Cigarette Smoking and Risk of Hodgkin Lymphoma: A Population-Based Case-Control Study

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Abstract

Background: **Studies have inconsistently reported an association between tobacco smoking and Hodgkin lymphoma (HL) risk. The conflicting findings may reflect etiologic heterogeneity between HL subtypes, warranting further characterization of the relationship.**

Methods: **We collected information on tobacco-smoking habits in 586 classic HL cases and 3,187 population controls in a Danish-Swedish case-control study. HL EBV status was established for 499 cases by standard techniques. Odds ratios (OR) for an association with cigarette smoking were calculated by logistic regression for HL overall and stratified by age, sex, major histology subtypes, and tumor EBV status, adjusting for known confounders.**

Results: **Compared with never smokers, current cigarette smokers were at an increased overall HL risk (adjusted OR, 1.57; 95% confidence interval (95% CI), 1.22-2.03). The association was strongest for EBV-positive HL (adjusted OR, 2.36; 95% CI, 1.51-3.71), but also applied to EBV-negative HL (adjusted OR, 1.43; 95% CI, 1.05-1.97; $P_{\text{homogeneity EBV-pos versus EBV-neg}} = 0.04$). The association did not vary appreciably by age, sex, or histologic subtype, the apparent EBV-related difference present in all strata. There was no evidence of a dose-response pattern, whether by age at smoking initiation, daily cigarette consumption, number of years smoking, or cumulative number of cigarettes smoked. Similar results were obtained in analyses using non-HL patients (n = 3,055) participating in the founding study as comparison group.**

Conclusion: **The observed association between cigarette smoking and HL risk is consistent with previous findings and biologically plausible. Although not easily dismissed as an artifact, the limited evidence of a dose-response pattern renders the overall evidence of causality weak.** (Cancer Epidemiol Biomarkers Prev 2007;16(8):1561–6)

Introduction

Because of its characteristic bimodal age distribution, Hodgkin lymphoma (HL) is one of the most common malignancies in adolescents and young adults in industrialized societies (1-3). Its etiology has thus far evaded clarification, and it is therefore of some concern that an increasing incidence of HL has been reported in young adults in a number of Western countries (4-6).

The association between tobacco smoking and risk of HL has been studied in several investigations with ambiguous results. Although most report no association between history of tobacco smoking and overall HL risk (7-15), others report significantly decreased (16) or increased risks (17-22). Besides generally being characterized by a limited number of study subjects, previous studies may have been hampered by etiologic heterogeneity within the group of HL. Accordingly, in addition to the distinction between nodular lymphocytic predominance and the subtypes of classic HL (23, 24), the latter entity possibly should be divided further according to age at diagnosis and/or the presence or absence of EBV nucleic acids and proteins in the neoplastic Hodgkin-Reed-Sternberg (HRS) cells (25, 26). According to this view on HL, EBV-positive tumors may arise either in the wake of primary EBV infection, leading to EBV-positive HL incidence peaks in childhood and young adulthood, or following the loss of immunologic control of latent EBV infection, causing EBV-positive HL incidence to increase with age in the elderly. In contrast, less is known about the causes of EBV-negative HL, which exhibits a unimodal age distribution with a peak in young adulthood (25, 26).

It follows from this novel understanding of HL that the results of previous investigations where EBV status of the tumor was not determined may be misleading because etiologic differences between EBV-positive and EBV-negative HL may obscure putative associations with either disease group. It is therefore noteworthy that smoking recently was associated with increased risks of either mixed cellularity HL, of which a substantial proportion are EBV positive (19), or specifically of EBV-positive HL (14, 18, 27). Interestingly, in three of these studies (14, 18, 19), the increased HL risk was restricted to current cigarette smokers, possibly indicating a carcinogenesis-promoting effect of tobacco smoking (19).

To increase our understanding of the natural history of HL, we assessed the association between cigarette smoking and risk of HL in a large Danish-Swedish case-control study encompassing 586 patients with incident classic HL, taking HL EBV status into consideration, and 3,187 population controls. The founding study also included 3,055 non-HL (NHL) cases (28), who were used as a second comparison group in the present analyses.

Received 2/1/07; revised 5/8/07; accepted 5/15/07.

Grant support: NIH (5 ROI CA 69269), Nordic Cancer Union (16-02-D), and Plan Danmark. The funding sources were not otherwise involved in the study.

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doi:10.1158/1055-9965.EPI-07-0094

Table 1. Distribution of classic HL patients and population and NHL controls according to sex, country, educational level and smoking status and tumor EBV status

	Controls		Classic HL		
	Populations (*N* = 3,187)	NHL (*N* = 3,055)	Overall (*N* = 586)	EBV-positive lymphoma (*N* = 142)	EBV-negative lymphoma (*N* = 357)
Country, *n* (%)					
Denmark	1,186 (37)	1,075 (35)	247 (42)	64 (45)	144 (40)
Sweden	2,001 (63)	1,980 (65)	339 (58)	78 (55)	213 (60)
Age at interview (y), median (range)	59 (18-76)	61 (18-76)	35 (18-77)	37 (20-75)	34 (18-74)
Sex, *n* (%)					
Male	1,767 (55)	1,819 (60)	306 (52)	91 (64)	167 (47)
Female	1,420 (45)	1,236 (40)	280 (48)	51 (36)	190 (53)
Educational level (y),* *n* (%)					
≤9	919 (29)	1,020 (34)	92 (16)	24 (17)	44 (12)
10-12	1,466 (47)	1,327 (44)	334 (57)	87 (61)	204 (57)
≥13	752 (24)	676 (22)	157 (27)	31 (22)	106 (30)
Cigarette smoking status*,†, *n* (%)					
Never	1,460 (47)	1,367 (46)	299 (52)	61 (46)	192 (54)
Ever	1,665 (53)	1,628 (54)	275 (48)	73 (54)	163 (46)
Former	949 (57)	950 (59)	92 (34)	24 (33)	55 (34)
Current	712 (43)	673 (41)	182 (66)	49 (67)	107 (66)

*Numbers may not add up due to missing information.
† For 134 (2%) of the study subjects, cigarette smoking status could not be accurately defined; these were excluded from the analyses.

Materials and Methods

Study Subjects. The investigation was part of the Scandinavian Lymphoma Etiology (SCALE) study, a large Danish-Swedish case-control study of risk factors for malignant lymphomas (28, 29). Briefly, the HL study base encompassed the entire Danish population aged 18 to 74 years in the period June 1, 2000, to August 30, 2002, and the corresponding Swedish population in the period from October 1, 1999, to April 15, 2002. Participants recruited in a Danish regional pilot phase starting November 1, 1999, were also included, as were prevalent cases of HL diagnosed since January 1, 1999, in either country. In both Denmark and Sweden, the source population was further restricted to persons with sufficient knowledge of the Danish/Swedish language, and with no history of organ transplantation, HIV infection, or history of other hematopoietic malignancies.

All patients diagnosed with malignant lymphoma, including HL (23, 24), during the study period were eligible for inclusion into the study. The patients were identified through a rapid case ascertainment system. Specifically, a network of contact physicians was established for all departments where malignant lymphomas are diagnosed and treated (internal medicine, hematology, oncology, and clinical pathology), involving a total of 39 departments in Denmark and 118 in Sweden. Continuous collaboration with the national pathology registry in Denmark and the six regional cancer registries in Sweden ensured complete reporting through the network. The estimated coverage of the Danish Pathology Register and the Swedish cancer registries is close to 100% (28).

Controls were randomly sampled from the entire Danish and Swedish populations using continuously updated computerized population registers. A subset of controls was sampled every 6 months during the study period and frequency-matched within each country on the expected age (10-year strata) and sex distribution of lymphoma patients.

Classification of Cases, Histology, and EBV Status. Tumor biopsies from participating HL patients were retrieved from Danish and Swedish pathology departments for diagnostic validation and EBV detection. Cases that could not be retrieved were classified according to the original histopathologic description. Because nodular lymphocytic predominant HL is believed to constitute a unique HL subgroup (24), such cases were omitted from the present analyses.

The retrieved tumor biopsies were analyzed for the presence of EBV in the neoplastic HRS cells by immunohistochemical staining for EBV latent membrane protein (LMP)-1 and/or *in situ* hybridization for EBV-encoded small RNAs (EBER). Antibodies used for EBV analyses were from DAKO. In Denmark, paraffin sections were stained using standard EnVision (DAKO) immunohistochemistry, and EBV LMP-1 was detected in HRS cells with antibody cocktail CS 1-4. Antigen was retrieved by microwave superheating in TEG buffer [10 mmol/L Tris, 0·5 mmol/L EGTA (pH, 9)]. EBERs were detected by *in situ* hybridization using single-stranded digoxenin-labeled riboprobes or equivalent commercial EBER probes (30). In Sweden, LMP-1 staining and EBER *in situ* hybridization were done with a Ventana Benchmark (LMP-1) and a Ventana Benchmark XT (EBER) machine. The same primary antibody for LMP-1 as in Denmark was used and visualized with a Ventana kit, and a Ventana kit was used for EBER *in situ* hybridization. Two slightly different approaches for EBV classification were pursued in Denmark and Sweden. In Denmark, all cases were tested by both described methods and were classified as EBV positive when both tests (LMP-1 and EBER) were positive. In Sweden, the majority of cases were first tested for LMP-1, and all cases with negative or ambiguous test results were then analyzed for EBERs. A total of 126 Swedish cases were tested only for EBERs. Swedish cases were classified as EBV positive upon a positive test for either EBER or LMP-1.

Exposure Information. Information on suspected risk factors for malignant lymphoma was obtained through standardized telephone interviews, identical in the two countries and conducted by trained interviewers. The interviewers could not be blinded to the case-control status of the participants, but were unaware of the hypotheses under study. Recorded information included family characteristics (sib-ship size and birth order), parental and personal education, childhood housing conditions, history of infectious mononucleosis, and smoking. Specifically, participants were asked if they had ever smoked tobacco daily for at least 1 year, and if so, what kind of tobacco (cigarettes and/or other tobacco products). In addition, information was obtained on current smoking status [current or former smoker (at the time of diagnosis for cases)] and, for cigarette smokers, age at initiation, average daily consumption, and where relevant, age at cessation (31).

Statistical Analyses. We used unconditional multiple logistic regression to assess the association between cigarette smoking and HL risk. Results are presented as odds ratios (OR) with 95% confidence intervals (95% CI). We assessed the association between cigarette smoking and risk of HL comparing ever with never smokers. We furthermore categorized cigarette smokers according to current or former smoking. Former smokers were defined as persons who had ceased smoking 1 year or more before diagnosis (patients) or interview (controls). Among current smokers, we assessed smoking intensity (≤9, 10-19, or ≥20 cigarettes per day), smoking duration (≤9, 10-29, ≥30 years), and cumulative cigarette exposure (≤149, 150-299, ≥300 cigarette years). Among former smokers, the association with time since cigarette smoking cessation (1-4, 5-9, and ≥10 years) was assessed.

Potential confounders were considered based on prior knowledge of risk factors for HL within the SCALE study (32). Thus, all statistical analyses were adjusted for the matching variables [age (in 10-year categories), sex, and country], number of younger and older siblings, history of infectious mononucleosis, mother's age at participant's birth, country-specific measures of mother's level of education, subject's level of education, and familial history of hematopoietic cancer (33).

Two series of analyses were carried out in parallel. Specifically, we compared cigarette smoking patterns among HL patients with those among population controls, and also those among NHL patients. The latter comparison was conducted to assess putative effects of selection bias and differential misclassification of exposure between cases and population controls, and was potentially informative because cigarette smoking was not associated with risk of NHL in SCALE (31).

Analyses were carried out for all types of classic HL combined, for the major histologic subtypes (mixed cellularity and nodular sclerosis), for younger (18 to 44 years) and older (45-74 years) adults, for men and women, and for EBV-positive and EBV-negative HL. Statistical significance of independent variables was tested by the likelihood-ratio test. Trends in exposure effects were assessed using the underlying continuous exposure variables in the regression analyses. All statistical tests were two-sided, and P values <5% were considered statistically significant. Confidence limits were based on Wald tests. Tests for homogeneity of the effect of current smoking on EBV-positive and EBV-negative HL were done in a polytomous regression model, with EBV-positive HL, EBV-negative HL, and control status as outcomes. Each parameter in this model was the log OR of EBV-negative HL or EBV-positive HL compared with control status for each exposure level versus a reference level, and homogeneity was tested with a likelihood ratio test.

The study was approved by regional ethics committees in both countries, and informed consent was obtained from each participant before interview.

Table 2. Multivariate ORs with 95% CIs for the association between cigarette smoking and risk of classic HL overall and by tumor EBV status in a comparison with population controls

	Controls	Classic HL			
	Number	HL overall		EBV-positive lymphoma	EBV-negative lymphoma
		Number	OR (95% CI)	OR (95% CI)	OR (95% CI)
Never smokers	1,460	299	Reference	Reference	Reference
Ever smokers	1,665	275	1.18 (0.94-1.48)	1.62 (1.08-2.43)	1.13 (0.86-1.49)
$P_{homogeneity}$*			0.15	0.01	0.39
Former smokers	949	92	0.80 (0.59-1.08)	0.95 (0.55-1.65)	0.80 (0.55-1.17)
Current smokers	712	182	1.57 (1.22-2.03)	2.36 (1.51-3.71)	1.43 (1.05-1.97)
$P_{homogeneity}$†			<0.0001	<0.001	0.01
Age at initiation (y)‡					
≤14	164	57	1.84 (1.22-2.77)	2.25 (1.10-4.61)	2.06 (1.25-3.41)
15-19	362	91	1.43 (1.04-1.98)	1.86 (1.04-3.35)	1.32 (0.89-1.96)
≥20	177	33	1.61 (1.02-2.56)	3.83 (1.95-7.53)	1.05 (0.55-1.97)
P_{trend}			0.68	0.27	0.14
Intensity (cigarettes/day)‡					
1-9	141	31	1.12 (0.69-1.83)	1.42 (0.59-3.41)	1.08 (0.60-1.94)
10-19	357	103	1.85 (1.35-2.54)	3.10 (1.81-5.29)	1.59 (1.07-2.35)
≥20	201	46	1.49 (0.97-2.57)	2.16 (1.06-4.42)	1.43 (0.84-2.42)
P_{trend}			0.58	0.93	0.58
Duration (y)‡					
≤9	31	34	1.61 (0.89-2.91)	2.39 (0.95-6.04)	1.38 (0.70-2.71)
10-29	144	82	1.41 (0.98-2.05)	1.77 (0.91-3.44)	1.26 (0.81-1.95)
≥30	528	65	1.72 (1.20-2.46)	3.14 (1.66-5.93)	1.68 (1.04-2.70)
P_{trend}			0.81	0.53	0.64
Cumulative exposure (cigarette years)‡					
≤149	69	53	1.63 (1.03-2.57)	1.68 (0.75-3.75)	1.51 (0.89-2.54)
150-299	118	42	1.33 (0.84-2.11)	1.83 (0.79-4.23)	1.14 (0.65-1.99)
≥300	511	85	1.66 (1.20-2.31)	3.14 (1.81-5.46)	1.53 (1.00-2.34)
P_{trend}			0.36	0.65	0.87
Time since cessation (y)§					
1-4	126	15	0.72 (0.37-1.37)	0.75 (0.22-2.57)	0.40 (0.15-1.06)
5-9	136	24	0.86 (0.49-1.51)	1.42 (0.56-3.57)	0.90 (0.45-1.77)
≥10	687	54	0.86 (0.56-1.15)	0.87 (0.45-1.69)	0.91 (0.58-1.42)
P_{trend}			0.66	0.64	0.60

NOTE: All analyses are adjusted for matching variables [age (in 10-y categories), sex, and country], number of younger and older siblings, history of infectious mononucleosis, mother's age at subject's birth, country-specific measure of mother's education, subject's education, and familial history of hematopoietic cancer.

*Test for homogeneity of effect of smoking history (ever versus never).

† Test for homogeneity of effect of smoking status (former, current, never).

‡ Among current smokers only.

§Among former smokers only.

Table 3. Multivariate ORs with 95% CIs for the association between cigarette smoking and risk of classic HL overall and by tumor EBV status in a comparison with NHL patient controls

	NHL patients	Classic HL			
	Number	HL overall		EBV-positive lymphoma	EBV-negative lymphoma
		Number	OR (95% CI)	OR (95% CI)	OR (95% CI)
Never smokers	1,367	299	Reference	Reference	Reference
Ever smokers	1,628	275	1.21 (0.95-1.54)	1.87 (1.20-2.89)	1.14 (0.84-1.54)
$P_{homogeneity}$*			0.14	0.005	0.41
Former smokers	950	92	0.87 (0.64-1.20)	1.11 (0.62-1.97)	0.90 (0.60-1.33)
Current smokers	673	182	1.56 (1.18-2.08)	2.75 (1.69-4.47)	1.35 (0.95-1.92)
$P_{homogeneity}$†			0.001	0.0001	0.12
Age at initiation (y) ‡					
≤14	116	57	2.49 (1.55-4.00)	3.34 (1.50-7.47)	2.80 (1.58-4.97)
15-19	354	91	1.36 (0.96-1.94)	2.21 (1.19-4.11)	1.18 (0.76-1.82)
≥20	201	33	1.33 (0.81-2.16)	3.32 (1.65-6.69)	0.81 (0.40-1.60)
P_{trend}			0.05	0.80	0.001
Intensity (cigarettes/day) ‡					
1-9	124	31	0.95 (0.54-1.68)	1.46 (0.57-3.76)	0.79 (0.40-1.57)
10-19	362	103	1.82 (1.29-2.56)	3.71 (2.08-6.62)	1.52 (0.99-2.33)
≥20	180	46	1.60 (1.01-2.52)	2.59 (1.21-5.56)	1.51 (0.85-2.68)
P_{trend}			0.96	0.80	0.68
Duration (y) ‡					
≤9	11	34	1.50 (0.65-3.46)	2.40 (0.75-7.67)	1.36 (0.54-3.43)
10-29	102	82	1.28 (0.84-1.95)	1.99 (0.94-4.22)	1.06 (0.65-1.74)
≥30	558	65	1.79 (1.25-2.58)	3.58 (1.90-6.76)	1.66 (1.02-2.71)
P_{trend}			0.48	0.65	0.87
Cumulative exposure (cigarette years) ‡					
≤149	46	53	1.29 (0.73-2.25)	1.32 (0.52-3.37)	1.11 (0.59-2.07)
150-299	83	42	1.31 (0.76-2.23)	2.37 (0.94-5.97)	1.08 (0.57-2.05)
≥300	537	85	1.75 (1.25-2.45)	3.83 (2.15-6.80)	1.58 (1.01-2.45)
P_{trend}			0.53	0.71	0.66
Time since cessation (y)§					
1-4	97	15	0.68 (0.33-1.43)	0.53 (0.11-2.43)	0.33 (0.12-0.96)
5-9	152	24	0.91 (0.50-1.66)	1.53 (0.56-4.13)	1.10 (0.53-2.25)
≥10	701	54	0.91 (0.63-1.31)	1.16 (0.59-2.27)	1.04 (0.65-1.65)
P_{trend}			0.32	0.44	0.62

NOTE: All analyses are adjusted for matching variables [age (in 10-y categories), sex, and country], number of younger and older siblings, history of infectious mononucleosis, country-specific measure of mother's age at subject's birth, mother's education, subjects' level of education, and familial history of hematopoietic cancer.

*Test for homogeneity of effect of smoking history (ever versus never).

† Test for homogeneity of effect of smoking status (former, current, never).

‡ Among current smokers only.

§Among former smokers only.

Results

Demographic characteristics of the participating lymphoma patients and controls are shown in Table 1. The sex, age, and country distribution differed between HL patients and population controls because the controls were sampled to match also the 3,055 patients with NHL (28). Overall, the participation rates were 91% among eligible HL patients, 81% among eligible NHL patients, and 71% among controls (28). Of the total of 586 patients with classic HL included in the study, tumor EBV status was established for 499 (85%) (Table 1).

History of ever-smoking cigarettes was not associated with a statistically significantly increased risk of HL overall, whether compared with population controls or NHL patients (Tables 2 and 3). Analyses stratified according to smoking status at interview, however, suggested an increased HL risk among current cigarette smokers, whereas no association was observed in former cigarette smokers (Tables 2 and 3). This association with current smoking was seen both in younger adults (<45 years of age; adjusted OR, 1.38; 95% CI, 0.97-1.97) and older adults (adjusted OR, 1.89; 95% CI, 1.29-2.78), in women (adjusted OR, 1.32; 95% CI, 0.91-1.91) and men (adjusted OR, 1.83; 95% CI, 1.28-2.61), and for both mixed cellularity (adjusted OR, 1.91; 95% CI, 1.14-3.21) and nodular sclerosis HL (adjusted OR, 1.43; 95% CI, 1.06-1.93). Except for the higher risk compared with never and former smokers, there was no evidence of a dose-response pattern among current smokers in any analysis, i.e., HL risk did not vary by age at smoking initiation, cumulative cigarette consumption, whether measured as number of years smoked or estimated total number of cigarettes smoked or by number of cigarettes smoked per day among current smokers. In addition, among former smokers, the risk of HL did not vary by time since cessation of cigarette smoking (Tables 2 and 3).

When analyses were stratified according to tumor EBV status, the increased risk of HL among current smokers was particularly strong for the EBV-positive subgroup, but was also apparent for the EBV-negative subgroup (Tables 2 and 3). This variation in association with tumor EBV status was seen across all investigated strata, i.e., age, sex, and histologic subtype, in some analyses of borderline statistical significance (Table 4). Except for an inverse association between age at smoking initiation and risk of EBV-negative HL in the comparison with NHL patients, detailed analyses showed no evidence of dose-response patterns, regardless of tumor EBV status (Tables 2 and 3).

Discussion

In the present investigation, current cigarette smokers were at an increased risk of HL overall, compared with never-smokers. Although the increased risk was particularly pronounced for EBV-positive HL, i.e., more than 2-fold increased, current cigarette smoking also entailed an increased risk of EBV-negative HL.

The observed association between current cigarette smoking and risk of EBV-positive HL is consistent with recent observations (14, 18, 19, 27). EBV can be shown in the neoplastic HRS cells in a proportion of HL, varying by age, sex, histologic subtype, and socioeconomic status (34, 35). Evidence suggests that EBV-positive and EBV-negative HL may differ etiologically. This includes a preponderance of EBV-positive HL after infectious mononucleosis (32, 36, 37), elevated anti-EBV antibody titers preceding development of virus-positive HL (38), and emerging evidence of tumor EBV-specific heritability patterns (39). In addition, recent molecular investigations make a role for EBV in HL development biologically credible (40, 41). Regardless, the role of the virus in HL pathogenesis remains uncertain (42). Immune impairment, whether acquired (43, 44) or congenital (45), is associated with an increased risk of HL, which is most often of the EBV-positive type in the context of profound immune suppression (46, 47). Tobacco smoking modulates the immune system in several ways (48), and accordingly, an increased risk of EBV-positive HL associated with cigarette smoking is not biologically inconceivable. The literature on the effect of tobacco smoking on EBV infection is scarce, but it is noteworthy that we recently observed a correlation between tobacco smoking and elevated titers of anti-EBV viral capsid antigen immunoglobulin G antibodies (49), previously associated with an increased risk of HL (50).

Although risk was borderline statistically significantly more increased for EBV-positive HL than EBV-negative HL, the association with current cigarette smoking in our study was not restricted to EBV-positive HL, but also applied to EBV-negative HL. This observation renders the interpretation of our findings less straightforward. Although the difference in risk could suggest etiologic heterogeneity between EBV-positive and EBV-negative HL, alternative explanations must also be considered. For neither EBV-positive or EBV-negative HL, there was evidence of an increased risk among former smokers, irrespective of the time elapsed since smoking cessation. Accordingly, if the observed association between current smoking and HL risk were true, tobacco smoking would most likely affect late stages in HL development (19), possibly similar or even identical for EBV-positive and EBV-negative HL. Although not supportive of etiologic heterogeneity between EBV-positive and EBV-negative HL (25, 26), such a mechanism would not necessarily conflict with the speculation either.

We found no evidence of dose-response patterns for the effect of cigarette smoking in the present investigation as suggested by some previous investigations (8, 9, 18, 19, 21, 22), whether for HL overall or for any of the investigated subgroups. Other, noncausal mechanisms should therefore also be considered as potential explanations for our findings. Case-control studies may be affected by selection bias resulting from, e.g., unwillingness to participate among smokers. Such bias is more likely to apply to controls than to patients and could therefore result in spurious positive associations. The proportions of current smokers among the controls closely matched those within the source population, differing <3% in Danish and Swedish women and in Swedish men (51, 52), whereas among Danish men, smoking was less commonly reported (26%) than in official statistics (38%; ref. 52). However, in supplementary analyses, current smoking conferred increased risks of similar magnitudes in Swedish and Danish men (data not shown). In addition, in analyses excluding Danish men, current smoking remained associated with a statistically significantly increased risk of HL (adjusted OR, 1.47; 95% CI, 1.22-2.03), i.e., only marginally different from the one observed for the entire study population. Moreover, when we compared smoking patterns in HL patients with that of the large group of patients with NHLs participating in the SCALE investigation (28), results essentially identical to those of the population control comparison were observed. Accordingly, it is difficult to attribute our observations solely to participation bias among the population controls, even more so as a similar bias would have to affect the participation of NHL patients. The HL versus NHL comparison, moreover, also renders recall bias an unlikely explanation for our findings because HL and NHL patients are unlikely to have recalled cigarette smoking in systematically different ways, particularly after stratification by age group and sex. Finally, the results did not change materially when analyses were restricted to participants interviewed within 6 months after diagnosis, emphasizing the limited impact of survival bias among the cases (data not shown). As expected, education was statistically significantly inversely correlated with smoking prevalence among the controls ($P < 0.0001$). Because all analyses were adjusted for subject education, we believe that neither uncontrolled confounding from this source is likely to explain our findings.

The strengths of our investigation include its population-based setting with a rapid case ascertainment, histopathologic review of nearly 90% of the cases in connection with EBV typing, classification of all cases of HL according to the WHO classification, and a high participation rate among both cases and controls. Conducted simultaneously in two ethnically similar populations, all observations could also be validated by comparison of population-specific findings. Thus, we found no evidence of heterogeneity of the association between current cigarette smoking and HL risk between the two countries.

In conclusion, current cigarette smoking was associated with an increased risk of HL in the present investigation. The increased risk was the strongest for EBV-positive HL, but a modestly increased risk was also observed for EBV-negative

Table 4. Multivariate ORs with 95% CIs for the association between current cigarette smoking and risk of classic HL by tumor EBV status in a comparison with population controls

	EBV-positive lymphoma	EBV-negative lymphoma	$P_{homogeneity}$
	OR (95% CI)	OR (95% CI)	EBV-positive versus -negative
Overall	2.36 (1.51-3.71)	1.43 (1.05-1.97)	0.04
Sex			
Men	3.00 (1.66-5.44)	1.49 (0.94-2.37)	0.05
Women	1.70 (0.83-3.48)	1.35 (0.88-2.09)	0.46
Age (y)			
<45	1.94 (1.05-3.62)	1.22 (0.81-1.81)	0.22
≥45	3.23 (1.63-6.38)	2.01 (1.18-3.44)	0.11
Subtype			
Nodular sclerosis	2.24 (1.24-4.07)	1.32 (0.93-1.87)	0.08
Mixed cellularity	3.08 (1.41-6.70)	1.59 (0.72-3.52)	0.30

NOTE: All analyses are adjusted for matching variables [age (in 10-y categories), sex, and country], number of younger and older siblings, history of infectious mononucleosis, mother's age at subject's birth, country-specific measure of mother's education, subject's education, and familial history of hematopoietic cancer.

HL. Although the observed associations are consistent with previous findings and have biological credibility, the limited evidence of a dose-response pattern renders the overall evidence of causality weak.

Acknowledgments

The authors kindly thank all of the doctors and nurses in Denmark and Sweden who participated in our rapid case ascertainment system.

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Cancer Epidemiol Biomarkers Prev 2007;16:1561-1566.