Tobacco Use, Body Mass Index, and the Risk of Leukemia and Multiple Myeloma: A Nationwide Cohort Study in Sweden

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Abstract

In a prospective cohort study of more than 330,000 Swedish construction workers, we explored the effect of tobacco smoking, oral moist snuff use, and body mass index (BMI) on the risk of developing leukemia (excluding chronic lymphocytic leukemia) and multiple myeloma (MM). Study subjects were participants of a health surveillance system within the building industry. Record linkage to the nationwide Swedish cancer registry, migration registry, and cause of death registry made a comprehensive follow-up available. A total of 372 incident cases of leukemia and 520 subjects with MM was ascertained. An increase in risk of acute myelogenous leukemia (AML) was observed in current smokers (incidence rate ratio, 1.50; 95% confidence interval, 1.06–2.11). Furthermore, there was an indication of a possible association between smoking intensity and risk of acute lymphocytic leukemia. Results on snuff use as well as BMI showed no association. This study confirms the role of smoking as a risk factor for AML and gives no support to the hypothesis of a role of snuff use or BMI level on the risk of leukemia or MM. [Cancer Res 2007;67(12):5983–6]

Introduction

Leukemias are a heterogeneous group of malignancies arising from cells of the hematopoietic system. Modern classification distinguishes between four main leukemia subtypes: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). CLL belongs to B-cell lymphomas (1). The etiology of leukemia has not yet been fully elucidated. The most well established risk factor is ionizing radiation (2, 3), such as therapeutic and diagnostic radiation (4, 5). Infection with human T-cell lymphotrophic virus, type I is a well-established factor of importance for the development of adult T-cell leukemia/lymphoma (6), and exposure to benzene an established risk factor for AML (7). Tobacco smoking is today an established risk factor for AML (8).

Multiple myeloma (MM) evolves from the B-cell line of the lymphatic system producing altered plasma cells that infiltrate the bone marrow. The great majority of findings related to tobacco as a causative agent of MM have not shown any association (9–16). However, one study has reported a positive association (17).

Studies that have addressed the relation between use of smokeless tobacco products and hematopoietic malignancies are very limited and have in general not revealed a positive association (12, 18). Several reports on body mass index (BMI) and leukemias and MM suggest that there may be a weak positive association (19–22). However, there is no conclusive evidence as other studies have failed to confirm such a relationship (23, 24).

Given the conflicting results in previous studies and the increasing concern about the effect of lifestyle factors on the global burden of disease, we conducted a cohort study on Swedish construction workers with the aim of investigating the effect of tobacco use and BMI on the incidence of leukemia and MM.

Materials and Methods

Subjects. From 1969 to 1992, the Construction Industry's Organization for Working Environment, Safety and Health (25) provided outpatient medical services to all blue and white collar employees within the building industry throughout Sweden. On average, each cohort member underwent 2.6 health checkups during the period. Data from these health checkups were then put together in a computerized central registry (25).

Exposure information. From 1971 until 1975 and from 1978 until 1992, information on tobacco use, BMI, as well as other factors was acquired by a self-administered 200-item questionnaire accompanied by face-to-face interviews by a nurse. In 1975 to 1977, no exposure information on tobacco use was collected. The quality of the smoking data has been reviewed previously (26).

Definition of the cohort. The original cohort consisted of 361,280 individuals. A total number of 24,899 (7%) was excluded due to female gender (n = 17,458), cancer before entry (n = 1,229), incorrect national identification number (n = 388), missing information on BMI (n = 3,032), and inconsistencies during record linkages (n = 2,792). A total of 336,381 individuals was considered eligible for data analyses. A minor part of data investigating tobacco use only have been published previously (12). However, the follow-up was terminated in 1991 and leukemia subtypes were not investigated explicitly in that report.

Follow-up. The unique 10-digit national registration number assigned to all Swedish residents is an inimitable personal identifier and was used for follow-up by linkage to the National Causes of Death Registry, Migration Registry, and Cancer Registry. The essentially complete Swedish Cancer Registry initiated in 1958 codes malignant neoplasms according to the International Classification of Diseases.

Each worker of the complete cohort was followed from date of entry (first visit) until emigration, death, date of cancer diagnosis, or December 31, 2004, whichever occurred first, for a total of 7,475,628 person-years of observation.

Statistical analyses. Information on tobacco smoking, snuff use, and BMI was restricted to that collected at first visit. We used Cox proportional hazards regression model to estimate relative risks [incidence rate ratio (IRR)] together with corresponding 95% confidence intervals (95% CI) adjusted for attained age and BMI. Because age is an important risk factor for almost all cancer types, we used attained age (in years) as the time scale. Therefore, all estimates were implicitly adjusted for the attained age. Analyses

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of smoking status (current/former) were restricted to never snuff dippers and adjusted for attained age and level of BMI. Pure use of diverse smoking tobacco products and daily amount of tobacco smoking, respectively, were analyzed in the same manner. Tests for trend for amount of smoking tobacco were conducted using the median value of different strata as the score.

We used four categories for classification of BMI: ≤18.5 kg/m^2 (underweight), 18.6 to 24.9 kg/m^2 (normal weight), 25.0 to 29.9 kg/m^2 (overweight), and ≥30.0 kg/m^2 (obese). BMI analyses were adjusted for attained age, snuff use, and daily amount of tobacco smoking. Intercooled STATA Release 9.2 was used for all statistical procedures.

This study was approved by the institutional review board at Karolinska Institutet.

Results

At baseline, the cohort members had a mean age of 34.3 years (range, 14–82 years) and were followed up for an average of 22.2 years (range, 0–33.5 years). About 56,179 workers (16.7%) were past smokers of one or several types of tobacco products (cigarette, pipe, cigar) and 137,311 (40.8%) were current smokers at entry into the cohort. Moreover, 29% of the cohort members were pure cigarette smokers, 12% were pure snuff dippers, 5% were pure pipe smokers, and 0.6% were pure cigar smokers. Mixed users consisted 23% of the study population. A total number of 4,247 (1.3%) had a BMI classified as underweight at time of enrollment, 210,081 (62.5%) were of normal weight, 105,793 (31.5%) were overweight, and 16,260 (4.8%) were obese. During follow-up, we identified 47 individuals with ALL, 224 with AML, 101 with CML, and 520 individuals with MM.

We did not detect any association between current or former smoking and the risk of ALL (Table 1). A 50% increased risk of AML was observed for current smokers (IRR, 1.50; 95% CI, 1.06–2.11). Current smokers and ex-smokers did not have an increased risk of CML or MM.

Smokers of more than 20 g tobacco per day had a 2-fold, although not statistically significant, excess risk of ALL (Table 2). No trend in risk of AML, CML, and MM was apparent for smoking intensity.

Exclusive use of cigarettes, pipe, snuff, or mixed use was not linked to a greater risk of ALL, AML, CML, or MM (Tables 2 and 3).

We did not reveal any apparent effect by having a BMI classified as overweight or obese on the risk of ALL, AML, CML, or MM compared with individuals of normal weight (Table 4).

Discussion

In this cohort study, including more than 330,000 male construction workers in Sweden, we observed an increased risk of AML in current smokers and an indicative association between amount of smoking and risk of ALL. The risk of CML and MM was not associated with tobacco smoking. Snuff use was not associated with the risk of leukemia or MM, and BMI did not seem to modify the risk of any of the neoplasias under study.

The IARC have concluded that smoking is weakly associated with an increased risk of leukemia but that there is insufficient support for an increased risk of lymphoid leukemia linked to smoking (8). Results from cohort studies provide the most convincing evidence for an association between myeloid leukemia and cigarette smoking. In addition, some case-control studies have reported an increased risk of AML (22, 27–29). Nonetheless, the internal validity of the exposure data in two of these studies (28, 29) can be questioned due to usage of interviews by proxy responders.

Inconsistent with many other findings, though, two previous cohort studies did not detected any significant associations between tobacco smoking and risk of leukemias (12, 30). However, both these cohort studies were limited by not analyzing leukemia subtypes independently.

Our results support the general evidence that there is no association between MM and tobacco smoking (11, 12, 14, 15). However, one recent study has shown conflicting results (31).

The effect of snuff on the risk of AML, ALL, CML, or MM has been investigated previously in one cohort study (12) and in three case-control studies, which found that snuff dipping was unrelated to the risk of developing leukemia (18, 32) and MM (11).

Table 1. IRRs for tobacco smoking of leukemia subtypes and MM

	Smoking status		
	Never tobacco users (reference)	Ex-smokers	Current smokers
No. individuals	101,959	33,374	106,264
Person-years, accumulated (in millions)	2.24	0.78	2.40
ALL			
No. cases	10	7	19
IRR* (95% CI)	Reference	1.56 (0.58–4.20)	1.80 (0.83–3.90)
AML			
No. cases	52	30	92
IRR (95% CI)	Reference	0.94 (0.60–1.48)	1.50 (1.06–2.11)
CML			
No. cases	35	10	28
IRR (95% CI)	Reference	0.64 (0.32–1.32)	0.69 (0.42–1.14)
MM			
No. cases	143	102	168
IRR (95% CI)	Reference	1.11 (0.86–1.43)	0.96 (0.77–1.20)

NOTE: When analyzing smoking, we restricted to never snuff dippers.
*Adjusted for age and BMI.

Table 2. IRRs for smoking intensity and use of specific types of tobacco of acute leukemia

Tobacco use	No. individuals	Person-years, accumulated (in millions)	ALL		AML	
			No. cases	IRR (95% CI)	No. cases	IRR (95% CI)
Never tobacco users (reference)	101,959	2.24	10	Reference	52	Reference
Current smokers						
<10 g/d*	49,465	1.39	5	1.00 (0.34–2.96)	50	1.58 (1.07–2.34)
10–20 g/d	33,607	1.05	9	2.66 (1.07–6.64)	25	1.21 (0.75–1.96)
>20 g/d	20,429	0.62	4	2.29 (0.71–7.37)	16	1.59 (0.90–2.79)
P for trend				0.11		0.59
Pure cigarette smoker	98,183	2.20	18	1.94 (0.89–4.21)	64	1.29 (0.89–1.86)
Pure pipe smoker	16,988	0.38	2	0.84 (0.18–3.92)	25	1.38 (0.85–2.24)
Mixed users	76,381	1.81	12	1.41 (0.61–3.29)	69	1.38 (0.96–1.98)

NOTE: Analyses of smoking intensity as well as specific types of smoking tobacco were adjusted for age and BMI. We equated one cigarette to contain 1 g and one cigar to contain 6 g of tobacco on average. Pipe smoking was measured in grams per week. Mixed users were defined as users of at least two tobacco products, either snuff and smoking tobacco or more than one type of smoking tobacco.
*Analyses of smoking intensity were restricted to current smokers. The number of cases for amount of smoking does not add up to that of current smokers for all outcomes due to missing information on amount.

One case-control study has reported an increased risk of MM, although based on small numbers (18).

Obesity has been considered to increase the risk leukemias by some investigators. This includes a population-based, case-control study of adult leukemia in Canada (22), where there was a positive association for AML and CML among overweight and obese people. Further support of an increased risk of leukemia, particularly AML, with level of BMI was observed in a cohort of Iowa women (21). In contrast, no association between obesity and leukemia risk was observed in a large cohort of hospitalized patients from Sweden with a discharge diagnosis of obesity (24) as well as a 10-year follow-up of a cohort of Korean men (23). Two previous cohort studies did not reveal any association between obesity and MM (23, 24), whereas conflicting results have been published in a few other studies (19, 33, 34).

Previous studies on BMI and risk of hematopoietic malignancies had some limitations that might affect the interpretation of the results. Case-control studies could suffer from recall bias. Furthermore, BMI of cases may be affected by disease development.

Table 3. IRRs for use of snuff of leukemia subtypes and MM

	Snuff status	
	Never tobacco users (reference)	Pure snuff dippers
No. individuals	101,959	40,932
Person-years, accumulated (in millions)	2.24	0.80
ALL		
No. cases	10	4
IRR* (95% CI)	Reference	1.24 (0.39–4.01)
AML		
No. cases	52	10
IRR (95% CI)	Reference	0.81 (0.41–1.60)
CML		
No. cases	35	12
IRR (95% CI)	Reference	1.17 (0.60–2.28)
MM		
No. cases	143	26
IRR (95% CI)	Reference	0.92 (0.61–1.40)

NOTE: Analyses of snuff use were restricted to pure users of snuff.
*Adjusted for age and BMI.

Table 4. IRRs for BMI of leukemia subtypes and MM

	Level of BMI		
	18.5–25	25.1–30	>30
No. individuals	210,081	105,793	16,260
Person-years, accumulated (in millions)	4.74	2.31	0.33
ALL			
No. cases	25	19	3
IRR* (95% CI)	Reference	1.43 (0.76–2.69)	1.46 (0.43–4.98)
AML			
No. cases	112	94	18
IRR (95% CI)	Reference	1.07 (0.80–1.42)	1.30 (0.77–2.17)
CML			
No. cases	66	27	8
IRR (95% CI)	Reference	0.69 (0.43–1.09)	1.35 (0.64–2.84)
MM			
No. cases	256	236	27
IRR (95% CI)	Reference	1.04 (0.86–1.24)	0.70 (0.46–1.06)

NOTE: Due to the small number of subjects and number of cases in the stratum (n = 4,247), BMI of <18.5 is not presented in the table.
*Adjusted for age and tobacco use.

One cohort study (21) was restricted to older women, which limits the external validity of the study. Moreover, conflicting results could partly be explained by the use of random digit dialing when enrolling controls, causing selection bias (22). In addition, in several studies (19–22), height and weight were self-reported, which could potentially lead to misclassification bias.

Tobacco smoke is known to consist of moderately high levels of benzene. Benzene has been shown to cause chromosomal aberrations, which in turn could be of importance in the causal pathway of AML (8). The mechanisms by which obesity could play an etiologic role in leukemia development are still not fully clarified. One potential causative pathway could be through elevated levels of insulin and insulin-like growth factor-I (IGF-I) among obese individuals (35) IGF-I promotes cell proliferation and inhibits apoptosis as well as increases propagation of bone marrow progenitor cells and receptors for IGF-I, which have been shown present on explanted leukemic cells (36).

To our knowledge, this study is one of the largest of its kind, with high quality of exposure and outcome data and a thorough and extensive follow-up. The study design ensures a very high internal validity, which is not affected by issues of "'representativeness" of the study population. Because there are no strong effect modifiers that are related to social class, we believe that our study also ensures external validity.

Although this makes it a highly valuable cohort, there are also limitations that should not be disregarded. The number of incident cases in some strata is too low to get adequate statistical precision. Furthermore, the data on BMI and tobacco use were obtained only at baseline, which makes interpersonal variability over the study period possible. However, such fluctuations in exposure status are most likely to be nondifferential and would bias the results toward the null.

In conclusion, we confirmed the presence of an association, likely to be causal, between tobacco smoking and AML risk, whereas an association with ALL risk cannot be excluded. Tobacco smoking does not affect or modify the risk of CML or MM. Snuff use and BMI level do not seem to affect risk of leukemia or MM.

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