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Cigarette smoking associated with lung adenocarcinoma in situ in a large case-control study (SFBALCS)

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Abstract

Introduction—Adenocarcinoma in situ (AIS, formerly bronchioloalveolar carcinoma [BAC]) is an uncommon subtype of lung adenocarcinoma and accounts for approximately 3–4% of lung cancers. Compared with other lung cancer histologies, AIS cases are less likely to be smokers, yet associations with other lung cancer risk factors and differences by gender have not been determined.

Methods—A total of 338 AIS (formerly BAC) cases and frequency matched controls from the parent study (cases=6039, controls=2073) were included in these analyses. Odds ratios and 95% confidence intervals as estimates of the relative risk were obtained from multivariable unconditional logistic regression analyses.

Results—Risk of AIS was associated with ever smoking (OR=2.7, 95% CI: 2.1, 3.6), increased 20–30% for each 10-year increase in pack-years of smoking and decreased with increased years since quitting (P for trend <0.0001). There was no evidence that risk differed by gender but there was some suggestion that risk may differ by asbestos and by second-hand tobacco smoke exposure in whites.

Conclusion—There is an association between AIS and smoking that is smaller in magnitude than other subtypes of non-small cell lung cancer. Our findings suggesting that effects may differ by asbestos and second-hand tobacco smoke exposure should be interpreted conservatively and warrant validation and further evaluation in larger studies of AIS.

Keywords

Adenocarcinoma in situ; case-control; epidemiology; smoking; second-hand tobacco smoke

Introduction

Smoking accounts for approximately 80–90% of lung cancer cases and in developed countries incidence rates, particularly among men, have decreased in recent years consistent with a decrease in cigarette smoking in earlier decades [1]. Bronchioloalveolar carcinoma (BAC) as defined by the 1999 and 2004 WHO classifications, is an uncommon subtype of lung adenocarcinoma that accounts for approximately 3–4% of all lung cancers.

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In the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) lung cancer classification, it was recommended that use of the term BAC be discontinued and the term adenocarcinoma in situ (AIS) be used instead[2]. Per the IASLC/ATS/ERS classification, AIS is specifically categorized as a pre-invasive lesion and consistent with the 1999 and 2004 definition of BAC, which is defined as a small localized adenocarcinoma having lepidic growth without stromal, vascular or pleural invasion[2]. The IASLC/ATS/ERS review committee further recommended that these cases should now be referred to as "AIS (formerly BAC)" and this terminology should be applied to analyses of cancer registry data as well as clinical data.

AIS has a unique tumor biology, better prognosis, survival and response to treatment compared with other lung cancers [3]. Epidemiological studies that use the 2011 classification of lung cancer have not yet been published. However, earlier epidemiological studies using older classifications showed that BAC also differs from other lung cancers with a disproportionate number of cases reported to occur in women, Asians, and non-smokers [4]. Based on a limited number of published studies, 17–40% of patients with BAC have never smoked, compared with about 5% of patients with squamous cell lung cancers and 10% of patients with adenocarcinoma[4–7]. A recent pooled analysis showed that tobacco smokers had an approximate 2- to 4-fold increased odds of BAC, depending on the amount of lifetime tobacco use[5]. Results also showed that the proportion of BAC attributable to smoking was greater in men than in women[5].

The molecular basis for the differential susceptibility for AIS relative to other lung cancers is unknown. Understanding the relationship between tobacco exposure and AIS development is a critical first step to understanding the unique biology of AIS. Although AIS is more common among never-smokers than are other lung cancers, it is unknown whether smoking-related exposures differ between AIS and non-AIS NSCLC patients. Moreover, it is unknown whether never-smokers or very light smokers have a higher amount of second-hand tobacco smoke (ETS) exposure compared with never-smokers with non-AIS NSCLC or age-matched controls. Finally, although data show that women are more likely to be never-smokers, no study has documented whether the association between tobacco smoking and AIS differs by gender.

Materials and methods

Case ascertainment

Lung cancer cases included in these analyses were participants from the San Francisco Bay Area Lung Cancer Study (SFBALCS), a population-based case–control study that was conducted to investigate molecular, behavioral, and occupational factors associated with lung cancer etiology focusing on minority populations of Hispanic/Latino and African-American descent[8]. Cases were residents of 5 Bay Area counties who were newly diagnosed with lung cancer [International Classification of Diseases (ICDO-3 C340–C349] from September 1998 to March 2003 (phase I) or July 2005 to March 2008 (phase II) and identified through the Greater Bay Area Cancer Registry rapid case ascertainment. Additional cases were identified through Alta Bates/Summit Hospital in phase I and Northern California Kaiser Permanente Medical Group in phase II. A total of 6,032 cases (49.9% women, 50.1% men) completed a screening interview. Proxy screening interviews were conducted for 31% of cases (deceased, too ill) and no screening interview was conducted for approximately 5% of deceased cases. A total of 338 AIS cases (ICDO-3 codes 8250–8254) identified from SEER abstracts in the SFBALCS study are included in these analyses.

Control ascertainment

Control recruitment has been described in detail previously[8] for phase I of the SFBALCS. Briefly, 3 strategies to ascertain and recruit controls were used including random-digit dialing, random sampling of Health Care Financing Administration (now the Center for Medicaid & Medicare Services) records and community-based recruitment (e.g. senior centers, churches, and health fairs). Phase II consisted of utilizing the Northern California Kaiser Permanente Medical Group membership to identify potential controls. For Phase I, the emphasis was on minority recruitment and controls were frequency matched to African Americans and Latinos by age and gender in a 1:2 case-control ratio. For Phase II, controls were frequency-matched on age and gender in a 1:2 case-control ratio for African Americans and Latinos and a 1:1 ratio for whites.

All participants provided informed consent to interview. The SFBALCS was approved by the University of California, San Francisco Committee on Human Research.

Analytic variables

Data on patient factors were collected from the screening interview, the main questionnaire (cases and controls) or the cancer registry abstracts (cases only). The screening and main interview data included socio-demographic data, usual occupation in addition to history of having worked in several specific occupations/industries, asbestos exposure (based on job exposure), second-hand tobacco smoke exposure (binary variable based on self-reported response to total years of exposure at an indoor workplace and lifetime years exposed to a smoker at home), tobacco smoking including age started, age stopped, years smoked, average number of cigarettes smoked per day, pack-years ([number of packs per day] × [number of years smoked]), and first-degree family history of lung cancer. Cancer registry data included year of diagnosis, age, marital status, residence at diagnosis, cancer stage, histological subtype (ICDO-2) and initial treatment. Taqman genotype data was available for 1740 cases and 572 controls that were genotyped as part of a previously published study of lung cancer[9].

Statistical analysis

Data were analyzed using SASv9.2 (Cary, NC). Unadjusted analyses of continuous factors associated with AIS were assessed using non-parametric statistics (Wilcoxon rank sum test) and categorical data were assessed based on Fisher's exact or Chi-square statistics. Continuous data were grouped for analyses using cut-points based on the quartiles of the frequency distribution among controls or on *a priori* categories that would enable comparison with previously published data. Referent groups were comprised of participants without the exposure of interest or those in the lowest quartile of exposure. Unconditional logistic regression analysis adjusted for matching factors was used to obtain odds ratios as estimates of the relative risk of the association between tobacco-related exposures and risk of AIS. Asbestos exposure (ever/never/unknown), history of second-hand tobacco smoke exposure (ever/never/unknown), and family history of lung cancer were evaluated as potential confounding factors in models of tobacco smoking associated with AIS risk. Trends in risk were based on a chi-square statistic obtained from a multivariable logistic model where the categorical exposure factor of interest was modeled as an ordinal variable. Stratified analyses were conducted to explore whether the association between tobacco-related main effects and AIS risk differed by race (white vs. non-white) or sex. Formal tests of statistical interaction were based on a log-likelihood ratio statistic comparing nested multivariable logistic models with and without the cross-product term. Additional case-only analyses were conducted to assess smoking characteristics associated with AIS compared with non-AIS NSCLC, lung adenocarcinoma and squamous cell lung cancers. Data are not

presented in the tables for factors with <5 in a cell. Results were considered statistically significant for a two-side $P<0.05$ and somewhat significant for $0.05\leq P\leq 0.10$.

Results

A total of 338 (5.6%) of all lung cancer cases (N=6,032) were diagnosed with AIS. Median age at diagnosis was 69.8 for all lung cancer cases and 70.5 for AIS patients (data not shown). Sixty-three percent of AIS patients were women in contrast to 49.9% of all lung cancer cases (Table 1) and whites comprised the majority of both AIS (68.0%) and all lung cancer cases (68.8%). Asians (12%) and African-Americans (11%) comprised the majority of non-white cases. The proportion of AIS cases with a family history of lung cancer, history of asbestos exposure, and second-hand tobacco smoke exposure was not different from controls or all lung cancers.

Further, although both AIS and all lung cancers were more likely to have a history of tobacco smoking compared with controls, a greater proportion of AIS cases were never smokers and a lower proportion were current smokers relative to all lung cancer (Table 1, Supplemental Table 1). AIS patients also smoked for fewer years and had fewer pack-years of smoking than did all lung cancer cases but for a greater number of years and pack-years compared with controls (Table 1, Supplemental Table 2).

The frequency of second-hand tobacco smoke exposures was similar in AIS and non-AIS NSCLC patients, where all exposure types combined totaled 91.2% vs. 92.8% respectively (Supplemental Table 3). However, second-hand tobacco smoke exposure was unknown for a greater proportion of non-AIS NSCLC cases.

Smoking characteristics by race and by gender

Results from analyses adjusted for age, gender and race, showed an increased odds of AIS among ever smokers (OR=2.7, 95% CI: 2.1, 3.6, $P<0.0001$, data not shown). Race-stratified analyses showed that this risk was greater in white than non-white ever-smokers (adjusted ORs: whites, OR=3.5; non-whites, OR=1.8; Table 2). Odds of AIS increased with increasing pack-years of smoking for both whites and non-whites (Table 2); compared with never smokers, those in the highest quartile of pack-years of smoking had a 4 to 6-fold increased risk of AIS (non-whites and whites respectively, Table 2). AIS risk was inversely associated with years since quit smoking although data were sparse in non-whites. Compared with never smokers, white participants who had quit smoking more than 20 years before diagnosis had an approximate 2-fold increased risk of AIS whereas risk among non-whites was not different from unity (Table 2).

Sparse data among non-whites restricted analyses by specific non-white race groups. However, in contrast to other race and gender groups, a greater proportion of Asian women were never smokers (76% of all lung cancer cases, 96% of AIS cases, and 91% of controls; data not shown). In adjusted analyses, risk estimates for tobacco-smoking characteristics between AIS and non-AIS NSCLC patients (Supplemental Table 4) were consistent with those observed between AIS and all lung cancer (Table 2).

In sex-stratified analyses, AIS risk increased with increased pack-years of smoking in both women and men (each P_{trend} <0.0001, Table 3). Risk among the heaviest smokers was similar by sex and there was no evidence of statistical interaction between pack-years smoking and sex ($P_{interaction}=0.54$). AIS risk decreased with increased years since quit smoking with risks remaining elevated even among those who had quit smoking for 20 or more years (Men: OR=2.3, Women: OR=1.7). There was no evidence that the association between AIS risk and years since quit smoking differed by sex ($P_{interaction}=0.99$).

To further evaluate the relationships between AIS and lung cancer risk factors unrelated to smoking, we assessed statistical interaction between smoking history and second-hand tobacco smoke exposure or asbestos exposure in multivariable models stratified by race and by sex. Among whites, the risk of AIS was greatest among ever smokers with any second-hand tobacco smoke exposure ($P_{interaction}$=0.05, data not shown). Among men, risk of AIS was greatest among ever smokers who had no asbestos exposure ($P_{interaction}$ =0.02, data not shown). Results should be interpreted with caution as some cell sizes were small in some statistical assessments and second-hand tobacco smoke exposure was unknown for a large proportion of non-whites.

AIS, non-AIS NSCLC, lung adenocarcinoma, and squamous cell lung cancer

The association with pack-years smoking was stronger for all lung cancer and for lung cancers other than AIS and small cell carcinomas (non-AIS NSCLC) than for AIS (Figure 1). The associations were similar by race but small sample size precluded our ability to conduct detailed analyses among non-whites (Supplemental Table 4) AIS cases were less likely than non-AIS NSCLC cases to be heavy smokers both for men and women (4^{th} quartile >31.5 pack-years: Men, OR=0.31, P_{trend}<0.0001; Women, OR=0.30, P_{trend}<0.0001; Table 4). Analysis of years since quitting smoking showed that compared with never smokers AIS cases were less likely than patients with non-AIS NSCLC, lung adenocarcinoma, and squamous cell lung cancer to be current smokers or to have smoked within the past 20 years (P_{trend}<0.0001 for both men and women, data not shown).

AIS and variants in lung cancer risk SNPs

There was no association between AIS susceptibility and genetic variation in specific SNPs known to be associated with lung cancer (Chr5p15: rs2736100, rs402710; Chr6p: rs2256543, rs4324798) or with both lung cancer and nicotine dependence (Chr15q25 rs8034191, rs16969968). Interestingly, the magnitude and direction of the risk estimates for the two Chr15q25 SNPS with AIS were consistent with those observed for all lung cancer and for adenocarcinoma in our earlier analyses[10] (P<0.05, Supplemental Table 5).

Discussion

Our results show that AIS was more common in women than men and that AIS cases smoked less than other lung cancer patients. Results also confirmed that as for other lung cancer histologies, AIS was associated with a history of smoking, risk increased with increased pack-years of smoking and decreased with years since quitting, although risk remained elevated even after more than 20 years since quitting. There was no evidence that the association between tobacco-smoking characteristics and AIS risk differed by sex and sparse data restricted our ability to robustly assess associations among non-white participants. Genetic variants in several known lung cancer susceptibility SNPs were not statistically significantly associated with AIS.

We use the terms AIS and BAC synonymously in this study because according to WHO classification neoplasms with lepidic growth without invasion are to be classified as BAC and many studies, especially institutional studies, have classified neoplasms with foci of invasion or adenocarcinomas with foci of lepidic as BAC. To date there have been a few epidemiologic studies of tobacco-related exposures and BAC risk. These include two small U.S. hospital-based studies (<100 BAC cases each)[6, 11] and a recent pooled analysis of 799 BAC cases from 7 U.S. case-control studies (3 hospital-based, 4 population-based) [5]. Cases from the earliest studies [6, 11] were diagnosed from 1977 to 1989, before the WHO classification revisions for lung cancer [12, 13] whereas the pooled analysis included a mix of studies conducted before and after the classification revision [5]. The two small hospital-based

studies reported similar approximately 4-fold risk of BAC associated with ever smoking as well as increased risks with increased duration and amount of cigarette smoking [6, 11]. In addition, one of these studies found a reduced risk with increased years since quitting[6]. In the second of these two small studies, there was no association with years since quitting[11] that upon further evaluation was likely due to the inclusion of hospital-based controls with smoking-related diseases [14]. Results from the recent pooled analysis showed a 2.5-fold increased odds of BAC in ever smokers, an increasing trend with pack-years of smoking and a decreasing trend with years since quitting smoking[5]. Although the overall results from the pooled analysis are consistent with the findings in our study, the magnitude of some OR estimates differed. These variations may be related to differences in study designs and population characteristics.

To the best of our knowledge, no previous studies have published results for second-hand tobacco smoke exposure associated with risk of BAC. In our study, second-hand tobacco smoke exposure was not an independent risk factor for AIS but among whites, the smoking-related risk of AIS was greatest for those with a history of second-hand tobacco smoke exposure. The association between asbestos exposure and BAC has not been evaluated in previous BAC studies despite an established synergistic effect of smoking and asbestos exposure on lung cancer risk. There was some evidence that smoking-related AIS risk in men and in whites was greatest for those without a history of asbestos exposure. Given the small number of cases exposed to asbestos and unexposed to second-hand tobacco smoke, and multiple hypothesis testing, these results should be interpreted conservatively and warrant confirmation in larger studies of AIS.

Genome-wide association studies of lung cancer have identified regions of genome-wide significance on chromosomes 5p15, 6p21, and 15q25 that include the SNPs that were investigated in our analyses[15–20]. No study has been published that explores genetic variation and susceptibility for BAC. However, the potential association of some lung cancer candidate SNPs with AIS is supported by studies that showed associations specifically with lung adenocarcinoma[21, 22], within different ethnic groups[10, 21, 23, 24], and with patient subgroups that may be characteristic of AIS *i.e.* Asians and non-smokers [21, 25]. Specifically, the *TERT-CLPMT1L* region on Chr5p15 was associated with risk of lung adenocarcinoma among nonsmoking Asian women[25]. In contrast, variants on Chr15q25 associated with nicotine dependence SNPs have been inconsistently associated with lung cancer in non-smokers and in Asians[9, 17, 26, 27]. Results from additional analyses of lung cancer susceptibility with SNPs in the 6p21 region also have been more variable[9, 16, 20, 25, 27–30]. Despite evidence in our total study population that the Chr15q25 SNPs were associated with increased susceptibility for all lung cancer and with all adenocarcinoma, they were not associated with risk of AIS. However, the magnitude and direction of the associations for Chr15q25 SNPs were consistent with those for all adenocarcinoma in our population and with other published results. Thus in our exploratory analyses, the small sample size and low power to detect an association may explain the null findings for the association between candidate SNPs and AIS. Given the consistency with results from previous studies, further investigation in studies with a large number of AIS cases is needed to determine the role of these SNPs in AIS susceptibility

Interviews were conducted in-person by trained interviewers and basic data about non-responders was collected allowing us to determine the generalizability of our study population. Potential misclassification of second-hand tobacco smoke exposure particularly among non-smokers is a concern. We would expect that analysis of past second-hand smoke exposure as a binary variable would diminish misclassification effects that might be present for more detailed data e.g. frequency and duration. Evidence from cardiovascular disease studies suggest that misclassification of second-hand smoke exposure among non-smokers is

likely to be non-differential resulting in risk estimates biased toward the null.[31, 32] However, it is unclear how these results pertain to studies of lung cancer and if non-smoking cases were more likely to recall exposure to second-hand smoke or to incorrectly self-report as non-smokers then our results are biased away from the null. Lung cancer histologic subtypes were determined from SEER registry abstracts and misclassification of non-AIS adenocarcinoma as AIS would have resulted in risk estimates away from the null as adenocarcinoma are most strongly associated with smoking. AIS is comprised of two major subtypes, mucinous and non-mucinous (~80%), with evidence that the etiology (K-ras versus EGFR driven) and prognosis (non-mucinous better prognosis) of these cancers differ[33, 34]. However, we were unable to conduct subtype analyses within AIS as only 13% of cases had SEER ICD-O codes for mucinous/non-mucinous types, and a re-review of pathology materials was not performed. The use of the Greater Bay Area Cancer Registry data allowed for complete ascertainment of lung cancer cases diagnosed in the San Francisco Bay Area. Although patients with high grade disease and poor prognosis who died shortly after diagnosis are likely to be under-represented in our study population, AIS tends to have good prognosis and therefore survival bias is unlikely to have influenced our results.

Overall our results confirm that never-smokers and women comprise a greater proportion of AIS cases relative to other lung cancers and that smoking, and dose of smoking are positively associated with AIS risk whereas risk of AIS decreases with years since quitting smoking. In addition, we were able to directly show that compared with other histologic subtypes of lung cancer, AIS cases were less likely to be ever smokers or heavy smokers. Our results suggesting that second-hand tobacco smoke exposure may alter the association between a history of ever smoking and AIS should be interpreted cautiously and require validation in other studies. Continued investigation of the epidemiologic and genetic risk factors for AIS is warranted with a focus on assessing the associations by the AIS subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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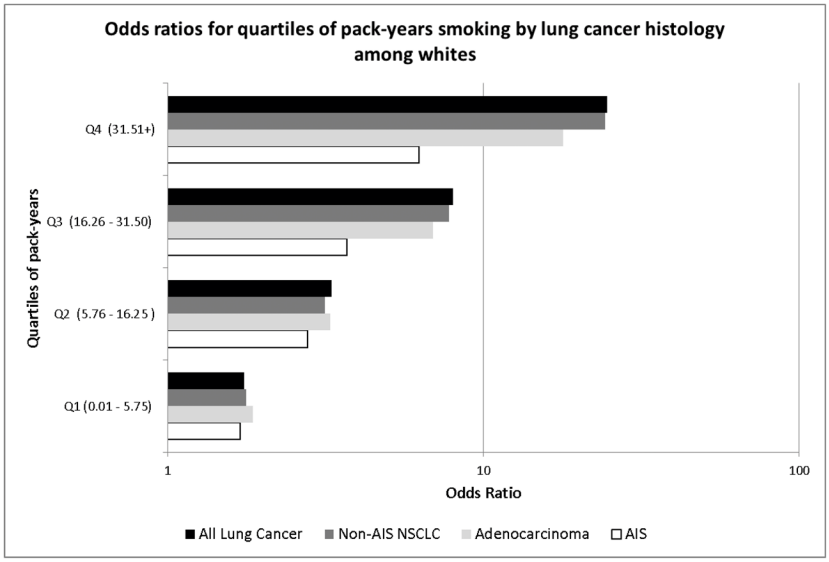

Figure 1.

Age and gender adjusted odds ratios (OR) for all lung cancer, adenocarcinoma in situ (AIS, formerly bronchioloalveolar carcinoma [BAC]), non-AIS non-small cell lung cancer (NSCLC), and lung adenocarcinoma associated with pack-years of smoking (quartiles based on distribution in control cigarette smokers) among whites. Never smokers are the referent group.

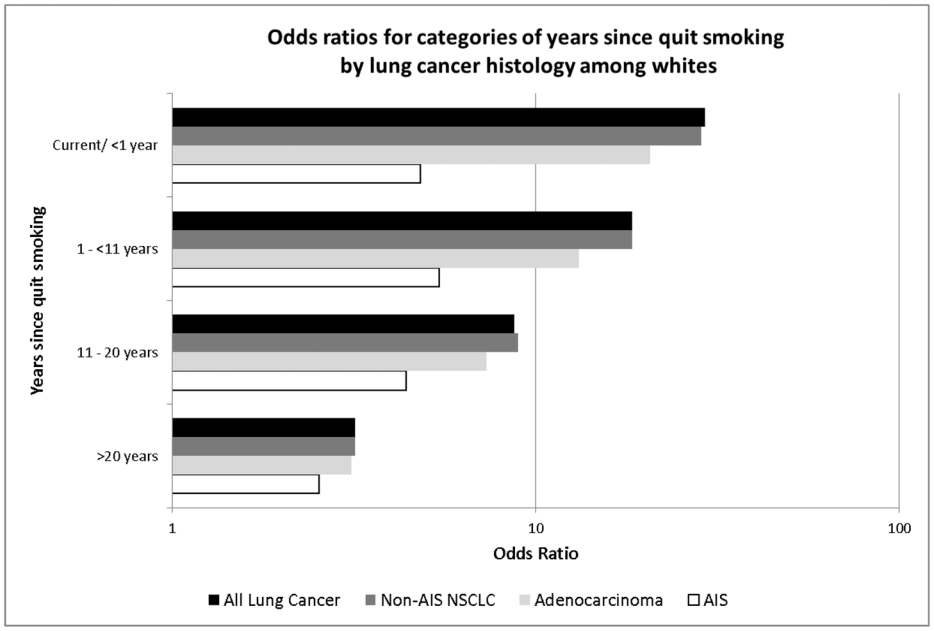

Figure 2.

Age and gender adjusted odds ratios (OR) for all lung cancer, adenocarcinoma in situ (AIS, formerly bronchioloalveolar carcinoma [BAC]), non-AIS non-small cell lung cancer (NSCLC), and lung adenocarcinoma associated with years since quit smoking (current smokers include those who quit within one year of diagnosis [cases] or interview [controls] and are grouped separately), among whites. Never smokers are the referent group.

Table 1

Demographic and smoking-related characteristics among all lung cancer cases, adenocarcinoma in situ (AIS, formerly BAC) patients and controls; Bay Area Lung Cancer Study 1998–2003 and Northern California Lung Study 2005–2008

Characteristic	Cases (N=6032)		AIS-Cases (N=338)		Controls (N=2073)			
	N	%	N	%	N	%	*P*-value[a]	*P*-value[b]
Sex								
Male	3025	50.1	125	37.0	1009	48.7	<0.0001	<0.0001
Female	3007	49.9	213	63.0	1064	51.3		
Race								
African American	655	10.9	30	8.9	463	22.3	<0.65	<0.0001
Latino	421	7.0	25	7.4	326	15.7		
White	4151	68.8	230	68.0	1091	52.6		
African American and White	4	0.1	0	0.0	7	0.3		
Asian	736	12.2	50	14.8	140	6.8		
Other	56	0.9	3	0.9	38	1.8		
Unknown	9	0.1	0	0.0	8	0.4		
Family history of lung cancer								
Yes	991	16.4	40	11.8	219	10.6	<0.055	0.46
No	4682	77.6	279	82.5	1749	84.4		
Unknown/missing	359	6.0	19	5.6	105	5.1		
Asbestos exposure								
Yes	1077	17.9	42	12.4	349	16.8	0.007	0.12
No	4067	67.4	250	74.0	1583	76.4		
Unknown/missing	888	14.7	46	13.6	141	6.8		
Second-hand tobacco smoke exposure								
Yes (work or home)	4467	74.1	258	76.3	1356	65.4	<0.43	0.09
No	591	9.8	34	10.1	249	12.0		
Unknown/missing	974	16.1	46	13.6	468	22.6		
Smoking								
Never smoker	814	13.5	95	28.1	1071	51.7	<0.0001	<0.0001
Former smoker	2900	48.1	175	51.8	805	38.8		
Current smoker	2030	33.7	50	14.8	178	8.6		

Characteristic	Cases (N=6032)			AIS-Cases (N=338)			Controls (N=2073)				
		N	%		N	%		N	%	*P*-value[a]	*P*-value[b]
Smoking unknown		288	4.8		18	5.3		19	0.9		
	N	Median	IQR	N	Median	IQR	N	Median	IQR	*P*-value [a]	*P*-value[b]
Smoking characteristics (ever smokers)											
Smoke years	4969	40.0	20.0	233	33.0	22.0	981	24.0	23.0	<0.0001	<0.0001
Pack-years	4825	42.0	36.25	226	30.0	32.5	934	16.2	26.0	<0.0001	<0.0001
Maximum cigarettes/day	4912	20.0	10.0	227	20.0	10.0	943	15.0	11.0	<0.0001	<0.0001

Abbreviations: BAC, bronchioloalveolar carcinoma; Std err, standard error; IQR, interquartile range

[a] *P*-value from Wilcoxon-rank sum test for analysis of continuous variables and from Chi-square test for analysis of discrete variables, AIS cases and non-AIS cases

[b] *P*-value from Wilcoxon-rank sum test for analysis of continuous variables and from Chi-square test for analysis of discrete variables, AIS cases and controls

Table 2

Adjusted[a] Odds Ratios (OR) and 95% Confidence Intervals (CI) for smoking and non-smoking related factors associated with lung cancer and with adenocarcinoma in situ (formerly BAC) by race, Bay Area Lung Cancer Study 1998–2003 and Northern California Lung Study 2005–2008

		Whites					Non-Whites				
Histology	**Factor**	**Cases**	**Controls**	**OR**	**95% CI**	**p-value**	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value**
All lung cancer	Ever Smoked	4119	1091	9.8	8.3, 11.6	<0.0001	1854	974	4.0	3.4, 4.8	<0.0001
	Pack-years (per 10 pack-years)	3903	1050	1.7	1.6, 1.8	<0.0001	1736	951	1.5	1.5, 1.6	<0.0001
	SHS[b]	3927	1075	0.88	0.68, 1.1	0.34	1099	530	0.83	0.64, 1.1	0.16
	Asbestos exposure[b]	3580	1015	1.0	0.86, 1.3	0.62	1529	912	0.90	0.72, 1.1	0.39
	Family history lung cancer[b]	3905	1030	1.3	1.1, 1.6	0.01	1727	933	1.7	1.3, 2.2	0.0003
	$P_{smoking*asbestos}$					0.55					0.20
	$P_{smoking*sex}$					0.78					<0.0001
	$P_{smoking*shs}$					0.18					0.30
AIS (formerly BAC)	Ever Smoked[a]	226	1091	3.5	2.5, 5.0	<0.0001	103	974	1.8	1.2, 2.8	0.0045
	Pack-years (per 10 pack-years)[a]	219	1050	1.3	1.2, 1.3	<0.0001	102	951	1.2	1.1, 1.4	<0.0001
	SHS[b]	220	1075	0.95	0.57, 1.6	0.86	66	530	1.1	0.60, 2.1	0.71
	Asbestos exposure[b]	200	1015	0.71	0.45, 1.1	0.16	86	912	0.75	0.39, 1.4	0.38
	Family history lung cancer[b]	213	1030	0.94	0.59, 1.5	0.78	97	933	1.6	0.83, 2.9	0.17
	$P_{smoking*asbestos}$					0.07					0.89
	$P_{smoking*sex}$					0.61					0.42
	$P_{smoking*shs}$					0.05					0.50
	Never smoker	51	520	1.0			44	551	1.0.		
	Current smoker[c]	30	88	4.6	2.6, 8.0		20	90	3.1	1.7, 5.7	
	Former smoker[c]	137	474	3.2	2.3, 4.7		38	331	1.6	0.99, 2.7	
	Pack-years (quartiles)[c]										
	Q1 (<=5.75)	18	116	1.9	1.0, 3.5		13	110	1.8	0.92, 3.5	
	Q2 (5.76–16.25)	31	134	3.0	1.8, 5.1		6	108	0.59	0.21, 1.7	
	Q3 (16.26–31.5)	36	122	3.2	1.9, 5.4		17	109	2.2	1.2, 4.2	
	Q4 (>31.5)	83	158	6.4	4.1, 9.8		22	77	4.7	2.5, 8.7	

		Whites					Non-Whites				
Histology	**Factor**	**Cases**	**Controls**	**OR**	**95% CI**	**p-value**	**Cases**	**Controls**	**OR**	**95% CI**	***P*-value**
	P for trend				<0.0001					<0.0001	
	Years since quit[C]										
	≥ 21	69	285	2.7	1.8, 4.1		14	178	1.1	0.61, 2.4	
	11 – <21	38	114	3.4	2.1, 5.7		13	87	2.0	0.98, 4.2	
	1 – <11	30	75	5.5	3.1, 9.8		11	66	2.0	0.87, 4.5	
	Current/quit <1 year	30	88	4.7	2.7, 8.2		20	90	3.5	1.8, 6.5	
	P for trend				<0.0001					<0.0001	

Abbreviations: AIS, adenocarcinoma in situ BAC, bronchioloalveolar carcinoma; OR, odds ratio; CI, confidence interval; SHS, second-hand tobacco smoke

[a]All models adjusted for age and sex

[b]Additionally adjusted for ever smoking

[c]Never smokers also are the referent group for analyses of quartiles of pack-years and years since quit; also adjusted for asbestos exposure in whites and non-whites

Table 3

Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for adenocarcinoma in situ (AIS, formerly BAC) associated with cigarette smoking characteristics in men and in women, Bay Area Lung Cancer Study 1998–2003 and Northern California Lung Study 2005–2008

	Women and Men				Men				Women			
Smoking factors[a]	**AIS (n=338)**	**Controls (n=2073)**	**OR**	**95% CI**	**AIS (n=125)**	**Controls (n=1009)**	**OR**	**95% CI**	**AIS (n=213)**	**Controls (n=1064)**	**OR**	**95% CI**
Never smoker	95	1071	1.0		22	429	1.0		73	642	1.0	
Ever smoker	234	998	2.9	2.2, 3.8	100	577	3.1	1.9, 5.1	134	421	2.6	1.9, 3.5
Current smoker	50	178	3.9	2.6, 5.8	25	106	4.9	2.6, 9.1	25	72	3.2	1.9, 5.5
Former smoker	175	805	2.6	2.0, 3.4	72	464	2.7	1.6, 4.5	103	341	2.4	1.7, 3.3
Pack-years (quartiles)[b]												
Q1 (<=5.75)	31	226	1.7	1.1, 2.6	11	114	2.0	0.93, 4.3	20	112	1.8	1.0, 3.2
Q2 (5.76–16.25)	37	242	2.0	1.3, 3.0	12	144	1.6	0.74, 3.4	25	98	2.3	1.3, 3.9
Q3 (16.26–31.5)	53	231	2.9	2.1, 4.2	20	141	2.4	1.2, 4.8	33	90	3.2	1.9, 5.4
Q4 (>31.5)	105	235	5.7	4.2, 7.9	53	148	6.5	3.7, 11.6	52	87	5.1	3.2, 8.2
P for trend				<0.0001				<0.0001				<0.0001
Years since quit[b]												
≥ 21	89	512	2.0	1.5, 2.8	37	271	2.3	1.3, 4.0	46	192	1.7	1.2, 2.6
11 – <21	45	152	3.6	2.4, 5.4	21	110	3.1	1.6, 6.0	30	91	2.7	1.6, 4.4
1 – <11	41	141	3.8	2.5, 5.8	14	83	3.1	1.5, 6.7	27	58	4.1	2.4, 7.0
Current/quit <1 year	50	178	4.0	2.7, 5.8	25	106	4.4	2.3, 8.5	25	72	3.3	1.9, 5.5
P for trend				<0.0001				<0.0001				<0.0001

Abbreviations: AIS, adenocarcinoma in situ; BAC, bronchioloalveolar carcinoma; OR, odds ratio; CI, confidence interval

[a] All models adjusted for age and race; current smokers includes participants who had quit smoking <1 year prior to interview/diagnosis.

[b] Never smokers also are the referent group for analyses of quartiles of pack-years and years since quit. Pack-years and years quit also adjusted for any exposure to second-hand tobacco smoke and asbestos in gender-stratified analyses

Table 4

. Adjusted Odds Ratios (OR)and 95% Confidence Intervals (CI) for adenocarcinoma in situ (AIS, formerly BAC; N=125 men, N=213 women) compared with non-AIS non-small cell lung cancer (NSCLC), adenocarcinoma, and squamous cell lung cancer associated with cigarette smoking by sex, Bay Area Lung Cancer Study 1998–2003 and Northern California Lung Study 2005–2008

Men		**Non-AIS NSCLC (n=2562)**		**Adenocarcinoma (N=970)**		**Squamous (N=677)**	
	Smoking factors [a]	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
	Never smoker		1.0		1.0		1.0
	Ever smoker	0.41	0.25, 0.67	0.59	0.35, 0.98	0.18	0.10, 0.33
	Current smoker	0.27	0.15, 0.50	0.44	0.24, 0.82	0.10	0.05, 0.21
	Former smoker	0.54	0.32, 0.90	0.72	0.42, 1.2	0.26	0.14, 0.50
	Pack-years (quartiles) [b]						
	Q1 (<=5.75)	1.2	0.54, 2.6	1.2	0.59, 2.9	0.67	0.26, 1.7
	Q2 (5.76–16.25)	0.61	0.29, 1.3	0.74	0.34, 1.6	0.33	0.14,0.79
	Q3 (16.26–31.5)	0.48	0.24, 0.93	0.69	0.36, 1.3	0.24	0.11, 0.52
	Q4 (>31.5)	0.31	0.18, 0.54	0.50	0.29, 0.87	0.13	0.07, 0.25
	P for trend		<0.0001		0.003		<0.0001
	Years since quit [c]						
	≥21	1.1	0.57, 2.0	1.0	0.57, 1.9	0.63	0.30, 1.3
	11 – <21	0.54	0.28, 1.1	0.72	0.36, 1.4	0.22	0.10, 0.51
	1 – <11	0.25	0.12, 0.52	0.42	0.20, 0.85	0.09	0.04, 0.21
	Current/quit <1 year	0.26	0.14, 0.48	0.44	0.24, 0.82	0.09	0.04, 0.19
	P for trend		<0.0001		0.0003		<0.0001
Women		Non-AIS NSCLC (n=2457)		Adenocarcinoma (N=1176)		Squamous (N=444)	
	Never smoker		1.0		1.0		1.0
	Ever smoker	0.41	0.30, 0.57	0.57	0.40, 0.80	0.13	0.08, 0.21
	Current smoker	0.19	0.12, 0.31	0.26	0.16, 0.43	0.05	0.03, 0.10
	Former smoker	0.58	0.41, 0.81	0.79	0.55, 1.1	0.19	0.12, 0.32
	Pack-years (quartiles)						
	Q1 (<=5.75)	1.3	0.75, 2.3	1.2	0.67, 2.1	1.0	0.40, 2.5
	Q2 (5.76–16.25)	0.74	0.44, 1.3	0.79	0.47, 1.3	0.31	0.16, 0.63

Men		Non-AIS NSCLC (n=2562)		Adenocarcinoma (N=970)		Squamous (N=677)	
	Smoking factors [a]	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
	Q3 (16.26–31.5)	0.48	0.29, 0.76	0.64	0.40, 1.0	0.17	0.09, 0.31
	Q4 (>31.5)	0.30	0.19, 0.45	0.41	0.27, 0.62	0.07	0.04, 0.12
	P for trend		<0.0001		<0.0001		<0.0001
	Years since quit [c]						
	≥ 21	1.1	0.69, 1.7	0.97	0.62, 1.5	0.56	0.30, 1.1
	11 – <21	0.58	0.35, 0.96	0.84	0.51, 1.4	0.22	0.11, 0.42
	1 – <11	0.37	0.22, 0.62	0.57	0.35, 0.94	0.10	0.05, 0.18
	Current/quit <1 year	0.20	0.12, 0.34	0.26	0.16, 0.43	0.05	0.03, 0.10
	P for trend		<0.0001		<0.0001		<0.0001

Abbreviations: AIS, adenocarcinoma in situ; BAC, bronchioloalveolar carcinoma; OR, odds ratio; CI, confidence interval; NSCLC, non-small cell lung cancer

[a]All models adjusted for age and race; never smokers also are the referent group for analyses of pack-years and years since quit; ORs are for the specific lung cancer subtype compared with patients with AIS

[b]Also adjusted for exposure to asbestos and second-hand tobacco smoke exposure for lung adenocarcinoma

[c]Also adjusted for exposure to asbestos and second-hand tobacco smoke exposure for squamous cell lung cancer