

IS CIGARETTE SMOKING A RISK FACTOR FOR NON-HODGKIN'S LYMPHOMA OR MULTIPLE MYELOMA? RESULTS FROM THE LUTHERAN BROTHERHOOD COHORT STUDY

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Abstract—Among 17633 U.S. white male insurance policy holders whose use of tobacco was characterized in a 1966 self-administered questionnaire, there were 49 deaths from non-Hodgkin's lymphoma (NHL) and 21 from multiple myeloma (MM) during a 20-year follow-up. Men who had ever smoked cigarettes had an elevated mortality from NHL (RR = 2.1; CI = 0.9-4.9), with risk almost four-fold greater among the heaviest smokers (RR = 3.8; CI = 1.4-10.1) compared with those who used no tobacco. In contrast, risk of MM was only slightly elevated among those who had ever smoked Cigarettes (RR = 1.3; CI = 0.4-3.9) and without evidence of a dose-response trend. Since this is the first cohort study suggesting a link between cigarette smoking and NHL and findings from case-control studies have been inconsistent, additional clarification should be sought from larger incidence-based cohort investigations.

Key words: Cigarette smoking, non-Hodgkin's lymphoma, multiple myeloma, prospective study, United States.

INTRODUCTION

SINCE 1950, age-adjusted incidence rates for non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) have increased at least two-fold in the U.S. [1]. Although rates rose for males and females in most age groups, increases were most notable for the oldest groups, while plateaus or small declines have occurred in recent years among middle-age groups. Reason for these changes are largely unknown, although similar types of environmental factors (including ionizing radiation, solvents, pesticides, and other chemicals) have been postulated in the etiology of both lymphoproliferative malignancies [2, 3] as well as the leukemias [4]. As evidence linking cigarette smoking with both myeloid [5-10] and lymphoid [6, 7, 11] leukemia has increased, the role of cigarette smoking in other hematolymphoproliferative cancers needs evaluation. An examination of cigarette smoking and NHL and MM is

presented here using data from a cohort study of 17633 American men.

MATERIALS AND METHODS

The methods of this study have been described in detail elsewhere [12]. Eligible subjects were white male policy holders of the Lutheran Brotherhood Insurance Society. A mailed questionnaire sent to members aged 35 and older was completed by 68.5% of the subjects. Respondents differed little from non-respondents in age, urban/rural residence, policy status, and cancer mortality [13]. Information on tobacco use, diet, and demographic background was collected in the questionnaire. Most study subjects resided in the upper midwest and northeast regions of the United States. Compared with the U.S. population, a higher proportion of subjects were farmers from rural areas and of Scandinavian heritage [14].

In 286 731 person-years of follow-up during 1967-1986, there were 4513 deaths. Death certificates were coded for underlying and contributory causes of death by the nosologist of the Minnesota State Department of Health. Twenty-three percent of the cohort (4027 subjects) were lost to follow-up due to lapsed policies or discontinuation of policies after premium maturity. The smoking habits of these subjects did not differ from those remaining in the cohort.

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TABLE 1. RISK OF DEATH FROM NON-HODGKIN'S LYMPHOMA AND MULTIPLE MYELOMA ASSOCIATED WITH CIGARETTE SMOKING HISTORY. LUTHERAN BROTHERHOOD COHORT, 1967-86

Tobacco use*	No. person-years	Non-Hodgkin's lymphoma		Multiple myeloma	
		RR† (95% CI)	No. deaths‡	RR (95% CI)	No. deaths
Never any tobacco	58 888	1.0 ---	6	1.0 ---	4
Any tobacco, excluding cigarettes	21 680	1.1 (0.3-4.4)	3	0.4 (0.1-3.8)	1
Ever cigarettes§	190 640	2.1 (0.9-4.9)	38	1.3 (0.4-3.9)	14
≤10 cigs/day	63 575	1.0 (0.3-3.0)	7	1.5 (0.4-5.2)	7
11-20 cigs/day	80 230	2.3 (0.9-5.9)	17	1.6 (0.5-5.6)	7
>20 cigs/day	43 268	3.8 (1.4-10.1)	13	—	0
(<i>p</i> for trend)		<i>p</i> < 0.005		<i>p</i> = 0.70	

* All categories refer to ever users.

† Adjusted for age.

‡ Missing data not included.

§ Includes current and ex-smokers.

A Poisson regression program for modeling hazard functions was used to calculate age-adjusted relative risks, with the hazard function assumed to be constant in each age interval [15, 16]. Five-year age intervals were used, with relative risks calculated for each age stratum and summarized over all strata for the selected variables. Person-years, were accumulated up to death, loss to follow-up, or 1986.

RESULTS

There were 49 deaths from non-Hodgkin's lymphoma and 21 from multiple myeloma during the 20-year follow-up. Risk of death from NHL or from MM did not vary significantly by level of education, urban/rural status, occupation/industry, or place of birth (data not shown).

Subjects who used any type of tobacco had an elevated risk of NHL (RR = 1.9; 95% CI = 0.8-4.5) but little increase in MM (RR = 1.1; 95% CI = 0.4-3.3). When smokers were classified by number of cigarettes smoked daily, a statistically significant dose-response pattern was observed for NHL, with risk increasing to 3.8 among those smoking more than one pack per day (Table 1). Risks were similar for current and ex-smokers, although the numbers of deaths were sparse (data not shown). Risk of MM was increased by 30% among cigarette smokers, although there was no dose-response, and lower than expected among users of pipes and cigars only (Table 1).

DISCUSSION

To our knowledge, this is the first cohort study to show a dose-response relationship between cigarette smoking and non-Hodgkin's lymphoma. In contrast, mortality from multiple myeloma was not notably increased among cigarette smokers nor associated with amount smoked, although these findings are based on small numbers.

No significant excess of NHL was found among cigarette smokers in a cohort study of American male college students [5] nor was risk of combined categories of hematolymphoproliferative neoplasms (NHL not separately considered) significantly elevated among U.S. veterans [17] or British male physicians [18]. Mortality from malignant lymphoma (including Hodgkin's disease) was 38% higher among men aged 35-64, but not elevated among those aged 65-79, who ever smoked compared with those who never regularly smoked in a follow-up study of American Cancer Society volunteers [19]. Some case-control studies have reported an excess risk for NHL of 30-60% among cigarette smokers, but none found a gradient with amount smoked [20-22]. Other case-control investigations have found no association [23, 24].

Multiple myeloma was not separately evaluated, but included in combined groupings of hematolymphoproliferative malignancies, in some earlier cohort studies which showed no excess of these neoplasms among cigarette smokers [17, 18]. In other cohort investigations of cancer occurrence among

cigarette smokers, findings for **MM** were not shown (even as part of combined group of hematolymphoproliferative neoplasms) [5, 19]. Recently, Mills *et al.* reported a significant increase and dose-response trend for multiple myeloma based on 9 ex-smokers and 2 current smokers (11 myeloma cases who had ever smoked cigarettes) in a six-year follow-up of 34 000 U.S. Seventh Day Adventists [8]. No excess of **MM** has been found in the 26-year follow-up 293 916 U.S. veterans (Heineman *et al.*, personal communication). Case-control studies of multiple myeloma in both the U.S. [20, 25, 26] and Canada [27] have generally shown no associations, although a Swedish study reported an increased risk among former cigarette smokers [28].

Incidence trends for NHL during the past several decades are consistent with an etiologic role for tobacco use. Incidence rose dramatically among the elderly, and to a lesser extent among middle-aged persons, with the rate of increase among the latter apparently peaking during the 1970s.

Our cohort data add to the accumulating evidence that NHL, but not **MM**, is associated with cigarette smoking. Although some postulated risk factors (ionizing radiation, solvents, pesticides, other chemicals) for the hematolymphoproliferative malignancies (NHL, **MM**, and the leukemias) appear to overlap and both these neoplasms have been found to occur in excess in certain occupational cohorts (farmers, chemical manufacturing workers, styrene and butadiene workers, persons exposed to ethylene oxide), there are also several indications of important etiologic differences among these malignancies [2-4].

The small number of multiple myeloma, and to a lesser extent, NHL deaths and resulting wide confidence limits must be taken into account in interpreting the risk estimates. In addition, 23% of the cohort members ($N=4027$) were lost to follow-up due to lapsed or discontinued insurance policies. However, at 11.5 years of follow-up, there were no significant differences in cancer mortality between those lost to follow-up and those with known vital status [13]. Because smoking history was ascertained only once, in 1966, the category of 'current smokers' probably included a substantial proportion of men who subsequently quit smoking, as has been documented among middle-aged Americans [29]. Thus, the risks reported here for smokers may be underestimates of true levels among continuing smokers. The study subjects may also have an under-reported level of cigarette smoking on the questionnaire because of concerns about insurance eligibility despite assurances of confidentiality by the investigators. Knowledge of scientific reports linking smoking with cancer risk may have caused the sub-

jects to minimize the actual level of cigarettes smoked daily.

In summary, our cohort study shows evidence suggesting a causal link between cigarette smoking and **NHL**. Findings do not support such an association for **MM**. Additional confirmation of our results is needed. Cohort and case-control investigations with substantial numbers of histologically verified incident cases of NHL and **MM** would be helpful, particularly if emphasis is given to subtype specification of **NHL**.

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