0.66, 2.67). In contrast, the positive association between smoking cessation soon before entering the cohort and follicular lymphoma (HR = 1.68; table 3) was statistically significant for women (HR = 2.02, 95 percent CI: 1.11, 3.68) but not for men (HR = 1.28, 95 percent CI: 0.58, 2.84).

DISCUSSION

This large, prospective cohort study did not provide evidence for a substantial role of smoking in the etiology of non-Hodgkin's lymphoma or major B-cell lymphoma subtypes. However, although based on a small number of cases, a clearly elevated risk of Hodgkin's lymphoma in relation to smoking was observed.

The weak or null result for non-Hodgkin's lymphoma is in line with data from recent European case-control studies (12, 14, 23). Contrary to several reports (9–11, 13, 15, 18–20) that provided evidence for a role of smoking in the etiology of follicular lymphoma, particularly among women, we found no elevated risk of follicular lymphoma for ever or current smokers of either gender. However, smoking cessation recent to entry into the cohort was associated with a statistically significant risk of follicular lymphoma among women.

Hodgkin's lymphoma is a B-cell neoplasm characterized by Reed-Sternberg giant cells replacing the normal lymphoid structure. The World Health Organization classification differentiates four subtypes whose etiology appears to be heterogeneous. All Hodgkin's lymphoma subtypes combined show a bimodal age structure, with peaks at ages 15–34 years and more than 60 years in most countries (32). Besides Epstein-Barr virus infection and some occupational exposures, smoking has repeatedly been discussed as a potential risk factor (14, 21–27). Previous cohort (17, 21, 22, 26) and case-control (14, 23, 25, 27) studies have shown an association between ever and/or current smoking and Hodgkin's lymphoma risk, although not all associations were statistically significant. Two studies in Europe and the United States, each involving about 340 cases, reported a 40 percent (95 percent CI: 4, 87) to 80 percent (95 percent CI: 30, 190) increased Hodgkin's lymphoma risk for current smokers (23, 25). Smoking seemed to be particularly relevant for older-onset Hodgkin's lymphoma (odds ratio for current smoking = 2.35, 95 percent CI: 1.52, 3.61) (23). A US study provided some evidence for a role of smoking in Epstein-Barr virus–infected subgroups (27); young adult women positive for the Epstein-Barr virus were at elevated risk if they were current smokers (adjusted odds ratio = 2.9, 95 percent CI: 1.03, 8.0).

Overall, our prospective data are in line with those from the majority of studies that found some indication for an increased risk of Hodgkin's lymphoma for smokers. Tobacco contains more than 4,500 compounds, including five known human carcinogens and a number of toxic agents (33). Some, such as formaldehyde and benzene, have been implicated in the etiology of lymphomas and some subtypes (34, 35). Besides a direct carcinogenic effect of tobacco-related agents, smoking may also affect lymphomagenesis indirectly by modulating immune responses (33, 36). Smoking has been shown to increase lymphocyte subset counts and impair their function, down-regulate natural killer cell activity, and induce T-cell anergy and inflammatory cytokines. A positive relation between smoking and positive Epstein-Barr virus status has been reported (37). One can speculate that the association of smoking particularly with Hodgkin's lymphoma risk may be related to an effect on clearance or reactivation of Epstein-Barr virus or other undetected viruses putatively implicated in Hodgkin's lymphoma etiology. Innate as well as adaptive immunity appears to be affected by smoking. It can be envisioned that particularly the down-regulated T-cell–mediated immunity in charge of a functioning antiviral and antitumor immune response may underlie the elevated Hodgkin's lymphoma risk for smokers. T-cell–mediated immunity is required for the control of Epstein-Barr virus infections and elimination of Epstein-Barr virus–infected B-cells. Impairment of

TABLE 1. Baseline characteristics of cases and noncases, European Prospective Investigation into Cancer and Nutrition, 1992–2005

	Incident cases	Noncases	Person-years
Total no.	1,371	417,111	3,567,410
Italy	132	45,264	391,265
Spain	113	40,675	409,507
United Kingdom	269	79,203	681,432
The Netherlands	92	36,930	322,789
Greece	38	26,000	186,475
Germany	126	50,307	418,075
Sweden	299	49,022	523,472
Denmark	257	55,832	429,280
Norway	45	33,878	205,115
Age (years) at recruitment (mean (SD*))	57.3 (8.7)	51.0 (10.4)	
Length (years) of follow-up (mean (SD))	4.9 (2.8)	8.5 (2.0)	
Educational level (%)			
None	3.5	4.7	
Primary school completed	32.1	32.1	
Technical/professional school	26.5	26.5	
Secondary school	14.2	18.6	
University degree	19.1	21.7	
Not specified	3.6	2.7	
Smoking variables (mean, (SD))			
Average smoking intensity (cigarettes/day)†,‡	14.0 (8.5)	13.3 (8.4)	
Duration of smoking (years)†,§	27.8 (13.2)	24.2 (12.3)	
Pack-years of smoking†,¶	20.6 (15.3)	17.1 (14.4)	
Age (years) at onset of smoking†,#	19.1 (5.7)	19.1 (5.6)	
Years since quitting**	15.7 (11.6)	14.1 (10.4)	
Males (no.)	666	145,570	
Average smoking intensity (cigarettes/day) (mean (SD))	16.3 (8.9)	16.3 (9.4)	
Duration (years) (mean (SD))	29.6 (13.3)	26.4 (12.4)	
Pack-years (mean (SD))	24.8 (16.4)	22.3 (16.8)	
Age (years) at onset of smoking (mean (SD))	18.0 (4.4)	18.2 (5.0)	
Years since quitting (mean (SD))	16.1 (11.9)	14.6 (10.6)	
Females (no.)	705	271,541	
Average smoking intensity (cigarettes/day) (mean (SD))	11.0 (6.7)	11.2 (6.9)	
Duration (years) (mean (SD))	25.3 (12.6)	22.4 (11.8)	
Pack-years (mean (SD))	15.1 (11.6)	13.3 (11.0)	
Age (years) at onset of smoking (mean (SD))	20.8 (6.8)	19.8 (5.9)	
Years since quitting (mean (SD))	15.0 (10.9)	13.7 (10.2)	

* SD, standard deviation.
† Among current and former smokers only.
‡ Information was missing for 58,960 subjects.
§ Information was missing for 18,658 subjects.
¶ Information was missing for 58,961 subjects.
# Information was missing for 15,105 subjects.
** Among former smokers only.

T-cell–mediated immunity allows latently infected B-cells to progress toward malignant transformation.

In this prospective study, it would be interesting to explore whether baseline smoking is associated with aberrant

TABLE 2. Risk (hazard ratio) of lymphomas associated with smoking, European Prospective Investigation into Cancer and Nutrition, 1992–2005

	Hodgkin's lymphoma			Non-Hodgkin's lymphoma			B-cell non-Hodgkin's lymphoma			T-cell non-Hodgkin's lymphoma		
	No.	HR*,†	95% CI*	No.	HR†	95% CI	No.	HR†	95% CI	No.	HR†	95% CI
Never smoked	18	1.00	Reference	532	1.00	Reference	475	1.00	Reference	17	1.00	Reference
Ever smoked	49	2.14	1.18, 3.87	772	1.06	0.94, 1.19	681	1.05	0.92, 1.12	30	1.06	0.56, 1.98
Current smokers	23	2.54	1.30, 4.96	239	0.93	0.79, 1.09	211	0.92	0.77, 1.09	11	1.11	0.50, 2.45
Former smokers	21	1.94	0.99, 3.82	439	1.12	0.98, 1.28	387	1.11	0.97, 1.28	14	0.90	0.43, 1.89
Cigar/pipe smokers	1			37	1.17	0.83, 1.66	35	1.25	0.88, 1.79	1		
Other smokers‡	4	2.11	0.65, 6.79	57	1.13	0.85, 1.50	48	1.08	0.78, 1.47	4	2.41	0.77, 7.59
Average smoking intensity§		1.03	1.00, 1.06		1.01	1.00, 1.01		1.00	1.00, 1.01		1.02	0.98, 1.05
0–<10 cigarettes/day	11	1.95	0.85, 4.47	157	0.99	0.82, 1.19	148	1.02	0.84, 1.24	4	0.59	0.19, 1.77
10–<20 cigarettes/day	18	2.50	1.18, 5.30	209	1.02	0.85, 1.22	188	1.01	0.84, 1.22	13	1.35	0.61, 2.96
≥20 cigarettes/day	8	2.18	0.86, 5.54	121	1.21	0.97, 1.50	103	1.12	0.89, 1.42	6	1.22	0.45, 3.33
Smoking duration§		1.04	1.02, 1.06		1.00	1.00, 1.01		1.00	1.00, 1.01		1.01	0.99, 1.03
0–<10 years	3	1.05	0.30, 3.64	78	1.12	0.88, 1.42	72	1.17	0.91, 1.50	1		
10–<20 years	5	0.96	0.34, 2.72	104	0.88	0.71, 1.09	88	0.84	0.67, 1.06	5	1.02	0.37, 2.84
≥20 years	37	2.90	1.52, 5.54	519	1.08	0.95, 1.23	461	1.07	0.94, 1.23	21	1.07	0.54, 2.12
Pack-years§		1.03	1.01, 1.04		1.00	1.00, 1.01		1.00	1.00, 1.01		1.01	0.99, 1.03
0.075–15	11	1.26	0.55, 2.90	214	1.00	0.84, 1.19	200	1.04	0.87, 1.24	5	0.51	0.18, 1.44
>15–30	16	3.48	1.58, 7.69	165	1.10	0.91, 1.34	146	1.07	0.88, 1.31	12	1.68	0.75, 3.75
>30	10	4.13	1.64, 10.4	108	1.06	0.84, 1.33	93	1.00	0.77, 1.26	6	1.33	0.48, 3.66
Age at onset of smoking§		0.85	0.77, 0.95		0.99	0.98, 1.00		0.99	0.98, 1.01		0.97	0.90, 1.04
≤16 years	24	2.96	1.45, 5.88	232	1.08	0.92, 1.28	199	1.04	0.87, 1.25	12	1.44	0.65, 3.21
>16 years	22	1.58	0.81, 3.08	485	1.04	0.91, 1.18	435	1.04	0.91, 1.19	16	0.87	0.43, 1.78
Years since quitting§,¶		0.97	0.93, 1.02		1.00	0.99, 1.00		0.99	0.98, 1.00		1.00	0.95, 1.05
0–<10	12	2.71	1.25, 5.91	156	1.25	1.04, 1.50	141	1.26	1.04, 1.53	6	1.07	0.41, 2.79
10–<20	6	1.69	0.63, 4.53	127	1.11	0.91, 1.36	110	1.08	0.87, 1.34	4	0.90	0.29, 2.78
≥20	3	1.02	0.28, 3.66	156	1.06	0.88, 1.28	136	1.05	0.86, 1.28	4	0.79	0.25, 2.55

* HR, hazard ratio; CI, confidence interval.
† Adjusted for educational level (binary: high/low), stratified by center, sex, and age at recruitment (1-year steps).
‡ Cigarette smokers for whom amount or duration of smoking or date of quitting smoking was unknown.
§ Continuous variable (trend).
¶ Former smokers only.

immune response against Epstein-Barr virus, which then results in exuberant proliferation, increases the chances for errors made during DNA replication, and subsequently results in Hodgkin's lymphoma. Abnormal seroresponse to Epstein-Barr virus has been previously observed preceding the development of lymphoma (38, 39), and a prospective setting would be helpful to elucidate the temporal relation among smoking, Epstein-Barr virus replication, and Hodgkin's lymphoma risk.

For some lymphoma subtypes for which an inflammatory rather than infectious etiology is discussed, the indicated anti-inflammatory effect of some cigarette compounds, such as carbon monoxide or nicotine (33), may attenuate a carcinogenic effect of moderate smoking. This possibility might explain why only high intensity of smoking, but not long-term smoking, presented an elevated risk of, for example, DLBCL.

One of the strengths of this study is its prospective design, with the advantage that both smoking behavior and the reporting of smoking behavior were not influenced by disease status. When we excluded from analysis cases of disease that occurred in the first 2 years of follow-up, we obtained essentially the same results. The positive association of smoking with Hodgkin's lymphoma risk was still statistically significant (HR = 2.61, 95 percent CI: 1.22, 5.58).

The cases were categorized according to the actual World Health Organization classification of lymphoid neoplasms (1). Unfortunately, 21.9 percent of the cases of non-Hodgkin's lymphoma could not be further specified given the available data. In addition, we were not able to verify all lymphoma diagnoses. Therefore, we cannot rule out the occurrence of some misclassification of lymphoma subtype. The number of observed cases of some lymphoma subtypes

TABLE 3. Risk (hazard ratio) of non-Hodgkin's lymphoma subtypes associated with smoking, European Prospective Investigation into Cancer and Nutrition, 1992–2005

	Follicular B-cell non-Hodgkin's lymphoma			Diffuse large B-cell non-Hodgkin's lymphoma			B-cell chronic lymphocytic lymphoma			Plasma cell neoplasm		
	No.	HR*,†	95% CI*	No.	HR†	95% CI	No.	HR†	95% CI	No.	HR†	95% CI
Never smoked	66	1.00	Reference	58	1.00	Reference	98	1.00	Reference	135	1.00	Reference
Ever smoked	77	0.88	0.62, 1.25	105	1.27	0.90, 1.79	140	0.95	0.73, 1.26	170	0.94	0.74, 1.20
Current smokers	26	0.78	0.49, 1.26	26	0.81	0.50, 1.30	40	0.77	0.52, 1.12	53	0.88	0.63, 1.23
Former smokers	45	0.99	0.67, 1.48	62	1.50	1.03, 2.19	78	1.01	0.74, 1.38	104	1.06	0.81, 1.39
Cigar/pipe smokers	2			7	1.95	0.85, 4.46	9	1.17	0.58, 2.39	6	0.74	0.32, 1.71
Other smokers‡	4	0.65	0.23, 1.84	10	1.99	0.98, 4.02	13	1.41	0.77, 2.57	7	0.47	0.22, 1.03
Average smoking intensity§		1.00	0.97, 1.02		1.02	1.00, 1.04		0.99	0.98, 1.01		1.00	0.99, 1.02
0–<10 cigarettes/day	24	1.03	0.63, 1.68	20	0.96	0.56, 1.63	31	0.91	0.59, 1.38	27	0.78	0.50, 1.21
10–<20 cigarettes/day	26	0.94	0.58, 1.53	30	1.14	0.71, 1.83	33	0.70	0.46, 1.07	50	1.11	0.77, 1.61
≥20 cigarettes/day	12	0.99	0.51, 1.92	25	2.00	1.18, 3.39	23	0.92	0.54, 1.50	26	1.09	0.68, 1.75
Smoking duration§		1.00	0.99, 1.01		1.00	0.99, 1.01		1.00	0.99, 1.00		1.00	0.99, 1.01
0–<10 years	8	0.86	0.41, 1.80	9	1.27	0.62, 2.59	15	1.20	0.69, 2.09	19	1.15	0.70, 1.87
10–<20 years	7	0.47	0.21, 1.04	19	1.51	0.89, 2.57	21	0.91	0.56, 1.48	22	0.76	0.48, 1.20
≥20 years	57	1.01	0.69, 1.48	65	1.14	0.78, 1.66	89	0.88	0.65, 1.20	120	1.02	0.78, 1.33
Pack-years§		1.00	0.98, 1.01		1.01	1.00, 1.02		1.00	0.98, 1.01		1.00	0.99, 1.01
0.075–15	32	1.02	0.65, 1.60	32	1.19	0.75, 1.88	40	0.89	0.60, 1.31	39	0.84	0.57, 1.23
>15–30	23	1.13	0.68, 1.89	23	1.15	0.69, 1.93	27	0.77	0.49, 1.21	39	1.19	0.80, 1.76
>30	7	0.59	0.26, 1.32	20	1.47	0.84, 2.58	20	0.76	0.45, 1.27	25	1.03	0.64, 1.67
Age at onset of smoking§		1.00	0.96, 1.05		1.01	0.97, 1.08		1.00	0.97, 1.03		1.01	0.97, 1.05
≤16 years	18	0.71	0.41, 1.23	35	1.29	0.82, 2.03	36	0.78	0.52, 1.17	56	1.11	0.80, 1.55
>16 years	55	0.95	0.65, 1.39	58	1.14	0.78, 1.67	93	1.00	0.74, 1.34	103	0.91	0.69, 1.19
Years since quitting§,¶		0.96	0.93, 0.99		1.00	0.96, 1.01		1.00	0.98, 1.02		1.00	0.98, 1.02
0–<10	25	1.68	1.04, 2.73	25	1.72	1.06, 2.80	29	1.12	0.73, 1.73	30	1.02	0.68, 1.53
10–<20	11	0.82	0.42, 1.57	19	1.64	0.96, 2.79	18	0.81	0.48, 1.36	39	1.34	0.92, 1.95
≥20	9	0.60	0.29, 1.22	18	1.30	0.75, 2.25	31	1.03	0.67, 1.57	35	0.91	0.61, 1.34

* HR, hazard ratio; CI, confidence interval.
† Adjusted for educational level (binary: high/low), stratified by center, sex, and age at recruitment (1-year steps).
‡ Cigarette smokers for whom amount or duration of smoking or date of quitting smoking was unknown.
§ Continuous variable (trend).
¶ Former smokers only.

was also small; thus, the statistical power for subtype-specific analysis was relatively low. The same holds true for further stratified analysis. Given the number of analyses we performed, some of the results may have arisen because of chance. Participants have been interviewed and queried about their smoking habits and other lifestyle characteristics at entry into the cohort. Repeated interviews have not been performed at all centers. Consequently, it is not known how many individuals began smoking during follow-up or quit smoking during that time. Furthermore, smokers may have been under closer surveillance for cancer, which may have influenced their being diagnosed with early lymphoma. However, we cannot think of any specific reason why Hodgkin's lymphoma should be diagnosed early among smokers.

In conclusion, the EPIC study supports recently accumulating evidence for a role of smoking in the etiology of Hodgkin's lymphoma, whereas B-cell non-Hodgkin's lymphoma risk is not considerably affected by smoking. A longer follow-up of the cohort with more incident cases is needed to better assess the relevance of heavy smoking in the etiology of DLBCL. Future studies would greatly benefit from a combined evaluation of smoking parameters, genetic susceptibility factors, and biomarkers of infectious agents.

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APPENDIX

Classification of Lymphoma Subgroups

- Hodgkin's lymphoma (includes ICD-O-2 codes 9650/3, 9651/3, 9652/3, 9653/3, 9654/3, 9655/3, 9659/3, 9663/3, 9664/3, 9665/3, 9667/3)
- Non-Hodgkin's lymphoma not otherwise specified (ICD-O-2 code 9590/3)
- B-cell acute lymphatic leukemia (includes acute lymphoblastic leukemia) (ICD-O-2 codes 9727/3, 9835/3, 9728/3, 9836/3)
- DLBCL (includes Burkitt) (ICD-O-2 codes 9680/3, 9684/3, 9679/3, 9687/3, 9826/3)
- Follicular lymphoma (all grades) (ICD-O-2 codes 9675/3, 9690/3, 9691/3,9695/3, 9698/3)
- B-cell chronic lymphatic leukemia (includes chronic lymphocytic leukemia, prolymphocytic leukemia) (ICD-O-2 codes 9670/3, 9823/3, 9832/3, 9833/3)
- Lymphoplasmocytic lymphoma/Waldenstroem disease (ICD-O-2 codes 9671/3, 9761/3)
- Multiple myeloma/plasmacytoma (ICD-O-2 codes 9731/3, 9732/3, 9734/3)
- Marginal zone B-cell lymphoma (ICD-O-2 codes 9699/3, 9689/3)
- Hairy cell lymphoma (ICD-O-2 code 9940/3)
- B-cell lymphoma, other (ICD-O-2 codes 9673/3, 9765/1)
- T-cell acute lymphoblastic leukemia (includes acute lymphoblastic leukemia and adult T-leukemia) (ICD-O-2 codes 9837/3, 9729/3, 9827/3)
- Mycosis fungoides, Sezary syndrome (ICD-O-2 codes 9700/3, 9701/3)
- Peripheral T-cell lymphoma not otherwise specified (ICD-O-2 code 9702/3)
- Cutaneous T-cell lymphoma (ICD-O-2 codes 9709/3, 9708/3, 9718/3)
- Other T-cell lymphomas (ICD-O-2 codes 9705/3, 9834/3, 9831/3, 9714/3, 9716/3, 9717/3, 9719/3, 9948/3)