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ORIGINAL REPORT

Meta-Analysis of the Association Between Cigarette Smoking and Incidence of Hodgkin's Lymphoma

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ABSTRACT

Introduction
Previous studies have suggested a relationship between smoking and Hodgkin's lymphoma (HL). The main objective of this study was to evaluate this potential association with a meta-analysis of observational studies.

Patients and Methods
A literature search was undertaken through December 2010 looking for observational studies evaluating the association between smoking and HL. From 714 articles, 17 were included in this study. Outcome was calculated and reported as odds ratio (OR). Heterogeneity was assessed by using the I^2 index. Publication bias was evaluated by trim-and-fill analysis. Quality assessment was performed with the Newcastle-Ottawa scale.

Results
Our analysis showed an OR of developing HL of 1.35 (95% CI, 1.17 to 1.56; $P < .001$) in current smokers. Former smokers did not have an increased risk of HL. In subset analyses of current smokers, men and older individuals had ORs of HL of 1.78 (95% CI, 1.46 to 2.17; $P < .001$) and 1.77 (95% CI, 1.23 to 2.54; $P = .002$), respectively. In addition, the OR of HL was increased in individuals who smoke more than 20 cigarettes per day, have smoked more than 20 years, or have smoked more than 15 pack-years at 1.51 (95% CI, 1.16 to 1.98; $P = .002$), 1.84 (95% CI, 1.47 to 2.32; $P < .001$), and 1.97 (1.53 to 2.54; $P < .001$), respectively. Meta-regression analyses showed a relative OR of HL of 1.007 (95% CI, 1.001 to 1.013; $P = .025$) per cigarette per day and of 1.013 (95% CI, 1.006 to 1.019; $P < .001$) per year of smoking.

Conclusion
Smoking seems to increase the odds of developing HL in current smokers. The risk of HL is higher in men and older individuals and increases with higher intensity and longer duration of smoking.

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INTRODUCTION

Hodgkin's lymphoma (HL) constitutes approximately 10% to 15% of the cases of lymphoma in the United States. HL has a bimodal distribution, affecting mainly adolescents or young adults and adults older than age 55 years.[1] According to Surveillance, Epidemiology, and End Results (SEER) data, the age-adjusted incidence rate is 2.8 per 100,000 person-years.[2] Modern chemotherapeutic regimens with or without radiation are associated with high cure rates in patients with HL.[3] However, HL affects individuals during their most productive and reproductive years, and the treatment can be associated with debilitating short- and long-term adverse effects.[4,5]

Little is known about risk factors for the development of HL, and a wide variety of factors have been studied. Among them, the association between smoking and HL has been evaluated with conflicting results. Since smoking-related complications can be preventable, the association between smoking and the development of HL is worth investigating further.

We hypothesized that there is a relationship between smoking status and incidence of HL. Since this question will unlikely be answered by means of a randomized, controlled trial, the main goal of this study was to investigate the epidemiologic relationship, if any, between smoking and HL by using a meta-analysis.

PATIENTS AND METHODS

Literature Search

Two authors independently performed literature searches by using PubMed and the Cochrane Database through December 2010. The keywords used were "(smoking OR tobacco OR cigarette) AND lymphoma." The titles and abstracts of the resulting articles were examined and, after excluding nonrelated articles, full-text articles were retrieved. If an article was selected for inclusion, the references were scrutinized for additional studies.

Inclusion and Exclusion Criteria

An article was relevant if it originated from case-control or cohort studies and reported original data, regardless of language, on the association between cigarette smoking and the development of HL. Any discrepancies between reviewers on inclusion of a study were resolved by joint evaluation of the manuscript. If there were multiple publications from the same study, the most relevant was selected, by using the other publications to clarify methodology, if necessary. Reviews or letters to the editor without original data, editorials, case reports, and cross-sectional studies were excluded.

Data Extraction

Data extraction was performed independently by two reviewers and included author, year of publication, country of origin, sample size, method of ascertainment of smoking, and method of diagnosis of HL. For case-control studies, we extracted years of inclusion, the source and definition of cases and controls, the outcome measured with 95% CIs, and the variables used for matching and adjustment. For cohort studies, we extracted the source of the cohort, years of follow-up, the outcome measured with 95% CIs, and the variables used for adjustment. Any discrepancies were addressed by a joint reevaluation of the original article with a third reviewer.

Quality Assessment

The quality of each study was assessed independently by two reviewers who used the Newcastle-Ottawa Scale (NOS).[6] The NOS consists of three parameters of quality: selection, comparability, and exposure (case-control studies) or outcome (cohort studies). The NOS assigns a maximum of four points for selection, two points for comparability, and three points for exposure/outcome. Therefore, nine points reflects the highest quality. Any discrepancies were addressed by a joint reevaluation of the original article with a third reviewer.

Data Synthesis and Analysis

Because the risk of HL is low, the relative risk in prospective cohort studies mathematically approximates the odds ratio (OR),[7] therefore permitting the combination of case-control and cohort studies. The primary outcome in this meta-analysis is reported as OR with 95% CI of developing HL in smokers. The outcome was analyzed for the unadjusted (crude) and the maximally adjusted association between ever, current, and former smokers and HL. We measured the outcome by using the random-effects model.[8] The random-effects model accounts for heterogeneity between studies, which is expected in an analysis of this nature. Subset analyses were performed by study type, age, sex, cigarettes smoked per day, years of smoking, pack-years, and Epstein-Barr virus (EBV) status.

We assessed for heterogeneity between studies by using the I^2 statistic[9]; values of 25%, 50%, and 75% represent mild, moderate, and severe heterogeneity, respectively. Since positive studies are more likely to be published than negative ones and the simple observation of a funnel plot is subjective, the trim-and-fill method was used to address publication bias.[10] The trim-and-fill method assumes that the effect sizes of all the studies distribute normally around the center of a funnel plot; if asymmetry is found, it adjusts for the potential effect that nonpublished (imputed) studies might have had on the measured outcome. Intensity and duration of smoking were evaluated by using meta-regression methods. The value assigned to each category was the midpoint for closed categories. For open categories, we assumed a maximum of 60 cigarettes per day and 50 years for intensity and duration of smoking, respectively. All calculations and graphs were obtained by using Comprehensive Meta-Analysis (CMA) version 2.2.050 (Biostat, Englewood, NJ). Data from this meta-analysis are presented in accordance with the checklist proposed by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group.[11]

RESULTS

Search Results

A total of 17 articles were selected for our meta-analysis, corresponding to three prospective cohort[12-14] and 14 case-control studies.[15-28] Our search flow is shown in Figure 1.

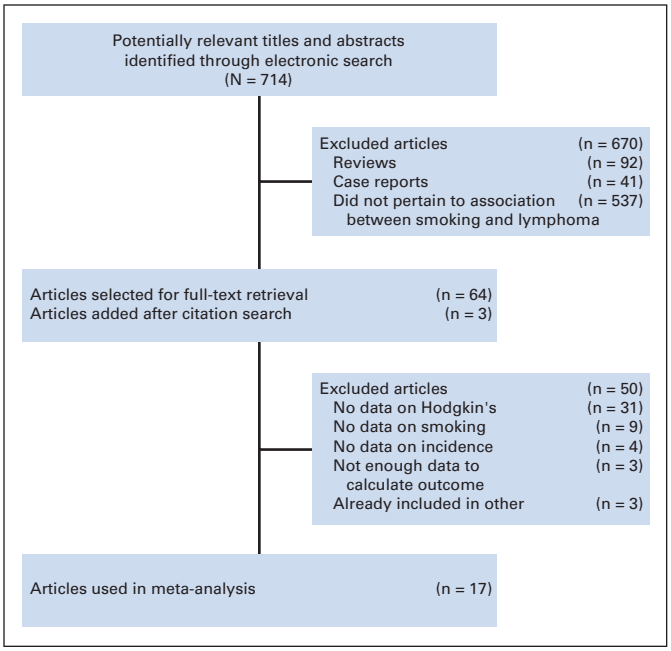

Fig 1. Search results.

Characteristics of the Cohort Studies

The main characteristics of the cohort studies are listed in Table 1. Studies were published between 2006 and 2008. One study originated from the United States,[13] one from Sweden,[12] and one was a European multinational study.[14] A total of 285 cases of HL in a cohort of 1,228,078 individuals, accounting for approximately 12 million person-years, were included in this meta-analysis. Two studies reported a positive association between smoking and HL.[13,14] All studies assessed HL diagnosis through cancer registry data and assessed smoking habits through a self-administered questionnaire.

Characteristics of the Case-Control Studies

The main characteristics of the case-control studies are provided in Table 2. Studies were published between 1974 and 2009. Four studies originated from the United States,[17,18,20,24] two studies from Canada,[22,26] and the remaining eight studies from Europe: two from England,[15,28] two from Italy,[19,27] one from France,[23] one from Germany,[25] one from Sweden and Denmark,[21] and one from a European multinational effort.[16] At least 3,385 cases and 13,281 controls are included in this meta-analysis. Five studies reported a positive association between smoking and incidence of HL.[16-18,25,28] Three studies had a pathologic confirmation of HL in less than 100% of their cases.[16,22,25] Smoking habits were ascertained by personal interviews in eight studies,[16,20,23-28] telephone interviews in three,[17,18,21] and mailed questionnaires in one.[22]

Quality Assessment Results

With regard to case-control studies, 93% were of high quality (NOS score $>$ 6), with an average NOS score of 7.8. One study had a score of 6.[22] The most common selection bias was less than 100% pathologic assessment of patients with HL in three studies.[16,22,25] The most common exposure bias was no designation of nonresponse rates in eight studies (57%). In the cohort studies, all had an NOS score of 8.

Table 1. Main Characteristics of Cohort Studies Evaluating the Association Between Smoking and Hodgkin's Lymphoma

Study	Year	Country	Source of Cohort	Hodgkin's Lymphoma Assessment	Smoking Assessment	Median Follow-Up (years)	Follow-Up Period	Total Cohort	Total Person-Years	No. of Patients	Adjustments
Fernberg et al[12]	2006	Sweden	Construction Industry Organization for Working Environment Safety and Health	Swedish Cancer Registry and Cause of Death Registry	Interview and 200-item questionnaire	19	1971-1992	335,612	6,804,539	160	BMI, age, tobacco use
Lim et al[13]	2007	United States	NIH-AARP Diet and Health study	Cancer Registry data and National Death Index	Interview and questionnaire	5.2	1995-2000	473,984	2,060,611	58	Age at entry, sex, ethnicity, alcohol and tobacco consumption, BMI, height, physical activity
Nieters et al[14]	2008	Europe	European Prospective Investigation into Cancer and Nutrition (EPIC)	Health insurance records, cancer and pathology registries, active follow-up of study patients, and next-of-kin information	Interview and questionnaire	8.5	1992-2005	418,482	3,567,410	67	Education level, center, sex, age at recruitment

Abbreviations: AARP, American Association of Retired Persons; BMI, body mass index; NIH, National Institutes of Health.

The most common bias was ascertainment of exposure; all the studies assessed smoking by self-administered questionnaires.

Outcome Results

The crude association analysis showed an increased OR of developing HL in current smokers (OR, 1.37; 95% CI, 1.22 to 1.54; $P < .001$), a decreased OR in former smokers (OR, 0.72; 95% CI, 0.61 to 0.86; $P < .001$), and no association in ever smokers. The heterogeneity among studies was mild to moderate in all groups. The trim-and-fill analysis identified two imputed studies, which would not have altered our results. The maximally adjusted association analysis showed an increased OR in current (OR, 1.35; 95% CI, 1.17 to 1.56; $P < .001$) and ever smokers (OR, 1.13; 95% CI, 1.01 to 1.27; $P = .03$), but no association was found in former smokers. There was moderate heterogeneity among studies, but no publication bias was identified. Complete results are given in Table 3.

Subset Analyses

Because of the increased OR of developing HL in current smokers, the subset analyses focused on this group of individuals.

Study type. On the basis of retrospective studies, the OR of HL in current smokers was 1.35 (95% CI, 1.13 to 1.61; $P = .001$). There was moderate heterogeneity ($I^2 = 52.4\%$) but no publication bias. In cohort studies, the OR of HL in current smokers was 1.56 (95% CI, 1.11 to 2.20; $P = .01$). There was moderate heterogeneity ($I^2 = 54.3\%$) but no publication bias.

Sex. Five studies reported data on men.[12,17,21,25,28] The OR of HL in male current smokers was 1.78 (95% CI, 1.46 to 2.17; $P < .001$; Fig 2B) with minimal heterogeneity ($I^2 = 15.0\%$) and no publication bias. Five studies reported data on women.[12,20,21,25,28] The OR of HL in female current smokers was 1.16 (95% CI, 0.89 to 1.51; $P = .28$) without heterogeneity ($I^2 = 0\%$). The trim-and-fill analysis detected one imputed study, which would have not affected our results.

Age at HL diagnosis. Six studies[14,16-18,20,21] reported data on patients according to age. Because of heterogeneity in the reports, the ORs will be reported in patients who were younger than age 30 to 40 years at diagnosis of HL and patients who were older than 30 to 40 years. In younger patients, the OR of HL in current smokers was 1.28 (95% CI, 1.06 to 1.55; $P = .01$) with mild heterogeneity ($I^2 = 21.7\%$) and no publication bias. In older patients, the OR of HL was 1.77 (95% CI, 1.23 to 2.54; $P = .002$; Fig 2C) with moderate heterogeneity ($I^2 = 61.4\%$) but no publication bias.

Smoking intensity. An empirical cutoff of 20 cigarettes per day was used to facilitate analysis. In current smokers who smoked fewer than 20 cigarettes per day, the OR of HL was 1.27 (95% CI, 1.09 to 1.49; $P = .002$). There was moderate heterogeneity ($I^2 = 39.4\%$) but no publication bias. In current smokers who smoke more than 20 cigarettes per day, the OR of HL was 1.51 (95% CI, 1.16 to 1.98; $P = .002$; Fig 3A). There was moderate heterogeneity ($I^2 = 59.5\%$) but no publication bias. In an exploratory analysis, the OR of HL in current smokers who smoke fewer than 10 cigarettes per day was 1.09 (95% CI, 0.88 to 1.35; $P = .45$). There was mild heterogeneity ($I^2 = 22.5\%$) and no publication bias. Meta-regression analysis that included 12 studies showed a relative OR (rOR) of 1.007 (95% CI, 1.001 to 1.013; $P = .025$) per cigarette per day. Hence, the rOR for smoking 20, 40, or 60 cigarettes per day would be 1.15 (95% CI, 1.02 to 1.3), 1.32 (95% CI, 1.04 to 1.68), and 1.52 (95% CI, 1.06 to 2.18), respectively.

Duration of smoking. An empirical cutoff of 20 years of smoking duration was selected. In individuals who smoked for fewer than 20 years, the OR of HL was 1.12 (95% CI, 0.93 to 1.36; $P = .23$) with moderate heterogeneity ($I^2 = 41.1\%$). In individuals who smoked for more than 20 years, the OR was 1.84 (95% CI, 1.47 to 2.32; $P < .001$; Fig 3B) with moderate heterogeneity ($I^2 = 64.8\%$). The trim-and-fill analysis identified two imputed studies, which would have not affected our results. In an exploratory analysis, the OR of HL in individuals who smoked for more than 30 years was 2.04 (95% CI, 1.68 to 2.49; $P < .001$). There was no heterogeneity ($I^2 = 6.9\%$) and no publication bias. Meta-regression analysis that included 10 studies showed an rOR of 1.013 (95% CI, 1.006 to 1.019; $P < .001$) per year of smoking. Hence, the rORs for smoking for 10, 20, or 30 years would be 1.14 (95% CI, 1.06 to 1.21), 1.3 (95% CI, 1.13 to 1.46), and 1.48 (95% CI, 1.2 to 1.77), respectively.

Number of pack-years. A cutoff of 15 pack-years was used to facilitate analysis. In current smokers who have smoked fewer than 15 pack-years, the OR of HL was 1.15 (95% CI, 0.95 to 1.40; $P = .16$). There was no heterogeneity ($I^2 = 0\%$) and no publication bias. In individuals

Table 2. Main Characteristics of Case-Control Studies Evaluating the Association Between Smoking and Hodgkin's Lymphoma

Study	Year	Country	Ascertainment Period	Source of Cases	No. of Cases	Source of Controls	No. of Controls	Smoking Assessment	Hodgkin Assessment	Matching and Adjustments
Newell et al[24]	1973	United States	Unknown	Several hospitals in New Orleans and Los Angeles	32	Siblings or from same hospital or clinic as cases	176	Face-to-face interview	Pathologic confirmation all cases	Age within 3 years, sex, race, socioeconomic status
Bernard et al[15]	1987	England	1979-1984	Cancer Registry and Histopathology Lymphoma panel	134	Hospital-based cases	N/R	Interview, not specified	Pathologic confirmation all cases	Health district, sex, age within 3 years
Siemiatycki et al[26]	1995	Canada	1979-1985	Montreal metro area	43	Electoral lists in Montreal	N/R	Face-to-face interview	Pathologic confirmation all cases	Age
Stagnaro et al[27]	2001	Italy	1990-1993	Hospital and hematology databases in 12 Italian areas	200	Florence, Forli, and Ragusa	811	Face-to-face interview	Pathologic confirmation all cases	Sex, age within 5 years
Briggs et al[17]	2002	United States	1984-1988	Eight US cancer registries, part of the SEER program	217	Random-digit dialing	602	Telephone interview	Pathologic confirmation all cases	Age within 5 years, area
Chang et al[18]	2004	United States	1997-2000	Age 15-79 years, physicians from Greater Boston and CT	565	Town books in Boston, MA; random-digit dialing in CT	679	Telephone interview	Pathologic confirmation all cases	Age within 5 years, sex, state of residency
Gallus et al[19]	2004	Italy	1984-1992	Hospitalized patients in Greater Milan	78	Hospital admission information in Greater Milan area	142	Interview, not specified	Pathologic confirmation all cases	Age, sex, study center
Glaser et al[20]	2004	United States	1988-1994	Patients from nine counties in Northern California	100	Random-digit dialing	186	Face-to-face interview	Pathologic confirmation all cases	Age (5-year groups), race/ethnicity
Besson et al[16]	2006	Europe	1998-2004	Cancer registry data in France, Czech Republic, Germany, Ireland, Italy, and Spain	203	Random population registers, hospitalized patients	1,095	Face-to-face interview	Pathologic confirmation 20% of cases	Sex, age (5-year groups), area of residence
Nieters et al[25]	2006	Germany	1999-2002	Hospitalized patients from six regions in Germany	69	Population registry of the six regions	314	Face-to-face interview	Pathologic confirmation 10% of cases	Sex, age, study region
Hjalgrim et al [21]	2007	Sweden and Denmark	1999-2002	Contact departments in Sweden and Denmark	275	Computerized population registers, random selection	1,460	Telephone interview	Pathologic confirmation all cases	Age (10-year groups), sex
Willett et al[28]	2007	England	1998-2003	Multiple English counties around Yorkshire	156	Random entries from population registry	465	Face-to-face interview	Pathologic confirmation all cases	Sex, date of birth, area of residence
Monnereau et al[23]	2008	France	2000-2004	Patients admitted to one of five hospitals in France	88	Patients admitted to hospitals in same five cities as cases	156	Face-to-face interview	Pathologic confirmation all cases	Center, sex, age within 3 years, area of residence
Karunanayake et al[22]	2009	Canada	1991-1994	Cancer registries and hospital records from six provinces	182	Provincial health insurance records and phone lists	526	Mailed questionnaire	Pathologic confirmation 49% of cases	Age within 2 years

Abbreviations: CT, Connecticut; N/R, not reported; SEER, Surveillance, Epidemiology, and End Results.

who have smoked more than 15 pack-years, the OR was 1.97 (95% CI, 1.53 to 2.54; $P < .001$; Fig 3C). There was moderate heterogeneity ($I^2 = 56.5\%$) but no publication bias. Meta-regression analysis was not performed because of the small number of studies (n = 6).

EBV status. In current smokers, the OR for EBV-positive HL was 2.26 (95% CI, 1.69 to 3.02; $P < .001$) without heterogeneity ($I^2 = 0\%$). The trim-and-fill analysis identified two imputed studies, which would not have altered our results. The OR for EBV-negative HL was 1.40 (95% CI, 1.08 to 1.81; $P = .01$) without heterogeneity ($I^2 = 0\%$). The trim-and-fill analysis identified one imputed study, which would not have altered our results.

DISCUSSION

Although several risk factors for the development of HL have been evaluated, this is a field of ongoing investigation.[1] Cigarette smoking is a known risk factor for cancer incidence and mortality.[29] The current literature does not provide a definitive link between smoking and HL;

Table 3. Meta-Analysis Evaluating the Unadjusted (crude) and Maximally Adjusted Association Between Ever, Current, and Former Smokers and Hodgkin's Lymphoma

Status of Smokers	No. of Studies	Crude Association OR	95% CI	*P*	I^2 (%)	Maximally Adjusted Association OR	95% CI	*P*	I^2 (%)
Ever	15	1.01	0.91 to 1.12	.87	41.5	1.13	1.01 to 1.27	.01	49.7
Former	14	0.72	0.61 to 0.86	< .001	58.6	0.95	0.81 to 1.10	.48	43.1
Current	14	1.37	1.22 to 1.54	< .001	32.9	1.35	1.17 to 1.56	< .001	48.9

Abbreviations: I^2, an index for assessing heterogeneity; OR, odds ratio.

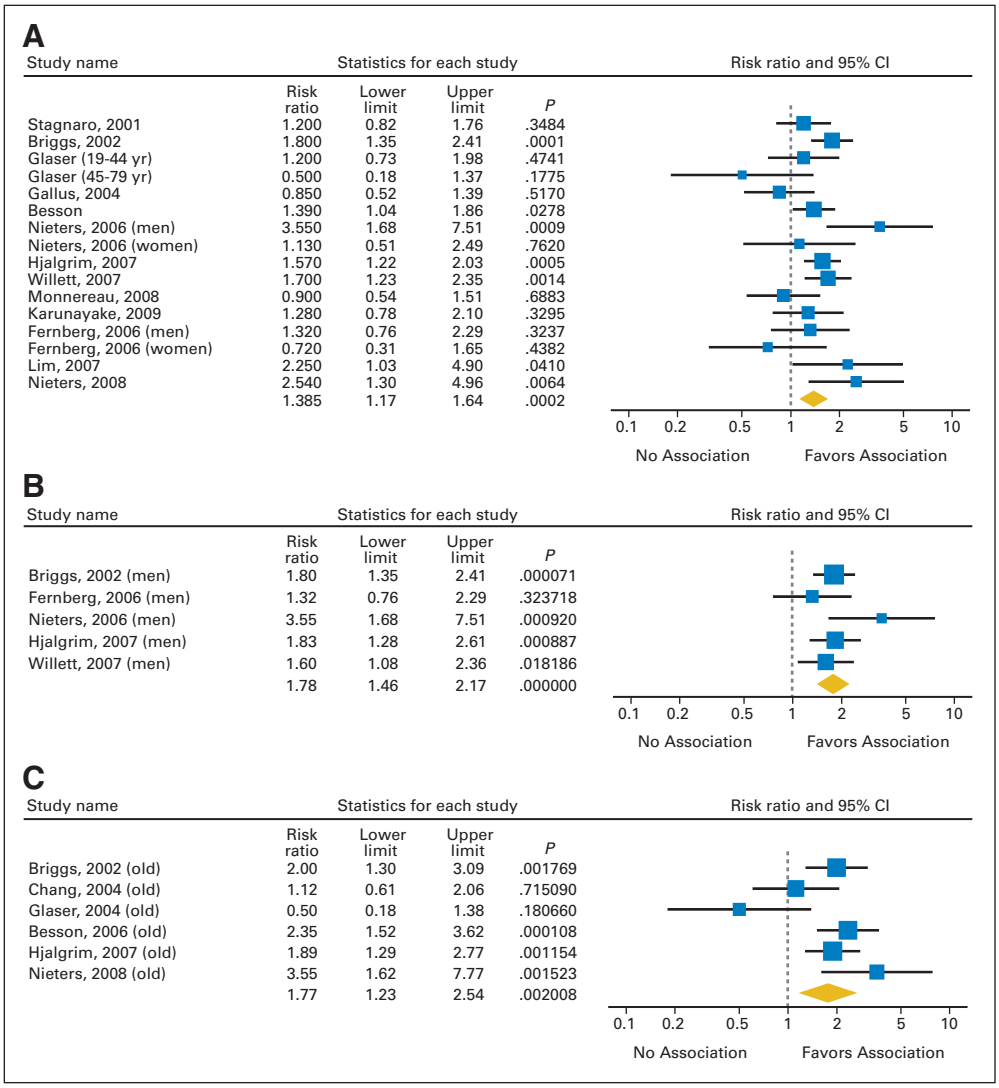

Fig 2. Estimates of the odds ratio of developing Hodgkin's lymphoma for (A) current smokers, (B) male current smokers, and (C) older current smokers. yr, years.

hence, the attempt on evaluating this potential association with a meta-analysis. Our study revealed several points worth discussing.

First, our study shows a statistical association between current smoking and an increased incidence of HL. Individuals who currently smoke have a 39% higher risk of developing HL than never smokers. Former smokers did not seem to have an increased risk of HL. It is important to note that in the studies included, a uniform definition of former and current smokers was not established. Hence, it is possible there is a threshold after stopping smoking at which the risk of HL decreases; however, there were not enough data to evaluate this further.

In subset analyses on current smokers, men and older individuals had a higher risk of HL. Male sex has been associated with a worse outcome in HL, and it is one of the components of the International Prognostic Score (IPS), a tool for stratifying patients with advanced HL by risk.[30] Our study shows that men who currently smoke have a 78% increased risk of HL. The risk of HL was nonsignificant in women. In our study, older patients who currently smoke had a 76% increased risk of HL. Of note, for the age subanalysis, the age groups did not match perfectly. We have used an age range of younger than 30 to 40 years as "younger" and an age range of older than 30 to 40 years as "older." This approach might have introduced bias into our analysis; however, most of the studies included patients with ages ranging between 15 and 80 years. Therefore, although some overlap is likely between the groups, our finding is unlikely to be the result of unequal age distribution.

Interestingly, there seems to be a direct relationship between higher numbers of cigarettes smoked per day, years of smoking, and pack-years and an increased risk of developing HL. There was no apparent increased risk of HL in individuals who smoke fewer than 10 cigarettes per day, but this risk increased to 27% in individuals who smoke up to 20 cigarettes per day and 51% in people who smoke more than 20 cigarettes per day. In addition, meta-regression analysis showed a linear relationship between intensity of smoking and relative OR of developing HL. Similarly, individuals who have smoked for fewer than 20 years had a nonsignificant 12% risk of HL that increased to 84% if smoking continued for more than 20 years and went up to 104% if smoking continued for more than 30 years. Meta-regression analysis was consistent with these results. Finally, when evaluating number of pack-years, smoking fewer than 15 pack-years did not show an increased risk of HL but smoking more than 15 pack-years increased the risk of HL to 97%. Altogether, these findings show internal

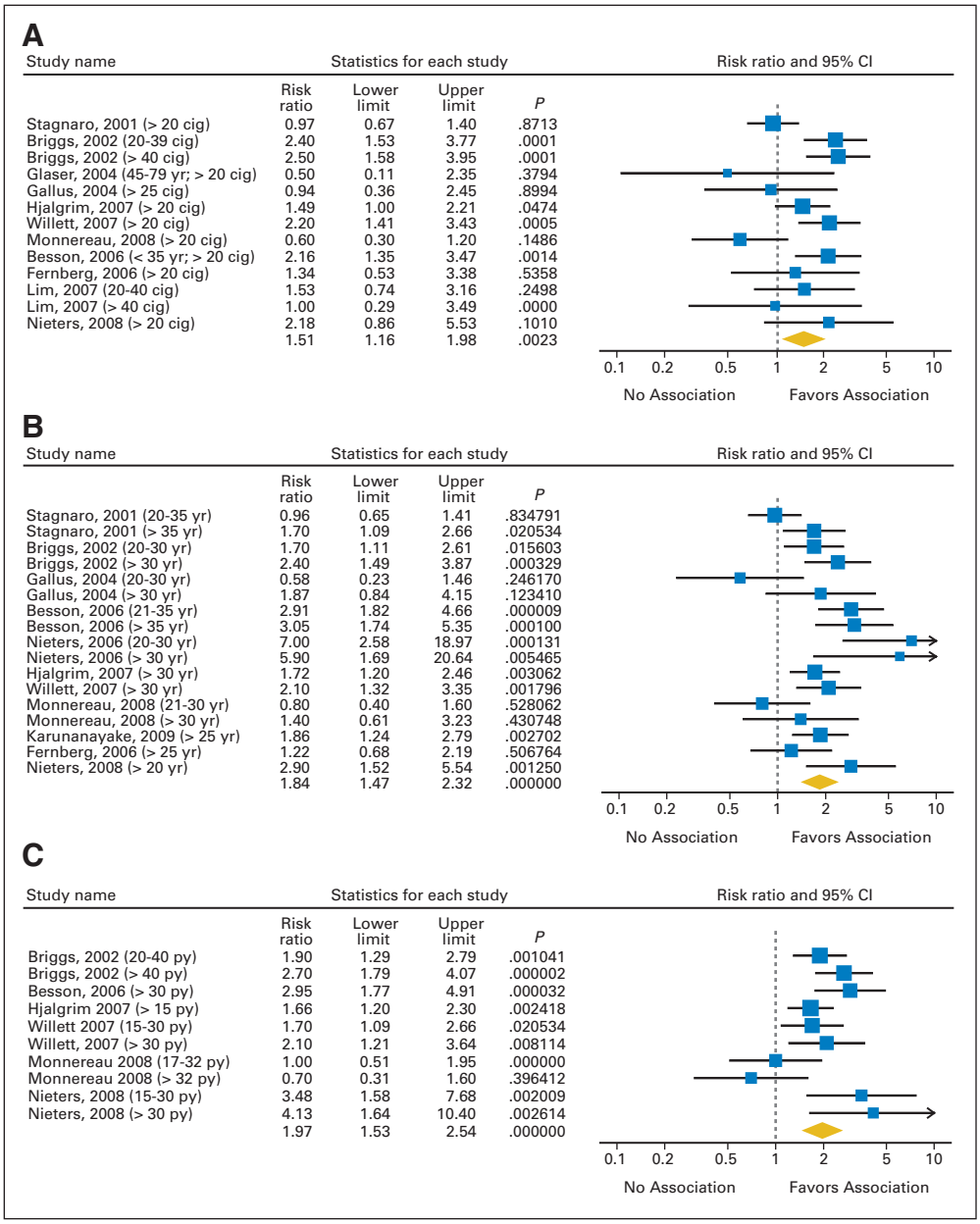

Fig 3. Estimates of the odds ratio of developing Hodgkin's lymphoma for (A) individuals smoking more than 20 cigarettes (cig) per day, (B) individuals smoking for more than 20 years (yr), and (C) individuals smoking more than 15 pack-years (py).

consistency and support the validity of our findings. On the basis of our results, not only the intensity but also the duration of smoking seems to play a role in the development of HL.

In smaller subset analyses, current smoking was also associated with EBV status and histologic subtypes. Current smokers have a 126% increased risk of developing EBV-positive HL and a 40% increased risk of developing EBV-negative HL. This is suggestive of a relationship between smoking and EBV infection. Given the small number of individuals included in these subanalyses, these findings should be considered preliminary.

There are several potential mechanisms that could support smoking as a risk factor for HL. In general, direct oncogenic effects of smoking could be mediated by various chemicals contained in cigarettes such as benzene, formaldehyde, and chromium.[17] More specifically, at the cellular level, smoking has been shown to affect the function of B cells, T cells, natural killer cells, and macrophages, not only potentially promoting but also rendering a microenvironment supportive of lymphomagenesis.[31-34] In addition, smoking is associated with decreased immunoglobulin production.[35] At the molecular level, smoking inhibits apoptosis by modulating Fas ligand in lymphocytes[36,37] and promotes activation of nuclear factor-kappa B and other proinflammatory cytokines associated with lymphomagenesis, such as interleukin 6 and tumor necrosis factor α.[33] Finally, smoking can induce an immunodeficiency state favoring reactivation of EBV, which could be associated with the development of HL.[17,18,21] Further research is needed to better understand these phenomena.

Our study has several strengths. First, it is the largest study to date evaluating the association between smoking and HL. Second, a large majority of the studies included were of high quality. And third, study-level data allowed meaningful subset analyses. However, our study also has several limitations. First, a few studies did not independently confirm a diagnosis of HL. This may have allowed non-HL patients to be included;

however, this was the minority of the studies, and, in such studies, random samples were taken in which a diagnosis of HL was demonstrated. Second, smoking habits were self-reported, which may have introduced a recall bias. More likely, smokers were reported as never smokers than the opposite. Therefore, the association between smoking and HL could be stronger than the one reported here. Third, not all the studies controlled for potential confounding variables, such as HIV infection and socioeconomic status. Fourth, many of the subset analyses, although specified a priori, were performed in small data sets and should be interpreted with caution. Finally, the number of patients from prospective studies could be considered small. However, on the basis of 285 cases found in approximately 12 million person-years, the incidence of HL was approximately 2.4 cases per 100,000 person-years, which is similar to SEER data.

In conclusion, our analysis shows that current cigarette smokers have an increased risk of developing HL. The risk of HL appears to be higher in men, in people older than 30 to 40 years of age, and in people with a higher number of cigarettes smoked per day, number of years smoking, and number of pack-years. The health implications of tobacco smoke are vast, having an impact on almost every organ system. Smoking cessation will have a positive impact on public health and should be advised globally. On the basis of the results of our study, it could also decrease the risk of developing HL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jorge J. Castillo, Samir Dalia
Collection and assembly of data: All authors
Data analysis and interpretation: Jorge J. Castillo
Manuscript writing: All authors
Final approval of manuscript: All authors

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