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Population-Based Case-Control Study of Amyotrophic Lateral Sclerosis in Western Washington State. I. Cigarette Smoking and Alcohol Consumption

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The associations of cigarette smoking and alcohol consumption with the risk of amyotrophic lateral sclerosis (ALS) were investigated in a population-based case-control study conducted in three counties of western Washington State from 1990 to 1994. Incident ALS cases (n = 161) were identified and were matched to population controls (n = 321) identified through random digit dialing and Medicare enrollment files. Conditional logistic regression analysis was used to compute odds ratios adjusted for age, gender, respondent type, and education. The authors found that alcohol consumption was not associated with the risk of ALS. Ever having smoked cigarettes was associated with a twofold increase in risk (alcohol-adjusted odds ratio (OR) = 2.0, 95% confidence interval (CI): 1.3, 3.2). A greater than threefold increased risk was observed for current smokers (alcohol-adjusted OR = 3.5, 95% CI: 1.9, 6.4), with only a modestly increased risk for former smokers (alcohol-adjusted OR = 1.5, 95% CI: 0.9, 2.4). Significant trends in the risk of ALS were observed with duration of smoking (p for trend = 0.001) and number of cigarette pack-years (p for trend = 0.001). The finding that cigarette smoking is a risk factor for ALS is consistent with current etiologic theories that implicate environmental chemicals and oxidative stress in the pathogenesis of ALS. *Am J Epidemiol* 2000;151:156–63.

alcohol drinking; amyotrophic lateral sclerosis; case-control studies; epidemiologic factors; risk factors; smoking

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is the most common motor neuron disease. The pathologic hallmark of ALS is the selective death of motor neurons in the brain and spinal cord that innervate skeletal muscles, with clinical symptoms of progressive weakness, muscle wasting, and spasticity. The apparent selectivity for motor neurons remains unexplained. Treatments that definitively alter the course of this devastating disease are lacking, and median survival time after clinical onset is 2–3 years (1). Although basic research has made exciting recent progress in delineating genetic factors involved in the development of ALS (2, 3), little research exists to determine whether lifestyle factors such as cigarette smoking, alcohol consumption, or diet influence the risk of developing this fatal motor neuron disease.

There have been relatively few case-control investigations of ALS, in part because of the rarity of the disease and the difficulties in assembling a large series of cases for study. Previous case-control studies have focused largely on the potential etiologic role of factors such as occupational exposures, fractures, and electric shock (4, 5–11). Despite the widely held view that environmental exposures are likely to contribute to the risk of neurodegenerative disorders, only a few studies have investigated lifestyle factors such as smoking and alcohol consumption (4, 7, 8, 12–15). None of the studies reported statistically significant associations with cigarette smoking or alcohol consumption; however, several methodological considerations may have limited the ability of these studies to detect associations. These include small sample sizes; the use of hospital control groups in which the frequency of smoking was high; and the use of spouse and/or friend controls, which may have introduced overmatching with respect to tobacco use and alcohol consumption.

Our objective was to investigate the associations of cigarette smoking and alcohol consumption with the risk of ALS by conducting a population-based case-control study of incident ALS cases in three counties of western Washington State.

MATERIALS AND METHODS

Study population

The study design and methods were described in prior publications (16–18). During a 4-year period

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Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; OR, odds ratio.

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beginning in 1990, we sought to identify all incident cases of ALS occurring in three counties of western Washington State (King, Pierce, and Snohomish). Potential cases of ALS were identified through a surveillance system consisting of multiple overlapping case ascertainment sources, including all practicing neurologists in the three-county region, the Muscular Dystrophy Association, and Muscular Dystrophy Association-supported clinics for ALS patients in the Seattle and Tacoma regions of western Washington State. Cases were also identified as a result of referrals from medical examiners, physiatrists, neurosurgeons, neuroradiologists, neuropathologists, and hospice organizations in the three-county region.

To be considered eligible, patients had to be residents of one of the three counties, aged 18 years or older, and newly diagnosed with ALS during the 4-year study period (16). All patients had been diagnosed by at least one neurologist, and their medical records were subsequently reviewed by the study neurologist to confirm the case definition. The case definition required patients to have a progressive motor neuron disease that affected both upper and lower motor neurons (i.e., classic ALS), lower motor neurons alone (i.e., progressive muscular atrophy), or bulbar motor neurons alone (i.e., progressive bulbar palsy). The latter two conditions are clinical subtypes of ALS classified according to the early clinical symptoms of the disease; patients with these variants ultimately demonstrate both upper and lower motor neuron involvement (1). Patients with primary lateral sclerosis (i.e., evidence of upper motor neuron involvement only) were excluded, as were patients whose diagnosis of ALS changed during the year following the initial diagnosis. To apply the same exclusion criteria as those applied for controls, we excluded cases who lacked a telephone or who did not speak English.

Two controls were matched to each case on gender and age within 5 years. One of two methods was used to identify controls from the base population. Because more than 95 percent of the region's households have telephones, random digit dialing was used to locate eligible controls, as detailed previously (17, 18). Random digit dialing proved to be inefficient for identifying elderly controls; therefore, partway through the study, we adopted an alternate strategy of using Medicare eligibility lists to identify controls older than age 65 years. Medicare eligibility lists for the target counties were obtained from the Health Care Financing Administration. Potential controls were selected randomly from the lists according to age and gender, and they were sent letters explaining the study and requesting their participation. Potential controls who did not speak English were excluded. The study was approved by the Human Subjects Committee of the University of Washington.

Over the 4-year study period, 180 newly diagnosed ALS patients met the case definition criteria, and 174 (97 percent) of them agreed to participate in the case-control study. The protocol for random digit dialing to identify potential controls required a minimum of nine calls (three weekday, three evening, three weekend) before a telephone number could be abandoned. A total of 4,858 residential numbers were reached (approximately 52 percent of the calls yielded residences), and persons in 4,209 (87 percent) of these households allowed a screening interview to determine whether a household member was eligible for the study. All 262 eligible controls identified by this method were invited to participate in the study, and 227 (87 percent) agreed. Of the 202 eligible controls who were identified from the Medicare eligibility lists, 179 were located by using the address information supplied by the Health Care Financing Administration; of these, 121 (68 percent) agreed to participate in the study. The combined response rate for eligible controls identified and contacted by using both methods was 79 percent (348/441). Twenty ALS cases died before interview; for each of these cases and their matched controls, information was obtained from a proxy respondent.

Data collection

Professional interviewers conducted structured in-person interviews to collect exposure data from study subjects. The interview included information on demographic factors, detailed cigarette smoking history, residential and occupational history, physical trauma and physical activity, height and weight, medical antecedents, and family history of neurodegenerative disorders. To exclude time periods that were not relevant to disease etiology, all questions referred to the time period before an assigned reference date. For each case, the reference date was the month and year of first ALS diagnosis. For each control, the reference date was the same as that for the matched case. Throughout the interview, a lifetime calendar of major personal events was used to enhance the completeness and accuracy of subjects' autobiographic recall. Questions pertaining to cigarette smoking included detailed information on whether the subject had ever smoked cigarettes (defined as having smoked 100 or more cigarettes during his or her lifetime), duration of cigarette smoking, average daily number of cigarettes smoked, and age at which smoking ceased (if applicable). From these variables, exposure measures were constructed for broad smoking categories (never, former, current), cigarette pack-years (number of years of smoking multiplied by average number of cigarettes

smoked per day divided by 20), and time since cessation of cigarette smoking (if applicable).

Alcohol consumption and caffeine intake were assessed by using a self-administered semiquantitative food frequency questionnaire (the National Cancer Institute's Health Habits and History Questionnaire) (19), in which cases and controls reported information about their consumption of 98 food items. For each case, alcohol and caffeine consumption habits were assessed during a 1-year period beginning 1 year prior to the onset of symptoms. The same dietary reference date was used for the two matched controls. This method was chosen to restrict the assessment to a time period prior to the onset of any significant biologic effects of ALS that could have affected lifestyle habits.

Information on caffeine intake was obtained by asking about the usual frequency of consumption and the serving size of caffeinated coffee, tea, and soft drinks. Information on alcohol consumption included the usual frequency of consumption and the serving size of wine, beer, and hard liquor. Estimates of caffeine and alcohol content were computed by using the University of Minnesota's Nutrient Data System, a commercially available nutrient software system (20). This system assigned 12.8 g of alcohol for each 12 ounce (355 ml) can of beer, 13.8 g of alcohol for each 6 ounce (177 ml) glass of wine, and 14.0 g of alcohol for each 1.5 ounce (44 ml) shot of liquor. Average daily alcohol consumption was computed by summing alcohol consumption from all three sources (beer, wine, and liquor). This average was divided by 14, the number of grams in an average drink, and grouped into three categories of consumption: nondrinker, less than or equal to two drinks per day, and more than two drinks per day. Measures were constructed to examine the associations by type of alcohol (beer, wine, liquor). For example, the beer measure was constructed by classifying beer drinkers into two categories of consumption (<1 beer/day, >1 beer/day) and comparing them with nondrinkers (referent group) and with persons who consumed other types of alcohol but not beer. Similar measures were constructed for wine and liquor consumption.

Information regarding alcohol consumption was available for all subjects who completed the food frequency questionnaire: 161/174 (93 percent) of the cases and 321/348 (92 percent) of the controls. The relation of cigarette smoking and alcohol consumption to the risk of ALS was evaluated for the subjects with complete information on both factors (161 cases and 321 controls). Of note, the prevalence of former and current cigarette smokers among cases and controls who did not complete the food frequency questionnaire was virtually identical to that of subjects who completed the questionnaire, indicating that restriction of analyses to subjects with complete information did not introduce a selection bias.

Data analysis

Statistical analyses were performed by using SAS (21) and EGRET (22) software. Case-control data were analyzed by using conditional logistic regression (23), a method that took into account the individual matching on age, gender, and respondent type (self vs. proxy). Statistical tests of the regression estimates were based on the chi-squared approximation for the likelihood ratio test statistic (24), and 95 percent confidence intervals were based on Wald's test. In our analyses of the relation between cigarette smoking and ALS, education and alcohol consumption were included in all logistic regression models to control for confounding. Other factors that were associated with disease risk in the overall study or that were related to smoking habits (e.g., dietary intake of fat and fiber, pesticide exposure, body mass index) were also evaluated as potential confounders. Because proxy respondents provided data for 11 percent of the cases and controls, statistical analyses were conducted according to published recommendations for data sets that include information from both self- and proxy respondents (25, 26). Analyses were initially conducted separately for the self-respondent and proxy-respondent strata, but as no significant differences were observed in effect estimates for these two strata, respondent type was included as a confounder in all analyses.

RESULTS

Table 1 compares the demographic and anthropometric characteristics of cases and controls. Because the study design matched on age, gender, and respondent type, the two groups were very similar with respect to those factors. Only a small number of subjects in both groups belonged to racial or ethnic groups other than non-Hispanic Whites; this finding reflects the composition of the underlying geographic region. The ALS cases had fewer years of formal education than the controls (mean, 13.5 years among cases vs. 14.0 years among controls), and cases were less likely to have a high school education (odds ratio (OR) = 0.7, 95 percent confidence interval (CI): 0.3, 1.3) or education beyond high school (OR = 0.4, 95 percent CI: 0.2, 0.8). Because a significant trend was observed for formal years of education (OR = 0.91 for each year of formal education, 95 percent CI: 0.84, 0.99; $p < 0.05$), this variable was included as a covariate in all analyses.

The proportion of drinkers was slightly higher among controls (59.8 percent) than among ALS cases (54.7 percent); however, alcohol consumption was not significantly related to the risk of ALS (table 2). A

TABLE 1. Demographic and anthropometric characteristics of ALS* cases and of controls, western Washington State, 1990–1994

Characteristic	ALS cases (n = 161)†			Controls (n = 321)†		
	No	%	Mean (SE*)	No.	%	Mean (SE)
Gender						
Male	89	55.3		171	53.3	
Female	72	44.7		150	46.7	
Age (years)			61.4 (1.0)			61.7 (0.7)
Respondent type						
Self	143	88.8		285	88.8	
Proxy	18	11.2		36	11.2	
Race						
Non-Hispanic White	152	96.2		304	95.6	
Other	6	3.8		14	4.4	
Education						
Less than high school	23	14.3		26	8.1	
High school	52	32.3		88	27.4	
More than high school	86	53.4		207	64.5	
Height‡ (inches§)			66.8 (0.36)			67.5 (0.30)
Weight‡ (pounds¶)			164.0 (2.89)			162.8 (1.88)
Body mass index‡ (kg/m^2)			25.5 (0.32)			25.0 (0.22)

* ALS, amyotrophic lateral sclerosis; SE, standard error.
† Because a few values were missing for some variables, the numbers may not sum to the total number of subjects in this category.
‡ Based on self-reported data for the 5-year period prior to the reference date (i.e., 5 years prior to ALS diagnosis for an ALS case and his or her matched controls).
§ 1 inch = 2.54 cm.
¶ 1 pound = 0.45 kg.

slight inverse association of alcohol consumption with ALS was present, but a trend with increasing numbers of drinks was not significant. When the associations with alcohol intake were examined according to type of alcohol, effect estimates were lowest for the highest levels of beer consumption and wine consumption but were not statistically significant.

Subjects who had ever smoked cigarettes had a twofold increased risk of ALS (table 3). Compared with never smokers, former smokers had a modestly increased risk, and current smokers had a significantly increased risk. The positive association of current smoking with ALS was observed for both men (education- and alcohol-adjusted OR = 3.7, 95 percent CI: 1.6, 8.4) and women (adjusted OR = 3.2, 95 percent CI: 1.3, 8.0), but the association with former smoking was observed for women only (adjusted OR = 2.3, 95 percent CI: 1.1, 4.9), not for men (adjusted OR = 1.0, 95 percent CI: 0.5, 2.0).

Significant dose-response trends were observed with duration of smoking (p = 0.001) and cigarette pack-years (p = 0.001) (table 3). To evaluate the timing- and dose-related aspects of the smoking association, we examined the effect of pack-years separately for former and current smokers (table 3, combination recency and dose measure). A dose-related effect of pack-years was not apparent for former smokers or current smokers. With respect to time since last cigarette for former smokers, the relation between time since last cigarette and ALS did not conform to an orderly trend. These analyses suggest that current cigarette smoking was the most important aspect related to disease risk. When the case and control ever smokers were compared, a lower proportion of the cases (56 percent) than the controls (76 percent) had quit smoking ($p < 0.001$).

Because of the correlation between cigarette smoking and alcohol consumption, we evaluated alcohol as a confounder of the association with smoking. The smoking-associated odds ratios increased after adjustment for alcohol consumption. This change occurred because the cases included more nondrinkers for whom the prevalence of smoking was lower than among drinkers (table 2). Adjustment for this effect predictably increased the magnitude of the smoking-associated odds ratios (table 3). Alcohol consumption was also examined as a potential effect modifier of the association with smoking, and the magnitude of the smoking-associated odds ratios was comparable for drinkers and nondrinkers (data not shown). Statistical adjustment for other potential confounders, including pesticide exposure, body mass

TABLE 2. Odds ratios for the association of alcohol consumption with the risk of ALS*, western Washington State, 1990–1994

Characteristic	ALS cases (n = 161)†		Controls (n = 321)†		Adjustment for education‡		Adjustment for education and smoking§	
	No.	%	No.	%	OR*	95% CI*	OR	95% CI
Alcohol consumption¶								
Nondrinker	73	45.3	129	40.2	1.0		1.0	
Drinker, ≤2 drinks/day	71	44.1	164	51.1	0.8	0.5, 1.3	0.8	0.5, 1.2
Drinker, >2 drinks/day	17	10.6	28	8.7	0.9	0.5, 1.8	0.7	0.3, 1.4
p for trend						0.49		0.22
Beer consumption								
Nondrinker	73	45.3	128	40.1	1.0		1.0	
Drinker, not beer#	32	19.9	67	21.0	0.9	0.5, 1.4	0.8	0.4, 1.3
Beer drinker, ≤1 beer/day	45	28.0	95	29.8	0.9	0.5, 1.5	0.9	0.5, 1.4
Beer drinker, >1 beer/day	11	6.8	29	9.1	0.6	0.3, 1.4	0.5	0.2, 1.2
p for trend						0.30		0.20
Wine consumption								
Nondrinker	73	45.6	128	40.1	1.0		1.0	
Drinker, not wine#	35	21.9	50	15.7	1.2	0.7, 2.2	1.2	0.7, 2.2
Wine drinker, ≤1 glass/day	41	25.6	108	33.9	0.7	0.4, 1.1	0.6	0.4, 1.0
Wine drinker, >1 glass/day	11	6.9	33	10.3	0.6	0.3, 1.3	0.5	0.2, 1.1
p for trend						0.08		0.03
Hard liquor consumption								
Nondrinker	73	45.6	128	40.1	1.0		1.0	
Drinker, not hard liquor#	39	24.4	82	25.7	0.9	0.5, 1.4	0.8	0.5, 1.4
Liquor drinker, ≤1 shot/day	32	20.0	82	25.7	0.7	0.4, 1.2	0.6	0.4, 1.1
Liquor drinker, >1 shot/day	16	10.0	27	8.5	1.0	0.5, 2.1	0.9	0.4, 1.9
p for trend						0.52		0.28

* ALS, amyotrophic lateral sclerosis; OR, odds ratio; CI, confidence interval.
† Because a few values were missing for some variables, the numbers may not sum to the total number of subjects in this category.
‡ Conditional logistic regression model included education (years).
§ Conditional logistic regression model included education (years) and cigarette smoking (pack-years).
¶ Average daily alcohol consumption in drinks per day (see text).
# Drinkers who did not consume this particular type of alcohol but who consumed other alcoholic beverages.

index, caffeine intake, and dietary factors (i.e., intake of fat, fiber, antioxidants), did not alter the associations with cigarette smoking. No relation was observed between caffeine intake and the risk of ALS (relative to the lowest quartile of caffeine intake, the odds ratios adjusted for age, gender, respondent type, education, and smoking were 0.9, 1.0, and 0.9 for the second through fourth quartiles of caffeine intake, respectively).

We considered potential effect modifiers of the association with smoking, including age and family history of ALS. The magnitude of the association between smoking and ALS did not vary according to age. Very few cases and controls had one or more relatives who were affected with ALS (nine cases and six controls), and exclusion of subjects with a positive family history did not materially alter the results.

DISCUSSION

In this population-based study, we observed a significant association between cigarette smoking, but not alcohol consumption, and the risk of ALS. Significant trends in the risk of ALS were observed with duration of smoking and number of cigarette pack-years. While having ever smoked was associated with a twofold increase in risk, the largest effect was due to the recent effects of cigarette smoking, with a greater than threefold increased risk for current smokers. The effects of current smoking were observed for both men and women and were not confounded by other disease-associated factors such as pesticide exposure or diet.

Although the hypothesis that environmental toxicants could contribute to disease risk is not new, few previous case-control studies have used detailed methods to assess the relation between lifestyle exposures and the risk of ALS. Several published studies collected some information related to cigarette smoking or alcohol consumption (4, 7, 8, 12–15); however, these studies focused on other risk factors and did not include detailed measures of tobacco use and alcohol consumption. None reported statistically significant associations with cigarette smoking or alcohol consumption,

TABLE 3. Odds ratios for the association of cigarette smoking with the risk of ALS*, western Washington State, 1990–1994

Characteristic	ALS cases (n = 161)†		Controls (n = 321)†		Adjustment for education‡		Adjustment for education and alcohol consumption§	
	No.	%	No.	%	OR*	95% CI*	OR	95% CI
Broad smoking category								
Never smoked	52	32.5	149	49.6	1.0		1.0	
Ever smoker	108	67.5	171	53.4	1.9	1.2, 2.9	2.0	1.3, 3.2
Former smoker	61	38.1	130	40.6	1.4	0.8, 2.2	1.5	0.9, 2.4
Current smoker	47	29.4	41	12.8	3.3	1.8, 5.8	3.5	1.9, 6.4
Duration of smoking								
Never smoked	52	32.7	149	46.7	1.0		1.0	
Smoked <20 years	35	22.0	67	21.0	1.5	0.9, 2.6	1.6	0.9, 2.7
Smoked ≥20 years	72	45.3	103	32.3	2.2	1.3, 3.5	2.3	1.4, 5.8
p for trend						0.003		0.001
Cumulative pack-years								
Never smoked	52	32.7	149	46.9	1.0		1.0	
<20 pack-years	47	29.6	84	26.4	1.6	1.0, 2.7	1.7	1.0, 2.9
≥20 pack-years	60	37.7	85	26.7	2.1	1.3, 3.6	2.3	1.4, 3.9
p for trend						0.003		0.001
Combination recency and dose								
Never smoked	52	32.7	149	46.9	1.0		1.0	
Former, <20 pack-years	34	21.4	77	24.2	1.3	0.7, 2.2	1.3	0.8, 2.3
Former, ≥20 pack-years	26	16.4	51	16.0	1.5	0.8, 2.8	1.6	0.9, 3.0
Current, <20 pack-years	13	8.2	7	2.2	4.4	1.6, 12.2	4.9	1.7, 13.7
Current, ≥20 pack-years	34	21.4	34	10.7	2.9	1.5, 5.6	3.2	1.6, 6.2
Time since last cigarette								
Never smoked	52	32.7	149	46.7	1.0		1.0	
Last smoked >20 years ago	31	19.5	60	18.8	1.6	0.9, 2.9	1.7	0.9, 3.1
Last smoked 10–20 years ago	12	7.6	38	11.9	0.8	0.4, 1.8	0.9	0.4, 1.9
Last smoked <10 years ago	17	10.7	31	9.7	1.6	08, 3.2	1.7	0.8, 3.4
Current smoker	47	29.6	41	12.9	3.2	1.8, 5.8	3.5	1.9, 6.4
p for trend						<0.001		<0.001

* ALS, amyotrophic lateral sclerosis; OR, odds ratio; CI, confidence interval.
† Because a few values were missing for some variables, the numbers may not sum to the total number of subjects in this category.
‡ Conditional logistic regression model included education (years).
§ Conditional logistic regression model included education (years) and alcohol consumption (nondrinker, ≤2 drinks/day, >2 drinks/day).

but small sample sizes (typically fewer than 100 cases) may have limited the statistical power of these studies. Other methodological features could have accounted for the failure to observe an association with cigarette smoking. Some studies used hospital control groups, which are known to have a higher prevalence of smoking than population controls do. Other studies used control groups such as spouses, friends, or neighbors, which may have introduced overmatching with respect to smoking history (4, 8, 15). Furthermore, most studies that have evaluated the association with smoking have included prevalent cases and have not clearly used methods to include only the smoking history prior to the clinical diagnosis of ALS.

One limitation of our study was the method used to assess alcohol consumption. Questions regarding drinking history were not included in the structured risk-factor interview, and the only method used to assess alcohol intake was the self-administered food frequency questionnaire. As a result, we were able to assess alcohol intake for only 1 recent year of adult life; information on lifetime drinking habits was not obtained. Nevertheless, to our knowledge this study is the first to collect and analyze information on specific types of alcohol (beer, wine, and liquor). A second limitation was the apparent low response rate among the controls older than age 65 years who were identified through the Medicare rolls. The response rate among

eligible Medicare controls was 68 percent compared with 87 percent among eligible controls identified through random digit dialing. Despite these differences, the magnitudes of the associations with smoking were similar for the controls identified by using both methods, suggesting that a nonresponse bias due to the inability to reach some Medicare controls was not likely to have influenced our study results.

A third potential limitation is that the prevalence of cigarette smoking could have been higher among eligible controls from both sources (random digit dialing and Medicare) who chose not to participate in the study. As a result, the smoking-associated odds ratios could have been elevated. A selection bias would have to be strong to eliminate the association that was observed with current cigarette smoking in our study. Even if the prevalence of current smoking was 50 percent higher among controls who refused participation than among those who participated, a more than 2.5-fold increased risk associated with current smoking would have been observed.

Despite these limitations, our study had several strengths that distinguishes it from previous epidemiologic studies of ALS. First, we enrolled a larger number of ALS cases than did all previous studies, obtained a high participation rate among eligible cases (97 percent), and improved the precision by selecting two controls for every case. Second, by using a population-based design, we avoided the problems associated with biased case selection from hospitals or referral centers and the attendant difficulties in identifying appropriate controls in such studies. Third, enrollment of incident rather than prevalent cases enabled us to investigate factors important in disease etiology and to assess exposures prior to the clinical diagnosis of ALS. Fourth, in contrast to the few published studies that have assessed cigarette smoking, we collected and analyzed detailed information regarding dose- and timing-related aspects of smoking.

At least two mechanisms exist by which cigarette smoke could contribute to the risk of ALS, one direct and one indirect. First, the chemical constituents of cigarette smoke could cause direct toxic injury to motor neuron cell components; however, naming a specific chemical culprit would be difficult, since more than 3,800 compounds have been identified in cigarette smoke (27). One often-unrecognized toxic constituent of tobacco is pesticides. Unlike with other crops, pesticides applied to tobacco crops are not subject to government regulation. Possibly, pesticides in tobacco could influence the risk of ALS, since pesticide exposure in the occupational setting was shown to be related to the risk of ALS in the overall study (age-, gender-, education-, and smoking-adjusted OR = 2.0, 95 percent CI: 1.1, 3.5).

Formation of free radical species during metabolism of the chemical constituents of cigarette smoke (28) is the second mechanism. Evidence is accumulating that oxidative stress may play an important role in the pathogenesis of ALS (29–31). Approximately 20 percent of patients with familial ALS have a missense mutation of the gene that codes for copper/zinc superoxide dismutase (32), an endogenous enzyme responsible for scavenging superoxide radicals in the body's tissues. Although superoxide dismutase gene mutations are rarely observed in ALS cases who do not have affected family members, it is plausible that impaired defenses against free radical toxicity may also play a role in the sporadic form of ALS. Mutant superoxide dismutase enzyme has been postulated to induce cell death either by catalyzing harmful peroxidase reactions (33) or by causing superoxide to bind with substrates (e.g., nitric oxide) that lead to the production of damaging nitrogen radical species (34, 35). Of potential relevance to the association with smoking is that the gas constituent of cigarette smoke is the largest exogenous source of nitric oxide to which humans are exposed (36). Many of the other chemical constituents of cigarette smoke (e.g., quinones, aldehydes, ketones, phenols, and polynuclear aromatic hydrocarbons) can generate harmful free radicals during metabolism (27). If the volume of free radical species exceeds the antioxidant capacity of a neuron, then damage may result to cellular constituents such as membrane lipids, DNA, and protein. Free radicals may produce additional deleterious effects by stimulating the release of excitatory amino acids such as glutamate, possibly contributing to a cascade of excitotoxic-induced cell injury (37).

The finding of a positive association between cigarette smoking and the risk of ALS is in contrast to the often-cited inverse association of smoking with Parkinson's disease, another neurodegenerative disorder for which smoking is associated with an approximate 50 percent reduction in risk among ever smokers compared with never smokers (38, 39). Nevertheless, ALS is a neurodegenerative disorder that affects a different population of nerve cells—motor neurons—and is likely to be characterized by distinct causal factors. The strength of the association and the apparent dose- and timing-related effects suggest that the relation between cigarette smoking and ALS could be causal; however, this hypothesis needs to be evaluated in further epidemiologic studies. The findings are biologically plausible and are consistent with two current etiologic theories of ALS pathogenesis that implicate environmental toxicants and oxidative stress in the pathogenesis of ALS. The association with current or recent smoking suggests that the aging motor neuron may be susceptible to the deleteri-

ous effects of toxic constituents of cigarette smoke or to smoking-induced oxidative stress.

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