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Cigarette smoking is associated with a small increase in the incidence of non-Hodgkin lymphoma: a meta-analysis of 24 observational studies

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Abstract

Previous studies have evaluated the association between cigarette smoking and incidence of non-Hodgkin lymphoma (NHL) with inconclusive results. Our main objective was to evaluate this relationship using a meta-analysis of observational studies. A literature search was undertaken through October 2011 looking for pertinent studies. Seven prospective cohort and 17 case–control studies were included in this meta-analysis. Outcomes were calculated using the random-effects model and are reported as odds ratio (OR). Meta-regression was used to evaluate the dose–response of intensity and duration of smoking in NHL incidence. Our study found an OR of 1.40 (95% confidence interval [CI] 1.14–1.73; $p = 0.001$) in current female smokers seen only in case–control studies. No increased odds of NHL was seen in men. There was no association between smoking and the most common NHL subtypes, with the exception of a statistical trend toward a higher incidence of T-cell lymphoma. In conclusion, there appears to be an increase in the odds of NHL in current female smokers.

Keywords: Smoking, non-Hodgkin lymphoma, meta-analysis, meta-regression

Introduction

The age-adjusted incidence rate of non-Hodgkin lymphoma (NHL) in the United States has progressively increased from 11 cases per 100 000 person-years in 1975 to 20 cases per 100 000 person-years in 1995 [1]. Although the incidence rate of NHL has stabilized somewhat in the last 10 years, potential causes for such a pattern in incidence rates remain unclear, and cannot be completely explained by the increased incidence of autoimmune conditions or the human immunodeficiency virus (HIV) pandemic [2–5].

Several infectious, genetic and/or environmental factors play a distinct role in the incidence patterns of NHL [6,7]. The association between cigarette smoking and NHL has been evaluated in numerous retrospective studies with conflicting results [8–17]. Furthermore, a relationship between smoking and follicular lymphoma (FL) has been suggested in a few case-control studies [8,17–19].

The main objective of this study was to evaluate the association, if any, between smoking and incidence of NHL using a meta-analysis of prospective cohort studies. A secondary objective was to evaluate the association between smoking and specific NHL subtypes such as FL, diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and T-cell lymphoma (TCL).

Methods

Literature search

The two authors independently performed a literature search using PubMed and the Cochrane Database of Systematic Reviews from 1 January 1950 to 31 October 2011. The keywords used were "(smoking OR tobacco OR cigarette) AND lymphoma." Additionally, a PubMed search using "(smoking OR tobacco OR cigarette) AND (incidence OR risk) AND cancer" was performed limiting our results to "Titles." The titles and abstracts of the resulting articles were examined, and after excluding non-related articles, full-text articles were retrieved. If a paper was selected for inclusion, the references were scrutinized to search for additional studies.

Inclusion and exclusion criteria

An article was deemed relevant to our study if it originated from prospective cohort or case–control studies and reported original data, regardless of its language, on the association between cigarette smoking and the development of NHL. Cross-sectional studies, case reports and reviews were excluded. Any discrepancies between the authors on inclusion or exclusion of a study were resolved by joint reevaluation of the manuscript. If there were multiple publications from the same study, the most relevant was selected, using the other publications to clarify methodology or characteristics of the population.

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Data extraction

The data extraction was performed independently by the two authors and included author, year of publication, country of origin, sample size, method of ascertainment of smoking, method of diagnosis of NHL, source of the exposed and non-exposed cohorts, source of cases and controls, years of follow-up, source of the expected incidence of NHL, the outcome measured with 95% confidence interval (CI), the variables used for matching and adjustment, and intensity (in number of cigarettes per day) and duration of smoking (in number of years). Intensity and duration of smoking were also gathered by NHL subtype, whenever possible. Any discrepancies between reviewers were addressed by a joint reevaluation of the original article.

Quality assessment

The quality of each study was assessed independently by two reviewers using the Newcastle–Ottawa Scale (NOS) [20]. The NOS consists of three parameters of quality: selection, comparability, and outcome (cohort studies) or exposure (case–-control studies). The NOS assigns a maximum of four points for selection, a maximum of two points for comparability, and a maximum of three points for exposure or outcome. Any discrepancies between reviewers were addressed by a joint reevaluation of the original article.

Data synthesis and analysis

Because the risk of NHL is low, the relative risk in prospective cohort studies mathematically approximates the odds ratio (OR), therefore permitting the combination of case–control and cohort studies. The primary outcome was calculated as the maximally adjusted OR with 95% CI of developing NHL in cigarette smokers. Never smokers were used as the reference group in all calculations. To measure the outcome, we used the random-effects model, which accounts for heterogeneity between and within studies [21]. We assessed for heterogeneity using the I^2 index [22]; I^2 values of 25%, 50% and 75% represent mild, moderate and severe heterogeneity, respectively. Publication bias was assessed using the trim-and-fill method [23], which assumes that the effect sizes of all the studies are distributed normally around the center of a funnel plot; if asymmetry is found, it adjusts for the potential effect that non-published (imputed) studies might have had on the measured outcome. Subset analyses were performed by smoking status (ever, current and former), study design (case–control and prospective cohort) and NHL subtypes (DLBCL, FL, CLL/SLL and TCL). Regression analyses were used to assess the dose–response relationship between intensity and duration of smoking (as continuous variables) and incidence of NHL. The value assigned to each category was the mid-point for closed categories. For open categories, we assumed a maximum of 60 cigarettes per day for intensity, 50 years for duration of smoking and 100 pack-years for cumulative smoking. All calculations and graphs were obtained using Comprehensive Meta-Analysis (Biostat, Englewood, NJ). Data are presented in accordance with the checklist proposed by the Meta-analysis of Observational Studies in Epidemiology group [24].

Results

Search results

A total of 753 articles were identified using the "lymphoma" search, and 1027 using the "cancer" search. Seven prospective cohort [25–31] and 17 case–control studies [8,12–16,32–42] were selected for our meta-analysis. Our search strategy is shown in Figure 1.

Characteristics of the prospective cohort studies

The main characteristics of the prospective cohort studies are shown in Table I. Studies were published between 1998 and 2011. Five studies originated from the USA [26,27,29–31], one from Sweden [25], and one was a European multinational study [28]. A total of 6461 cases (2795 in non-smokers and 3666 in smokers) of NHL were identified in a total cohort of 1 765 643 individuals. All the studies were of high quality (NOS >7). The most common bias was ascertainment of exposure; all the studies assessed smoking habits by self-administered questionnaires.

Characteristics of the case–control studies

The main characteristics of the case–control studies are shown in Table II. The studies were published between 1988 and 2010. Eleven studies originated from Europe [8,13,15,16,32–34,36,38,39,41], four from America [35,37,40,42], one from Japan [12], and one was a multinational study including centers from Europe and the USA [14]. A total of 19 111 cases and 31 939 controls were included. Nine studies were of acceptable quality (NOS <7) and nine were of high quality (NOS 7–9).

Outcome results

The OR of NHL for ever-smokers was 1.05 (95% CI 1.01–1.10; $p = 0.02$). There was minimal heterogeneity (22%), but seven imputed studies were identified to the left of the mean, resulting in an adjusted OR of 1.02 (95% CI 0.98–1.07). There was an increased OR of NHL in current female smokers seen in case–control studies (OR 1.40, 95% CI 1.14–1.73, $p = 0.001$; Figure 2) but not in prospective cohort studies. Otherwise, no other associations were seen according to study design, sex or smoking status. Complete outcome results are shown in Table III.

Dose–response analysis

Intensity of smoking

To optimize the available data, we categorized smoking intensity in three groups, <20, 20–40 and >40 cigarettes per day. There was no dose-dependent association between incidence of NHL and number of cigarettes smoked per day, and meta-regression did not show a linear association between NHL incidence and number of cigarettes. No associations were found when separately evaluating study design or sex.

Duration of smoking

We categorized duration of smoking in five groups, <10, 10–19, 20–29, 30–39 and ≥ 40 years. The only positive association was found in the group who had smoked for 20–29 years with OR of NHL at 1.09 (95% CI 1.02–1.16; $p=0.007$). Meta-regression

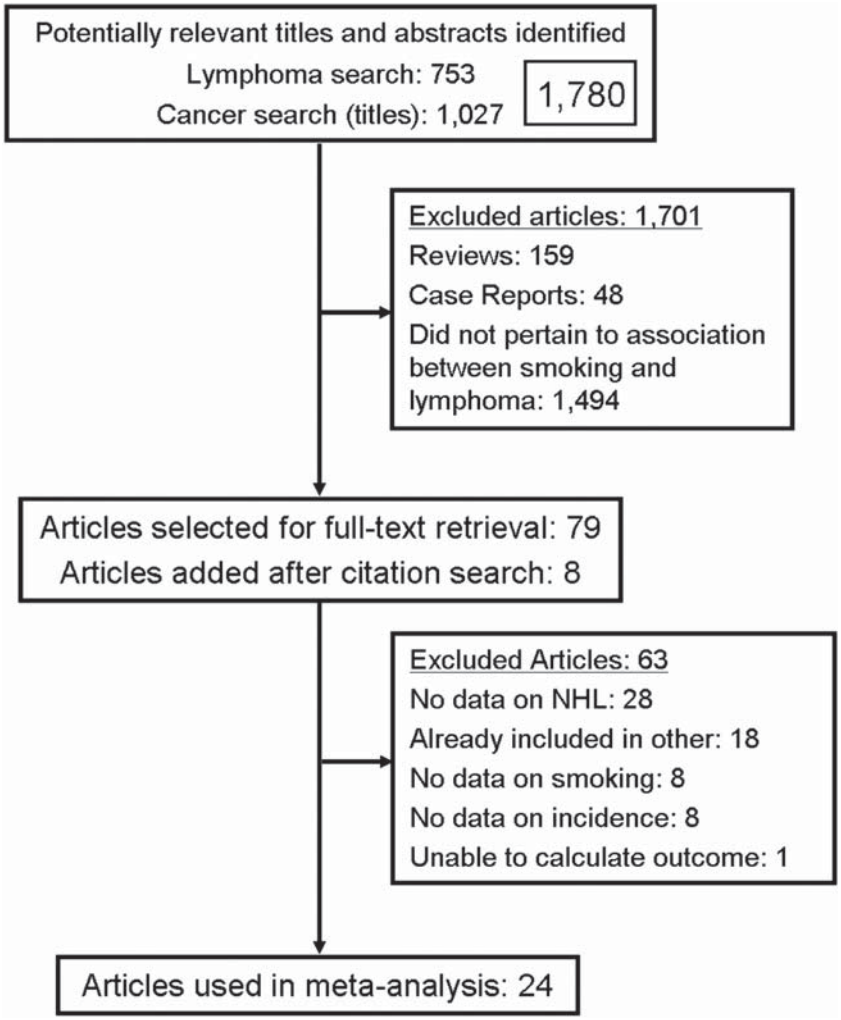

Figure 1. Search results.

showed a linear relationship between years of smoking and NHL incidence with a relative OR (rOR) of 1.003 for each year of smoking ($p = 0.001$). However, no associations were found when evaluating study design or sex separately.

Number of pack-years

Smokers were separated into three groups, < 25, 25–50 and > 50 pack-years of smoking. The only positive association was in the group who had smoked > 50 pack-years (OR 1.13, 95% CI 1.03–1.23; $p = 0.006$). Meta-regression showed a linear relationship between NHL incidence and number of pack-years with a rOR of 1.001 for each pack-year of smoking ($p < 0.001$). However, no associations were found when separately evaluating study design or sex.

NHL subtypes

When evaluating smoking status and the most common subtypes of NHL, we found no evidence that being an ever, former or current smoker increases the odds of developing FL, DLBCL or CLL/SLL. There was a statistical trend, however, toward a higher OR of TCL in smokers. Ever, former and current smokers had an OR of TCL of 1.23 (95% CI 1.00–1.52; $p = 0.05$), 1.18 (95% CI 0.98–1.42; $p = 0.08$) and 1.20 (95% CI 0.98–1.46; $p = 0.07$), respectively (Figure 3).

A subset analysis evaluating the OR of FL incidence by sex in case–control studies showed an OR of FL of 1.33 (95% CI 1.07–1.66; $p = 0.01$) in former female smokers. We found no evidence of increased odds of FL in women who were ever or current smokers, or in men. We were not able to perform meta-analyses on other NHL subtypes according to sex due to insufficient data.

Discussion

Clinically, biologically and molecularly, NHL is a heterogeneous disease, and it is likely that distinct NHL subtypes have distinct risk factors [6]. In fact, several factors have been associated with the development of NHL, such as infectious agents, autoimmune conditions, immunodeficient states, and environmental and iatrogenic exposures [7,43]. Cigarette smoking has been associated with higher rates of incidence of and mortality by a variety of cancers [44]. The association between cigarette smoking and the incidence of NHL has been addressed in multiple studies with contradicting results, hence our attempt to pool data from observational studies to evaluate this potential relationship.

We have conducted a large meta-analysis to evaluate the potential relationship between cigarette smoking and NHL.

Table I. Characteristics of seven cohort studies evaluating the association between smoking and non-Hodgkin lymphoma.

Author (year)	Country	Source of cohort	Median follow-up (period)	Lymphoma assessment	Smoking assessment	Total cohort (total person-years)	Number of cases	Adjustments	NOS
Herrinton (1998)	United States	Kaiser Permanente Medical Care Program	11 years (1964–1991)	Northern California Cancer Center, Kaiser Permanente cancer registry and hospitalization file	Questionnaire	252 836 (NR)	674	Age, sex, year of examination	7
Parker (2000)	United States	Iowa Women's Health Study	11 years (1986–1996)	State Health Registry of Iowa's Cancer Registry and National Death Index	Mailed questionnaire	37 336 (380 231)	200	Age, marital status, residence, alcohol and red meat intake, history of blood transfusion, diabetes	7
Fernberg (2006)	Sweden	Construction Industry Organization for Working Environment Safety and Health	19 years (1971–1992)	Swedish Cancer Registry and Cause of Death Registry	Self-administered questionnaire	335 612 (6 804 539)	1309	Age and BMI	9
Lim (2007)	United States	NIH-AARP Diet and Health study	5 years (1995–2000)	Cancer Registry data and National Death Index	Questionnaire	473 984 (2 060 611)	1381	Age, sex, ethnicity, alcohol intake, BMI, height, physical activity	8
Nieters (2008)	Europe	European Prospective Investigation into Cancer and Nutrition	9 years (1992–2005)	Health insurance records, cancer and pathology registries	Questionnaire	418 482 (3 567 410)	1304	Age, sex, educational level, center	8
Troy (2010)	United States	NCI Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	9 years (1993–2001)	Medical record review at screening center, state vital statistics and the National Death Index	Mailed, self-administered or telephone-administered questionnaires	142 982 (1 201 074)	1264	Age, sex, race/ethnicity, education	8
Lu (2011)	United States	California Teachers' Study	11 years (1995–2007)	Annual linkage with the California Cancer Registry	Self-administered questionnaire	121 246 (1 323 140)	626	Age, race, alcohol intake	8

AARP, American Association of Retired Persons; BMI, body mass index; NCI, National Cancer Institute; NIH, National Institutes of Health; NR, not reported.

Table II. Characteristics of 17 case–control studies evaluating the association between smoking and non-Hodgkin lymphoma.

Author (year)	Country	Source of cases (number)	Source of controls (number)	Period	Lymphoma assessment	Smoking assessment	Matching and adjustments	NOS
Cartwright (1988)	United Kingdom	Hospital admissions in Yorkshire (437)	Hospital-based (724)	1979–1984	Medical records (NR pathological confirmation)	Personal interview	Age, sex, region	6
Persson (1993)	Sweden	Regional Cancer Registry, University Hospital, Linkoping (93)	Population-based (204)	1975–1984	100% pathological confirmation	Mailed questionnaire	Age, other exposures	7
Hardell (1994)	Sweden	Department of Oncology in Umea (105)	Population-based (355)	1974–1978	100% pathological confirmation	Telephone interview	Age, sex, residence, vital status	7
Siemiatycki (1995)	Canada	All hospitals in Montreal (212)	Population-based (533)	1979–1985	100% pathological confirmation	Personal interview and mailed questionnaire	Age	6
Zahm (1997)	United States	Kansas, Iowa, Minnesota, Nebraska (1177)	Population-based (3625)	1983–1986	100% pathological confirmation	Personal interview	Age, sex, race, region	8
De Stefani (1998)	Uruguay	Instituto Nacional de Oncologia of Montevideo (163)	Hospital-based (163)	1988–1995	Medical records (NR pathological confirmation)	Personal interview	Age, sex, residence, beer and salted meat intake	6
Freedman (1998)	United States	Eight cancer registries (1193)	Population-based (1903)	1984–1988	100% pathological confirmation	Telephone interview	Age, residence	8
Fabbro-Peray (2001)	France	Hospitals in Languedoc-Rousillon (445)	Population-based (1025)	1992–1995	Medical records (NR pathological conformation)	Personal interviews	Age, sex, urban setting, education level	7
Besson (2003)	France	Three hospitals in Lyon (180)	Hospital-based (360)	1999–2001	Medical records (89% pathological confirmation)	Questionnaire	Age, sex, residence, welfare support	6
Morton (2005)	United States, Europe	International Lymphoma Epidemiology Consortium (6594)	Population-based, except Northern Italy (8892)	1990–2004	100% pathological confirmation	Mailed questionnaire and personal interview	Age, sex, race, study center	8
Schollkopf (2005)	Denmark, Sweden	Scandinavian Lymphoma Etiology study (3055)	Population-based (3187)	1999–2002	100% pathological confirmation	Telephone interview	Age, sex, country	8
Talamini (2005)	Italy	Hospital admissions in Pordenone and Naples (255)	Hospital-based (504)	1999–2002	Medical records (NR pathological confirmation)	Personal interview	Age, sex, center, education, place of birth, HCV	6
Besson (2006)	Europe	Spain, Germany, France, Italy, Ireland, Czech republic (1742)	Hospital and population-based (2465)	1998–2004	Medical records (20% pathological conformation)	Questionnaire	Age, sex, residence, educational level, alcohol intake	6
Nieters (2006)	Germany	Hospitalized patients from six regions (710)	Population-based (710)	1999–2002	Medical records (10% pathological confirmation)	Personal interview	Age, sex, study region	7
Casey (2007)	France	Three regions in France (298)	Hospital-based (276)	2000–2003	Pathology reports (20% pathological confirmation)	Personal interview	Age, sex, socioeconomic level, center	6
Monnereau (2008)	France	Bordeaux, Brest, Caen, Lille, Nantes, Toulouse (399)	Hospital-based (701)	2000–2004	Pathology reports (NR pathological confirmation)	Personal interview	Age, sex, center, residence	6
Kanda (2009)	Japan	Aichi Cancer Center Hospital, Nagoya (782)	Hospital-based (3484)	1988–2005	Medical records (NR pathological confirmation)	Personal interview	Age, sex, alcohol intake	6

HCV, hepatitis C virus; NOS, Newcastle–Ottawa Scale; NR, not reported.

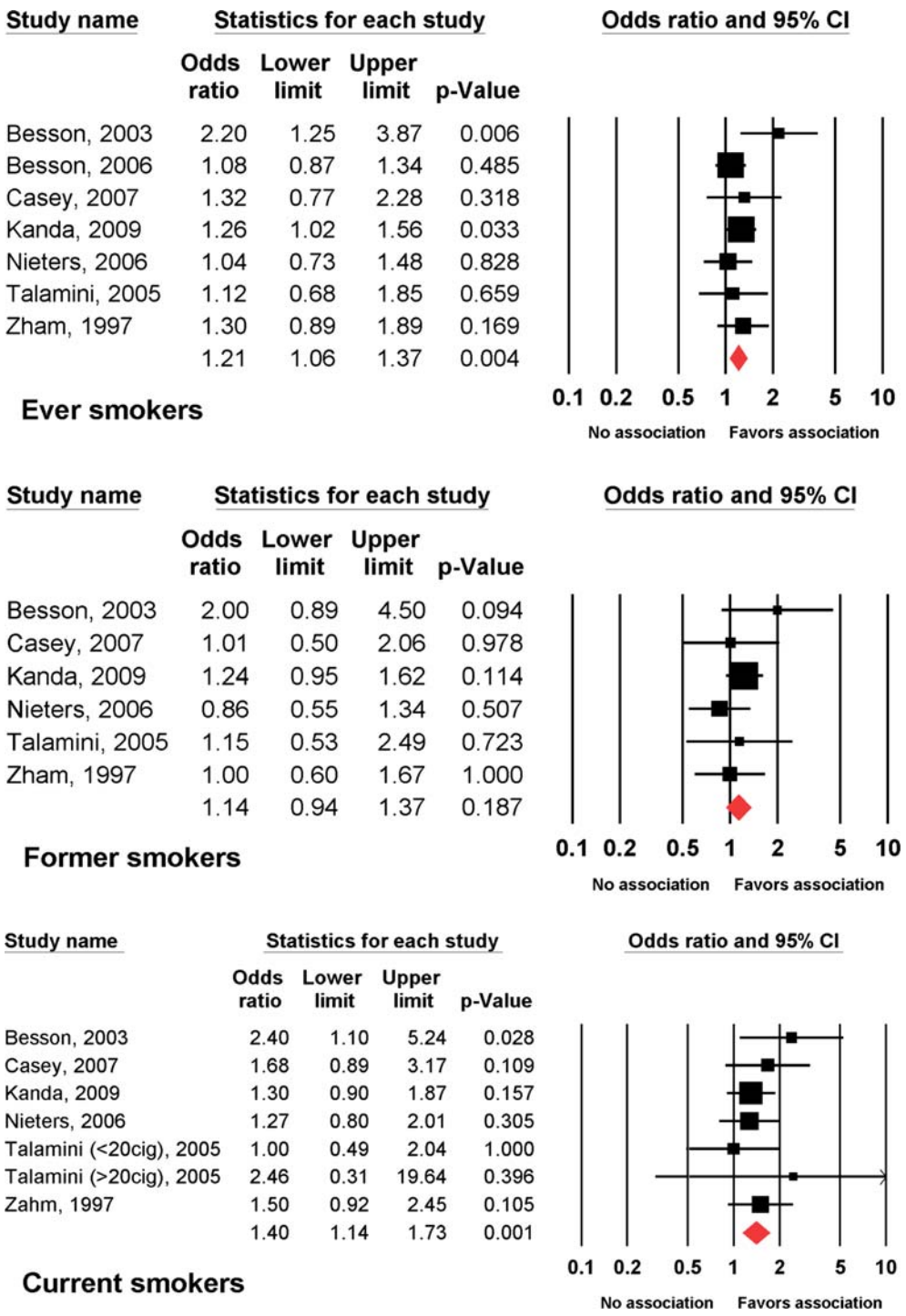

Figure 2. Forest plots of association between smoking and incidence of non-Hodgkin lymphoma in women (case–control studies), according to smoking status.

We found a mild increase in the odds of NHL in current female smokers of 40%. There was no association between smoking and NHL in male smokers. We also found a 9% increased odds of NHL only in individuals smoking for 20–29 years, and of 13% only in individuals who had smoked >50 pack-years. Hence, the dose–response analyses with regard to intensity, duration and cumulative smoking were not internally consistent. Meta-regression analysis did not show a linear association between incidence of NHL and number of cigarettes smoked per day and, although statistically significant, there did not seem to be a clinically important dose-dependent relationship with number of years or pack-years of smoking.

Similarly, there was no association between smoking status, duration or intensity and NHL subtypes, with the exception of former female smokers, in whom the odds of FL were increased at 43% when compared to non-smokers. The reasons why only former but not current or ever female smokers would have increased odds of developing FL are unclear. Also, in meta-regression analyses, a minimal increase in the

Table III. Meta-analyses of the incidence of NHL by smoking status, study design and sex.

Smoking status	Study type	OR (95% CI)	*p*-Value	I^2	No. of imputed studies	Adjusted OR (95% CI)
Ever smokers	All studies	1.05 (1.01–1.10)	0.02	22%	7 (left)	1.02 (0.98–1.07)
	Cohort	1.01 (0.95–1.08)	0.70	11%	2 (left)	1.00 (0.93–1.07)
	Men	1.00 (0.86–1.16)	0.99	0%	0	1.00 (0.86–1.16)
	Women	0.98 (0.63–1.53)	0.92	47%	0	0.98 (0.63–1.53)
	Case–control	1.01 (0.95–1.08)	0.70	11%	2 (left)	0.99 (0.93–1.07)
	Men	1.04 (0.93–1.17)	0.47	32%	1 (left)	1.03 (0.91–1.17)
	Women	1.21 (1.06–1.37)	0.004	8%	0	1.21 (1.06–1.37)
Former smokers	All studies	1.01 (0.97–1.05)	0.67	0%	2 (left)	1.01 (0.97–1.05)
	Cohort	1.00 (0.93–1.08)	0.93	27%	4 (left)	0.93 (0.85–1.02)
	Men	1.01 (0.85–1.21)	0.91	0%	0	1.01 (0.85–1.21)
	Women	1.12 (0.72–1.74)	0.62	4%	0	1.12 (0.72–1.74)
	Case–control	1.02 (0.96–1.07)	0.55	0%	0	1.02 (0.96–1.07)
	Men	0.98 (0.89–1.08)	0.68	0%	0	0.98 (0.89–1.08)
	Women	1.14 (0.94–1.37)	0.19	8%	1 (right)	1.20 (0.99–1.46)
Current smokers	All studies	1.06 (1.01–1.11)	0.03	11%	5 (left)	1.02 (0.97–1.08)
	Cohort	1.01 (0.94–1.08)	0.79	0%	2 (left)	0.99 (0.91–1.07)
	Men	1.00 (0.87–1.15)	1.00	0	0	1.00 (0.87–1.15)
	Women	0.98 (0.67–1.42)	0.91	0%	0	0.98 (0.67–1.42)
	Case–control	1.09 (1.02–1.16)	0.01	16%	2 (left)	1.08 (1.00–1.16)
	Men	1.15 (0.97–1.37)	0.11	43%	2 (left)	1.09 (0.90–1.31)
	Women	1.40 (1.14–1.73)	0.001	0%	2 (left)	1.34 (1.09–1.64)

CI, confidence interval; NHL, non-Hodgkin lymphoma; OR, odds ratio.

odds of DLBCL was observed with a higher number of years and pack-years of smoking. However, this was not confirmed when evaluating the same data in a categorical manner. Of interest is the statistical trend toward an increased risk of TCL found in smokers. This is a novel finding that needs further evaluation.

Overall, our study shows a statistical increase in the odds of developing NHL in ever and current female smokers. Beyond these findings, no additional meaningful association was found arguing in favor of a relationship between smoking and NHL. These results are in contrast with the findings from a recent meta-analysis from our group, which evaluated the relationship between cigarette smoking and Hodgkin lymphoma (HL) [45]. In that study, current smokers had a higher risk of developing HL than never smokers. Furthermore, there was a direct linear relationship between duration, intensity and cumulative smoking and a higher risk of HL.

Of interest is the relationship found between smoking and NHL in case–control studies, which was not consistent with the results from prospective cohort studies. Both statistical designs have their own strengths and weaknesses. Case–control studies suffer from exposure ascertainment (recall) bias, and a cause–effect relationship cannot be established. Prospective cohort studies are generally considered of higher quality than case–control studies; however, adequate follow-up is needed to guarantee that the outcome can be reliably measured. In our study, some of the cohort studies included had a relatively short follow-up of <10 years [27,28,30], which could have underestimated the association of smoking with indolent NHL subtypes, such as FL. Additionally, case–control studies included a three-times larger number of cases than prospective cohort studies, providing a higher statistical power. Hence, the moderately increased incidence of NHL found in smokers is most likely a real association.

There are several theoretical mechanisms, however, by which cigarette smoke inhalation could lead to the development of NHL. Primarily, there is a direct carcinogenic effect of substances found in cigarettes including benzene, which can lead to the inhibition of apoptosis. In heavy smokers, higher rates of t(14;18), a translocation seen in patients with FL, have been reported [46]; this promotes up-regulation of bcl-2, which in turn inhibits apoptosis [47]. Cigarette smoking has also been associated with both an immunodeficiency state and decreased immune responsiveness at the cellular level; B, natural killer (NK) and T-cell activity seem decreased in smokers, which could decrease cellular immune surveillance and lead to an oncogenic microenvironment [48,49]. Finally, cigarette smoking has been shown to promote oxidative stress and inflammation [50]. Chronic inflammatory states have also been shown to be associated with NHL.

Our study has several strengths. First, the number of cases of NHL included in this meta-analysis is large; hence, the likelihood that the lack of association between smoking and NHL is secondary to an underpowered sample size is low. Second, most of the studies provided pertinent data to enable subset analyses according to study design, smoking status, sex and NHL subtype. Finally, the analyses of heterogeneity and publication bias showed minimal impact on our results.

Our study, however, carries several limitations. First, smoking habits were assessed mainly by means of self-administered questionnaires and personal interviews, which could have introduced exposure bias. However, in a recent report from the National Health and Nutrition Examination Survey [51], it was found that self-reported smoking habits were reliable in $>99\%$ of smokers surveyed. Second, longer follow-up might have been necessary to start seeing the actual effect of cigarette smoking on the development of NHL in prospective cohorts. Finally, in a study of this nature,

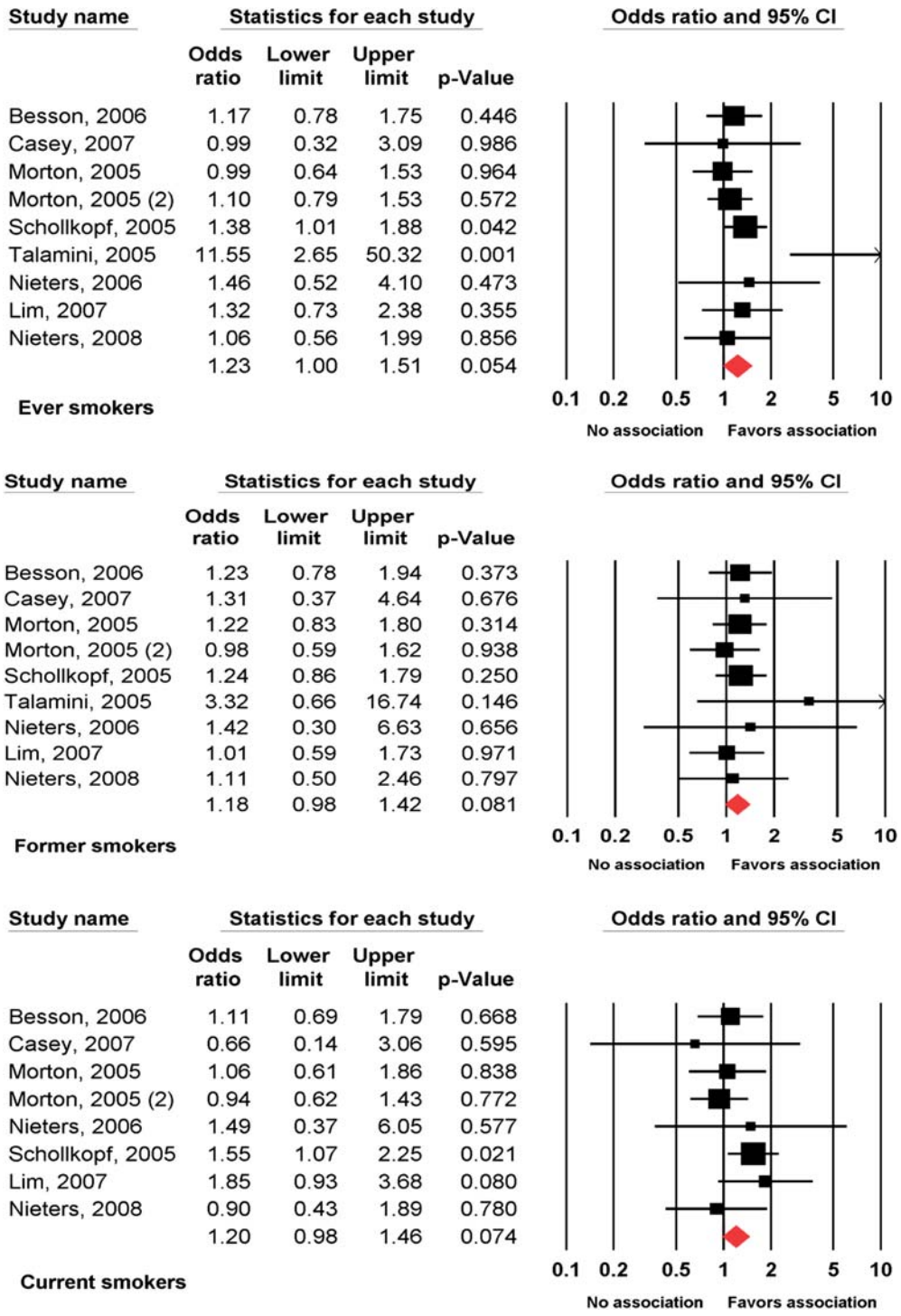

Figure 3. Forest plots of association between smoking and incidence of T-cell lymphoma, according to smoking status.

it is possible that the positive results found here were due to statistical multiplicity and not a real association. To support this statement is the fact that no significant dose–response relationship was observed between incidence of NHL and smoking duration or intensity.

In conclusion, based on the results of this meta-analysis of observational studies, cigarette smoking was associated with a small increase in the odds of developing NHL in female smokers. Furthermore, we found a statistical trend toward a higher incidence of TCL. Smoking cessation would impact positively on the health of the general population and should be advised globally.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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