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Cigarette Smoking and Risk of Lung Metastasis from Esophageal Cancer

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Abstract

Background—While extensive research has explored the impact of environmental factors on the etiology of specific cancers, the influence of exposures such as smoking on risk of site-specific metastasis is unknown. We investigated the association of cigarette smoking with lung metastasis in esophageal cancer.

Methods—We performed a case-control study of esophageal cancer patients from two centers, comparing cases with lung metastases to controls without lung metastases. Information was gathered from medical records on smoking history, imaging results, site(s) of metastasis, and other patient and tumor characteristics. We used logistic regression to assess association.

Results—We identified 354 esophageal cancer cases; smoking status was known in 289 (82%). Among patients with lung metastases, 73.6% (39/53) were ever smokers, versus 47.8% (144/301) of patients without lung metastases (p=0.001) (summary OR 2.52, 95%CI 1.17-5.45; stratified by histology). Smoking was associated with a nonsignificant increased adjusted odds of lung metastasis (OR 1.89, 95%CI 0.80-4.46). Upper esophageal subsite (OR 4.71, 95%CI 1.20-18.5) but not histology (squamous OR 0.65,95%CI 0.27-1.60) was associated with lung metastasis. Compared to the combined never/unknown smoking status group, smoking was associated with a significantly increased odds of lung metastasis (OR 2.35, 95%CI 1.11-4.97). There was no association between liver metastasis and smoking (OR 0.88, 95%CI 0.42-1.83)

Conclusions—Smoking is associated with increased odds of lung metastasis from esophageal cancer, and this relationship appears to be site-specific. Future studies are needed to determine whether smoking affects the tumor cell or the site of metastasis, and whether this changes the survival outcome.

Keywords

smoking; metastasis; esophageal cancer; epidemiology

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Introduction

While extensive research has investigated etiologic factors, both genetic and environmental, for most primary cancers, much less attention has focused on the reasons for the sites of metastasis associated with each cancer. In 1889, Stephen Paget first proposed the theory that cancer metastasis is site-specific, and a link exists between a primary tumor cell (the “seed”) and its site of metastasis (the “soil”) (1). In the past century, much progress has been made to further our knowledge of the behavior of the “seed” as it grows and spreads through the body (2). However, the endogenous and exogenous factors that relate the growth of a primary tumor and the characteristics of the distant site of metastasis are still incompletely understood.

There exists an emerging body of promising laboratory data on the prevention of cancer metastasis (3-7). Several novel targets have been identified as possible sites of therapeutic intervention as a means of preventing cancer spread (8-15). However, epidemiologic data that define high-risk patients for site-specific metastasis are lacking.

Esophageal cancer has a poor prognosis with a 15% 5-year survival (16); the vast majority of these patients die as a result of metastatic disease (17). The most common sites of metastasis are the regional lymph nodes, liver, lungs, and bone (18-20). Whether patterns of spread differ between adenocarcinoma and squamous cell cancer is not known. Retrospective studies have reported that 11-32% of esophageal cancer patients develop lung metastases, and 26-52% develop liver metastases (19-22). It is unclear whether the observed differences were due to cell type, study design, or the more proximal location of squamous cell cancers in the esophagus as compared to adenocarcinomas. There is also a higher prevalence of prior tobacco use among squamous cell cancer patients, and tobacco use itself may increase the risk of lung metastasis.

In order to evaluate the role of smoking on the risk of lung metastasis in esophageal cancer, we performed a retrospective hospital-based prevalent case-control study of patients with esophageal cancer.

Materials and Methods

Study sites

The study was conducted at Columbia University and Weill Cornell Medical Centers in New York, NY. Both are tertiary care centers with a large referral base for the management of Barrett's esophagus and esophageal cancer. The patient population is ethnically and socio-economically diverse and comes from the New York City tri-state area (New York, New Jersey, and Connecticut).

Study subjects

Esophageal cancer patients from Columbia were identified by searching the Department of Surgical Pathology database from 1997-2005. All tissue samples submitted for review (i.e., biopsies, surgical resections) at Columbia are entered into this database and assigned an ICD-9 code. Cases were identified by searching for ICD-9 codes 150.0-150.9 (neoplasm of the esophagus) and 151.0 (neoplasm of the gastro-esophageal (GE) junction).

Esophageal cancer patients from Cornell were identified from a database maintained by one of the investigators (NKA) from 1988 through April 2006 of patients who had undergone esophagectomy for histologically confirmed primary esophageal cancer. This database contains approximately 80% of all esophageal cancer cases seen at Weill Cornell Medical Center.

For purposes of analysis, cases were defined as any esophageal cancer patient who had or developed lung metastases. Controls were those esophageal cancer patients who did not have lung metastases (both those without metastasis and those with metastasis to non-lung sites).

Inclusion criteria

The following were the criteria for inclusion in the study: 1) histologically confirmed diagnosis of primary esophageal cancer (any cell type, any stage); and 2) metastatic work-up in the form of cross-sectional imaging (e.g. computed tomography) of the lungs at or after the time of diagnosis.

Smoking history

Smoking was recorded for all subjects as ever, never, or unknown. When smoking history was quantified in the medical records, ever smoker was defined as ≥1 lifetime pack years. The number of pack years of smoking or years since quitting was inconsistently recorded in the medical records.

Lung metastasis

Lung metastases, either present at diagnosis or developed during follow-up, were defined as follows: radiologic findings showing ≥2 suspicious masses in the lung parenchyma or findings consistent with lymphangitic carcinomatosis; or a pleural effusion with cytologic confirmation of malignant cells consistent with the primary esophageal tumor histology. The requirement for multiple lung masses was made to minimize the possibility of mislabeling a primary lung cancer as an esophageal cancer lung metastasis in this population with a high smoking prevalence.

Liver metastasis

As a comparison to lung metastasis, the association between smoking and liver metastasis was also examined. Liver metastasis was defined as any cross sectional imaging result with at least one mass in the liver deemed by the interpreting radiologist to be consistent with a metastatic lesion. Evidence of metastasis to any other distant organ site was also recorded.

Other data

Data were recorded on patient and tumor characteristics. Tumor histology and subsite as well as disease stage and year of diagnosis were recorded. Tumor subsite was categorized as GE junction, lower esophagus, mid-esophagus, or upper esophagus. Classification of subsite was made using a combination of endoscopy, operative, and pathology reports. When endoscopic measurements were provided for the tumor location, lower esophagus was defined as ≥30 cm from the incisors, mid-esophagus was defined as 25-29 cm from the incisors, and upper esophagus was defined as <25 cm from the incisors.

Notation was made as to disease stage at the time of diagnosis. Patients were classified as either stage 1-3 or stage 4 (metastasis at any distant organ site at the time of diagnosis). More detailed disease staging was not available from the medical records.

Statistical analysis

Categorical variables were analyzed using Fisher's exact test. Continuous variables were analyzed using two-sided Student's t-tests unless otherwise noted. Multivariable logistic regression modeling was performed to assess the adjusted association between smoking and metastasis. Interaction terms between smoking and tumor histology and smoking and sex were evaluated but not significant for the association with either lung or liver metastasis. These terms

were therefore not included in the final models. Disease stage did not alter the association between smoking and lung or liver metastases and was not included in the final models.

For 18.4% of the subjects, smoking information was missing. We conducted a sensitivity analysis in which we assumed that, when smoking information was not documented, the subject was a never smoker.

Alcohol history was available for 119 (33.6%) of the study subjects. Since alcohol use is correlated with smoking, multivariable logistic regression was also performed in the subset of patients in whom alcohol history was available to determine if there was a qualitative difference in the association between smoking and lung metastasis.

Statistical significance was defined as $p<0.05$ or a 95% confidence interval that did not cross 1.00. All analyses were performed using STATA 9.2 (StataCorp, College Station, TX). The study was approved by both the Columbia University and Cornell University Institutional Review Boards.

Results

We identified 354 patients (197 from Columbia, 157 from Cornell) with histologically confirmed primary esophageal cancer and available cross-sectional imaging results. The characteristics of these patients are shown in Table 1. The majority of subjects were male (76.3%), and the mean age was 63.8 years. Ever smokers comprised 51.7% (183/354) of the study population, and 18.4% (65/354) lacked documented smoking history. Slightly more than half of the tumors were adenocarcinomas (56.8%), and 70.6% of the tumors were located at either the GE junction or in the lower esophagus.

The associations between subject characteristics and lung metastasis are shown in Table 2. A significantly higher proportion of patients with lung metastases were ever smokers as compared to those without lung metastases (73.6% vs. 47.8%, p=0.001). Similarly, a greater percentage of ever smokers than never smokers had lung metastases (21.3% vs. 9.4%, p=0.009). The unadjusted odds ratio for the association between smoking and lung metastasis was 2.60 (95% CI 1.23-5.46). There were significantly fewer patients with lung metastases with more distal tumor subsite location (p for trend = 0.03). No differences were observed in the proportion of patients with lung metastasis as a function of sex, race/ethnicity, age, or study site.

Compared to never smokers, a higher proportion of ever smokers had stage 4 disease at the time of diagnosis (8.7% vs. 1.9%, p=0.02). After adjusting for stage at diagnosis, the odds ratio for the association between smoking and lung metastasis was 2.09 (95%CI 0.96-4.53).

There was no significant difference in the proportion of adenocarcinomas and squamous cell carcinomas with lung metastases (Table 2). A significantly higher proportion of patients with squamous cell as compared to adenocarcinoma were ever smokers (61.1% vs. 44.8%, respectively; p=0.005). The association between smoking and lung metastasis was higher in squamous cell (OR 5.83, 95%CI 1.27-53.8) than in adenocarcinoma (OR 1.63, 95%CI 0.61-4.68). However, the interaction term for smoking status and tumor histology was not statistically significant (p=0.16). Stratified by tumor histology, the Mantel-Haenszel combined odds ratio for the association between smoking and lung metastasis was 2.52 (95%CI 1.17-5.45). In a subset analysis of patients in whom alcohol history was documented, the association between smoking and lung metastasis was not qualtitatively different from the entire study population (OR 4.12, 95%CI 0.89-19.0).

In multivariable logistic regression analysis, smoking was associated with a nonsignificant increased odds of lung metastasis from esophageal cancer (OR 1.89, 95%CI 0.80-4.46) (Table

3). The odds ratio for lung metastasis progressively increased with more proximal tumor location. Squamous cell histology was not associated with a significantly altered odds of lung metastasis as compared to adenocarcinoma (OR 0.65, 95%CI 0.27-1.60). Patient sex, race/ethnicity, age, and study site were not associated with an altered risk of lung metastasis in esophageal cancer.

We hypothesized that there was a bias toward documentation of a positive smoking history. This is consistent with the observation that, among the 65 patients whose smoking status was unknown, there was a very low proportion of subjects with squamous cell carcinoma (21.5%). The adjusted odds ratio for the association between lung metastasis and unknown smoking status, compared to never smokers, was 0.93 (95%CI 0.14-6.24), consistent with our hypothesis that the subjects with missing smoking status were more likely to represent never smokers. We therefore repeated the multivariable analyses and included the missing smoking status subjects with the never smokers (Table 3). There was a significantly increased odds of lung metastasis in ever smokers (OR 2.35, 95%CI 1.12-4.96).

No association was found between smoking and liver metastasis. A total of 328 (93% of study subjects) patients had imaging results available for the evaluation of liver metastasis. Fifty-six (15.8%) of these patients had or developed liver metastases. Among those with liver metastases, 51.8% were smokers compared to 52.6% of those without liver metastases (p=0.37). A higher but non-significant proportion of adenocarcinomas versus squamous cell carcinomas had liver metastases (19.9% vs. 11.5%, respectively; p=0.07). In multivariable logistic regression, there was no significant association between smoking and odds of liver metastasis (OR 0.88, 95% CI 0.42-1.83) (Table 4). The odds ratio for liver metastasis progressively decreased with more proximal tumor location. There was no association between tumor cell type and liver metastasis.

Of all esophageal cancer patients initially presenting with stage 1-3 disease, 39.7% (131/330) developed a metastasis at any distant organ site. There was no significant difference in development of any metastasis between ever and never smokers (p=0.62). In multivariable logistic regression analysis of subjects presenting with stage 1-3 disease, there was no association between smoking and metastasis at any site (OR 1.24, 95%CI 0.68-2.26) or any non-lung metastasis (OR 0.81, 95% CI 0.43-1.54).

No qualitative difference was observed in the association between smoking and lung metastasis when controls were redefined as patients with non-lung metastases (OR 2.60, 95%CI 1.16-5.83). There was again no association between smoking and liver metastasis when controls were defined as those with non-liver metastases (OR 0.59, 95%CI 0.28-1.24).

Discussion

In this hospital-based retrospective prevalent case control study of patients with esophageal cancer, smoking was associated with a significantly increased odds of lung metastasis. This relationship existed independent of cell type and tumor subsite. This is the first study to evaluate the relationship between smoking and other patient and tumor characteristics with site-specific metastasis.

The effects of smoking on metastatic risk appeared to be specific to the lung. No association was observed between smoking and liver metastasis or any metastasis from esophageal cancer.

Interestingly, tumor cell type did not appear to be an independent predictor of site-specific metastasis in esophageal cancer. There were no significant differences between adenocarcinoma and squamous cell carcinoma with regard to lung and liver metastasis in both uni- and multivariate analyses. However, the association between smoking and lung metastasis

was higher in squamous cell than in adenocarcinoma. While tests for interaction were not statistically significant, this may have been due to a lack of power. Future studies will need to account for histology-specific effects of environmental exposures on metastasis.

Tumor subsite was strongly associated with site-specific metastatic risk. Proximal esophageal tumors were more likely to metastasize to the lungs, whereas distal tumors were more likely to spread to the liver. This is consistent with the patterns of lymph node spread by tumor subsite in esophageal cancer and with the vascular anatomy of the esophagus (19,22-24).

An association between smoking and lung metastasis was observed in two prior studies in breast cancer patients. Scanlon and colleagues conducted a nested case-control study of women breast cancer, in which a significantly higher proportion of ever smokers developed pulmonary metastases compared to never smokers (25). The investigators also found a dose-dependent relationship between cigarette smoking history and risk of pulmonary metastasis; those patients who smoked >20,000 packs in their lifetime had almost 4 times the risk of developing lung metastases compared to breast cancer patients who never smoked (RR 3.73, 95%CI 1.6-8.9).

A similar case-control study of women with breast cancer by Murin and Inciardi showed a non-significant increased risk of pulmonary metastasis among smokers (26). Active smokers were nearly twice as likely as nonsmokers to have pulmonary metastases (OR 1.96, 95%CI 0.96-4.02). Neither study examined whether the effect of smoking was specific to the lung. We are not aware of studies that examine the association between smoking and lung metastasis in other primary cancers that commonly spread to the lungs, such as renal cell carcinoma and sarcoma.

Our study does not directly address whether tobacco smoke alters risk of lung metastasis by acting at the level of the “seed” or the “soil”. However, our results suggest that smoking may exert its effect by acting on the site of metastasis. There is a 5-10 fold difference in the effect of smoking on the risk of squamous cell carcinoma as compared to adenocarcinoma of the esophagus (27-29). We found no evidence of significant interaction between smoking and cell type on the risk of lung metastasis. Additionally, the magnitude of association found between smoking and lung metastasis in esophageal cancer was similar to that reported in the abovementioned studies of breast cancer (25,26).

Tobacco exposure leads to lung damage and areas of relative hypoxia within the airways; this change in the “soil” may promote tumor seeding in the lungs. In normal cells, hypoxia leads to apoptosis and cell death. However, tumor cells may be resistant to apoptosis in the presence of hypoxia (30). The expression of key elements of tumor growth and survival, including VEGF and carbonic anhydrase IX (CA IX), is significantly increased under hypoxic conditions (31). In a mouse model, deletion of hypoxia-inducible transcription factor 1 (HIF-1), which regulates VEGF and CA IX expression, resulted in decreased pulmonary metastasis from breast cancer (32). A hypoxic environment, such as the diseased lung, could provide an ideal milieu to promote angiogenesis and tumor growth.

Smoking could increase the risk of lung metastasis via alternative mechanisms. Smokers have significantly higher levels of sputum VEGF and VEGF+ cells in lung tissue compared to nonsmokers, independent of lung function (33,34). The means by which smoking increases risk of lung metastasis is likely multifactorial.

The present study does have limitations. The relatively small sample size limits the ability to draw conclusions, particularly with regard to potential confounders. This is a retrospective chart review, and nearly 20 percent of the patients identified with esophageal cancer and a metastatic imaging work-up lacked a documented smoking history. This may have been due in part to physician bias toward recording a positive smoking history. Our sensitivity analyses

were consistent with this hypothesis, as the odds of lung metastasis in the missing smoking status group compared to the never smokers was close to 1.00. While not feasible in the present study, biochemical confirmation of smoking status may have improved smoking categorization.

Alcohol use and smoking are correlated; alcohol history was not available for many of the patients, potentially biasing the results. Additionally, alcohol use is a strong risk factor for squamous cell esophageal cancer (27). However, in our subset analysis of patients in whom an alcohol history was documented, inclusion of alcohol in the multivariable model did not qualitatively change the association between smoking and lung metastasis.

There were significant differences between the overall patient characteristics of the two study sites, the reasons for which are not entirely clear. However, after inclusion of study site in the logistic regression models, the association between smoking and lung metastasis was qualitatively unchanged. In the final model for liver metastasis, the Columbia study site was associated with a significantly decreased odds of liver metastasis as compared to the Cornell study site. It is not evident what the impact of this finding had on the relationship between smoking and liver metastasis.

Quantification of lifetime smoking was not available for many of the study subjects. As a result, demonstration of a dose-related effect of smoking on the risk of lung metastasis was not possible. Clinical follow-up was not reliably available and therefore not included in the analyses. Greater than 90% of the patients presented with stage 1-3 disease, and a significant proportion of these patients may have undergone surgery, radiation and/or chemotherapy. It is not known whether treatment would have altered the results. Prior body mass index would also have been interesting to evaluate, especially with regard to liver metastasis.

A significantly higher proportion of smokers had metastatic disease at the time of diagnosis. After adjusting for stage at diagnosis, there was no major qualitative difference in the association between smoking and lung metastasis. However, smoking may result in faster disease progression, and future studies should anlyze this element as well.

In this retrospective hospital-based study of patients with newly diagnosed esophageal cancer, smoking was associated with an increased risk of lung metastasis. This association appeared to be site-specific, as no association was seen between smoking and liver metastasis. Tumor subsite was also independently predictive of both lung and liver metastasis, consistent with knowledge of the lymphatic and hematogenous drainage of the esophagus. There was no observed association between tumor cell type and site-specific metastasis. It is unclear from this study whether smoking exerts its effects by acting on the primary tumor cell or on the site of metastasis, thus making it more susceptible to metastatic seeding. With greater knowledge of patient-related risk factors (e.g., smoking) for site-specific metastasis, future therapies and clinical trials could target those high risk patients for prophylaxis against tumor spread to a particular site. Future prospective studies are needed to gain a better understanding of risk factors for site-specific metastasis and the manner in which they exert their effects.

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Table 1

Characteristics of patients with esophageal cancer, Columbia University and Weill Cornell Medical Centers.

	Total	No. (%) Columbia	Cornell	p-value*
Number of patients	354 (100%)	197 (56%)	157 (44%)	
Mean age, years (S.D.)	63.8 (12.0)	66.2 (11.7)	60.8 (11.8)	<0.0001
Male sex	270 (76%)	140 (71%)	130 (83%)	0.01
Smokers (ever)				<0.001
Never	106 (30%)	33 (17%)	73 (46%)	
Ever	183 (52%)	99 (50%)	84 (53%)	
Unknown	65 (18%)	65 (33%)	0 (0%)	
Race/ethnicity				<0.001
White	260 (74%)	117 (59%)	143 (92%)	
Black	33 (9%)	25 (13%)	8 (5%)	
Hispanic	33 (9%)	33 (17%)	0 (0%)	
Other	27 (8%)	22 (11%)	5 (3%)	
Tumor histology				0.19
Adenocarcinoma	201 (57%)	104 (53%)	97 (62%)	
Squamous cell	131 (37%)	81 (41%)	50 (32%)	
Other	22 (7%)	12 (6%)	10 (6%)	
Tumor subsite				0.05
GE junction	65 (19%)	41 (21%)	24 (16%)	
Lower esophagus	182 (52%)	94 (48%)	88 (58%)	
Mid-esophagus	71 (20%)	38 (19%)	33 (22%)	
Upper esophagus	32 (9%)	24 (12%)	8 (5%)	
Site of metastasis†				
Lung	53 (15%)	28 (14%)	25 (16%)	0.66
Liver	56 (16%)	20 (10%)	36 (23%)	<0.001
Other	86 (24%)	32 (16%)	54 (34%)	<0.001
Stage at diagnosis				
1-3	330 (93%)	173 (88%)	157 (100%)	<0.001
4	24 (7%)	24 (12%)	0 (0%)	

*For comparison between Columbia and Cornell study sites.

†Some subjects had multiple sites of metastasis.

Table 2

Unadjusted associations of study subject characteristics with lung metastasis in esophageal cancer, Columbia University and Weill Cornell Medical Centers.

	% with lung mets	p-value
Smoking history		0.002
Never	9.4% (10/106)	
Ever	21.3% (39/183)	
Unknown	6.2% (4/65)	
Histology		0.57
Adenocarcinoma	13.9% (28/201)	
Squamous cell	17.6% (23/131)	
Other	9.1% (2/22)	
Sex		0.48
Female	11.9% (10/84)	
Male	15.9% (43/270)	
Race/Ethnicity		0.36
White	13.9% (36/260)	
Black	24.2% (8/33)	
Hispanic	18.2% (6/33)	
Other/Unknown	11.1% (3/27)	
Tumor subsite		0.03*
GE junction	10.8% (7/65)	
Lower esophagus	13.2% (24/182)	
Mid esophagus	15.5% (11/71)	
Upper esophagus	28.1% (9/32)	
Stage at diagnosis		<0.001
Stage 1-3	11.5% (38/330)	
Stage 4	62.5% (15/24)	
Age		0.74*
<50	14.9% (7/47)	
50-59	12.1% (8/66)	
60-69	16.3% (20/123)	
≥70	15.3% (18/118)	
Study site		0.66
Cornell	15.9% (25/157)	
Columbia	14.2% (28/197)	

* p-value for trend

Table 3

Multivariable logistic regression for the evaluation of risk factors for **lung** metastasis in esophageal cancer, Columbia University and Weill Cornell Medical Centers. Results are presented for smoking status categorized as ever/never/unknown as well as for ever/never (with unknowns grouped with never smokers).

	Site of metastasis = Lung			
	Original Model		Alternate Model*	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Smoking history				
Never*	1.00	Referent	1.00	Referent
Ever	1.89	0.80-4.46	2.35	1.11-4.97
Unknown	0.54	0.14-2.09	N/A	
Sex				
Female	1.00	Referent	1.00	Referent
Male	1.56	0.68-3.60	1.55	0.67-3.56
Race/Ethnicity				
White	1.00	Referent	1.00	Referent
Black	1.84	0.63-5.34	1.88	0.65-5.42
Hispanic	0.91	0.28-2.96	0.97	0.30-3.11
Other/Unknown	0.73	0.19-2.88	0.66	0.17-2.56
Histology				
Adenocarcinoma	1.00	Referent	1.00	Referent
Squamous cell	0.65	0.27-1.60	0.74	0.31-1.77
Other	0.42	0.08-2.10	0.27	0.05-1.59
Tumor subsite				
GE junction	1.00	Referent	1.00	Referent
Lower esophagus	1.71	0.66-4.42	1.65	0.64-4.24
Mid esophagus	2.08	0.61-7.16	1.92	0.56-6.53
Upper esophagus	4.71	1.20-18.5	4.37	1.11-17.1
Age				
<50	1.00	Referent	1.00	Referent
50-59	0.86	0.28-2.68	0.85	0.27-2.64
60-69	0.95	0.36-2.55	1.03	0.39-2.77
≥70	1.04	0.37-2.91	1.16	0.42-3.24
Year of diagnosis				
1988-1994	1.00	Referent	1.00	Referent
1995-2000	1.50	0.34-6.60	1.35	0.31-5.84
2001-2006	2.44	0.57-10.4	2.16	0.52-9.01
Study site				
Cornell	1.00	Referent	1.00	Referent
Columbia	0.95	0.42-2.16	0.82	0.38-1.78

* Unknown smoking status subjects grouped with never smokers

Table 4

Multivariable logistic regression for the evaluation of risk factors for **liver** metastasis in esophageal cancer, Columbia University and Weill Cornell Medical Centers. Results are presented for smoking status categorized as ever/never/unknown as well as for ever/never (with unknowns categorized as never smokers).

	Site of metastasis = Liver			
	Original Model		Alternate Model*	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Smoking history				
Never	1.00	Referent	1.00	Referent
Ever	0.88	0.42-1.83	0.86	0.44-1.69
Unknown	1.07	0.32-3.56	N/A	
Sex				
Female	1.00	Referent	1.00	Referent
Male	0.65	0.30-1.38	0.65	0.30-1.38
Race/Ethnicity				
White	1.00	Referent	1.00	Referent
Black	1.30	0.37-4.48	1.29	0.37-4.46
Hispanic	2.70	0.75-9.69	2.67	0.76-9.39
Other/Unknown	0.82	0.17-4.05	0.83	0.17-4.06
Histology				
Adenocarcinoma	1.00	Referent	1.00	Referent
Squamous cell	0.86	0.36-2.05	0.86	0.36-1.98
Other	0.30	0.04-2.45	0.30	0.04-2.66
Tumor subsite				
GE junction	1.00	Referent	1.00	Referent
Lower esophagus	0.49	0.22-1.06	0.49	0.23-1.07
Mid esophagus	0.26	0.08-0.85	0.26	0.08-0.85
Upper esophagus	0.29	0.06-1.46	0.29	0.06-1.46
Age				
<50	1.00	Referent	1.00	Referent
50-59	1.20	0.42-3.40	1.20	0.42-3.39
60-69	1.50	0.58-3.87	1.50	0.58-3.86
≥70	0.85	0.31-2.33	0.84	0.31-2.32
Year of diagnosis				
1988-1994	1.00	Referent	1.00	Referent
1995-2000	1.45	0.47-4.44	1.46	0.48-4.43
2001-2006	1.52	0.50-4.58	1.53	0.51-4.57
Study site				
Cornell	1.00	Referent	1.00	Referent
Columbia	0.30	0.13-0.72	0.31	0.14-0.67

* Unknown smoking status subjects grouped with never smokers