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Smoking and Risk of Non-Hodgkin Lymphoma Subtypes in a Cohort of Older Women*

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Although non-Hodgkin lymphoma (NHL) has not been considered to be a smoking-related malignancy, recent investigations suggest otherwise. We evaluated this association in a cohort of 37,336 women, aged 55–69 years, who reported in a mailed questionnaire in 1986 information regarding smoking history as well as demographic, medical history and dietary factors. Cancer and mortality experience through 1996 was determined by linkage to the Iowa Cancer Registry and other databases; there were 200 incident cases of NHL during the 380,231 total person-years of follow-up. Compared to never smokers, former (age-adjusted RR = 1.0; 95% CI 0.8–1.5) and current smokers (age-adjusted RR = 1.0; 95% CI 0.7–1.5) were not at elevated risk of NHL, and there was no trend with pack-years smoked (P_{trend} = 0.3). Multivariate adjustment for other NHL risk factors did not alter these findings. Age-adjusted analysis by NHL subtype revealed a suggestive positive association of smoking with follicular NHL [(RR_{former}= 1.3; 95% CI 0.6–2.8), ($RR_{current}$= 1.8; 95% CI 0.8–3.8)], which strengthened after multivariate adjustment [(RR_{former}= 1.6; 95% CI 0.7–3.4), ($RR_{current}$ = 2.3; 95% CI 1.0–5.0)]; there was no association for diffuse or small cleaved-cell NHL. Our study findings, which are consistent with other recent investigations, suggest that smoking may be associated with an increased risk of follicular NHL.

Keywords: Cohort study, etiology, non-Hodgkin lymphoma, smoking

INTRODUCTION

Between 1973 and 1994, there was an 81 percent increase in the incidence rate of non-Hodgkin lymphoma (NHL) in the United States, which constituted one of the largest increases among the major cancer sites (1). The American Cancer Society estimated that 55,400 new cases of NHL would be diagnosed in 1998, nearly double the number of incident cases in 1970 (2). While a portion of this increase in the NHL incidence rate has been attributed to better detection and the emergence of AIDS, neither of these factors

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can fully account for the increase in NHL incidence observed since the 1950's, or the continued increase in NHL rates among the elderly and the HIV negative population (3, 4).

Risk of NHL is clearly elevated by primary and iatrogenic immunodeficiency (5, 6). Other suggested risk factors include certain viruses (Epstein Barr Virus and the Human T Cell Lymphotrophic Virus Type I) (7), occupations dealing with chemicals and agriculture (8), blood translusion (9), nitrates in drinking water (10), and certain dietary (9) and lifestyle factors, including smoking. Although most early studies suggested little or no association between NHL and smoking (11–21), many recent reports (22–27) have suggested otherwise. In a large cohort study of white, male insurance policy holders in Utah, there was a strong association between smoking and NHL mortality, with heavy smokers experiencing almost a four fold increase in risk of death from NHL (24). In addition, analysis by NHL tumor subtype suggests a specific association of smoking with both high grade (23) and follicular (23, 26) NHL. One study combining the results from three population based case-control studies suggested that the association between smoking and NHL may be stronger among women than men (25). We present data from a large population-based cohort study of older Iowa women who reported their smoking history in a detailed baseline questionnaire and were subsequently followed using a state-wide cancer registry to determine their NHL experience.

MATERIALS AND METHODS

Details of the Iowa Women's Health Study have been reported previously (28). Briefly, in January 1986 a mailed questionnaire was completed by 41,837 of 98,030 (42.7%) women age 55–69 years who were randomly selected from the 1985 Iowa driver's license list. This sampling frame has been reported to cover over 95% of the target population (29). There were only minor demographic differences between respondents and non-respondents (28); however, respondents developed less smoking related disease than non-respondents during the first five years of follow up (30).

The baseline questionnaire asked each woman to report if she had ever smoked cigarettes on a regular basis. Women who answered "yes" were then asked to report the age at which they started smoking, the average number of cigarettes they smoked per day, their current (1986) smoking status, and the age they stopped smoking if they no longer smoked. Each woman also reported information on demographics, diet, and personal medical history, including history of any cancer.

Follow-up

Vital status and cancer incidence was determined through eleven years of follow up from 1986 through 1996. Follow up questionnaires were mailed in 1987, 1989, 1992 and 1997 to assess address changes and vital status. Deaths were determined through linkage of personal identifiers (name, address, social security number, birth date and maiden name) to Iowa death certificates, supplemented by data from the follow-up questionnaires, and for non-respondents, linkage to the National Death Index. Identification of incident cancer was accomplished through annual linkage by personal identifiers to the State Health Registry of Iowa's Cancer Registry, which is part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program (1). Tumor site and morphology were coded in the registry according to the International Classification of Diseases for Oncology (ICD-O), Second Edition (31).

The histologic subtypes recorded in the cancer registry were grouped according to the Working Formulation (32) into the following subtypes: low grade NHL (ICD-O codes 9670, 9671, 9691, 9693, 9695, or 9696), intermediate grade NHL (ICD-O codes 9672, 9673, 9675, 9680–9682, 9698), high grade NHL (ICD-O codes 9684, 9686), small lymphocytic NHL (ICD-O code 9670), follicular NHL (9690, 9691, 9693, 9695, 9696, or 9698), diffuse NHL (ICD-O codes 9595, 9672, 9673, 9675, 9680–9682, 9684 or 9686), and all other NHL (ICD-O codes 9590, 9671, or 9700). Those NHL cases that were not classified as low, intermediate or high grade, or were otherwise missing grade data, were categorized together as unclassified NHL.

Data Analysis

In order to provide a cancer-free cohort, we excluded from analysis 3,903 women who self-reported at baseline (1986) a history of any cancer, except non-melanoma skin cancer. This exclusion reduced the at-risk cohort to 37,934.

The smoking exposure data from the baseline questionnaire was used to categorize each women as a "current", "former" or "never" smoker and to calculate pack years of smoking. There were 598 women (1.6% of total) in the cohort who were excluded from analysis due to missing information on smoking status, reducing the at risk cohort further to a final total of 37,336 women. Pack-years of smoking were categorized *a priori* as none, < 20, 20–40 and > 40.

Each woman accrued person-years of follow-up from the date of receipt of their 1986 baseline questionnaire until: (1) date of NHL diagnosis, (2) date of emigration from Iowa, or (3) date of death. If none of these events occurred, person-years were accumulated to December 31, 1996.

Age-adjusted and multivariate relative risks (RR), along with 95% confidence intervals (95% CI), were calculated as measures of association between smoking and NHL incidence using Cox proportional hazards regression (33). Relative risks (RR) were generated for (1) all NHL; (2) nodal and extra-nodal NHL; (3) low, intermediate, high, and unclassified grade NHL; and (4) the following Working Formulation subtypes: follicular, diffuse, small lymphocytic and all other NHL. Variables considered in the multivariate analysis as potential confounders included age, alcohol consumption (nondrinker, < 3.6 grams/day, ≥ 3.6 grams/day), marital status (never, former, current), history of blood transfusion (yes, no, not sure), farm residence (yes, no), diabetes (yes, no), and red meat consumption (servings/month). Additional variables considered but found not to influence the results included education level, body mass index and consumption of animal fat and fruit; they are not reported here. The assumption for proportional hazards for smoking was tested and found not to be violated. Analyses were conducted using SAS statistical software (SAS Institute Inc., Cary, NC).

RESULTS

During 380,231 person-years of follow-up (median = 10.9 years) there were 200 incident cases of NHL. The mean age at diagnosis was 69 years (range, 57–81 years). At baseline, approximately 15% of the cohort reported that they were current smokers, 19% were former smokers and 66% were never smokers; 14% reported less than 20 pack years of smoking, 11% reported 20–39 pack-years of smoking and 9% reported greater than 40 pack-years of smoking.

Table I presents the distribution of potential confounding variables across categories of smoking status. Smokers were slightly younger than never smokers. Current smokers in general were more likely to engage in several dietary and lifestyle behaviors related to risk of developing NHL in this cohort than were never or former smokers. Specifically, current smokers ate slightly more red meat and animal fat (both risk factors), but consumed much less fruit (a protective factor). Current smokers were also less likely to be currently married, and to have been educated beyond high school. In contrast, smokers drank more alcohol (a protective factor) and were also less likely to live on a farm (a risk factor). There was little meaningful difference across smoking categories for a history of diabetes or blood transfusion (both risk factors).

There was no association between smoking history and risk of NHL overall (Table II). When the outcome was stratified by primary site (nodal versus extra-nodal), there also was no association with smoking history.

In the analysis of risk by grade of NHL, there was no association of smoking with either low or intermediate grade NHL. High grade NHL was positively associated with smoking, but was based on only five cases, which limits any conclusions.

TABLE I Baseline demographic, lifestyle and dietary factors according to smoking status, Iowa Women's Health Study, 1986

Factor	Never (n=24,602)	Former (n=7,191)	Current (n=5,543)
Age (years)	61.9	61.4	60.9
Red meat (servings/month)	42.2	29.5	33.0
Fruit (servings/month)	79.5	73.9	59.3
Animal Fat (grams/day)	39.9	37.7	40.5
Marital Status			
Current	79%	76%	69%
Former	18%	22%	30%
Never	3%	2%	2%
Education			
< High School	10%	7%	7%
High School	32%	30%	37%
> High School	58%	63%	56%
Farm Residence			
No	76%	90%	90%
Yes	24%	10%	10%
Transfusion History			
No	72%	70%	72%
Yes	26%	27%	25%
Not sure	3%	3%	4%
Alcohol Use			
None	64%	43%	41%
< 3.4 grams/day	22%	24%	20%
≥ 3.4 grams/day	14%	33%	39%
History of Diabetes			
No	93%	93%	94%
Yes	6%	7%	5%
Not Sure	1%	1%	1%

In the analysis by The Working Formulation tumor classification (32), there was no association between smoking history and diffuse or small lymphocytic NHL. There was a suggestive positive association, however, between smoking and development of follicular NHL in the age-adjusted models. After multivariate adjustment, relative risk estimates strengthened. Compared to never smokers, former (RR=1.6; 95% CI 0.7–3.4) and current smokers (RR=2.3; 95% CI 1.0–5.0) were at increased risk of follicular NHL (p_{trend} = 0.03) and there was a trend of increasing risk with increasing number of pack-years of smoking (p_{trend}=0.06). Further stratification of current smokers into those who smoked less than 20 cigarettes per day and those who smoked 20 or more cigarettes per day, revealed little difference in risk estimates for development of follicular NHL (data not shown). There were too few data to estimate the effects of pack-years smoked for current and former smokers separately or to estimate risk for time since quitting among former smokers.

TABLE II Age and multivariate-adjusted relative risks (RR) and 95% confidence intervals for non-Hodgkin lymphoma by smoking history, Iowa Women's Health Study, 1986–1996

	Smoking Status				Pack-years of smoking[a]			
	Never	Former	Current	p-trend	< 20	20–40	>40	p-trend
All NHL								
Cases	144	40	27		22	27	18	
Person-years	254,235	71,910	54,086		50,735	41,461	30,662	
Age RR[b]	1	1.1 (0.8–1.5)	1.0 (0.7–1.5)	0.8	0.9 (0.6–1.4)	1.3(0.9–2.0)	1.2 (0.7–1.9)	0.3
Multivariate RR[c]	1	1.2 (0.8–1.7)	1.1 (0.7–1.7)	0.4	1.0 (0.6–1.6)	1.5 (1.0–2.3)	1.2 (0.7–2.0)	0.2
Primary Site								
Nodal								
Cases	94	27	20		16	17	14	
Age RR	1	1.0 (0.7–1.6)	1.1 (0.6–1.7)	0.8	0.9 (0.5–1.5)	1.2 (0.7–1.9)	1.3 (0.7–2.2)	0.4
Multivariate RR	1	1.3 (0.8–2.0)	1.3 (0.8–2.0)	0.3	1.1 (0.6–1.8)	1.4 (0.8–2.4)	1.5 (0.8–2.7)	0.1
Extra nodal								
Cases	39	13	17		6	10	4	
Age RR	1	1.2 (0.7–2.3)	0.9 (0.4–2.1)	0.9	0.8 (0.3–1.9)	1.7 (0.8–3.4)	0.9 (0.3–2.5)	0.6
Multivariate RR	1	1.1 (0.6–2.2)	0.9 (0.4–2.1)	0.9	0.8 (0.3–2.0)	1.7 (0.8–3.4)	0.7 (0.2–2.1)	0.9
Grade								
Low								
Cases	43	11	8		6	8	5	
Age RR	1	0.9 (0.5–1.8)	0.9 (0.4–1.9)	0.8	0.7 (0.3–1.7)	1.2 (0.6–2.5)	1.0 (0.4–2.5)	0.9
Multivariate RR	1	1.1 (0.6–2.2)	1.1 (0.5–2.4)	0.7	0.9 (0.4–2.1)	1.5 (0.7–3.2)	1.2 (0.4–3.0)	0.5
Intermediate								
Cases	69	20	13		11	12	10	
Age RR	1	1.1 (0.6–1.7)	0.9 (0.5–1.7)	0.9	0.8 (0.4–1.6)	1.1 (0.6–2.1)	1.2 (0.6–2.4)	0.6
Multivariate RR	1	1.1 (0.6–1.8)	1.0 (0.5–1.8)	0.9	0.9 (0.5–1.7)	1.2 (0.6–2.3)	1.2 (0.6–2.4)	0.5
High								
Cases	3	2[d]						
Age RR	1	1.5 (0.2–8.8)		0.7				
Multivariate RR	1	2.4 (0.4–16)		0.4				
Not Classified								
Cases	18	7	6		5	6	2	
Age RR	1	1.4 (0.6–3.5)	1.7 (0.7–4.4)	0.2	1.5 (0.6–4.0)	2.2 (0.9–5.6)	1.0 (0.2–4.2)	0.3
Multivariate RR	1	1.6 (0.6–3.8)	1.9 (0.7–5.0)	0.1	1.6 (0.6–4.5)	2.4 (0.9–6.2)	1.1 (0.2–4.8)	0.3
Subtype								
Follicular								
Cases	25	9	9		6	8	4	
Age RR	1	1.3 (0.6–2.8)	1.8 (0.8–3.8)	0.1	1.2 (0.5–3.0)	2.0 (0.9–4.5)	1.4 (0.5–3.9)	0.2
Multivariate RR	1	1.6 (0.7–3.4)	2.3 (1.0–5.0)	0.03	1.5 (0.6–3.8)	2.6 (1.1–5.8)	1.6 (0.6–4.9)	0.06
Diffuse								

	Smoking Status				Pack-years of smoking[a]			
	Never	Former	Current	p-trend	< 20	20–40	>40	p-trend
Cases	73	21	11		11	12	9	
Age RR	1	1.1 (0.6–1.7)	0.8 (0.4–1.4)	0.5	0.8 (0.4–1.5)	1.1 (0.6–2.0)	1.1 (0.5–2.1)	0.9
Multivariate RR	1	1.1 (0.6–1.8)	0.8 (0.4–1.5)	0.6	0.9 (0.5–1.6)	1.1 (0.6–2.1)	1.0 (0.4–2.1)	0.9
Small lymphocytic								
Cases	18	3[d]						
Age RR	1	0.3 (0.1–1.2)		0.09				
Multivariate RR	1	0.4 (0.1–1.5)		0.2				
Other								
Cases	17	8	6		5	6	3	
Age RR	1	1.7 (0.7–4.0)	1.8 (0.7–4.6)	0.1	1.6 (0.6–4.3)	2.3 (0.9–5.9)	1.5 (0.4–5.2)	0.1
Multivariate RR	1	2.0 (0.8–4.8)	2.1 (0.8–5.4)	0.08	1.8 (0.7–5.1)	2.7 (1.0–7.0)	1.8 (0.5–6.3)	0.08

a. Referent group is never smokers
b. RR adjusted for age.
c. RR adjusted for age, marital status, residence on a farm, alcohol consumption, transfusion history, diabetes, and red meat consumption.
d. RR is for ever smoker.

DISCUSSION

In this population-based cohort of Iowa women, we found no overall association between smoking and risk of NHL. There was, however, a suggestive association between smoking and follicular NHL, which strengthened after multivariate adjustment for demographic, dietary and lifestyle risk factors for NHL.

There are strengths and limitations to these data. The low prevalence of smoking reported among these women, particularly for heavy smokers, limits our ability to fully define the dose-response relation. The most critical limitation of this study overall was the small sample size within many individual categories of NHL subtype. Small sample size also precluded our ability to evaluate time since quitting smoking or to evaluate the influence of pack-years of smoking in current versus former smokers. Strengths of the study include a large prospective study design, small loss to follow-up, use of a SEER Cancer Registry to determine cancer incidence, and the ability to control for NHL risk factors that were often not addressed in previous studies.

NHL subtypes in this study were derived from the Iowa SEER Cancer Registry data, which abstracts diagnostic pathology reports, and not by central review. A study conducted in Iowa from 1981 to 1984 found that panel review by light microscopy was of questionable value due to the inability of the expert panel to agree on many subtypes. However, the agreement between the reported diagnosis and the panel for small lymphocytic and follicular NHL was excellent (34).

Our finding of no overall association between smoking and NHL is consistent with most previous studies (11–21), although a few positive results have been reported. In a population-based case-control study of men conducted in Iowa and Minnesota (23), there was a positive association (OR=1.4; 95% CI 1.1–1.8) for all NHL, but no evidence for a dose-response relation. In the Selected Cancers Study, a population-based case-control study of men, there was no overall association with NHL, but there was a positive association for heavy (≥2.5 packs/day), long-term (30–39 years) smokers (OR=1.45) (27). Finally, in a large prospective cohort study in Utah there was a strong association between heavy cigarette smoking and death from NHL (RR=3.8; 95% CI 1.4–10.1) (24).

Of potential interest in our study was the finding that after multivariate adjustment, current smokers had a significant increase (~130%) in risk of developing follicular NHL compared to never smokers. There was some evidence for a dose response relation with pack-years of smoking, although the risk attenuated for the heaviest smokers, possibly due to competing mortality from other smoking related diseases, or a weakening of effect by inclusion of ex smokers in the pack-years analysis.

The potential existence of an association between smoking and particular subtypes of NHL has been reported previously (23, 25–27). In addition to finding an overall association between smoking and NHL, Brown et al (23) reported that current smokers appeared to be at greater risk of developing both follicular NHL (OR= 1.4; 95% CI 0.9–2.3) and high grade NHL (OR= 2.4; 95% CI 1.0–6.0), specifically. Herrinton and Friedman (26) also reported evidence of a specific NHL subtype association with smoking from a prospective cohort study of 253,000 Kaiser-Permanente Medical Care Program members ages 16–84 years (median follow-up = 11 years; 673 cases). Age and sex-adjusted analysis revealed no overall association with NHL, but a positive association was detected between smoking and follicular NHL [$RR_{current}$=1.4, 95% CI (0.9–2.2); RR_{former}=1.9, 95% CI (1.2–2.9)].

There are several potential mechanisms by which smoking might influence the development of NHL. It is well documented that cigarette smoke contains various lymphomagenic agents, including radioactive elements (i.e. polonium-210) and benzene (35). Other possible lymphomagens such as formaldehyde (36) and organic solvents (37) are also known constituents of tobacco smoke (38). The most plausible theory suggests that one of the many potential carcinogens in tobacco smoke could cause a mutagenic alteration in a lymphocyte precursor cell.

In addition to a possible initiation of lymphomagenesis by carcinogens found in cigarette smoke, there is also evidence of an indirect promotion effect of cigarette smoke. Lower percentages of natural killer cells have been shown to be associated with cigarette smoking (39). Reports have also suggested that lymphocytes from smokers make more mistakes in the repair of DNA damage than lymphocytes from non-smokers (40). This impairment of the body's intrinsic defense against tumorigenesis is favorable to the further development of NHL.

Little attention has been given to the biology behind the finding of a specific association between smoking and follicular NHL. It is well documented that greater than 85% of all follicular NHL tumors contain a unique translocation of the bcl-2 tumor-suppressor gene locus (41, 42). The chromosomal translocation t(14;18) (q32;q21) involves a juxtaposition of the bcl-2 gene with the immunoglobulin heavy-chain gene. The resulting translocation up-regulates the bcl-2 gene product and is thought to then delay or even eliminate apoptosis (43). A study by Bell et al (44) on a group of healthy men and women under the age of 52, found a strong association between cigarette smoking and detection by PCR of the t(14;18) chromosomal translocation in peripheral blood samples. Using logistic regression models, the authors reported that individuals classified as having 1–40 pack-years of smoking had an elevated odds of the bcl-2 translocation (OR=1.5; 95% CI 1.2–1.9), and those categorized as having greater than 40 pack-years of smoking were 3.9 times more likely to have an increased t(14;18) translocation frequency (95% CI 1.8–8.4). Bell and colleagues proposed that carcinogens from cigarette smoke could increase the rate of t(14;18) translocations by inducing breaks on chromosome 18. Alternatively, they suggested that the baseline rate of bcl-2 translocations are equal in smokers and non-smokers, but that cigarette smoke antigens may stimulate expansion of rare B-cells containing the mutations.

Our study supports the finding from several other investigations that there is no overall association between smoking and development of NHL. However, our data do suggest that smoking may be a risk factor for development of the follicular subtype of NHL.

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