Cigarette Smoking and Risk of Non-Hodgkin's Lymphoma Subtypes[1]

Lisa J. Herrinton[2] and Gary D. Friedman

Kaiser Permanente, Oakland, California 94611

Abstract

We examined the hypothesis that cigarette smoking increases the risk of non-Hodgkin's lymphoma (NHL) subtypes in a cohort of approximately 253,000 members of the Kaiser Permanente Medical Care Program, ages 16–84 years, who completed a self-administered questionnaire during the period 1964–1991 that ascertained smoking history. Using information from the Surveillance, Epidemiology, and End Results cancer registry that operates in the area and the Kaiser Permanente cancer registry, we identified 674 incident cases of NHL through 1993. We observed a positive association between smoking and risk of follicular lymphoma (compared with nonsmokers: former smokers, relative risk = 1.9 with 95% confidence interval = 1.2–2.9; current smokers, relative risk = 1.4 with 95% confidence interval = 0.9–2.2), although the strength of the association did not increase consistently with increasing duration and intensity of smoking. We observed no relationship between smoking status and the risks of small cell lymphocytic, diffuse, or high-grade lymphoma, nor was smoking related to the risk of all histological types of NHL combined. These results give limited evidence for a relationship between smoking and the risk of follicular lymphoma.

Introduction

NHL[3] comprises a heterogeneous group of malignancies that differ in their etiology. The greatly increased risk of lymphoma among persons with AIDS (1), primary immunodeficiency (2), and allogeneic organ transplant (3) is limited to diffuse large cell lymphoma, immunoblastic lymphoma, and, in the case of AIDS, Burkitt's lymphoma. The risk of small cell lymphocytic lymphoma, like chronic lymphocytic leukemia, to which it is pathogenetically related, has been reported to be increased in agricultural workers (4, 5), whereas the rate of follicular lymphoma has been noted to increase with migration from lower-risk Asian countries to the United States (6). Beyond these observations, little is understood about the etiology of the diverse diseases that comprise the rubric NHL.

We conducted a cohort study to investigate the relationship of cigarette smoking with risk of the more commonly occurring histological subtypes of NHL. Our work was motivated by the lack of understanding of the etiological basis of the entities that make up NHL and by recent reports that cigarette smoking is associated with the occurrence and mortality of NHL overall (7, 8).

Patients and Methods

The cohort included 252,836 persons ages 16–84 years who: (*a*) were members of the San Francisco or Oakland, California facilities of the Kaiser Permanente Medical Care Program; and (*b*) provided information about smoking history on at least one of five questionnaires that were administered during the period 1964–1991.

Four of the questionnaires that ascertained smoking history were included in the multiphasic examinations that have been offered free to Kaiser Permanente members since 1964. Although the multiphasic questionnaire was revised in 1972, 1977, and 1986, the four versions ascertained smoking history in nearly identical ways. They included six questions about smoking, using check boxes to ascertain current (yes or no) and past (yes or no) smoking of cigarettes, pipes, or cigars; years of regular cigarette smoking (<10, 10–20, and >20 years); and the average number of packs of cigarettes smoked per day (<1, 1–2, and >2). Although multiphasic examinations have been given since 1964, the questionnaires administered during the period from August 1973 through 1976 were not entered into a computerized database, and for this reason, they were not included in the present study. In addition to smoking history, data from the multiphasic check-ups on sex, race, marital status, and educational attainment were also obtained for the present study. The fifth questionnaire contained 47 items concerned primarily with tobacco use (9). It was given during the period 1979–1986 and included detailed questions on the years of smoking and average number of cigarettes smoked per day as well as other smoking characteristics. These data were recoded to be consistent with the data obtained from the multiphasic questionnaires. Persons who smoked pipes or cigars only were excluded from the present study, because their numbers were too few to consider in a separate analysis.

Persons diagnosed with NHL were identified from three sources: (*a*) the Northern California Cancer Center, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results program since 1973, was used to ascertain the 272 cohort members who were diagnosed with NHL during the period 1973–1987 and who resided in the five-county San Francisco Bay area at the time of their diagnosis; (*b*) we searched the Kaiser Permanente cancer registry, which has ascertained patients diagnosed since 1988, to identify the 402 cohort members who resided in any Northern California county and were diagnosed during the period 1988–1993. The Kaiser Permanente cancer registry maintains the case definition

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[2] To whom requests for reprints should be addressed, at Division of Research, Kaiser Permanente, 3505 Broadway Avenue, Oakland, CA 94611. E-mail: ljh@dor.kaiser.org.

[3] The abbreviations used are: NHL, non-Hodgkin's lymphoma; RR, relative risk; CI, confidence interval; ICD-O, International Classification of Diseases for Oncology.

standards of the Surveillance, Epidemiology, and End Results program; and (*c*) we searched the Kaiser Permanente computerized hospitalization file, which contains information on members throughout the Northern California region, for the period 1971–1987, but every one of the cases identified through the hospitalization records was also recorded in the cancer registry operated by the Northern California Cancer Center.

The histological subtypes recorded in the registry were assumed to be accurate and were grouped according to the Working Formulation (10) into the following subtypes: small cell lymphocytic lymphoma (ICD-O code 9670), follicular lymphoma (ICD-O codes 9690, 9691, 9693–9696, and 9698), intermediate-grade diffuse lymphoma (ICD-O codes 9592, 9593, 9672–9675, 9681, and 9682), and high-grade lymphoma (ICD-O codes 9684–9687). In addition, we considered the entity "diffuse, large cell lymphoma not otherwise specified" (9680). This entity, used frequently before 1988, when the Working Formulation was codified, is ambiguous, containing cases that today would be coded either as intermediate-grade diffuse disease (ICD-O code 9681 or 9682) or as high-grade disease (ICD-O code 9684). We considered this entity because it was assigned to a relatively large number of the NHL cases. We did not examine small cell plasmacytoid lymphoma (ICD-O code 9671), because there were only two cases.

Follow-up began on the date that the first questionnaire was completed and ended on the date of diagnosis of NHL, termination of membership, death, or December 31, 1993, whichever was earliest. The median follow-up period was 11 years. The Cox proportional hazards model was used to compute the maximum likelihood estimate of the RR and its 95% CI (11). The RRs were adjusted for sex, age (continuous), and year of multiphasic examination (continuous). We also examined race, marital status, and years of schooling using the categories shown in Table 1, but these were not confounders of the associations. We tested for a trend of risk with duration and intensity of smoking by replacing the binary smoking variables in the base model with an ordinal variable coded 1 (never smoked) through 7 (smoked 20 or more cigarettes per day for 20 years or longer), as indicated in Table 2.

Table 1 Demographic characteristics in relation to smoking history among 252,836 members[a] of the Kaiser Permanente Medical Plan, San Francisco and Oakland facilities, 1964–1993

Characteristic	Never smoker (113,192) %	Former smoker (51,998) %	Current smoker (85,745) %
Yr of birth			
1889–1919	20	26	18
1920–1929	15	20	19
1930–1939	15	18	20
1940–1949	24	23	26
1950–1973	26	13	16
Age at examination (yr)			
≤29	29	15	27
30–39	25	25	27
40–49	18	24	22
50–59	14	20	15
≥60	13	16	8
Yr of exam			
1964–1973	50	54	65
1977–1985	41	37	29
1979–1986	1	2	2
1986–1991	8	8	4
Gender			
Female	64	43	53
Male	36	57	47
Race			
Black	19	15	24
White	59	72	64
Other/unknown	23	13	12
Marital status[b]			
Single	38	29	37
Married	62	71	63
Yr of schooling			
≤12	29	26	37
13–14	25	24	27
≥15	32	31	21
Unknown	14	19	13

[a] Information on smoking status missing for 1,901 persons.
[b] Information on marital status missing for 2,132 never smokers, 1,525 former smokers, and 2,415 current smokers.

Results

As expected, a larger proportion of men than women reported a history of smoking (Table 1). Compared with nonsmokers and current smokers, former smokers tended to be older, married, white, and of higher educational attainment.

We observed no association of smoking status (never, former, or current) with the risk of small cell lymphocytic, diffuse, or high-grade lymphoma, nor was the risk associated with the duration and intensity of past smoking. However, smokers were at increased risk of follicular disease (compared with nonsmokers: former smokers, RR = 1.9 with 95% CI = 1.2–2.9; current smokers, RR = 1.4 with 95% CI = 0.9–2.2), although the trend of increasing risk of follicular disease with increasing duration and intensity of smoking was not entirely consistent (P trend = 0.10).

Discussion

Our study has several limitations. We obtained information on smoking history at only one point in time. Persons who were current smokers at the time of the initial questionnaire may have gone on to quit, and this misclassification would have diminished the RR for the "current smoker" category. In an unrelated study conducted in our population, it was observed that one-quarter of the 4345 smokers ages 40–49 years who completed two smoking questionnaires reported that they had quit smoking in the 4–6 intervening years (12). The somewhat low RR observed for current smokers (relative to the RR observed for former smokers) may have been a result of this misclassification. It is also possible that some individuals who reported not being smokers at the time of the initial questionnaire, particularly young persons, started smoking later. Had 5% of the subjects under 30 years of age later taken up smoking, then 1.5% of the subjects classified as "never smokers" would have in fact been smokers; thus, the bias resulting from this misclassification would have been negligible.

Pathologists may differ in their interpretation of NHL subtypes, particularly the diffuse large cell types. However, the broad categories that were used in the present study are readily distinguishable (13) and probably were classified consistently from case to case. This is particularly so because the majority of slides would have been read by Kaiser Permanente pathologists working in the San Francisco and Oakland facilities. On the other hand, high-grade lymphoma is a broad category that contains immunoblastic, lymphoblastic, and small noncleaved cell lymphoma, entities that may not share a common etiology. Thus, our negative result for high-grade lymphoma should be interpreted with caution. Another limitation is that we made

Table 2 RR[a] (95% CI) of NHL subtypes in relation to smoking history

	Smoking status			Duration and intensity of smoking					
				<10 yrs		10–20 yrs		>20 yrs	
	Nonsmoker	Former smoker	Current smoker	≤20 cigarettes/day	>20 cigarettes/day	≤20 cigarettes/day	>20 cigarettes/day	≤20 cigarettes/day	>20 cigarettes/day
NHL, all types combined	1.0[b]	1.1	1.1	0.9	1.1	1.1	1.2	1.1	1.0
		0.9–1.3[c]	0.9–1.3	0.6–1.2	0.8–1.5	0.8–1.6	0.9–1.7	0.8–1.4	0.8–1.3
	286[d]	182	206	47	87	39	46	69	103
Small cell lymphocytic lymphoma	1.0	1.0	0.5	[e]					
		0.5–1.8	0.3–1.1						
	29	16	11						
Follicular lymphoma	1.0	1.9	1.4	1.7	1.3	1.9	2.2	2.1	1.3
		1.2–2.9	0.9–2.2	0.9–3.0	0.7–2.4	1.0–3.8	1.2–4.2	1.2–3.7	0.7–2.3
	45	44	45	14	19	10	13	17	17
Intermediate-grade diffuse lymphoma	1.0	0.8	0.8	0.7	0.6	1.2	1.0	0.7	1.1
		0.5–1.3	0.6–1.3	0.4–1.5	0.3–1.1	0.6–2.4	0.5–2.1	0.3–1.4	0.7–1.8
	67	31	38	9	12	9	8	9	22
Large cell diffuse lymphoma not otherwise specified	1.0	1.2	1.1	1.1	1.0	0.8	1.2	1.3	1.2
		0.8–1.7	0.8–1.6	0.6–2.0	0.6–1.8	0.4–1.8	0.6–2.4	0.8–2.2	0.7–1.9
	71	43	52	15	18	7	11	19	26
High-grade lymphoma	1.0	0.8	0.8	0.4	0.8	0.8	1.1	0.9	0.7
		0.4–1.4	0.5–1.5	0.1–1.5	0.4–1.7	0.2–2.5	0.5–2.8	0.3–2.4	0.3–1.7
	30	15	20	3	11	3	6	6	7

[a] Adjusted for age (continuous), year of multiphasic examination (continuous), and sex.
[b] Reference group. The number of cases of "NHL, all types combined" is greater than the sum of the cases of specific subtypes because it includes unclassified cases.
[c] 95% CI.
[d] Number of cases in the category.
[e] Number of cases in the category was too few for meaningful analysis.

many comparisons, and in some of the comparisons, there were few cases. Thus, our positive findings for follicular lymphoma may have resulted from chance.

We did not have information on infection with HIV, which is modestly related to an increased prevalence of smoking (14, 15) and is strongly related to an increased risk of large cell diffuse, immunoblastic, and Burkitt's lymphoma (16). However, the data do not give evidence that HIV infection confounded the relationship of smoking with risk of NHL, because any confounding would have increased the RR, and the RRs we observed for large cell diffuse and high-grade disease were close to 1.0.

Only two other epidemiological studies have examined the relationship of smoking with NHL subtypes, and their data were combined in the report of Zahm *et al.* (8). In their combined analysis of population-based case-control studies of residents of Iowa, Minnesota, Nebraska, and Kansas, cigarette smoking was associated with NHL in women (self-respondents only, ever *versus* never: men, OR = 1.0 and 95% CI = 0.8–1.2; women, OR = 1.9 and 95% CI, 1.2–3.0), with some differences in risk being observed by subtype (both self-respondents and proxy respondents, women: follicular, OR = 1.3 and 95% CI = 0.7–2.5; diffuse, OR = 1.6 and 95% CI = 0.9–2.8; small lymphocytic lymphoma, OR = 3.4 and 95% CI = 0.7–16; Ref. 2). In addition, the authors reported a dose-response relationship in the association of years smoked with follicular lymphoma and small lymphocyte lymphoma among women (data not reported; P trend = 0.02). The present report, together with the results of Zahm *et al.* (8), is suggestive of a possible relationship and merits further investigation into the role of smoking with lymphoma subtypes.

Because the incidence of follicular lymphoma has been noted to increase with migration from China and Japan to the United States (6), it is of interest to examine the prevalence of smoking in these populations. In 1965, the prevalence of smoking was greater in Japan (75 and 15%) than in the United States (43% in men and 33% in women; Ref. 17), whereas during a similar period in Hawaii, the prevalence rates in persons of Japanese, Chinese, and European ancestry were 53, 37, and 61% in men and 24, 17, and 49% in women (18). These data indicate that smoking does not underlie the pattern of follicular lymphoma risk observed among Asian migrants to the United States.

One can only speculate about the possible biological role of smoking in the development of lymphoma. Most conceivable is that one of the many carcinogens in cigarette smoke could induce a mutation in a lymphoma precursor. However, we are not aware of any experimental data on this topic. Nonetheless, we believe that the possible role of smoking in the development of follicular lymphoma should be examined further because of the known carcinogenicity of cigarette smoke, the prevalence of smoking, the lack of knowledge of the etiology of follicular lymphoma, and the suggestive results observed in this study and that of Zahm *et al.* (8).

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