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Smoking, Snuff Dipping and the Risk of Amyotrophic Lateral Sclerosis – A Prospective Cohort Study

Fang Fang[a] Rino Bellocco[a, c] Miguel A. Hernán[b] Weimin Ye[a]

[a]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden;
[b]Department of Epidemiology, Harvard School of Public Health, Boston, Mass., USA;
[c]Department of Statistics, University of Milano-Bicocca, Milan, Italy

Key Words
Amyotrophic lateral sclerosis · Cigarette smoking · Snuff dipping

Abstract
Background: Little is known about the etiology of amyotrophic lateral sclerosis (ALS). The association between cigarette smoking, but not other types of smoking and snuff dipping, and the risk of ALS has been evaluated in several epidemiologic studies. The findings were inconclusive. ***Methods:*** We studied the association of smoking and snuff dipping with the risk of ALS in the Swedish Construction Workers Cohort, which includes 280,558 male construction workers enrolled between 1978 and 1993 with detailed information on tobacco use. Incident cases of ALS were identified through cross-linkage to the Swedish Inpatient Register. Relative risks and their corresponding 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model. ***Results:*** After a mean follow-up duration of 19.6 years, we identified 160 incident cases of ALS through 2004. Compared with non-tobacco use, the relative risk of ALS was 0.8 (95% CI 0.6–1.1) for tobacco smoking and 0.6 (95% CI 0.3–1.5) for snuff dipping, respectively. For tobacco smoking, further stratified analyses of smoking status or types of tobacco smoking did not reveal any excess risks in any strata. ***Conclusions:*** Our study provides no evidence that smoking or snuff dipping is associated with an increased ALS risk among men.

Introduction

Amyotrophic lateral sclerosis (ALS), a neurodegenerative disorder of motor neurons, is a highly lethal disease with a median survival time of about 1.5–3 years [1]. About 90% of ALS cases are sporadic, and little is known about its etiology [2]. In Sweden, mortality from ALS has increased steadily since the 1960s [3].

Cigarette smoke contains numerous neurotoxic substances, and thus cigarette smoking may be a risk factor for ALS. Epidemiological findings, mostly from retrospective case-control studies, are inconclusive [4–8], probably because of methodological differences and shortcomings [4–7]. In a recent cohort study, cigarette smoking was associated with a moderately increased risk of death from ALS in women, but not in men [9]. The relationship between snuff dipping, the most popular alternative to tobacco smoking in Sweden [10], and ALS risk has not been investigated.

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Weimin Ye, MD, PhD
Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Box 281
SE–171 77 Stockholm (Sweden)
Tel. +46 8 5248 6184, Fax +46 8 314 975, E-Mail weimin.ye@ki.se

We evaluated the association between cigarette smoking, snuff dipping and the risk of incident ALS in a large cohort study in Sweden.

Material and Methods

The Swedish Construction Workers Cohort, comprised mostly of male workers, was established using computerized data (from 1971 onward) by the Construction Industry's Organization for Working Environment, Safety and Health, a joint venture launched by construction trade unions and the Swedish Construction Employers' Association [11]. The organization provided outpatient medical services to construction workers throughout Sweden from 1969 to 1993. The basic units were stationary and mobile clinics, typically staffed by a few nurses and a physician. The main activity was preventive health check-ups; a questionnaire containing information about tobacco use was distributed meanwhile. Between 1971 and 1975, the questionnaire was simply self-administered, and between 1975 and 1977, it did not collect tobacco use information. Information about smoking and snuff dipping collected after 1977 was detailed and obtained through personal interviews by the nurses. Therefore, we included 300,637 workers who were first registered in the database during the period of 1978–1993 with detailed tobacco use information.

The national registration numbers assigned to all Swedish residents enabled us to ascertain incident ALS cases through record linkage to the Swedish Inpatient Register [12]. Because in Sweden private inpatient medical care is rare and the public health care system does not allow patients to use public hospitals outside their county of residence, the Inpatient Register effectively includes almost all the incident cases of ALS in each county. The completeness and correctness of the Swedish Inpatient Register are generally high. According to a study on hip fractures in Uppsala, Sweden, the overall underreporting rate of the register was less than 2% [13]. In a randomly selected sample, using diagnoses made by an expert panel based on the medical records as gold standard, the false-negative rates were 5, 7 and 3% and the false-positive rates 1, 2 and 2%, respectively, among diagnoses of trauma, ischemic heart disease and malignant tumors in the register [14]. The coverage of the Inpatient Register was 60% in 1969, 85% in 1983 and reached complete coverage in 1987. A complete coverage of the Inpatient Register in our study was defined as 2 years after the real completion time in each county to avoid possible prevalent ALS cases recorded at the beginning of the register. For workers who lived in a county without or with incomplete Inpatient Register coverage, cohort entry dates were reset to the date when the Inpatient Register was complete in that county if the worker did not move, or the date when the worker moved to a county with complete Inpatient Register.

Information on vital status and migration was ascertained through linkages to the nationwide Causes of Death Register or Migration Register. Each cohort member contributed person-time from the date of entry to the date of first ALS diagnosis, death, emigration, immigration to a county without or with incomplete Inpatient Register, or end of follow-up (December 31, 2004), whichever came first.

Of the 300,637 workers, we first excluded 14,982 female workers (5.0% of total), then 334 (0.1%) male workers with erroneous national registration numbers that did not match with those of any living, dead or emigrated persons, 3,924 (1.3%) without residence information, and 839 (0.3%) with observed inconsistencies among data from the registers (e.g., died or migrated before entry to the cohort). Thus, our final analyses included 280,558 (93.3%) male workers. On average, workers underwent 2.6 check-ups (range 1–9). Our analysis used exposure information collected at every worker's first registration into the cohort, which was on average 1 year earlier than the reset entry dates defined by complete Inpatient Register coverage. We did not update the smoking status during the follow-up period to avoid bias from missing data.

Age-standardized incidence rates (per 100,000 person-years) were obtained by applying the age-specific incidence rates observed in the six age categories (<40, 40–44, 45–49, 50–54, 55–59, 60+ years) of ALS within different exposure strata to a standard age distribution of the person-years experienced by the whole cohort. We used Cox proportional hazards regression models to estimate relative risks (RRs) and their corresponding 95% confidence intervals (CIs) after adjustment for the covariates, age (in 5-year categories) and county of residence (southern, middle and northern Sweden). We calculated the dose of tobacco in grams per day, assuming that one cigarette contained 1 g and one cigar 5 g of tobacco [15]. The daily pipe dose was derived from the weekly dose. The method based on Schoenfeld's partial residuals showed little indication of violation of the assumption of proportional hazards for any variables. Analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, N.C., USA).

Results

Among 280,558 construction workers, 66% of study subjects were younger than 40 years at entry (mean age at entry 35.5 years). Among these workers, 13.6% were pure snuff dippers, 37.7% pure smokers and 17.3% mixed smokers and snuff dippers. Snuff dipping was more common among young construction workers, while smoking was more common among older subjects (table 1). During a mean follow-up duration of 19.6 years, we documented 160 incident cases of ALS out of 5,505,849 person-years of observation (overall crude incidence rate = 2.91 per 100,000 person-years). Figure 1 shows the age-specific incidence rates of ALS; the incidence rate increased with age before 75 years and then dropped.

The age-standardized incidence rate of ALS was 3.50 per 100,000 person-years in non-tobacco users, 2.70 in tobacco smokers, and 1.64 in pure snuff dippers, respectively (table 2). Compared with non-tobacco use, the age-adjusted RR was 0.8 (95% CI 0.6–1.1) for tobacco smoking and 0.6 (95% CI 0.3–1.5) for pure snuff dipping. For tobacco smoking, further stratified analyses of smoking status and types of tobacco smoking did not reveal any

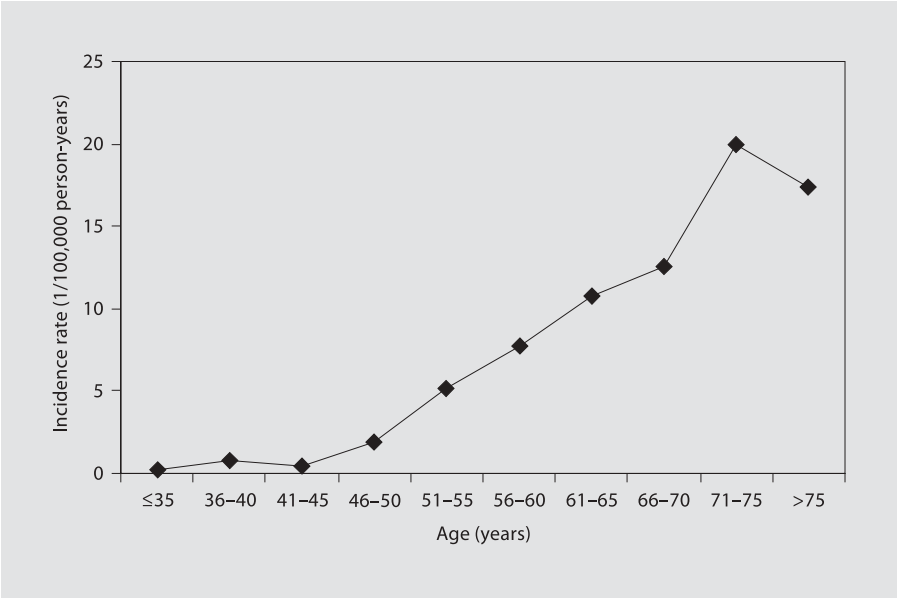

Fig. 1. Age-specific ALS incidence rates in men from the Swedish Construction Workers Cohort, 1978–1993, followed through 2004.

Table 1. Distribution of tobacco use at baseline by age and residence area in male workers from the Swedish Construction Workers Cohort, 1978–1993, followed through 2004

	Workers	Tobacco use status			
		non-tobacco use[1]	snuff dipping only	smoking only	both snuff dipping and smoking
Age at entry					
<40 years	185,209	62,235 (33.6)	34,104 (18.4)	57,491 (31.0)	31,379 (17.0)
40–49 years	47,455	12,690 (26.7)	2,209 (4.7)	23,274 (49.0)	9,282 (19.6)
50–59 years	33,073	9,133 (27.6)	1,075 (3.2)	17,483 (52.9)	5,382 (16.3)
>59 years	14,821	4,014 (27.1)	684 (4.6)	7,669 (51.7)	2,454 (16.6)
Residence area					
South	70,966	23,440 (33.0)	11,282 (15.9)	23,305 (32.9)	12,939 (18.2)
Middle	147,994	46,039 (31.1)	19,815 (13.4)	56,433 (38.1)	25,707 (17.4)
North	61,598	18,593 (30.2)	6,975 (11.3)	26,179 (42.5)	9,851 (16.0)
Total	280,558	88,072 (31.4)	38,072 (13.6)	105,917 (37.7)	48,497 (17.3)

Figures in parentheses are percentages.
[1] Never smoking and never snuff dipping.

excess risks. Further adjustment for the residence area had little influence on the observed associations (table 2).

Since it has been suggested that there might be a long preclinical period before ALS diagnosis [16], we reanalyzed our data after excluding the first 5 years of follow-up (142 ALS cases left). The results were not materially different from those derived from the main analyses. The age-adjusted RR was 0.7 (95% CI 0.5–1.1) for tobacco smoking and 0.6 (95% CI 0.2–1.5) for snuff dipping, respectively, compared with non-tobacco use.

Upon inspection of the Causes of Death Register (through December 31, 2003), we found that 103 (72%) of the 143 ALS cases identified from the Inpatient Register

Table 2. Association between tobacco use and ALS incidence in male workers from the Swedish Construction Workers Cohort, 1978–1993, followed through 2004

	Person-years	Cases	SIR (per 10^5 person-years)	Age-adjusted RR	Age and residence area-adjusted RR
Non-tobacco use	1,718,639	55	3.50	reference	reference
Tobacco smoking[1]	3,088,600	99	2.70	0.8 (0.6–1.1)	0.8 (0.6–1.1)
Smoking status					
Former	1,047,956	47	3.05	0.8 (0.6–1.2)	0.8 (0.6–1.2)
Current	2,040,644	52	2.45	0.7 (0.5–1.1)	0.7 (0.5–1.1)
Total amount of tobacco smoking[2]					
≤15 g/day	1,234,797	30	2.36	0.7 (0.5–1.1)	0.7 (0.5–1.1)
>15 g/day	716,620	21	2.54	0.8 (0.5–1.4)	0.8 (0.5–1.4)
Types of tobacco smoking[3]					
Pure smoking	2,106,140	69	2.54	0.7 (0.5–1.1)	0.7 (0.5–1.1)
Cigarette smoking	1,601,566	39	2.35	0.7 (0.5–1.1)	0.7 (0.5–1.1)
Cigar, pipe or mixed smoking	504,574	30	2.94	0.8 (0.5–1.3)	0.8 (0.5–1.3)
Mixed smoking and snuff dipping	974,957	30	3.10	0.9 (0.6–1.4)	0.9 (0.6–1.4)
Pure snuff dipping	698,611	6	1.64	0.6 (0.3–1.5)	0.6 (0.3–1.5)

Figures in parentheses are 95% CIs. SIR = Standardized incidence rate (standardized to the age distribution of the person-years experienced by the whole cohort).

[1] Any type of smoking (cigarette, cigar, pipe and mixed smoking), excluding pure snuff dipping.

[2] Because of missing data in the daily amount of cigarette, cigar or pipe smoking, we excluded 5,582 workers, contributing 89,227 person-years and 1 ALS case.

[3] Because of missing data in smoking types, we excluded 362 workers, contributing 7,503 person-years and no ALS case.

(through December 31, 2003) had died from ALS as the underlying cause. The mean (median) survival time from first diagnosis to death was 323.3 (147.0) days. We also discovered 32 additional individuals with ALS as the underlying cause of death. Of these 32 deaths, 7 had diagnoses of unspecified motor neuron diseases, 4 had diagnoses of suspected ALS, and 21 had other diagnoses or no records in the Inpatient Register. Although we decided not to include these potential ALS cases in our main analyses (because, in contrast to diagnoses detected through the Inpatient Register, there is no guarantee that a neurologist was involved in the diagnostic assessment), their inclusion did not materially change our results (data not shown).

Discussion

In this large prospective cohort study, we did not find an increased risk of ALS among male tobacco users, either smokers or snuff dippers, compared with non-users. The age-specific incidence rates of ALS in our cohort were comparable with those reported previously [17]. The small number of women in this cohort precluded the possibility to explore the relation between tobacco use and risk of ALS among women.

Several studies, mostly case-control studies, have investigated the association between cigarette smoking and risk of ALS [4–8]. The results of these studies are inconclusive, perhaps due to the relatively small sample sizes, the potential selection and recall biases, and the pooling of male and female individuals [4–7]. Recently, a prospective cohort study [9] estimated that the relative risks of ALS among current smokers compared with never-smokers were 1.67 (95% CI 1.24–2.24) in women and 0.69 (95% CI 0.49–0.99) in men.

Due to the prospective study design, recall bias might have had little influence on our results. However, we did not have enough information for adjustment of potential confounders, like social economic status and alcohol consumption, but adjustment of these factors in previous studies [2, 5, 7, 9] did not significantly change the observed association between smoking and risk of ALS. In addition, our results are based on a relatively large sample

size and the actual diagnosis of ALS rather than death from ALS. The short interval between diagnosis and death from ALS may raise some concern about delayed ascertainment of ALS cases. However, tobacco users generally have a larger chance to be hospitalized, thus a higher possibility of being identified via the Inpatient Register. This differential ascertainment would have led to upwards bias in the estimate. Our finding of a null association allays such concern. Finally, the decision not to update smoking status may have resulted in some small bias towards the null.

In conclusion, our findings provide no evidence to support that smoking or snuff dipping increases ALS risk in men. The search for possible causes of ALS among genetic or environmental (non-smoking-related) factors may be a more fruitful strategy.

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