American Journal of Epidemiology

Vol. 175, No. 12
DOI: 10.1093/aje/kwr465
Advance Access publication:
April 19, 2012

Original Contribution

Role of Tobacco Use in the Etiology of Acoustic Neuroma

Sadie Palmisano, Judith Schwartzbaum, Michaela Prochazka, David Pettersson, Tommy Bergenheim, Rut Florentzson, Henrik Harder, Tiit Mathiesen, Gunnar Nyberg, Peter Siesjö, and Maria Feychting*

* Correspondence to Dr. Maria Feychting, Institute of Environmental Medicine, Karolinska Institutet, Box 210, Stockholm 171 77, Sweden (e-mail: maria.feychting@ki.se).

Initially submitted July 6, 2011; accepted for publication November 15, 2011.

Two previous studies suggest that cigarette smoking reduces acoustic neuroma risk; however, an association between use of snuff tobacco and acoustic neuroma has not been investigated previously. The authors conducted a case-control study in Sweden from 2002 to 2007, in which 451 cases and 710 population-based controls completed questionnaires. Cases and controls were matched on gender, region, and age within 5 years. The authors estimated odds ratios using conditional logistic regression analyses, adjusted for education and tobacco use (snuff use in the smoking analysis and smoking in the snuff analysis). The risk of acoustic neuroma was greatly reduced in male current smokers (odds ratio (OR) = 0.41, 95% confidence interval (CI): 0.23, 0.74) and moderately reduced in female current smokers (OR = 0.70, 95% CI: 0.40, 1.23). In contrast, current snuff use among males was not associated with risk of acoustic neuroma (OR = 0.94, 95% CI: 0.57, 1.55). The authors' findings are consistent with previous reports of lower acoustic neuroma risk among current cigarette smokers than among never smokers. The absence of an association between snuff use and acoustic neuroma suggests that some constituent of tobacco smoke other than nicotine may confer protection against acoustic neuroma.

acoustic neuroma; cigarette smoking; smoking; snuff; snus; Swedish snuff; tobacco; vestibular schwannoma

Abbreviations: CI, confidence interval; OR, odds ratio; RR, risk ratio; TSNA, tobacco-specific nitrosamine.

Acoustic neuroma, also known as vestibular schwannoma, is a benign, slow-growing tumor affecting Schwann cells of the eighth cranial nerve. It comprises approximately 8%–10% of all intracranial tumors (1–3). Schwann cells are peripheral nervous system cells that produce a myelin sheath around neuronal axons. Common presenting symptoms for acoustic neuroma include hearing loss, tinnitus, and loss of balance; however, large untreated tumors can potentially lead to brain stem compression, hemorrhaging, and death, although these outcomes are rare (4). Incidence estimates vary from 1 to 20 cases per million per year (5), with more recent estimates placing incidence between 11 and 13 cases per million per year (2). Although the incidence appears to be increasing over time (3, 5–7), it is unclear whether this signals a true increase or is due to improved diagnostic technology, changes in completeness of reporting, or both.

Several risk factors for acoustic neuroma have been identified through previous research. The inherited genetic condition neurofibromatosis type 2 has been associated with bilaterally presenting acoustic neuroma cases; however, these bilateral tumors account for fewer than 5% of all acoustic neuroma diagnoses (6). Less is known about the etiology of acoustic neuroma cases presenting unilaterally, even though these 1-sided tumors account for the majority of cases. Studies of children who received doses of radiotherapy for tinea capitis (8) and atomic bomb survivors (9) have linked moderate to high doses of ionizing radiation to increased acoustic neuroma risk. Risk factors including loud noise (10–12), mobile phone use (13), and some occupational hazards (14) have also been investigated, but these results have been inconclusive.

Two studies found a protective effect of cigarette consumption on acoustic neuroma risk. Schoemaker et al. (15) noted that ever smokers were at a reduced risk of acoustic neuroma compared with never smokers (odds ratio (OR) = 0.7, 95% confidence interval (CI): 0.6, 0.9), and current smokers enjoyed even

greater protection (OR = 0.5, 95% CI: 0.4, 0.6). Using data from the Million Women Study in Great Britain, Benson et al. (16) confirmed that female current smokers were at a reduced risk of acoustic neuroma (risk ratio (RR) = 0.41, 95% CI: 0.24, 0.70), although ever smoking data were not presented. Nicotine, the primary psychoactive ingredient in cigarette smoke, has been inversely associated with Parkinson's disease (17), and both previous acoustic neuroma studies cited the neuroprotective effects of this chemical as 1 possible explanation of the relation between cigarette smoke and acoustic neuroma risk.

Swedish moist oral snuff (also called *snus*) users have blood levels of nicotine that are strikingly similar to those of cigarette smokers, but snuff users attain these levels without exposure to combustion products (e.g., carbon monoxide and tar) (18). Currently, there are no studies evaluating whether smokeless tobacco is inversely related to the development of acoustic neuroma, which could potentially provide information about the effects of the chemicals unique to the combustion process on tumor risk. The present study provides additional estimates of the association between cigarette consumption and acoustic neuroma and seeks to determine whether the protective effects of tobacco smoking on acoustic neuroma are also conferred on Swedish snuff users.

MATERIALS AND METHODS

A population-based nationwide case-control study of acoustic neuroma was conducted in Sweden between September 1, 2002, and August 31, 2007.

Case ascertainment

Eligible cases were patients diagnosed with acoustic neuroma (*International Classification of Diseases*, Tenth Revision, code C72.4, and *International Classification of Diseases for Oncology*, Second Edition, code 9560.0) between the ages of 20 and 69 years at the time of diagnosis. Diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. Cases were identified in collaboration with the hospital-based neurosurgery and/or otorhinolaryngology clinics responsible for patient treatment, as well as through population-based regional cancer registries. Reporting of acoustic neuroma cases to the Swedish National Cancer Registry is mandatory (19). The 6 regional cancer registries report data to the Swedish National Cancer Registry, and therefore these regional registries are updated earlier than the national registry. In addition, the Uppsala and Linköping regions have locally established acoustic neuroma registries at their otorhinolaryngology clinics. These local registries are more complete than the regional cancer registries, as clinics sometimes wait for histologic confirmation before sending notification of cases to the regional cancer registry, and the delay between the first acoustic neuroma diagnosis and a subsequent diagnostic surgical procedure can be substantial. Also, some patients undergo stereotactic radiation without prior histologic examination. In Stockholm for the period from January 1, 2005, to August 31, 2007, the medical records of all patients diagnosed with benign neoplasm of the cranial nerves (*International Classification of Diseases*, Tenth Revision, code D33.3) at neurosurgery clinics were scrutinized to identify additional cases with acoustic neuroma. Because of the scope and thoroughness of our case ascertainment methods, it is likely that we were able to capture a greater proportion of diagnosed cases than most previous population-based studies.

Medical records for all cases were examined to confirm the diagnosis, to establish a date of diagnosis, and to determine tumor laterality. The first medical examination (usually the first radiologic examination) resulting in an acoustic neuroma diagnosis was used as the date of diagnosis and defined as the reference date for exposure assessment.

Patients diagnosed with neurofibromatosis or tuberose sclerosis were excluded from the study.

Controls

Two controls per case were randomly selected from the Swedish nationwide population registry and stratified on age in 5-year categories, sex, and place of residence (6 geographic regions corresponding to the regional cancer registries). If neither of the 2 invited controls agreed to participate, 2 additional controls were selected according to the same principles. The reference date for controls was the date of diagnosis for the matching case.

Data collection

Data collection started in October 2007. Permission to contact the patient was obtained from the treating physician or from the head of the patient's clinic before contact was made. Each case and control received an invitation letter with information about the study and thereafter a mailed questionnaire regarding environmental exposures and lifestyle information. Three reminders, 2 by mail and 1 by telephone, were sent in 2-week intervals. A second copy of the questionnaire was included with the second mail reminder. Returned questionnaires were checked for completeness and, if needed, study participants were contacted by telephone for missing details.

Statistical analysis

We used conditional logistic regression to estimate odds ratios. For cigarette smoking, we analyzed each gender separately; for snuff tobacco, we restricted analysis to male users (78 cases, 119 controls) because we did not have enough female snuff users in the sample (1 case, 9 controls) to justify analysis. We conditioned on matched sets (matched on sex, region, and age within 5 years) and further adjusted for snuff use among male smokers, smoking among male snuff users, and education, using this last variable as an indicator of social class. We also evaluated the data for residual confounding by including age as a continuous variable in the regression models (controls were matched to cases within 5 years of age) and found no evidence of this bias (data not shown). Dose categories for both cigarette smoking and snuff tobacco use were similar. Ever smoking and ever snuff tobacco use were defined as 1 cigarette daily or 1 pinch or pouch of snuff daily for 6 months or longer. Because acoustic neuroma is a slow-growing tumor, current use was defined as those who were smoking or using snuff regularly 1 year prior to the reference date, which was the date of diagnosis of the case and the same date for the matched

controls (Schoemaker et al. (15) used the same definition). Conversely, past use was defined as those who had quit smoking or using snuff more than 1 year prior to the reference date.

Tests for trend were conducted on multilevel categorical variables by using the Wald chi-square test. All presented *P* values are 2-sided. All analyses were performed with the SAS statistical software package (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Over the course of the study period, 538 acoustic neuroma cases and 1,089 controls were identified. Participation rates were 84% ($n = 451$) for cases, and 65% ($n = 710$) for controls. For the conditional logistic regression analysis, we used only complete, informative strata—matched on age (within 5 years), sex, and region—leading to a final sample of 423 cases and 645 controls. The characteristics of participating cases and controls are summarized in Table 1. Matching of cases and controls is reflected by similarities across the matched strata between these groups. High school was the highest level of educational attainment for a greater percentage of cases than controls (cases = 20.33%, controls = 15.17%) and, therefore, as would be expected, fewer cases than controls had attended university and beyond (cases = 26.24%, controls = 29.77%); however, we adjusted for education so these distributional differences are accounted for in the analysis. Additionally, lower levels of educational attainment have recently been associated with a decreased risk of acoustic neuroma (20), further justifying adjustment for this covariate. Marital status was similar between cases and controls; thus, we did not adjust for it.

A strong protective association of current smoking with acoustic neuroma risk was found among males (OR = 0.41, 95% CI: 0.23, 0.74) (Table 2), and a less potent association, with a wider confidence interval, was found among females (OR = 0.70, 95% CI: 0.40, 1.23). Past smoking was not related to acoustic neuroma risk for either gender, so the reduced risk associated with ever smoking is attributable to current smoking.

Men with 20 or more pack-years of smoking showed a decreased acoustic neuroma risk (OR = 0.46, 95% CI: 0.26, 0.81) (Web Table 1, which is posted on the *Journal*'s website (http://www.aje.oxfordjournals.org/)). However,

Table 1. Characteristics of Acoustic Neuroma Cases and Controls, Sweden, 2002–2007[a]

Characteristics	Men				Women				All			
	Cases		Controls		Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at reference date, years												
<35	21	9.09	36	10.03	18	9.38	25	8.74	39	9.22	61	9.46
35–44	29	12.55	41	11.42	28	14.58	43	15.03	57	13.48	84	13.02
45–54	57	24.68	83	23.12	47	24.48	75	26.22	104	24.59	158	24.50
55–64	89	38.53	138	38.44	69	35.94	104	36.36	158	37.35	242	37.52
>64	35	15.15	61	16.99	30	15.63	39	13.64	65	15.37	100	15.50
Region												
Stockholm	43	18.61	69	19.22	39	20.31	57	19.93	82	19.39	126	19.53
Uppsala	58	25.11	84	23.40	50	26.04	70	24.48	108	25.53	154	23.88
Umeå	24	10.39	40	11.15	13	6.77	23	8.04	37	8.75	63	9.77
Linköping	38	16.45	62	17.27	47	24.48	72	25.17	85	20.09	134	20.78
Göteborg	39	16.88	57	15.88	30	15.63	45	15.73	69	16.31	102	15.81
Lund	29	12.55	47	13.09	13	6.77	19	6.64	42	9.93	66	10.23
Marital status												
Single	27	11.69	50	13.93	16	8.33	34	11.89	43	10.17	84	13.02
Married/cohabitating	180	77.92	284	79.11	153	79.69	200	69.93	333	78.82	484	75.04
Separated/divorced	16	6.93	17	4.74	14	7.29	25	8.74	30	7.09	42	6.51
Widowed	8	3.46	8	2.23	9	4.69	27	9.44	17	4.02	35	5.43
Highest attained educational level												
Elementary school	65	28.14	108	30.08	50	26.04	76	26.57	115	27.19	184	28.53
2-year secondary	61	26.41	92	25.63	49	25.52	68	23.78	110	26.00	160	24.81
Minimum 3-year high school	57	24.68	61	16.99	29	15.10	42	14.69	86	20.33	103	15.17
University/college or postgraduate	47	20.35	94	26.18	64	33.33	98	34.22	111	26.24	192	29.77

[a] The number of observations throughout the table varies by characteristic category because of missing values.

Table 2. Risk of Acoustic Neuroma in Relation to Regular Cigarette Smoking, Sweden, 2002–2007[a,b]

Factor	Men						Women						All					
	Cases		Controls		OR[c]	95% CI	Cases		Controls		OR[d]	95% CI	Cases		Controls		OR[d]	95% CI
	No.	%	No.	%			No.	%	No.	%			No.	%	No.	%		
Ever regular smoker																		
No	127	54.98	168	46.93	1.0[e]		106	55.50	148	52.48	1.0[e]		233	55.21	316	49.38	1.0[e]	
Yes	104	45.02	190	53.07	0.73	0.51, 1.05	85	44.50	134	47.52	0.88	0.59, 1.29	189	44.79	324	50.63	0.80	0.61, 1.04
Smoking status																		
Former smoker	85	36.80	125	34.92	0.97	0.64, 1.46	59	30.89	81	28.72	0.98	0.63, 1.50	144	34.12	206	32.19	0.98	0.73, 1.32
Current smoker[f]	19	8.23	63	17.60	0.41	0.23, 0.74	26	13.61	52	18.44	0.70	0.40, 1.23	45	10.66	115	17.97	0.54	0.36, 0.81
Age started smoking, years																		
<15	15	6.49	16	4.47	1.45	0.64, 3.32	6	3.14	23	8.16	0.41	0.16, 1.05	21	4.98	39	6.09	0.82	0.46, 1.47
15–19	62	26.84	129	36.03	0.64	0.42, 0.97	49	25.65	69	24.47	1.00	0.64, 1.57	111	26.30	198	30.94	0.78	0.57, 1.05
≥20	27	11.67	45	12.57	0.73	0.42, 1.27	30	15.71	42	14.89	0.96	0.53, 1.75	57	13.51	87	13.59	0.84	0.56, 1.26
P_{trend} (all subjects)						0.09						0.32						0.41
P_{trend} (ever smokers)						0.95						0.04						0.20
Years since started smoking																		
<20	7	3.03	9	2.51	1.16	0.42, 3.20	7	3.66	11	3.90	1.09	0.39, 3.02	14	3.32	20	3.13	1.13	0.55, 2.33
20–29	9	3.90	20	5.59	0.54	0.22, 1.37	10	5.24	18	6.38	0.75	0.32, 1.77	19	4.50	38	5.94	0.62	0.33, 1.18
30–39	36	15.58	61	17.04	0.74	0.43, 1.27	40	20.94	56	19.86	1.07	0.62, 1.85	76	18.01	117	18.28	0.89	0.61, 1.31
≥40	52	22.51	100	27.93	0.68	0.42, 1.11	28	14.66	49	17.38	0.68	0.37, 1.26	80	18.96	149	23.28	0.70	0.48, 1.02
P_{trend} (all subjects)						0.38						0.69						0.25
P_{trend} (ever smokers)						0.90						0.95						0.91
Total years smoked																		
<10	25	10.82	40	11.17	0.83	0.47, 1.48	18	9.42	29	10.28	0.94	0.49, 1.81	43	10.19	69	10.78	0.90	0.59, 1.38
10–19	28	12.12	36	10.06	1.05	0.58, 1.90	21	10.99	26	9.22	1.14	0.59, 2.21	49	11.61	62	6.69	1.09	0.70, 1.70
20–29	18	7.79	36	10.06	0.71	0.37, 1.35	12	6.28	28	9.93	0.58	0.28, 1.19	30	7.11	64	10.00	0.66	0.40, 1.07
≥30	29	12.55	68	18.99	0.54	0.32, 0.93	28	14.66	43	15.25	0.78	0.43, 1.43	57	13.51	111	17.34	0.64	0.43, 0.96
P_{trend} (all subjects)						0.20						0.56						0.11
P_{trend} (ever smokers)						0.50						0.56						0.33

Table continues

Table 2. Continued

Factor	Men						Women						All					
	Cases		Controls		OR[c]	95% CI	Cases		Controls		OR[d]	95% CI	Cases		Controls		OR[d]	95% CI
	No.	%	No.	%			No.	%	No.	%			No.	%	No.	%		
Years since stopped smoking																		
≥30	20	8.66	26	7.26	1.18	0.60, 2.32	9	4.71	11	3.90	1.32	0.48, 3.66	29	6.87	37	5.78	1.24	0.71, 2.18
20–29	28	12.12	36	10.06	1.07	0.58, 1.97	18	9.42	23	8.16	1.12	0.56, 2.24	45	10.66	59	9.22	1.12	0.71, 1.76
10–19	19	8.23	39	10.89	0.73	0.39, 1.38	12	6.28	24	8.51	0.73	0.35, 1.52	31	7.35	31	4.84	0.74	0.46, 1.19
5–9	9	3.90	12	3.35	0.97	0.38, 2.51	8	4.19	13	4.61	0.69	0.27, 1.78	17	4.03	17	2.66	0.78	0.39, 1.54
>1–4	7	3.03	10	2.79	1.00	0.36, 2.78	8	4.19	8	2.84	1.54	0.52, 4.57	15	3.55	14	2.19	1.22	0.58, 2.56
Current smoker[e]	19	8.23	63	17.60	0.43	0.24, 0.77	26	13.61	52	18.44	0.71	0.40, 1.26	45	10.66	115	17.97	0.56	0.37, 0.84
P_{trend} (ever smokers)						0.05						0.56						0.12
Smoking pack-years																		
<10	44	19.05	70	19.55	0.83	0.51, 1.34	41	21.47	55	19.50	1.06	0.65, 1.71	85	20.14	125	19.53	0.96	0.68, 1.34
10–19	31	13.42	42	11.73	0.99	0.58, 1.69	17	8.90	38	13.48	0.55	0.29, 1.06	48	11.37	80	12.50	0.78	0.51, 1.17
20–29	9	3.90	31	8.66	0.36	0.15, 0.82	13	6.81	16	5.67	1.17	0.52, 2.62	22	5.21	47	7.34	0.64	0.37, 1.12
≥30	16	6.93	33	99.22	0.54	0.27, 1.08	7	3.66	15	5.32	0.53	0.20, 1.46	23	5.45	48	7.50	0.58	0.33, 1.01
P_{trend} (all subjects)						0.10						0.29						0.20
P_{trend} (ever smokers)						0.24						0.43						0.13

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Smoking is defined as at least 1 cigarette daily for 6 months or longer.

[b] The number of observations throughout the table varies by smoking category because of missing values. Each factor in the table represents a different regression coefficient with different covariates.

[c] Odds ratios from conditional logistic regression models stratified by matched set. Cases and controls were matched on gender, age (within 5 years at the reference date), and region. Odds ratios were adjusted for the highest level of education and snuff use (never vs. ever).

[d] Odds ratios for women were similarly constructed but were not adjusted for snuff use because of lack of snuff users in the population.

[e] Reference category for the entire table.

[f] Current smoker odds ratios are not identical because they are based on the regressions with different covariates.

44% of these men were current smokers, whereas current smokers comprised only 10% of male smokers with fewer than 20 pack-years. To determine whether the effect of smoking pack-years on acoustic neuroma risk was attributable to the dose and duration of cigarette consumption or to current smoking, we dichotomized both male and female current smokers for whom we could calculate pack-years ($n = 157$) into 2 categories: fewer than 20 pack years and greater than or equal to 20 pack-years, based on the median pack-years found among ever smoker controls (Web Table 1). We observed differences of association between the genders. Among men, most of the dose-response association was found among former smokers (although the number of current smokers among cases with fewer than 20 pack-years is small). Among women, there appeared to be no dose-response association.

In Table 2, we also examined the age at which participants began smoking, years since started smoking, total years of smoking, and number of years since stopped smoking but found no relation between these factors and acoustic neuroma risk.

We evaluated snuff tobacco use only among males, because the sample size for female snuff tobacco users was too small for meaningful inferences. There was no relation between having ever used snuff tobacco, or being a current or past user, and acoustic neuroma risk when compared with never snuff users (Table 3). We also examined the age at first snuff use, years since started using snuff, total years of usage, and years since stopped using snuff, and we found no association with acoustic neuroma risk when comparing the distribution of these variables with that among never snuff users.

DISCUSSION

We found that the risk of acoustic neuroma was greatly reduced in male current smokers and moderately reduced in female current smokers. A previous study that included both men and women did not report gender-specific results; however, our results for ever smokers for both genders combined are similar to this study (15). Our results for female smokers are in the same direction as those reported in the Million Women Study (16), where the risk ratio was 0.41 (95% CI: 0.24, 0.70) for current versus never female smokers, although our effect estimates are weaker in magnitude. We observed no evidence of a role for snuff tobacco consumption in acoustic neuroma etiology. The disparity between the effects of smoking tobacco and snuff use on risk of acoustic neuroma suggests that the potentially protective benefits of smoking tobacco are caused by something other than nicotine, the most prominent shared ingredient of the 2 tobacco intake methods.

As previously noted, our results for cigarette smoking mirror those of previous studies. Using case-control data from the Nordic countries and the United Kingdom, Schoemaker et al. (15) found ever smoking versus never smoking to be protective against acoustic neuroma (OR = 0.7, 95% CI: 0.6, 0.9). These authors reported an even stronger inverse relation when comparing current smokers with never smokers (OR = 0.5, 95% CI: 0.4, 0.6). Schoemaker et al. did not present separate data for men and women; however, their reported odds ratios for ever smoking versus never smoking and current smoking versus never smoking are strikingly similar to the combined odds ratios in our study.

Our study did not confirm all of the findings of Schoemaker et al. (15). We found neither an inverse dose-response relation between cigarette smoking pack-years and acoustic neuroma risk (the Schoemaker et al. $P_{\text{trend}} < 0.001$) nor a dose-response relation linking the total number of years smoked to decreased risk of acoustic neuroma (the Schoemaker et al. $P_{\text{trend}} < 0.001$). However, the study by Schoemaker et al., while similar to ours in terms of case sample size, had greater than 3 times the number of controls. It is possible that their increased statistical power allowed them to identify effects that we could not.

Data from the Million Women Study in Great Britain were also used to evaluate the relation between cigarette smoking and acoustic neuroma risk. In a prospective cohort, Benson et al. (16) found that current smokers enjoyed protection against acoustic neuroma (RR = 0.41, 95% CI: 0.24, 0.70). In addition, the investigators detected a dose-response relation among current smokers: Women who smoked 15 or more cigarettes per day had a lower risk of acoustic neuroma (RR = 0.27, 95% CI: 0.11, 0.66) than did women who smoked fewer than 15 cigarettes per day (RR = 0.53, 95% CI: 0.28, 1.00). It should be noted that, because this was a prospective study of a rare condition, the case sample size was small: Risk ratios were derived from data on only 16 current smokers (11 of whom smoked fewer than 15 cigarettes per day, and 5 of whom smoked 15 or more cigarettes per day), although they contributed over 10.2 million person-years of follow-up time. In contrast, the present study had an appreciably larger sample of cases from which to draw, including 191 female acoustic neuroma cases, 25 of whom were current smokers 1 year before their diagnoses. In addition, unlike the analyses of Benson et al., all of our participants were matched on variables representing age, gender, and region, which increased the statistical power of our analyses.

It should be noted that there are important physical and chemical differences between Swedish and American snuff. American companies produce 3 different types of snuff (chewing tobacco, moist snuff, and dry snuff), whereas Swedish companies produce moist snuff almost exclusively (21). American snuff is fermented during the manufacturing process, potentially leading to increased levels of tobacco-specific nitrosamines (TSNAs), which are known carcinogens (21). In contrast, Swedish snuff tobacco is traditionally treated with steam for a period of 24–36 hours, in a process similar to pasteurization, which can largely prevent microbial activation of TSNAs. One study reported that, although sampled Swedish snuff had between 2.8 and 11.2 μg of TSNAs per gram of moist snuff, American snuff had between 3.7 and 127.9 μg of TSNAs per gram (22). In light of these differences, the present study's findings apply only to Swedish snuff.

Peak blood nicotine levels are similar among habitual cigarette smokers and Swedish snuff users (18), so our findings therefore suggest that nicotine is not the source of acoustic neuroma risk reduction among cigarette smokers. A notable difference between cigarette smoking and snuff use is that, while the nicotine in snuff is absorbed orally, cigarettes rely on combustion to deliver nicotine. Cigarette combustion, with its byproducts of carbon monoxide and other chemicals, has a hypoxic effect on human tissue (23). A recent study

Table 3. Risk of Acoustic Neuroma in Relation to Regular Snuff Use, Sweden, 2002–2007[a,b]

Factor	Men					
	Cases		Controls		OR[c]	95% CI
	No.	%	No.	%		
Ever snuff user						
No	152	66.09	239	66.76	1.0[d]	
Yes	78	33.91	119	33.24	0.99	0.65, 1.51
Snuff user status						
Former snuff user	37	16.09	44	12.29	1.22	0.71, 2.10
Current snuff user[e]	40	17.39	71	19.83	0.94	0.57, 1.55
Age started using snuff, years						
<15	10	4.35	11	3.07	1.21	0.36, 4.07
15–19	28	12.17	42	11.73	0.95	0.53, 1.68
≥20	40	17.39	66	18.44	1.01	0.60, 1.68
P_{trend} (all subjects)						0.58
P_{trend} (ever snuff users)						0.98
Years since started using snuff						
<10	7	3.04	16	4.47	0.80	0.31, 2.06
10–19	15	6.52	25	6.98	1.00	0.45, 2.19
20–29	26	11.30	25	6.98	1.60	0.77, 3.28
≥30	30	13.04	53	14.80	0.86	0.51, 1.65
P_{trend} (all subjects)						0.47
P_{trend} (ever snuff users)						0.63
Total years using snuff						
<10	19	8.26	30	8.38	0.913	0.47, 1.77
10–19	21	9.13	29	8.10	1.20	0.60, 2.42
20–29	16	6.96	24	6.70	0.96	0.45, 2.06
≥30	16	6.96	27	7.54	0.91	0.46, 1.82
P_{trend} (all subjects)						0.65
P_{trend} (ever snuff users)						0.97
Years since stopped using snuff						
≥20	12	5.22	12	3.35	1.29	0.53, 3.13
10–19	7	3.04	16	4.47	0.64	0.24, 1.68
>1–9	16	6.96	15	4.19	1.56	0.68, 3.59
Current snuff user[e]	40	17.39	71	19.83	0.89	0.54, 1.47
P_{trend} (all subjects)						0.59
P_{trend} (ever snuff users)						0.57

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Snuff use is defined as at least 1 packet or dose daily for 6 months or longer.

[b] The number of observations throughout the table varies by snuff use category because of missing values. Each factor in the table represents a different regression coefficient with different covariates.

[c] Odds ratios from conditional logistic regression models stratified by matched set. Cases and controls were matched on gender, age (within 5 years at the reference date), and region. Odd ratios were adjusted for highest level of education and smoking status as of the reference date (never user, past user, and current user).

[d] Reference category for the entire table.

[e] Current snuff use odds ratios are not identical because they are based on regressions with different covariates.

by Zhu et al. (24), which investigated the effects of hypoxia and reoxygenation on Schwann cells in vitro, found that hypoxia and reoxygenation induce apoptosis and reduce cell viability. Because acoustic neuroma is characterized by an overproliferation of Schwann cells, this is a possible explanation as to why cigarette smoke protects against acoustic neuroma risk and snuff use does not.

Nonetheless, several studies have investigated the antiinflammatory effects of nicotine therapy, thus potentially implicating nicotine as the chemical agent responsible for reduced

incidence of acoustic neuroma among smokers. In 1 study, investigators treated intratracheal lipopolysaccharide (50 μg)-challenged mice with nicotine doses (either 0.2 or 0.4 mg/kg, subcutaneously) (25). After 24 hours, the study authors obtained bronchoalveolar lavage fluid and found attenuated levels of inflammatory cells. In a separate in vivo study, nicotine administration (2 mg/kg, subcutaneously) suppressed the severity of experimental autoimmune encephalomyelitis (26). Although our snuff findings do not mirror the effects found in these studies, this attenuated inflammatory response suggests that nicotine could be the chemical substance inducing the protective effects of smoking tobacco on acoustic neuroma genesis. Odds ratios in the present study may have been distorted by selection bias, a source of bias in case-control studies. Potential controls (65% participated) were less likely to agree to participate in the study than were cases (84% participated). Nonparticipants are more likely to be characterized by low socioeconomic status (27) that is also associated with cigarette and snuff intakes (28). At the same time that socioeconomic status is associated with cigarette smoking and snuff use, it is also probably independently related to acoustic neuroma risk, making it a potentially confounding variable. The relations among socioeconomic status, education, tobacco use, and acoustic neuroma are complex; however, it is probably safe to assume that equal case-control participation would have strengthened the inverse association between cigarette smoking and acoustic neuroma, because smokers were less likely to participate than were nonsmokers. It is also possible that our failure to observe an effect of snuff use is attributable to selection bias, which might have been more strongly affected by unequal case-control selection than was cigarette consumption.

Another potential source of distortion is detection bias, defined as the preferential diagnosis of individuals with higher socioeconomic status. As noted before, those with lower socioeconomic status are more likely to be smokers and snuff users (28). Thus, if present, this bias would artificially lower smoking and snuff use rates in our case sample and lead to a spurious inverse relation between both smoking and snuff use and acoustic neuroma. Although we found a strong inverse relation among male smokers, we found no relation among male snuff users, indicating that detection bias did not influence our results.

It is worth noting that our findings, as in any observational study, may reflect both causal patterns and biases. We therefore restrict our discussion to the strongest results and await further confirmation from subsequent studies to develop detailed descriptions of underlying mechanisms. We thus avoid ''overinterpreting'' our data or constructing causal explanations for random or systematic bias. For example, although previous studies have not presented separate odds ratios for men and women with regard to cigarette smoking and acoustic neuroma risk, we felt that the difference in the magnitude of the effects was large enough to justify reporting. However, because we are the first to report such a difference, we are not sure whether this reflects a true gender difference or is due to some form of bias or random variation and, thus, have refrained from forming a premature biologic justification when none is clearly apparent.

The public health hazards associated with cigarette smoking are both well known and well documented; as such, it is not our intention to endorse smoking as a means of protection against acoustic neuroma development. However, the consistency with which cigarette smoking has been shown to reduce acoustic neuroma risk, in both the present study and those of others (15, 16), provides rare clues into the etiology of a tumor about which relatively little is known. Accordingly, we encourage researchers to investigate the mechanism by which some constituent of tobacco smoke appears to reduce acoustic neuroma risk.

Further studies are needed to confirm the difference in the magnitude of effects found between men and women in relation to smoking and risk of acoustic neuroma. Additionally, our snuff results for men should be validated, and the relation between snuff use among women and acoustic neuroma risk should be analyzed. To test the effects of hypoxia on the risk of acoustic neuroma, investigators in future observational studies could identify the rates of acoustic neuroma at disparate altitudes, to see whether higher, less oxygen-rich environments reduce acoustic neuroma risk.

ACKNOWLEDGMENTS

Author affiliations: Division of Epidemiology, College of Public Health, Ohio State University, Columbus, Ohio (Sadie Palmisano, Judith Schwartzbaum); Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Michaela Prochazka, David Pettersson, Maria Feychting); Department of Neurosurgery, Umeå University Hospital, Umeå, Sweden (Tommy Bergenheim); Department of Otorhinolaryngology, Sahlgrenska University Hospital, Göteborg, Sweden (Rut Florentzson); Department of Otorhinolaryngology, Linköping University Hospital, Linköping, Sweden (Henrik Harder); Department of Clinical Neuroscience, Karolinska Hospital, Stockholm, Sweden (Tiit Mathiesen); Department of Neurosurgery, Uppsala University Hospital, Uppsala, Sweden (Gunnar Nyberg); and Department of Neurosurgery, Lund University Hospital, Lund, Sweden (Peter Siesjö).

This study was funded by the Swedish Council for Working Life and Social Research.

The authors wish to thank the regional cancer registers for their collaboration.

Conflict of interest: none declared.

REFERENCES

1. Lanser MJ, Sussman SA, Frazer K. Epidemiology, pathogenesis, and genetics of acoustic tumors. *Otolaryngol Clin North Am*. 1992;25(3):499–520.
2. Tos M, Stangerup SE, Cayé-Thomasen P, et al. What is the real incidence of vestibular schwannoma? *Arch Otolaryngol Head Neck Surg*. 2004;130(2):216–220.
3. Propp JM, McCarthy BJ, Davis FG, et al. Descriptive epidemiology of vestibular schwannomas. *Neuro Oncol*. 2006;8(1):1–11.
4. Yates CW, Weinberg M, Packer MJ, et al. Fatal case of tumor-associated hemorrhage in a large vestibular schwannoma. *Ann Otol Rhinol Laryngol*. 2010;119(6):402–405.
5. Howitz MF, Johansen C, Tos M, et al. Incidence of vestibular schwannoma in Denmark, 1977–1995. *Am J Otol*. 2000;21(5):690–694.

6. Evans DG, Moran A, King A, et al. Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. *Otol Neurotol*. 2005;26(1):93–97.
7. Larjavaara S, Feychting M, Sankila R, et al. Incidence trends of vestibular schwannomas in Denmark, Finland, Norway and Sweden in 1987–2007. *Br J Cancer*. 2011;105(7):1069–1075.
8. Ron E, Modan B, Boice JD Jr, et al. Tumors of the brain and nervous system after radiotherapy in childhood. *N Engl J Med*. 1988;319(16):1033–1039.
9. Preston DL, Ron E, Yonehara S, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. *J Natl Cancer Inst*. 2002;94(20):1555–1563.
10. Edwards CG, Schwartzbaum JA, Lönn S, et al. Exposure to loud noise and risk of acoustic neuroma. *Am J Epidemiol*. 2006; 163(4):327–333.
11. Edwards CG, Schwartzbaum JA, Nise G, et al. Occupational noise exposure and risk of acoustic neuroma. *Am J Epidemiol*. 2007;166(11):1252–1258.
12. Schlehofer B, Schlaefer K, Blettner M, et al. Environmental risk factors for sporadic acoustic neuroma (Interphone Study Group, Germany). *Eur J Cancer*. 2007;43(11):1741–1747.
13. Ahlbom A, Feychting M, Green A, et al. Epidemiologic evidence on mobile phones and tumor risk: a review. ICNIRP (International Commission for Non-Ionizing Radiation Protection) Standing Committee on Epidemiology. *Epidemiology*. 2009;20(5): 639–652.
14. Prochazka M, Feychting M, Ahlbom A, et al. Occupational exposures and risk of acoustic neuroma. *Occup Environ Med*. 2010;67(11):766–771.
15. Schoemaker MJ, Swerdlow AJ, Auvinen A, et al. Medical history, cigarette smoking and risk of acoustic neuroma: an international case-control study. *Int J Cancer*. 2007;120(1):103–110.
16. Benson VS, Green J, Pirie K, et al. Cigarette smoking and risk of acoustic neuromas and pituitary tumours in the Million Women Study. *Br J Cancer*. 2010;102(11):1654–1656.
17. Hernán MA, Takkouche B, Caamaño-Isorna F, et al. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol*. 2002;52(3):276–284.
18. Holm H, Jarvis MJ, Russell MA, et al. Nicotine intake and dependence in Swedish snuff takers. *Psychopharmacology (Berl)*. 1992;108(4):507–511.
19. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol*. 2009;48(1):27–33.
20. Schüz J, Steding-Jessen M, Hansen S, et al. Sociodemographic factors and vestibular schwannoma: a Danish nationwide cohort study. *Neuro Oncol*. 2010;12(12):1291–1299.
21. Rodu B, Jansson C. Smokeless tobacco and oral cancer: a review of the risks and determinants. *Crit Rev Oral Biol Med*. 2004; 15(5):252–263.
22. Osterdahl BG, Jansson C, Paccou A. Decreased levels of tobacco-specific *N*-nitrosamines in moist snuff on the Swedish market. *J Agric Food Chem*. 2004;52(16):5085–5088.
23. Jensen JA, Goodson WH, Hopf HW, et al. Cigarette smoking decreases tissue oxygen. *Arch Surg*. 1991;126(9):1131–1134.
24. Zhu H, Li F, Yu WJ, et al. Effect of hypoxia/reoxygenation on cell viability and expression and secretion of neurotrophic factors (NTFs) in primary cultured schwann cells. *Anat Rec (Hoboken)*. 2010;293(5):865–870.
25. Mabley J, Gordon S, Pacher P. Nicotine exerts an anti-inflammatory effect in a murine model of acute lung injury. *Inflammation*. 2011;34(4):231–237.
26. Nizri E, Irony-Tur-Sinai M, Lory O, et al. Activation of the cholinergic anti-inflammatory system by nicotine attenuates neuroinflammation via suppression of Th1 and Th17 responses. *J Immunol*. 2009;183(10):6681–6688.
27. Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol*. 2007;17(9):643–653.
28. Adler NE, Boyce T, Chesney MA, et al. Socioeconomic status and health. The challenge of the gradient. *Am Psychol*. 1994;49(1): 15–24.