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Original Article

Smoking and subsequent risk of leukemia in Japan: The Japan Public Health Center-based Prospective Study

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ABSTRACT

Background: Cigarette smoking has been reported to be associated with an increased risk of leukemia. Most epidemiological evidence on the association between cigarette smoking and leukemia risk is from studies conducted in Western populations, however, and evidence from Asian populations is scarce.
Methods: We conducted a large-scale population-based cohort study of 96,992 Japanese subjects (46,493 men and 50,499 women; age 40–69 years at baseline) with an average 18.3 years of follow-up, during which we identified 90 cases of acute myeloid leukemia (AML), 19 of acute lymphoblastic leukemia (ALL), and 28 of chronic myeloid leukemia (CML). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a Cox regression model adjusted for potential confounders.
Results: When we adjusted for age, sex, and study area, our findings showed no significant association or increasing dose–response relationship between risk of AML and cigarette smoking overall. However, after further adjustment for body mass index and occupation, current smokers with more than 30 pack-years of cigarette smoking had a significantly increased risk of AML compared to never smokers among men (HR 2.21; 95% CI, 1.01–4.83). This increased risk was not clear among women.
Conclusions: Our results suggest that cigarette smoking increases the risk of AML in Japanese men. The associations of smoking with AML among women, and with CML and ALL among men and women, should be assessed in future studies.

Introduction

The association between cigarette smoking and risk of leukemia has been investigated in epidemiological studies. Recent meta-analyses showed that cigarette smoking is a significant risk factor for the development of acute myeloid leukemia (AML).[1,2] In 2004, the Surgeon General of the United States and the International Agency for Research on Cancer (IARC) reported that smoking is associated with an increased risk of AML,[3,4] while there is insufficient supporting evidence for the risk of lymphoid leukemia. Most epidemiological evidence on the association between cigarette smoking and leukemia risk has been obtained from studies in Western populations, however, and evidence from Asian populations is scarce.

Here, we investigated the effect of cigarette smoking on the risk of leukemia, including AML, acute lymphoblastic leukemia (ALL), and chronic myeloid leukemia (CML), in a large-scale population-based cohort study of a Japanese population.

Methods

Study population

The design of the Japan Public Health Center-based Prospective Study has been detailed elsewhere.[5] Briefly, the study was launched

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in 1990 for cohort I and in 1993 for cohort II. Cohort I covered five prefectural public health center (PHC) areas (Iwate, Akita, Nagano, Okinawa, and Tokyo) and cohort II covered six areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka). In the present analysis, we excluded all subjects in the Tokyo area because their incidence data were not available, and we also excluded some in the Osaka area because different definitions of the study population had been applied to them. A baseline survey was conducted in 1990 for cohort I and in 1993–1994 for cohort II, with a high response rate (81%). Participants with a self-reported history of cancer at baseline ($n = 2302$) were excluded. Subjects were followed from the date of the baseline survey to December 31, 2012. Residence status and survival were confirmed annually through the resident registry in each area, or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Data for subjects who had missing values for smoking status ($n = 524$) were excluded from this analysis, leaving a total of 96,992 subjects (46,493 men and 50,499 women) for analysis. The study protocol was approved by the institutional review boards of the National Cancer Center, Japan and Aichi Cancer Center Research Institute.

Outcome

Study outcomes were defined as the incidence of newly occurring leukemia diagnosed during the study period. Leukemia was identified using active patient notification from major local hospitals in the study area and data collection from population-based cancer registries, with approval. We used death certificate files, with permission, as a supplement. The proportion of cases where incidence was ascertained using death certificate only was 15.8% for total leukemia and 6.7% for all types of cancer. Leukemia was coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). We defined the ICD-O-3 topology code C42.1, with morphology codes 9840, 9861, 9866, 9867, 9873, 9874, 9875, 9891 and 9896 as AML; 9875 and 9863 as CML; and 9832, 9833, 9834 and 9835 as ALL. Chronic lymphocytic leukemia (CLL), hairy cell leukemia, prolymphocytic leukemia, and adult T cell lymphoma/leukemia (ATL) were excluded because they were classified into mature lymphoid neoplasms in ICD-O-3. Chronic myelomonocytic leukemia was also excluded because it was classified into myelodysplastic/myeloproliferative diseases. The earliest date of diagnosis was used for patients who developed multiple primary neoplasms at different times. We coded cases as multiple primaries when both a chronic and an acute neoplasm were diagnosed simultaneously or within 21 days according to the rules of the Surveillance Epidemiology and End Results (SEER) Program.[6]

Exposure data

Exposure data were based on a baseline self-administered questionnaire survey on various life-style factors, including smoking habit. Regarding smoking, subjects were categorized as never, former, or current smokers. In JPHC Study I, participants were asked whether they had ever smoked. If not, they were classified as never smokers. Ever smokers were further asked if they smoked at the time of the baseline survey. Those with positive and negative responses to the question were categorized into current smokers and former smokers, respectively. In JPHC Study II, participants were first asked whether they smoked at baseline. Subjects who reported smoking at baseline were defined as current smokers. Those who had quit smoking and did not smoke at baseline were requested to indicate the age at cessation, the number of cigarettes smoked per day during the smoking period, and the age at starting smoking. Those with or without responses to these questions were classified as former smokers or never smokers, respectively. Smoking intensity for current smokers and ever smokers was evaluated using pack-years, defined by multiplying the number of years of smoking by the number of cigarettes per day divided by 20. We classified current smokers using the two smoking intensity categories of <30 pack-years and ≥30 pack-years. We also classified ever smokers using the four smoking intensity categories of <10 pack-years, 10–19 pack-years, 20–29 pack-years, and ≥30 pack-years. Body mass index (BMI) was calculated from the self-reported height and weight by dividing the weight in kilograms by the square of height in meters.

Statistical analysis

Person-years for leukemia incidence were accrued from the date of the baseline survey until the date of occurrence of leukemia, emigration from the study area, death, or end of the study period, whichever came first. Subjects lost to follow-up were censored at the last confirmed date of presence in the study area. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model as a measure of association between the risk of leukemia associated with smoking categories at baseline (never smokers, former smokers, pack-years in current smokers [<30 and ≥ 30 pack-years], and pack-years in ever smokers [<10, 10–19, 20–29 and ≥ 30 pack-years]). We set never smokers as the reference category. However, when we performed analysis of ALL, we set never and former smokers as the reference category because no male never smoker was diagnosed with ALL during the follow-up period. We estimated two types of HRs: 1) adjusted for age at baseline (continuous), sex, and study area (10 PHC areas); and 2) adjusted for age at baseline, sex, BMI (<18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m^2), occupation (professional or office worker, sales clerk or other, farmer, manual laborer, unemployed and missing), and study area (10 PHC areas). We considered occupation as an indicator of individual socioeconomic conditions. The *p*-values for trends were assessed by assigning ordinal variables in each category. All statistical analyses were done using Stata version 13.1 software (Stata Corp., College Station, TX, USA), with a P value < 0.05 considered to be statistically significant.

Results

During 1,782,762 person-years of follow-up (average, 18.3 years) for the 96,992 subjects (46,493 men and 50,499 women), 90 AML cases (55 men and 35 women), 19 ALL cases (11 men and 8 women), and 28 CML cases (19 men and 9 women) were newly diagnosed. Baseline characteristics of study subjects according to smoking status are shown in Table 1. At baseline, 24.2%, 23.8%, and 52.1% of the men were never smokers, former smokers, and current smokers, respectively. In contrast, most of the women (92.4%) were never smokers, with only 1.5% and 6.1% being former smokers and current smokers, respectively. In pack-year categories, a smaller number of women were heavy smokers than men. Mean BMI was approximately 23 kg/m^2 in each smoking category in both men and women. Distributions of occupation at baseline are also shown in Table 1.

Table 2 shows the adjusted HRs for AML and CML by smoking category. When we adjusted for age, sex, and study area, we failed to observe a significant association or increasing dose–response relationship between AML risk and cigarette smoking overall. However, after further adjustment for BMI and occupation, current smokers with more than 30 pack-years of cigarette smoking had a significantly increased risk of AML compared to never smokers among men (HR 2.21; 95% CI, 1.01–4.83). This risk increase was not clear among women. An association with smoking was not

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