Cigarette Smoking and Nasopharyngeal Cancer : an Analysis of the Relationship According to Age at Starting Smoking and Age at Diagnosis

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To examine whether the association between smoking and nasophayngeal cancer varies according to age at starting smoking and age at diagnosis of the disease, we compared 113 men with nasopharyngeal cancer diagnosed between 31 and 59 years old who lived within eight cancer registry areas to 1,910 controls selected by random-digit telephone dialing. Compared to smoking which began at the age of 22 years or older, the risk estimates were 0.4 (95% confidence interval (CI) 0.2-0.9) and 0.8 (95%CI 0.4-1.5) for smoking begun at the ages of 18-21 and 17 years or younger, when adjusted for pack-years smoked and other potential confounders (p for trend > 0.8). In contrast, the risk estimates adjusted for age at starting smoking and other variables were 1.3 (95%CI 0.7-2.6), 1.9(95%CI 0.9-4.0) and 3.0(95%CI 1.4-6.2) for 15-29.9, 30-44.9 and 45 or over, relative to 15 or less pack-years smoked (p for trend < 0.005). The analyses were repeated for subgroups in terms of age at diagnosis. The relative risks of ever-smoking and the dose-effect relation between pack-years and the risk of the disease were not significantly different between men whose cancer was diagnosed at the age 49 or younger and those whose tumor was diagnosed between the ages 50 and 59. This study suggests that the magnitude of the risk for nasopharyngeal cancer may not vary significantly with the age at which smoking begins, and age at which the disease is diagnosed. *J Epidemiol*, 1997 ; 7 : 107-111.

age, case-control study, nasopharyngeal cancer, smoking

Age-related factors in carcinogenesis have been widely studied in animals and human beings [1]. It has been suggested that age is related to target-tissue sensitivity to the level of DNA damage, the efficacy and rate of its repair, and the proliferative activity of tissues[2]. Therefore, the effect of carcinogens may differ, depending upon age at exposure. On the other hand, carcinogenic mechanisms may be related to age at development of cancer. Hereditary effects and effects of other carcinogens may differ between patients with cancers developing at an earlier age and those presenting at an older age [3,4].

The smoking/nasopharyngeal-cancer association has been found in some previous investigations including ours [5-9]. Because of the possible relatedness of age to carcinogenesis, it is plausible to assume that the smoking/nasopharyngeal-cancer association may vary depending upon age at starting smoking and age at diagnosis. However, only two studies have ever addressed either age at starting smoking [10] or age at diagnosis of nasopharyngeal cancer [11]. In the present report, we provide additional data bearing on this question, using pathologically-confirmed new cases and considering more potential confounders.

MATERIAL AND METHODS

This study was based on the data from a case-control investigation conducted by the Selected Cancers Cooperative Study

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Group[12]. In the original study, tumors of interest included lymphoma, nasal cancer, nasopharyngeal cancer, primary liver cancer and sarcoma. Men diagnosed with these cancers during 1984-88 were eligible for the study if they were 31 to 59 years old and lived in the areas covered by eight cancer registries in the US (Atlanta, Detroit, San Francisco, Seattle, Miami, Connecticut State, Iowa State, and Kansas State). Control men, who were frequency-matched to cases with lymphoma (a tumor of most interest in the original study) by geographic area covered by cancer registry and 5-year date-of-birth intervals, were selected through random-digit telephone dialing.

The present analyses included as cases 113 men pathologically diagnosed with nasopharyngeal cancer. The histologic types of the cancers included squamous cell cancer (n=83), unspecified carcinoma (n=17), unspecified malignant lymphoma (n=8), diffuse histiocytic lymphoma (n=1), Hodgkin's disease with mixed cellularity (n=1), malignant melanoma (n=1), adenoid cystic carcinoma (n=1), and unspecified papillary cystadenocarcinoma (n=1). Two thousand, two hundred and ninety-nine men were identified to be eligible as controls through random-digit-dialing, among whom 83.1% completed the interview (n=1910) and were used in the analysis.

Information was collected primarily through telephone interviews. In-person interviews (6.2% of cases and 1.9% of controls) and next-of-kin interviews (9.7% of cases) were made when necessary or when a case had died. Primary data collection included demographic characteristics (date of birth, ethnic background, education level, marital status, religion preference, and family income), relevant medical history (malaria, mononucleosis, systemic lupus erythematosis, allergy, tonsillectomy, immunodeficiency, sinus problems, or nasal polyps), occupations (working with or around chemical solvents, wood, asbestos, or dust), exposures to radiation, pesticides or other chemical materials (chemotherapy, or nose drops or sprays), personal habits (smoking and alcohol consumption), drug abuse, and military service history.

In this study, we analyzed age at starting smoking and pack-years (daily number of packs of cigarettes smoked multiplied by the number of years the subject smoked.) in relation to nasopharyngeal cancer, using logistic regression[13, 14]. Age at starting smoking and intensity of smoking were adjusted for each other in the analyses because of their positive correlation [15]. We merged age groups with similar odds ratio (OR) estimates from preliminary analyses. As a result, three groups of age at starting smoking were formed: 22 or older, 18-21, and 17 years old or younger. Because there can be no value for age at starting smoking when pack-year is zero (non-smoking), it is impossible to estimate the risk of age at starting smoking relative to non-smoking while adjusting pack-year to zero. We therefore estimated the pack-year-adjusted odds of each group of age at starting smoking compared to its baseline exposure level (22 years or older) among smokers. A test for trend was used to examine whether the risks for the groups were significantly different from that of baseline level. The same rationale was applied when estimating the risks of pack-year adjusted for age at starting smoking. We also repeated the analyses, using the number of years smoked and the number of packs smoked per day instead of pack-years.

In our data, men with nasopharyngeal cancer were more likely to be Asian (27.4%) and less likely to be white (56.6%), compared with controls (3.5% and 81.5%, respectively). While 27-28% of cases had a college degree or $50,000 or more of annual household income, the corresponding proportions were 38-39% for controls. Cases also tended to be older than controls [9]. Therefore, age, ethnicity, educational level and annual income were included as covariables in models, in addition to the mutual adjustment of age at starting smoking and the intensity of smoking. We also chose as the potential confounders the variables that were significantly associated with the risk of nasopharyngeal cancer and that logically can be thought to confound the smoking-nasopharyngeal cancer relationship.

Subgroup analyses included restriction to nasopharyngeal squamous cell carcinoma or a certain range of age at diagnosis. For the latter, we divided study subjects into age groups of 31-49 and 50-59 years to avoid a small number of cases in each group. Odds ratio estimates were calculated for the two groups, respectively, and tests for heterogeneity of the OR estimates were performed.

RESULTS

There were 78.8% of cases and 66.8% of controls who had ever smoked cigarettes. Relative to non-smoking, the risk for men who started smoking at the age of 22 or older and smoked less than 15 pack-years (the baseline exposure levels for both variables) was 2.2 (95% Confidence interval (CI) 1.1-4.4). However, the relative risk adjusted for pack-years and other potential confounders was not increased with younger age at initiating smoking: the p-value for trend test was greater than 0.80 for the OR estimates comparing the younger age at exposure to the age 22 or older (Table 1). This tendency was similar when we controlled for the number of years or the number of packs per day that a man smoked, instead of pack-years. On the other hand, odds ratio estimate for the disease, adjusted for age at starting smoking, was consistently higher as pack-years increased (p for trend <0.005). The patterns in OR for pack-years were similar when only nasopharyngeal squamous cell carcinoma was analyzed as an outcome (table 1). Although the CI of the OR was wide, however, the risk tended to be higher for men who started smoking at the age of 17 or younger, compared with those who began smoking at older age.

We estimated odds ratios for the subgroups defined according to age at diagnosis, adjusted for the matching variables, the

Table 1. The odds ratio estimates[1] for nasopharyngeal cancer, according to age at starting smoking and pack-years, The Selected Cancers Study, 1984-1988.

Variable	Adjusted OR[2]	
	All histologic types (110 cases, 1890 controls)	Squamous cell carcinoma (80 cases, 1890 controls)
Age at starting smoking (year)		
>=22	1.0 (reference)	1.0 (reference)
18-21	0.4 (0.2-0.9)	0.8 (0.3-1.9)
<=17	0.8 (0.4-1.5)	1.4 (0.5-3.4)
	P for trend>0.80	*P for trend>0.20*
Pack-years		
<15	1.0 (reference)	1.0 (reference)
15-	1.3 (0.7-2.6)	1.1 (0.5-2.4)
30-	1.9 (0.9-4.0)	1.4 (0.6-3.3)
>=45	3.0 (1.4-6.2)	2.7 (1.2-6.3)
	P for trend>0.005	*P for trend>0.025*

[1] Odds compared to reference level of exposure; [2]Adjusted for year of birth, area covered by registry, existence of home phone, educational level, ethnic background, annual household income, growing in an urban/suburban environment, medical history (mononucleosis, tonsillectomy, sinus infection, other sinus problems, nasal polyps, and blood transfusion), exposure to asbestos or woodwork, and alcohol consumption in addition to the mutual adjustment of age at starting smoking and pack-years. The subjects with "unknown" on any of these variables were excluded.

Table 2. The odds ratio estimates[1] for nasopharyngeal cancer, according to age at diagnosis, age at starting smoking and pack-years, The Selected Cancers Study, 1984-1988.

Variable	Adjusted OR[2]	
	Age at diagnosis <50 years (66 cases, 1182 controls)	Age at diagnosis 50-59 years (44 cases, 709 controls)
Age at starting smoking (year)		
>=22	1.0 (reference)	1.0 (reference)
18-21	0.5 (0.2-1.5)	0.3 (0.1-0.8)
<=17	1.0 (0.4-2.6)	0.5 (0.2-1.4)
	P for trend>0.99	*P for trend>0.40*
Pack-years		
<15	1.0 (reference)	1.0 (reference)
15-	2.0 (0.8-4.9)	0.7 (0.2-2.2)
30-	1.7 (0.6-4.8)	1.5 (0.5-4.3)
>=45	5.7 (2.1-15.5)	1.3 (0.5-3.9)
	P for trend>0.005	*P for trend>0.20*

[1] Odds compared to reference level of exposure; [2]Adjusted for year of birth, area covered by registry, existence of home phone, educational level and ethnicity in addition to the mutual adjustment of age at starting smoking and pack-years.

existence of home phone, educational level and ethnicity. Compared to non-smoking, the risk of ever-smoking, adjusted for the potential confounders, was 1.5 (95% CI 0.8-2.8) and 2.3 (95% CI 0.9-5.9) for tumors diagnosed at the age of 31-49 and 50-59, respectively. The two OR estimates were not heterogeneous based on the test for the effect modification of age at diagnosis on smoking. Table 2 shows the results of age at starting smoking and pack-years for the two subgroups defined by age at diagnosis. The dose-effect relation in the risk associated with pack-years was more prominent among men whose cancer was diagnosed at the age of 31-49 years, while the ORs for smoking started at ealier ages, as compared with smoking started at the age of 22 years or older, tended to be lower among men with a tumor diagnosed between 50 and 59 years old. However, our tests of the effect modification of age at diagnosis on age at starting smoking or pack-years did not show that the differences were significant. The results were similar when more potential confounders (refer to Table 1) were controlled.

DISCUSSION

Our results do not support the hypothesis that an earlier age at starting smoking increases the overall risk of nasopharyngeal cancer. This contrasts with the results of Chow et al [10]. On the other hand, higher risks with increasing pack-years were still found while controlling for age at smoking initiation.

Failure to find a dose-effect relation between age at beginning smoking and the risk of nasopharyngeal cancer in our study is not unexpected. In the two epidemiological studies of the smoking-lung cancer association, in which age at starting smoking was analyzed with an adjustment for intensity of smoking, one found a higher risk of lung cancer associated with an earlier age at starting smoking [16] and the other did not show the association [17]. A possible explanation for the lack of association is that people who began smoking at an earlier age might inhale less deeply or be more likely to smoke filter cigarettes [18]. However, we do not exclude the possibility that the magnitude of the risk for nasopharyngeal cancer does not vary with age at starting smoking. The higher risks for nasopharyngeal cancer for higher pack-years smoked, while adjusted for age at smoking initiation, simply suggest that intensity of cigarette smoking has a stronger dose-response effect on the occurrence of the disease.

This study also does not suggest overall differences in the risk associated with smoking between tumors diagnosed at different ages, although the overall risk of smoking tended to be higher and the trends in the risk of nasopharyngeal cancer associated with pack-years smoked might be less prominent for tumors diagnosed at the age of 50-59 years. The latter result contrasts with that of another previous study in which the dose-response relation between smoking and the disease was more striking among people who were older [11]. More studies are needed to address the relationship between age at diagnosis and the smoking/nasophatyngeal-cancer association, using more nasopharyngeal cancer patients.

We are concerned about the effect of proxy interviews for deceased cases on the study results. If information about cigarette smoking including age at starting smoking is inaccurate for deceased cases for whom interviews with next-of-kin were carried out, the results might be biased. However, a low proportion of proxy interviews (9.7%) and the similar distributions in the smoking-related variables between proxy-interviews cases and the rest of cases suggest that the effects might not be substantial. However, insufficient study power due to a relatively small number of cases might exist for subgroup analyses using squamous carcinoma as an outcome or by age at diagnosis. These subgroup results, such as slightly higher risk of smoking at the age of 17 or younger, relative to that at older age, for nasopharyngeal squamous carcinoma, need to be confirmed in studies with more patients.

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