

Association of Cigarette Smoking and Asbestos Exposure with Location and Histology of Lung Cancer

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Prior studies have suggested that lung cancers that arise in association with cigarette smoking favor an upper-lobe location while those associated with asbestos exposure favor a lower-lobe location. An excess of adenocarcinomas has also been reported among cases not exposed to cigarette smoke as well as among those exposed to asbestos. However, these studies typically have not adjusted adequately for potential confounders such as the patient's age, sex, race, or family history of cancer. To better examine the effects of cigarette smoking and asbestos exposure on location and histology of lung cancer, we analyzed data from a large case-control study that included 456 patients with stage I or II lung cancer. Patients with upper-lobe tumors tended to have had more exposure to tobacco as assessed by pack-years smoked (54.7 versus 46.2, $p = 0.07$) and less time since quitting smoking (3.0 versus 5.5 yr, $p = 0.05$). In contrast to some prior reports, asbestos exposure was also associated with an upper-lobe location of tumor. Among those with upper-lobe tumors, 14.6% had a history of significant asbestos exposure compared with 5.4% of those with lower-lobe tumors ($p < 0.01$). The relationship between asbestos exposure and upper-lobe location of tumor was also statistically significant whether stratified by smoking or analyzed by multivariable logistic regression modeling. Adenocarcinomas were more likely among those with less exposure to cigarette smoke based on fewer pack-years smoked (41.5 versus 61.8, $p = 0.0001$) and more time since quitting smoking (5.0 versus 3.0 yr, $p = 0.02$). The proportion of patients with significant exposure to asbestos was lower among those with adenocarcinomas but was not statistically significant (9.5 versus 15.3%, $p = 0.09$). In multivariable logistic regression analysis, longer time since smoking exposure remained a significant predictor of adenocarcinomas ($p < 0.02$), but history of asbestos exposure did not predict tumor histology. Thus, in patients with lung cancer, both cigarette smoking and asbestos exposure histories favor an upper-lobe location of tumor. Longer time since smoking exposure favors adenocarcinomas, but the history of asbestos exposure does not appear to influence the tumor histology.

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Lung cancer is currently the leading cause of cancer death in the United States. In 1995, more than 157,000 deaths were attributed to lung cancer (1). The two major known risk factors for bronchogenic carcinoma in humans are smoking and asbestos exposure (2, 3). Investigators have reported a 10-fold increase in the risk of lung cancer with smoking and a 3- to 4-fold increase associated with asbestos exposure (4, 5). Cur-

rent epidemiologic data favor a synergistic model for the two risk factors (6) so that individuals who are exposed to both tobacco smoke and asbestos have roughly a 30- to 50-fold increase in risk of developing lung cancer (4).

Tumors that arise in association with tobacco smoke exposure tend to occur in the upper lobes with a typical upper:lower ratio of roughly 2.5:1.0 (7-11). For example, among the 15,477 histologically proven cases of primary lung cancer among white men in the Surveillance, Epidemiology, and End Results (SEER) Study, 65% of the tumors originated in the upper lobes compared with 35% in the middle or the lower lobes (10). Among asbestos-exposed individuals, some studies have reported an inversion of this ratio, with a higher proportion of tumors occurring in the lower lobes (12-20). For example, in a study of 108 patients undergoing lobectomy or pneumonectomy for lung cancer, 62% of asbestos-exposed patients

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had lower-lobe tumors, in contrast to 25% of the nonexposed patients ($p < 0.0001$) (19). In a case-control study, the ratio of upper-lobe to lower-lobe tumors was 0.57 among 36 lung cancer patients exposed to asbestos and 2.23 among 42 lung cancer patients not exposed to asbestos (15). The higher prevalence of lower-lobe tumors among asbestos-exposed individuals has been attributed to the tendency of the tumor to arise from heavily fibrosed areas of the lung, which is most typically in the dependent portions of the lung (17, 21). In contrast to these studies, others have reported an upper-lobe predominance of cancer in asbestos-exposed individuals, a pattern similar to lung cancer arising in the general population with cigarette exposure (11, 13, 22–25). For example, in a study involving 196 lung cancer patients who were occupationally exposed to asbestos, 62% of the tumors originated in the upper lobes and 34% originated in the middle or the lower lobes (23). Among 29 lung cancers associated with asbestos exposure in another study, 66 and 34% were found in upper and lower lobes, respectively, which did not differ significantly from the distribution of tumor among 87 control subjects (71 and 25%, respectively) (24). Similarly, in a study involving 346 consecutively diagnosed cases of lung cancer, 58% of the tumors among asbestos-exposed individuals originated in the upper lobes as did 70% of the tumors among nonexposed individuals (p value not significant [NS]) (13). However, none of these studies showing upper-lobe predominance had adequately controlled for smoking (13, 23, 24). Therefore, there are conflicting data on the association between asbestos exposure and lobe of origin of lung cancer.

Some studies have reported an excess of adenocarcinomas among asbestos-exposed individuals (14, 24, 26) while other studies have failed to confirm such an association (11, 15, 19, 25, 27–29). These studies had not adequately adjusted for confounding variables such as sex or smoking history, which have been shown to affect the histology of tumor (30–33). Such debates regarding the more likely location and the histology of bronchogenic tumors associated with asbestos exposure are not trivial in that these features of a patient's tumor have been used to argue for or against one's tumor being attributable to asbestos exposure (18). In this study, we examined data from a large case-control study of 456 patients with stage I or II lung cancer in which detailed occupational and smoking histories were obtained.

METHODS

This study is part of a large case-control study of incident cases of lung cancer at the Massachusetts General Hospital (MGH), which involved genotyping for metabolic polymorphisms and determination of DNA adduct levels from peripheral leukocytes and lung tissue (34). Thus, all case subjects had surgically resected lung cancer; eligible cases included all patients with newly diagnosed primary lung cancers (stages I or II) presenting to the thoracic surgery service at MGH between December 1, 1992 and August 15, 1996. The study was approved by the Human Subjects Committees at MGH and the Harvard School of Public Health. All cases were confirmed by histologic examination of the surgically resected tumor sample. Of the 562 eligible cases during the study period, 42 refused to participate, 34 were missed, 26 were unable to participate, and four agreed to participate but did not complete the questionnaires. Thus, 456 (81%) remaining cases were included in this analysis.

Demographic information from case and control subjects (gender, age, race, education, and family history of cancer) was collected by an extensive questionnaire administered by trained interviewers at the hospital. The race of the subjects was categorized as white versus non-white. Patients with at least some college education were considered to have a "high" level of education and those completing up to high school education were considered to have a "low" level of education.

A patient with any biological parent or sibling with a history of any known cancer, other than nonmelanomatous skin cancers, was considered to have a family history of cancer.

Smoking history and other occupational or environmental exposure information were collected using a modified standardized American Thoracic Society respiratory questionnaire (35). This questionnaire included information on current smoking status, total pack-years of smoking exposure, number of years since quitting smoking, and period and frequency of exposure to other environmental or occupational substances such as asbestos and solvents. Patients were assigned a current smoking status based on whether they had never smoked (nonsmokers), had not smoked for more than 1 yr (ex-smokers), or were smoking at the time of the study (current smokers). Those who had quit smoking for less than 1 yr were classified as current smokers for the purposes of this analysis. The number of years since quitting smoking was considered to be zero for current smokers, and the age of the patient was used for this value for those who had never smoked. Primary tumors located in the right lower lobe, right middle lobe, or the left lower lobe were classified as lower-lobe tumors. Primary tumors located in the right upper lobe or the left upper lobe were classified as upper-lobe tumors. Histology of the tumor was dichotomized as adenocarcinomas versus other tumors (squamous cell, large cell, or small cell) because adenocarcinoma was reportedly associated with asbestos exposure in some prior studies (14, 24, 26), and fewer than 9% of the tumors were large cell or small cell carcinomas.

Asbestos exposure was assessed using a previously described asbestos exposure index (36). This index was derived based on knowledge of asbestos exposure in the New England building construction trades. The heaviest asbestos exposure occurred prior to 1965. By 1965, the use of fiberglass insulation for new insulation application became well established and widespread. Therefore, after 1965, exposure to asbestos occurred mainly during repair, remodeling, or renovation work. After 1972, the use of asbestos for new insulation and fireproofing was discontinued. The promulgation of the permissible exposure limit for asbestos by the Occupational Safety and Health Administration in 1972 also helped to reduce workplace exposures further. Thus, the weighted duration of asbestos exposure was calculated for each subject based on the duration of work during these three time periods: a weight of 4 was given to each year of asbestos exposure prior to 1965, a weight of 2 was given to each year worked from 1965 to 1972, and a weight of 1 was given to each year worked after 1972. In addition, specific jobs were assigned a weight (intensity factor) ranging from 4–6 depending on the type of exposure. For example, a weight of 4 was assigned to the following types of exposure: automobile repair, brake mechanic, building maintenance, carpentry, demolition of buildings, drywall hanging, fire fighting, smelting, tunnel construction, and welding; a weight of 5 was assigned to the following types of exposure: boiler making, foundry work, iron/steel manufacturing, pipe fitting, construction work; a weight of 6 was assigned to the following types of exposure: insulation installation, pipe covering/

TABLE 1
BASELINE CHARACTERISTICS OF PATIENTS WITH RESPECT
TO THE LOCATION OF LUNG CANCER

	Lower-lobe Tumors	Upper-lobe Tumors	p Value
Number of subjects	117	280	
Mean age, yr	68.1 (9.6) [†]	66.1 (10.1) [†]	0.07*
Mean height, cm	170.2 (9.9) [†]	170.2 (10.3) [†]	> 0.95*
Mean weight, kg	73.4 (17.7) [†]	75.8 (17.4) [†]	> 0.20*
Sex, % female	48.7	46.1	> 0.65 [‡]
Race, % nonwhite	2.6	3.6	> 0.75 [‡]
Family history of cancer, %	15.3	24.1	0.08 [‡]
Education, % low education	54.9	59.2	> 0.45 [‡]
Adenocarcinoma, %	60.2	61.5	> 0.80 [‡]
Squamous cell, %	31.5	29.6	> 0.80 [‡]
Large cell, %	4.6	6.2	> 0.80 [‡]
Small cell, %	3.7	2.7	> 0.80 [‡]

* Unpaired *t* test.

[†] Standard deviation.

[‡] Fisher exact test.

TABLE 2
BASELINE CHARACTERISTICS OF PATIENTS WITH RESPECT TO
THE HISTOLOGY OF LUNG CANCER

	Adenocarcinoma	Other Tumors	p Value
Number of subjects	246	172	
Mean age, yr	65.0 (10.8) [†]	67.7 (9.2) [†]	< 0.008*
Mean height, cm	169.6 (10.0) [†]	170.3 (10.1) [†]	> 0.50*
Mean weight, kg	72.8 (16.2) [†]	75.6 (16.8) [†]	0.10*
Sex, % female	52.0	38.4	0.007 [†]
Race, % nonwhite	4.9	1.2	0.05 [†]
Family history of cancer, %	21.2	22.1	0.90 [†]
Education, % with high education	44.6	35.3	0.07 [†]
Location, % in lower lobe	29.2	30.3	> 0.80 [†]

* Unpaired *t* test.

[†] Standard deviation.

[†] Fisher exact test.

insulating, ship building/repair. Finally, a cumulative index (asbestos exposure index) representing the intensity as well as the weighted duration of asbestos exposure was calculated for each subject by multiplying the number of years of exposure, the weight based on specific years of exposure, and the intensity factor. Thus, a subject who had worked year-round for 2 yr as a shipbuilder before 1965 would have an index score of 48 ($2 \times 4 \times 6$) and a subject who had worked year-round as an automobile mechanic for 3 yr after 1972 would have an index score of 12 ($3 \times 1 \times 4$). Based on this score, subjects were assigned one of seven categories of asbestos exposure: score of zero; 1–5; 6–20; 21–40; 41–80; 81–160; and > 160. Subjects with a score > 20 were defined to have had “significant” exposure and those with a score ≤ 20 were defined to have had “nonsignificant” exposure to asbestos. The cut-off point was selected based on our observation of a step-up increase in lung cancer risk when the asbestos exposure score exceeded 20 and the lack of a demonstrable increase in lung cancer risk when the score was ≤ 20. Patients were also assigned a smoking-asbestos exposure interaction category as follows: (1) nonsmokers without significant asbestos exposure; (2) ex-smokers without significant asbestos exposure; (3) current smokers without asbestos exposure; (4) ex-smokers with significant asbestos exposure; and (5) current smokers with significant asbestos exposure. Because there was only one nonsmoker who had significant asbestos exposure, this subject was assigned to category 2 along with ex-smokers without significant asbestos exposure. Questions about current habits were referred to time of diagnosis for cases and time of interview for controls.

Initially, univariate analysis was used to examine the potential associations of age, height, weight, sex, race, level of education, family history of cancer, smoking history, asbestos exposure history, and tumor histology on the location of tumor among 397 patients whose lobe of origin was known. Similar analyses were performed to examine the potential associations of age, height, weight, sex, race, level of education, family history of cancer, smoking history, asbestos exposure history, and tumor location on the histology of tumor among 418 patients whose tumor histology was known. Statistical analysis was performed using two-tailed *t* test for unpaired data to compare the means of continuous normal variables such as age, height, and weight. The Wilcoxon rank-sum test was used to compare continuous non-normal variables such as pack-years of smoking, and years since quit-

ting smoking. The Fisher exact test was used to analyze categorical variables such as sex, race, family history of cancer, and level of education. The Mantel-Haenszel test for trend was used to compare ordinal variables such as current smoking status or the smoking-asbestos interaction category.

The variables found to have significant influence on the location of the tumor in univariate analysis were included in a multivariable logistic regression model to account for the effects of potential confounders and effect-modifiers. Similarly, the variables found to have significant influence on tumor histology in univariate analysis were included in a multivariable logistic regression model to account for the effects of potential confounders and effect-modifiers. All statistical analyses were performed on SAS software (SAS Institute Inc., Cary, NC).

RESULTS

The descriptive characteristics of the patients included in the analysis are summarized in Tables 1 and 2. The 280 patients with upper-lobe tumors (70.5% of subjects) tended to be somewhat younger (66.1 versus 68.1 yr, $p = 0.07$) and more likely to have a family history of cancer (24.1 versus 15.3%, $p = 0.08$) in contrast to the 117 patients with lower-lobe tumors (29.5% of subjects). There were no significant differences between the two groups with regard to height, weight, sex, race, education level, and tumor histology. The 246 patients with adenocarcinoma (58.8% of subjects) were younger (65.0 versus 67.7 yr, $p < 0.008$), more likely to be female (52.0 versus 38.4%, $p = 0.007$), nonwhite (4.9 versus 1.2%, $p = 0.05$), and tended to be better educated (44.6 versus 35.3% with high education, $p = 0.07$) than the 172 patients with other types of tumors (41.2% of subjects). Among men, 52.7% had adenocarcinomas, and 47.3% had other types of tumors; among women, 66.0% had adenocarcinomas, and 34.0% had other types of tumors ($p = 0.007$). There were no significant differences between the two groups with regard to height, weight, family history of cancer, and tumor location.

Tumor Location

Smoking history had a strong influence on tumor location (Table 3, Figure 1). Patients with upper-lobe tumors tended to have had more exposure to tobacco based on median pack-years smoked (54.7 versus 46.2, $p = 0.07$) as well as a lower median time since quitting smoking (3.0 versus 5.5 yr, $p = 0.05$) than those with lower-lobe tumors. In addition, the proportion of patients with upper-lobe and lower-lobe tumors, respectively, varied from 56.5 and 43.5% among nonsmokers, to 68.8 and 31.2% among ex-smokers, and to 75.7 and 24.3% among current smokers (Mantel-Haenszel trend test, $p = 0.04$).

History of asbestos exposure also had a strong influence on the location of the tumor (Table 3 and Figure 2). In contrast to some prior reports, patients with upper-lobe tumors tended to have had more exposure to asbestos based on a higher mean asbestos exposure index score (23.1 versus 16.6 yr, $p < 0.05$) and a higher proportion of patients with significant exposure to asbestos (14.6 versus 5.4%, $p < 0.01$; OR = 3.00; 95% CI: 1.28–7.04) compared with those with lower lobe tumors. Stated

TABLE 3
RELATIONSHIP BETWEEN SMOKING, ASBESTOS EXPOSURE, AND THE LOCATION OF LUNG CANCER

	Lower-lobe Tumors	Upper-lobe Tumors	p Value
Median pack-years of smoking	46.2	54.7	0.07*
Median time since quitting smoking, yr	5.5	3.0	0.05*
Mean asbestos exposure index score, yr	16.6	23.1	< 0.05*
Significant exposure to asbestos, %	5.4	14.6	< 0.01 [†]

* Wilcoxon rank-sum.

[†] Fisher exact test.

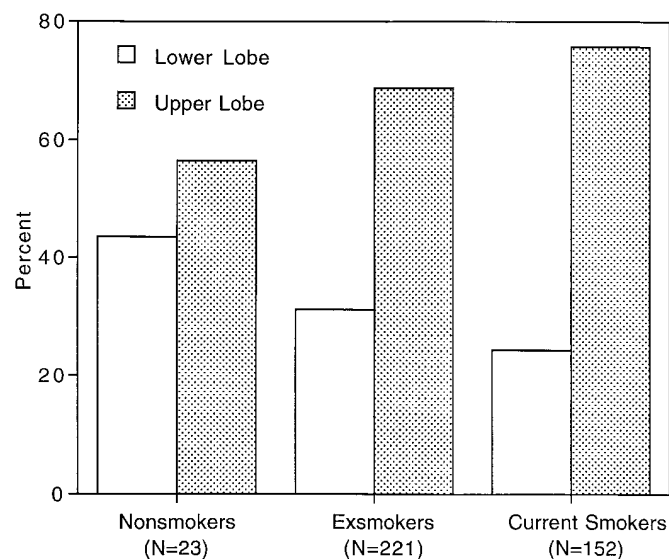


Figure 1. Relationship between current smoking status and location of tumor. Mantel-Haenszel trend test, $p = 0.04$.

another way, among those with a history of significant exposure to asbestos (score > 20), 87.2% of the tumors were found in the upper lobes and 12.8% were found in the lower lobes; of those without a history of significant exposure to asbestos, 69.5% of the tumors were found in the upper lobes and 30.5% were found in the lower lobes ($p < 0.01$).

Four patients in our study had a clinical diagnosis of asbestosis; all had an asbestos exposure index score > 20 (range 126–672). All four patients had upper-lobe tumors, three in right upper lobe, and one in left upper lobe.

The combined influence of smoking and asbestos exposure histories on the location of tumor is demonstrated in Figure 3. The proportion of patients with upper-lobe tumors increased in a stepwise fashion (Mantel-Haenszel trend test, $p = 0.001$) from 54.6% among those in category 1 (nonsmokers with no significant asbestos exposure); 67.6% among those in category

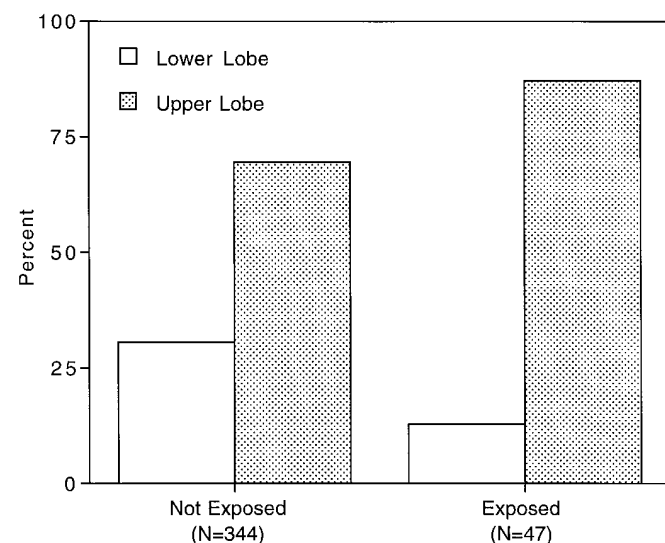


Figure 2. Relationship between asbestos exposure and location of tumor. Fisher exact, $p < 0.01$.

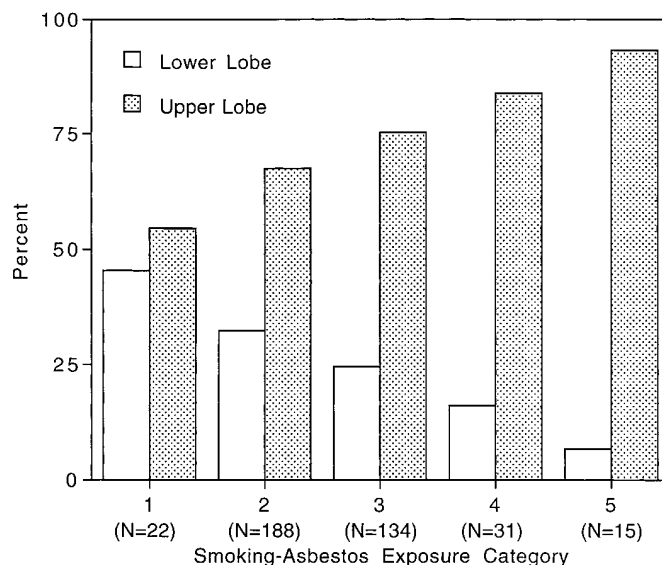


Figure 3. Relationship between smoking-asbestos exposure category and location of tumor. Mantel-Haenszel test for trend, $p = 0.001$. (See text for explanation of categories.)

2 (ex-smokers with no significant asbestos exposure or nonsmokers with significant asbestos exposure); 75.5% among those in category 3 (current smokers without significant asbestos exposure); 83.9% among those in category 4 (ex-smokers with significant asbestos exposure); to 93.3% among those in category 5 (current smokers with significant asbestos exposure history).

The relationship between asbestos exposure and upper-lobe tumor location remained significant ($\beta = 1.54$; OR = 4.66, 95% CI: 1.60–13.57; $p < 0.005$) when adjusted for age, family history of cancer, current smoking status, and time since quitting smoking in a multivariable logistic regression model (Table 4). Thus, the relationship between asbestos exposure history and upper-lobe location of the tumor was significant whether based on univariate analysis (OR = 3.00; 95% CI: 1.28–7.04; $p = 0.01$), stratified by smoking (OR = 3.03; 95% CI: 1.28–7.18; $p = 0.01$), or analyzed by multivariable logistic regression modeling (OR = 4.66; 95% CI: 1.60–13.57; $p < 0.005$).

Tumor Histology

Smoking history had a strong influence on tumor histology (Table 5, Figure 4). In univariate analysis, patients with ade-

TABLE 4
MULTIVARIABLE LOGISTIC REGRESSION MODEL OF LUNG CANCER LOCATION IN RELATION TO HISTORY OF ASBESTOS EXPOSURE

	β	p Value	OR (95% CI)*
Age	-0.02	0.18	0.98 (0.96–1.01)
Smoking status: ex-smoker	1.82	0.08	6.18 (0.78–48.71)
Smoking status: current smoker	2.28	0.07	9.79 (0.86–110.96)
Time since quitting smoking	0.02	0.20	1.02 (0.99–1.05)
History of significant asbestos exposure	1.54	< 0.005	4.66 (1.60–13.57)
Family history of cancer	0.41	0.22	1.51 (0.77–2.94)

Model: $\text{Log}(\rho)/(1 - \rho) = \beta_0 + \beta_1(\text{age}) + \beta_2(\text{ex-smoker}) + \beta_3(\text{current smoker}) + \beta_4(\text{time since quitting smoking}) + \beta_5(\text{asbestos exposure}) + \beta_6(\text{family history of lung cancer})$; ρ = probability of upper-lobe location of tumor.

* 95% confidence interval.

TABLE 5
RELATIONSHIP BETWEEN SMOKING, ASBESTOS EXPOSURE, AND THE HISTOLOGY OF TUMOR

	Adenocarcinoma	Other Histology	p Value
Median pack-years of smoking	41.5	61.8	0.0001*
Median time since quitting smoking, yr	5.0	3.0	0.02*
Mean asbestos exposure index score, yr	15.4	28.6	> 0.50*
Significant exposure to asbestos, %	9.5	15.3	0.09†

* Wilcoxon rank-sum.

† Fisher exact test.

nocarcinomas tended to have had less exposure to tobacco based on median pack-years smoked (41.5 versus 61.8, $p = 0.01$) and more time since quitting smoking (median of 5.0 versus 3.0 yr, $p = 0.02$) compared with those with other types of tumors. In addition, the proportion of patients with adenocarcinomas tended to decrease from 80.0% among nonsmokers, to 58.8% among ex-smokers, and to 55.8% among current smokers (Mantel-Haenszel trend test, $p = 0.08$).

Asbestos exposure history did not have a clear influence on tumor histology in univariate analysis (Table 5, Figure 5). Among those with adenocarcinomas, 9.5% reported exposure to asbestos in contrast to 15.3% of those with other types of lung cancer, but the difference was not statistically significant (OR = 1.72; 95% CI: 0.95–3.12; $p = 0.09$). Stated another way, adenocarcinomas comprised 46.9% of the tumors among those exposed to asbestos compared with 60.3% of those not exposed to asbestos ($p = 0.09$). Of the four patients with a diagnosis of asbestosis, three patients had squamous cell carcinomas and one had an adenocarcinoma.

The combined influence of cigarette smoking and asbestos exposure on tumor histology is demonstrated in Figure 6. The proportion of patients with adenocarcinomas tended to decrease in a stepwise fashion (Mantel-Haenszel trend test, $p < 0.03$) from 79.2% among those in category 1 (nonsmokers with no significant asbestos exposure); 61.3% among those in category 2 (ex-smokers with no significant asbestos exposure or nonsmokers with significant asbestos exposure); 56.2% among those in category 3 (current smokers without significant asbestos exposure); 40.6% among those in category 4 (ex-

smokers with significant asbestos exposure); to 56.3% among those in category 5 (current smokers with significant asbestos exposure history).

As shown in Table 6, longer time since smoking exposure remained a significant predictor of adenocarcinomas in a multivariable logistic regression model which adjusted for age, sex, race, education, and asbestos exposure ($\beta = -0.04$, $p < 0.02$). However, the relationship between asbestos exposure and tumor histology remained statistically nonsignificant ($\beta = 0.33$, $p = 0.33$) in the multivariable logistic regression model.

DISCUSSION

Our analysis of patients with stage I or II lung cancer supports previous reports of an association between upper-lobe location of lung cancer and smoking (7–11). Patients with upper-lobe tumors tended to have had more pack-years of tobacco exposure as well as shorter median time since quitting smoking. In addition, and exposure-response relationship could be demonstrated between the proportion of patients with upper-lobe tumors and current smoking status of the patients. Among nonsmokers, the proportion of tumors in the upper lobes versus the lower lobes was statistically similar. In contrast, the proportion of tumors in the upper lobes was 68.8% among ex-smokers and 75.7% among current smokers (Mantel-Haenszel trend test, $p = 0.04$). In multivariable logistic regression analysis which adjusted for asbestos exposure, age, and family history of lung cancer, the relationship between smoking exposure and upper-lobe predominance of lung cancer was of border-

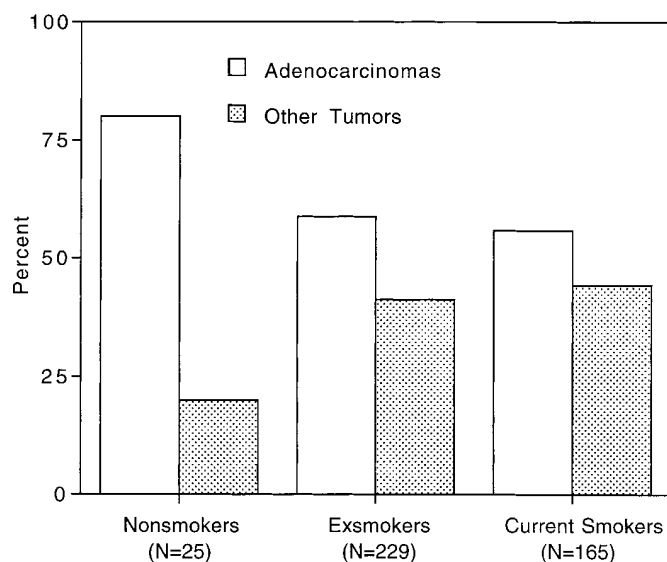


Figure 4. Relationship between current smoking status and histology of tumor. Mantel-Haenszel trend test, $p = 0.08$.

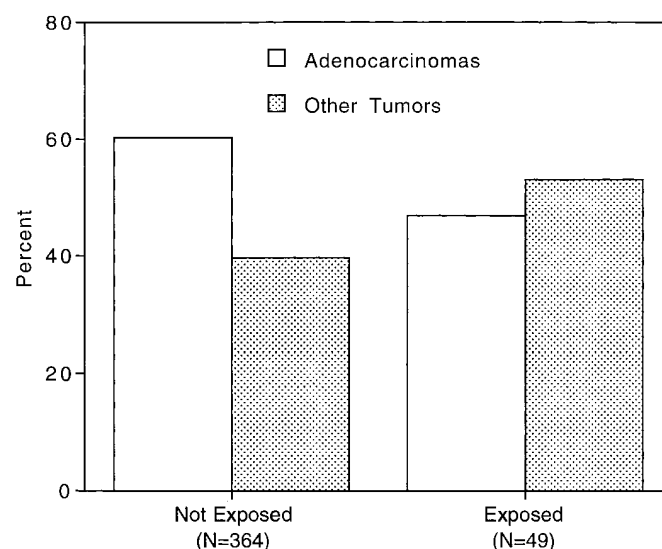


Figure 5. Relationship between asbestos exposure history and histology of tumor. Fisher exact, $p = 0.09$.

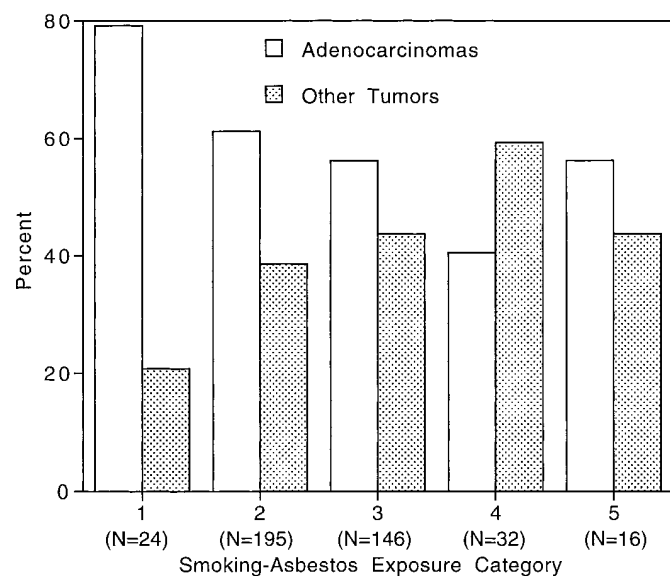


Figure 6. Relationship between smoking-asbestos exposure category and tumor histology. Mantel-Haenszel test for trend, $p < 0.03$. (See text for explanation of categories.)

line statistical significance ($p = 0.07$ for ex-smokers and $p = 0.08$ for active smokers). However, the borderline statistical significance may have been in part due to inadequate power of the study. When nonsignificant predictors were removed from the saturated multivariable logistic regression model, the relationship between smoking and upper-lobe location was statistically significant ($p < 0.05$).

The pathophysiological basis for the predominance of upper-lobe location of lung cancer among smokers is not known but a similar upper-lobe predominance is observed for emphysema among smokers. For both emphysema and lung cancer, an upper-lobe predominance is observed despite the fact that a higher proportion of the ventilation occurs in the lower lobes. It is possible that toxins and carcinogens may persist longer in the upper lobes due to less relative ventilation or less efficient lymphatic clearance. Alternatively, the delivery of protective substances via the circulation may be relatively lower in the upper lobes compared with the lower lobes per unit of toxin-carcinogen in cigarette smoke delivered via the airways. For example, numerous cohort and case-control studies have reported an inverse relationship between intake of

foods containing carotenoids and the risk of lung cancer (37–40) as well as a significant inverse relationship between serum β -carotene levels and lung cancer risk (41–43). Similar relationships have been reported with intake of vitamins C (44–46) and E (42, 43, 47). These observations lend support to the hypothesis that a circulating factor with possible antioxidant properties may be protective against lung cancer. Although recent prospective randomized controlled trials did not find supplemental intake of β -carotene to be protective against development of lung cancer in high-risk individuals (48, 49), it is still likely that other substances in vegetables and fruits are beneficial. If so, one can speculate that the balance between the protective substances delivered via the circulation (i.e., antioxidants) and the toxin-carcinogens delivered via the airways (i.e., components of cigarette smoke) would be less favorable in the upper lobes compared with the lower lobes, hence accounting for the predominance of upper-lobe tumors among smokers.

In contrast to some prior reports, exposure to asbestos was also associated with an upper-lobe location of lung cancer. Since lung cancers associated with smoking exposure tend to occur in the upper lobes and smoking and asbestos exposure have multiplicative effects on the risk of lung cancer, it is not surprising that asbestos exposure would also favor an upper-lobe location of lung cancer. In addition, the upper-lobe predominance of lung cancers associated with asbestos exposure is consistent with reports that the asbestos fiber concentration may be higher in the upper lobes than in the lower lobes. For example, in a carefully conducted study examining nine morphologically normal whole left lung specimens of subjects occupationally exposed to asbestos, the concentration of asbestos fibers determined by electron microscopy was highest in the apices and lowest in the bases (50). Since pulmonary fibrosis associated with asbestos exposure occurs in a lower-lobe distribution, the upper-lobe predominance of lung cancers associated with asbestos exposure suggests that the pathophysiologic mechanisms leading to pulmonary fibrosis versus development of lung cancer are not necessarily identical. It is possible that development of pulmonary fibrosis is associated primarily with delivery of inflammatory cells and mediators via the circulation (favoring a lower-lobe location). In addition to possibly greater deposition of asbestos fibers in the upper lobes (50), the development of lung cancer may be inversely associated with the amount of antioxidants delivered via the circulation (favoring an upper-lobe location). Thus, further studies aimed at examining the relationship between consumption of vegetables containing carotenoids or dietary intake vitamins A, C, and E and location of lung cancer would be of considerable interest, especially in regard to how the intake of these substances influences the effects of smoking and asbestos exposure on tumor location.

Some studies have reported an association between asbestos exposure and predominance of adenocarcinoma in patients with lung cancer (14, 24, 26). However, others have failed to support such findings (11, 15, 19, 25, 27). Our analysis adjusted for potential confounders and effect modifiers such as age, sex, race, education level, and smoking in a multivariable logistic regression model and did not reveal any statistically significant relationship between asbestos exposure and tumor histology. As in prior reports (31, 32), younger age, female sex, and absence of exposure to cigarette smoke were independent predictors of adenocarcinomas in our study.

The results of our study are in agreement with prior studies reporting no specific association between asbestos exposure and tumor histology (11, 15, 19, 25, 27). However, our results conflict with many studies that reported a lower-lobe predom-

TABLE 6
MULTIVARIABLE LOGISTIC REGRESSION MODEL OF
HISTOLOGY OF LUNG CANCER IN RELATIONSHIP TO
HISTORY OF ASBESTOS EXPOSURE

	β	p Value	OR (95% CI)*
Age	0.04	0.001	1.04 (1.02–1.06)
Sex	0.53	0.02	1.70 (1.08–2.66)
Race	–1.30	0.10	0.27 (0.06–1.31)
Education level	–0.41	0.08	0.67 (0.42–1.05)
Smoking status: ex-smoker	–1.02	0.33	0.36 (0.05–2.83)
Smoking status: current smoker	–1.24	0.30	0.29 (0.03–3.07)
Time since quitting smoking	–0.04	< 0.02	0.96 (0.94–0.99)
History of significant asbestos exposure	0.33	0.33	1.40 (0.71–2.72)

Model: $\text{Log}(\rho)/(1 - \rho) = \beta_0 + \beta_1(\text{age}) + \beta_2(\text{sex}) + \beta_3(\text{race}) + \beta_4(\text{education level}) + \beta_5(\text{ex-smoker}) + \beta_6(\text{current smoker}) + \beta_7(\text{time since quitting smoking}) + \beta_8(\text{asbestos exposure})$; ρ = probability of nonadenocarcinomas.

* 95% confidence interval.

inance of tumors associated with asbestos exposure (12–20). Most of these latter studies have been small in size or have not adjusted adequately for confounding variables such as age, family history of cancer, or smoking status (12–18). Of the studies that found an association between lower-lobe location of cancer and asbestos exposure, the only one to include more than 100 patients and to adjust adequately for confounding variables was the study by Karjalainen and coworkers (19). In that study, 62% of lung cancer patients exposed to asbestos had a tumor in the lower lobes in contrast to only 25% of those not exposed to asbestos. The difference was statistically significant ($p < 0.001$) and was reportedly adjusted for age and pack-years of smoking in a logistic regression model. In another report of 90 patients from the same investigators, the proportion of lower lobe tumors increased from 25% among subjects not exposed to asbestos, to 45% among those with < 15 yr of asbestos exposure, and to 82% among those with ≥ 15 yr of asbestos exposure (20). The reason why the lobar distribution of lung cancer in our study differs from these two Finnish reports is unclear. One potential reason is that their population may not have been representative of the general population with lung cancer since patients with more smoking exposure (≥ 40 pack-years) actually had less upper-lobe predominance of tumor in contrast to those with less smoking exposure (< 40 pack-years); 56% of those with ≥ 40 pack-years of smoking history had upper-lobe tumors compared to 65% of those with < 40 pack-years ($p = \text{NS}$) (19). Furthermore, description of the study subjects in the two Finnish studies (19, 20) suggests that data from same individuals may have been used in both studies. Thus, it would be more accurate to consider these reports as essentially one study rather than two independent observations.

There are several potential limitations to our study. The patients with upper-lobe tumors were not entirely comparable to those with lower-lobe tumors since patients with upper-lobe tumors tended to be older and more of them had family members with lung cancer. However, these differences were not statistically significant. Moreover, multivariable logistic regression analysis which adjusted for these factors did not change the relationships between smoking, asbestos exposure, and tumor location.

Another limitation is that our population was restricted to patients with operable tumors (stage I or II). However, there is no reported difference in the proportion of operable tumors based on the lobe-of-origin of the tumor (51) nor is there a reported difference in the proportion of operable tumors based on the asbestos exposure status (52). Therefore, it is unlikely that selection of only operable lung cancers would have biased the study in terms of tumor location. On the other hand, restricting the study to operable lung cancers would have affected the tumor histology since operability is based in part on tumor histology. Correspondingly, fewer than 3% of the patients in our study had small cell carcinoma. Since small cell carcinoma may be more common among female smokers (30, 33, 53, 54) and women are much less likely to have been exposed to asbestos, inclusion of only a few patients with small cell carcinoma in our study may have masked a positive association between asbestos exposure and adenocarcinoma. Nevertheless, our findings are consistent with most studies which have found no specific cell type predominating in asbestos-associated lung cancers (11, 15, 19, 25, 27–29), including the study by Kannerstein and Churg in which 78% of the samples were obtained nonsurgically (autopsy 66% or biopsy 12%) and small cell carcinomas comprised 25% of the case-control series (15).

Another limitation of our study is that patients with a his-

tory of asbestos exposure were not further analyzed for radiographic or histologic evidence of pulmonary or pleural fibrosis. It is possible that an association between lower-lobe location of tumor and asbestos exposure may only be apparent among those with asbestosis. Most of the earlier studies that reported lower-lobe predominance of cancer in asbestos-exposed patients had asbestosis (12–15). In contrast, most of the prior studies that reported an upper-lobe predominance of cancer among asbestos-exposed patients did not restrict the population to those with asbestosis (11, 13, 23–25). It is also possible that an association between adenocarcinoma cell type and asbestos exposure may only be apparent among those with asbestosis. For example, although the study by Karjalainen and coworkers did not find any difference in distribution of cell type among patients exposed and not exposed to asbestos, there was a predominance of adenocarcinomas among those with asbestosis. Although radiographic or histologic evidence of asbestosis was not part of our data set, four patients in our study had a diagnosis of asbestosis. All had an asbestos exposure index score > 20 (range 126–672), all had upper-lobe tumors, and only one had an adenocarcinoma. Although analysis of these four patients is not an adequate substitute for systemic study of patients with histologic or radiographic evidence of asbestosis, our data do not support the hypothesis that inclusion of more patients with asbestosis would have demonstrated a lower-lobe predominance of tumor or a predominance of adenocarcinoma. Furthermore, a recent study did not find any difference between asbestos-exposed patients with and without asbestosis in regard to tumor location (19).

In our analysis of surgical patients with stage I and II lung cancer, both cigarette smoking and asbestos exposure were associated with an upper-lobe location of tumor while absence and cessation of smoking tended to favor adenocarcinoma histology. However, asbestos exposure did not influence tumor histology. Further studies that include nonsurgical cases of lung cancer, more patients with small cell carcinoma, and more information about presence or absence of asbestosis may help to strengthen these observations.

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