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Article

ARTICLE

Factors Associated With Small Aggressive Non–Small Cell Lung Cancers in the National Lung Screening Trial: A Validation Study

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Abstract

Background: A small proportion of non–small cell lung cancers (NSCLCs) have been observed to spread to distant lymph nodes (N3) or metastasize (M1) or both, while the primary tumor is small (≤3 cm, T1). These small aggressive NSCLCs (SA-NSLSC) are important as they are clinically significant, may identify unique biologic pathways, and warrant aggressive follow-up and treatment. This study identifies factors associated with SA-NSCLC and attempts to validate a previous finding that women with a family history of lung cancer are at particularly elevated risk of SA-NSCLC.

Methods: This study used a case–case design within the National Cancer Institute's National Lung Screening Trial (NLST) cohort. Case patients and "control" patients were selected based on TNM staging parameters. Case patients (n = 64) had T1 NSCLCs that were N3 or M1 or both, while "control" patients (n = 206) had T2 or T3, N0 to N2, and M0 NSCLCs. Univariate and multivariable logistic regression were used to identify factors associated with SA-NSCLC.

Results: In bootstrap bias–corrected multivariable logistic regression models, small aggressive adenocarcinomas were associated with a positive history of emphysema (odds ratio [OR] = 5.15, 95% confidence interval [CI] = 1.63 to 23.00) and the interaction of female sex and a positive family history of lung cancer (OR = 6.55, 95% CI = 1.06 to 50.80).

Conclusions: Emphysema may play a role in early lung cancer progression. Females with a family history of lung cancer are at increased risk of having small aggressive lung adenocarcinomas. These results validate previous findings and encourage research on the role of female hormones interacting with family history and genetic factors in lung carcinogenesis and progression.

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Researchers from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) studied a small proportion of non–small cell lung cancers (NSCLCs) that were found to have spread to distant lymph nodes or metastasized, or both, while the primary tumor was relatively small in size (1). These cancers that were highly aggressive while the primary tumor remained relatively small were termed small aggressive non–small cell lung cancers (SA-NSLSCs). Due to their aggressive nature, these SA-NSCLCs carry a grave prognosis, as they are no longer surgically resectable with curative intent. It is hypothesized that these SA-NSCLCs may involve unique biological pathways. In the previous study, "small" cancers were considered T1 (<3 cm with minimal invasion of surrounding tissues) (1). Previous studies reported that as many as 10% of small (≤3 cm) lung cancers were advanced stage at diagnosis (stage IIIB/IV), that is, with involvement of distant lymph nodes (N3) and/or metastases (M1) (2–4). Overall, few studies have described or validated factors associated with SA-NSCLC.

The PLCO-based study by Tammemägi and colleagues found that factors associated with SA-NSCLC included age at diagnosis, ibuprofen use, sex, and sex by family history of lung cancer interaction (1). Comparing those diagnosed at age 65 years or older with those younger than age 65 years, the odds ratio (OR) for SA-NSCLC was 0.44 (95% confidence interval [CI] = 0.22 to 0.88) (1). The odds ratios for comparing women vs men with SA-NSCLC in those with and without a family history of lung cancer were 11.76 (95% CI = 2.00 to 69.22) and 1.86 (95% CI = 0.88 to 3.96), respectively. The sex by family history interaction was statistically significant ($P = .02$). Ibuprofen use was found to be inversely associated with SA-NSCLC (OR = 0.29, 95% CI = 0.11 to 0.76) (1). Ibuprofen use has been thought to be associated with reduced risk of lung cancer in general (5–10). Other risk factors identified as having a possible association in univariate modeling included smoking duration, history of heart disease/infarction, and histology (adenocarcinoma vs other NSCLC) (1). In the PLCO study, 10.4% of SA-NSCLCs occurred in never smokers (1). Validation of some of these findings may provide insight into lung carcinogenesis; in particular, validation of the sex-family history of lung cancer interaction may stimulate further research into developing an understanding of female hormone-gene interactions (1).

Overall, research on characterizing and identifying factors associated with aggressive forms of lung cancer is limited. Our first study aim was to carry out prespecified hypothesis testing to validate the previously observed associations between age at diagnosis and sex-family history of lung cancer interaction and the outcome of SA-NSCLC. Our second study aim was exploratory and attempted to identify associations between novel predictors and SA-NSCLC. Generally, small cell lung cancers (SCLCs) metastasize early, and therefore most are considered small aggressive lung cancers, while this is not generally true for NSCLC; therefore, NSLSCs are the focus of the current study.

Methods

Study Setting

This study used a case–case design nested within the National Cancer Institute's (NCI's) National Lung Screening Trial (NLST) cohort. The details of the NLST have been described elsewhere (11). In brief, the NLST was a randomized controlled screening trial that compared low-dose computed tomography (LDCT) with chest radiography (CXR) for screening of high-risk current and former smokers for lung cancer among 53 452 participants, enrolled during 2002–2004. On enrollment into NLST, informed consent was obtained from each participant. Institutional review board (IRB) approval was obtained at each participating site and the NCI. Eligibility criteria for enrolling high-risk individuals included age 55 to 74 years, 30 or more pack-years' smoking history, and smoking cessation of 15 or fewer years for former smokers. Three rounds of annual screening were scheduled. Upon enrollment, all participants completed a questionnaire querying information on demographics, exposures, medical history, and smoking behaviors. For those diagnosed with lung cancer, pathology and tumor-staging reports, records of operative procedures, and initial treatments were abstracted from medical records. Histology and disease stage were coded according to the International Classification of Diseases, third edition (ICD-O3) (12), and the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC), sixth edition (13), respectively. When the NLST was conducted, bronchioloalveolar carcinoma (BAC) was the accepted terminology assigned by pathologists, so we use it here. However, it should be noted that BACs are now referred to as adenocarcinoma with lepidic features. All NSCLCs occurring during the NLST follow-up (2002–2009) were eligible for study inclusion.

Study Design

The focus of this study was to identify factors associated with progression to aggressive spread while the primary tumor was still relatively small. SA-NSCLCs were considered case positive (case+), while large, less aggressive NSCLCs (referred to as "controls") were considered case negative (case−). SA-NSCLCs were defined as patients with T1 tumors that had spread to distant regional lymph nodes (N3), or metastasized (M1), or both. Controls (case−) were defined as tumors that had grown beyond T1, and excluded individuals with locally aggressive disease (T4), distant nodal disease (N3), or metastases (M1), resulting in a control group of patients with tumors that were T2 to T3, N0 to N2, and M0. Henceforth, the case- group is referred to as the control group. Tumor sizes were categorized (≤30 mm vs >30 mm) using pathology data, and in the absence of pathology data, clinical data were used. Large, aggressive (T2-T4/N3/M1, n = 161) and small, nonaggressive lung cancers (T1/N0-N2/M0, n = 641) are excluded from the study sample because their aggressive status at the time of transition from small to large was unknown.

Statistical Analysis

Categorical variables were assessed using contingency table analyses, and differences in distributions were evaluated using Fisher exact tests. For continuous variables, with approximately normal distributions, differences in distributions were tested using the Student independent sample t test, and Wilcoxon rank-sum tests were used where distributions were skewed. Univariate and multivariable models were prepared using logistic regression analyses to evaluate associations between predictors and SA-NSCLC. Candidate variables (Table 1) were identified for testing in multivariable models based on them approaching statistical significance ($P < .15$) in univariate models, having effect estimates clearly apart from the null, or by knowledge of their role in lung carcinogenesis. Potential nonlinear relationships between continuous covariates and the outcome were evaluated using multivariable fractional polynomial

Table 1. Variables evaluated for associations with SA-NSCLC*

Category of variable	Specific variables
Sociodemographics (n = 5)	Age at diagnosis Sex Race/ethnicity Marital status Education
Smoking exposures (n = 5)	Smoking status (former, current) Pack-years smoked Smoking duration, (y) Smoking intensity (average number of cigarettes smoked/d) Pipe/cigar smoking
Medical history (n = 19)	Family history of lung cancer, personal history of cancer, body mass index Comorbidities: adult asthma, asbestosis, bronchiectasis, childhood asthma, chronic bronchitis, COPD, diabetes, emphysema, heart attack/heart disease, hypertension, pneumonia, pulmonary fibrosis, sarcoidosis, silicosis, stroke, and tuberculosis
Interaction terms (n = 6)	Age*sex, age*FHLC, sex*FHLC, FHLC*smoking duration, FHLC*smoking intensity, sex*emphysema

*COPD = chronic obstructive pulmonary disease; FHLC = family history of lung cancer; n = subset number.

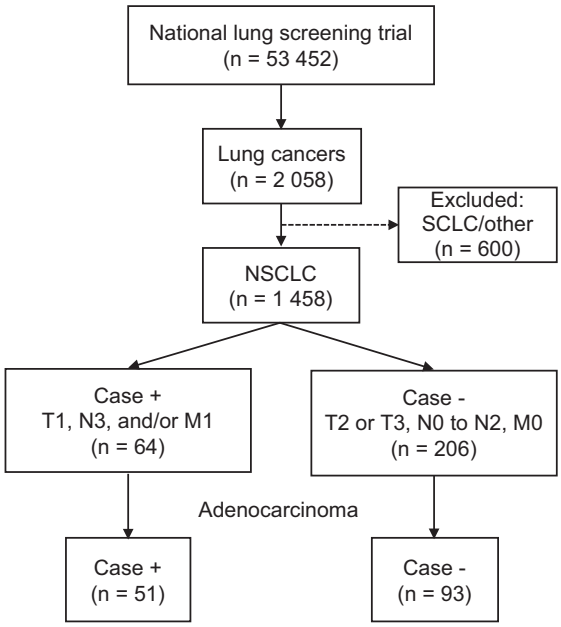

Figure 1. Flow chart depicting the sample selection for cases (small aggressive non–small cell lung cancers [SA-NSCLC] or case+) and controls (larger less-aggressive NSLSC or case−) from the National Lung Screening Trial cohort.

Table 2. TNM stage distribution in SA-NSCLC (light gray) and large non-SA-NSCLC (dark gray) for NSCLC and adenocarcinoma*

		NX No. (%)	N0 No. (%)	N1 No. (%)	N2 No. (%)	N3 No. (%)
NSCLC						
M0	T1					10 (15.6)
	T2		109 (52.9)	31 (15.0)	42 (20.4)	
	T3		13 (6.3)	1 (0.5)	10 (4.9)	
M1	T1	1 (1.6)	12 (18.8)	6 (9.4)	20 (31.3)	15 (23.4)
Adenocarcinoma						
M0	T1					9 (17.6)
	T2		56 (60.2)	9 (9.7)	21 (22.6)	
	T3		4 (4.3)	0 (0.0)	3 (3.2)	
M1	T1	1 (2.0)	9 (17.6)	4 (7.8)	15 (29.4)	13 (25.5)

*Percentages represent proportions among cases and controls separately. NSCLC = non–small cell lung cancer; SA-NSCLC = small aggressive non–small cell lung cancer; TNM = tumor-node-metastasis staging.

regression (14). No nonlinear relationships were identified, and they are not discussed further in this report. In evaluating interactions, the main effect terms were included along with the interaction term, and statistical significance of the interaction was evaluated using likelihood ratio tests (LRTs), comparing nested models including and excluding the interaction term. Type I (α) error was set at .05 for main effects and .10 for interaction terms, and reported *P* values are two-sided. Significance levels for interaction terms were loosened to compensate for reduced cell counts. Predictor variable inclusion in final multivariable models was restricted to those for which data were present for more than 95% of SA-NSCLCs, and where missing data did not differ significantly by case–control status. To evaluate the likelihood of overfitting models, the final model was internally validated using 1000 bootstrap replicates (15). Stata 14.2 software (StataCorp., College Station, TX) was used to conduct analyses.

Results

The NLST had 1458 NSCLCs, and 1338 of these had tumor sizes available from pathology or clinical data and were eligible for this study. Cases of SCLC (n = 286), carcinoid tumors (n = 9), unclassified tumors (n = 279), and other/missing (n = 26) were excluded. There were 64 SA-NSCLCs (4.8% of NSCLCs with size available), and 206 controls (large, less aggressive NSCLCs, 15.4%). Twenty-three of 195 SCLCs with size measurements (11.8%) were small aggressive lung cancers (T1, N3, and/or M1), compared with only 4.8% of NSCLCs ($P < .001$ for difference in proportions). Figure 1 describes the case–case selection process used in this study. Tumor-node-metastasis (TNM) distributions for the full and adenocarcinoma samples are described in Table 2. Most SA-NSCLCs were metastatic (M1/stage IV; 84.4%), with 15.6% of SA-NSCLCs diagnosed as nonmetastatic tumors with distant nodal spread (T1N3M0/stage IIIB). Most controls had T2N0M0/stage IB tumors (52.9%). Of 1338 eligible NSCLCs, 906 were primary tumors 30 mm or shorter in the long axis. Approximately 7.1% (64 of 906) of these were SA-NSCLCs. SA-NSCLCs ranged from 8 mm to 30 mm (median = 18.5 mm, interquartile range [IQR] = 14.0–24.5 mm) in the long axis, with few (n = 3) smaller than 10 mm and the smallest being 8 mm. The lesion size for the smallest primary tumor that was metastatic was 9 mm. The majority (95.3%) of SA-NSCLCs were at or beyond 10 mm. Most SA-NSCLCs (71.8%), and all SA-NSCLCs smaller than 10 mm (n = 3), were detected by CXR. Of the 64 SA-NSCLCs, 14 (21.9%) were diagnosed less than one year after study entry (T0), and 50 (78.1%) were diagnosed one to seven years after study entry (T1+), while among the 206 controls, 61 (29.6%) were T0 and 145 (70.4%) were T1+ diagnoses, respectively ($P = .265$). In total, 51.9% of cases and 45.3% of controls were detected during the screening phase of the study, and the difference was not significant ($P = .392$).

Table 3. Demographic and clinical characteristics of cases and controls (n = 270)*

Variable	Case− (n = 206, 76%)	Case+ (n = 64, 24%)	P†	OR (95% CI)‡
Sociodemographic				
Age at diagnosis, mean (SD), y	66.8 (5.8)	66.2 (4.9)	.412	0.98 (0.93 to 1.03)
Sex, No. (%)				
Male	147 (71.4)	39 (60.9)		
Female	59 (28.6)	25 (39.1)	.124	1.60 (0.89 to 2.87)
Race/ethnicity, No. (%)				
Nonwhite	20 (9.7)	2 (3.1)		
White	186 (90.3)	62 (96.9)	.118	3.33 (0.76 to 14.7)
Education level, No. (%)				
High school or less	79 (38.4)	23 (36.5)		
More than high school	127 (62.6)	40 (63.5)	.882	1.08 (0.60 to 1.94)
Medical history				
Body mass index, mean (SD), kg/m^2	27.2 (4.3)	26.6 (3.6)	.312	0.96 (0.90 to 1.04)
Family history of lung cancer, No. (%)				
No	146 (71.6)	43 (68.2)		
Yes	58 (28.4)	20 (31.8)	.636	1.17 (0.64 to 2.16)
Sex*FHLC interaction, No. (%)				
Male, no FHLC	103 (50.5)	29 (46.0)		
Male, FHLC	43 (21.1)	9 (14.3)		
Female, no FHLC	43 (21.1)	14 (22.2)		
Female, FHLC	15 (7.4)	11 (17.5)	.109	3.03 (0.84 to 10.97)
Emphysema§, No. (%)				
No	184 (89.3)	50 (79.4)		
Yes	22 (10.7)	13 (20.6)	.053	2.17 (1.02 to 4.62)
COPD§, No. (%)				
No	156 (75.7)	47 (73.4)		
Yes	50 (24.3)	17 (26.6)	.741	1.13 (0.60 to 2.14)
Chronic bronchitis§, No. (%)				
No	182 (8.4)	56 (88.9)		
Yes	24 (11.6)	7 (11.1)	1.000	0.95 (0.39 to 2.32)
Exposures				
Cigarettes/d, mean (SD)	30.6 (12.7)	31.8 (13.5)	.906	1.00 (0.98 to 1.02)
Years smoked, mean (SD)	44.7 (7.1)	44.5 (7.2)	.862	1.00 (0.96 to 1.04)
Pack-years, mean (SD)	68.4 (31.4)	68.2 (29.0)	.971	1.00 (0.99 to 1.01)
Smoking status, No. (%)				
Former	125 (60.7)	40 (62.5)		
Current	81 (39.3)	24 (37.5)	.884	1.08 (0.61 to 1.93)
Cancer-related				
Tumor size, mean (SD), mm	48.2 (15.9)	19.0 (6.1)	–	–
Histology, No. (%)				
Adenocarcinoma	88 (42.7)	49 (76.6)	<.001	4.77 (2.44 to 9.30)‖
Bronchioloalveolar carcinoma	5 (2.4)	2 (3.1)		
Squamous cell carcinoma	95 (46.1)	9 (14.1)		
Large cell carcinoma	13 (6.3)	2 (3.1)		
Other NSCLCs	5 (2.4)	2 (3.1)		
Screening-related				
Randomization group, No. (%)				
LDCT	90 (43.7)	18 (28.1)	.029	0.50 (0.27 to 0.93)
CXR	116 (56.3)	46 (71.9)		

*Odds ratios and 95% confidence intervals are from univariate logistic regression analyses. CI = confidence interval; COPD = chronic obstructive pulmonary disease; CXR = chest x-ray; FHLC = family history of lung cancer; LC = lung cancer; LDCT = low-dose computed tomography; NSCLC = non–small cell lung cancer; OR = odds ratio.
†Wilcoxon rank-sum test was used for age, cigarettes per day, years smoked, pack-years, tumor size; Student t test was used for body mass index; Fisher exact test was used for all categorical covariates.
‡Odds ratios for categorical covariates are aligned in the table with the level of interest.
§Lung comorbidities, such as COPD, chronic bronchitis, and emphysema, were determined through self-report.
‖In the logistic regression odds ratio estimation, adenocarcinomas (including bronchioloalveolar carcinomas) were compared with all other NSCLCs combined.

Demographic and clinical characteristics were generally similar between cases and controls (Table 3). Notable differences in distributions between cases and controls were found for histology, random assignment group (screening arm), and history of emphysema. Smoking covariates (status, intensity, duration, and pack-years) were similar between groups. Most SA-NSCLCs occurred in males (60.9%), though this proportion was lower than for larger, less aggressive NSCLCs (71.4%). SA-NSCLCs had a statistically significant univariate association with adenocarcinomas, which included bronchioloalveolar carcinomas (OR = 4.77, 95% CI = 2.44 to 9.30), compared with other NSCLCs (squamous cell carcinomas, large cell carcinomas, and other combined). This

Table 4. Demographic and clinical characteristics of cases and controls among those with adenocarcinoma (n = 144)*

Variable	Case− n = 93 (65%)	Case+ n = 51 (35%)	P†	OR (95% CI)‡
Sociodemographic				
Age at diagnosis, mean (SD), y	66.9 (5.5)	66.6 (5.1)	.760	0.99 (0.93 to 1.06)
Sex, No. (%)				
Male	63 (67.7)	31 (60.8)		
Female	30 (32.3)	20 (39.2)	.456	1.35 (0.67 to 2.76)
Race/ethnicity, No. (%)				
Nonwhite	6 (6.4)	2 (3.9)		
White	87 (93.6)	49 (96.1)	.712	1.70 (0.33 to 8.69)
Education level, No. (%)				
High school or less	29 (31.2)	18 (36.0)		
More than high school	64 (69.8)	32 (64.0)	.580	0.81 (0.39 to 1.66)
Medical history				
Body mass index, mean (SD), kg/m^2	27.5 (4.3)	26.2 (3.3)	.064	0.92 (0.83 to 1.01)
Family history of lung cancer, No. (%)				
No	68 (73.9)	33 (66.0)		
Yes	24 (26.1)	17 (34.0)	.338	1.46 (0.69 to 3.08)
Sex*FHLC interaction, No. (%)				
Male, no FHLC	44 (47.8)	23 (46.0)		
Male, FHLC	19 (20.6)	7 (14.0)		
Female, no FHLC	24 (26.1)	10 (20.0)		
Female, FHLC	5 (5.4)	10 (20.0)	.061	3.83 (1.02 to 15.78)
Emphysema§, No. (%)				
No	88 (94.6)	38 (76.0)		
Yes	5 (5.4)	12 (24.0)	.002	5.56 (1.83 to 16.87)
COPD§, No. (%)				
No	73 (78.5)	36 (70.6)		
Yes	20 (22.5)	15 (29.4)	.314	1.52 (0.70 to 3.32)
Chronic bronchitis§, No. (%)				
No	79 (85.0)	43 (86.0)		
Yes	14 (15.0)	7 (14.0)	1.000	0.92 (0.34 to 2.45)
Exposures				
Cigarettes/d, mean (SD)	31.1 (13.5)	30.9 (14.0)	.915	1.00 (0.97 to 1.02)
Years smoked, mean (SD)	43.7 (6.7)	45.3 (7.3)	.202	1.03 (0.98 to 1.09)
Pack-years, mean (SD)	68.1 (33.6)	69.0 (29.3)	.873	1.00 (0.99 to 1.01)
Smoking status, No. (%)				
Former	44 (47.3)	19 (37.2)		
Current	49 (52.7)	32 (63.8)	.293	1.51 (0.75 to 3.04)
Cancer-related				
Tumor size, mean (SD), mm	45.8 (14.5)	18.9 (6.2)	–	–
Screening-related				
Randomization group, No. (%)				
LDCT	39 (41.9)	16 (31.4)		
CXR	54 (58.1)	35 (68.6)	.282	0.63 (0.31 to 1.30)

*Odds ratios and 95% confidence intervals are from univariate logistic regression analyses. CI = confidence interval; COPD = chronic obstructive pulmonary disease; CXR = chest x-ray; FHLC = family history of lung cancer; LC = lung cancer; LDCT = low-dose computed tomography; OR = odds ratio.

†Wilcoxon rank-sum test was used for age, cigarettes per day, years smoked, pack-years, tumor size; Student *t* test was used for body mass index; and Fisher exact test was used for all categorical covariates.

‡Odds ratios for categorical covariates are aligned in the table with the level of interest.

§Lung comorbidities, such as COPD, chronic bronchitis, and emphysema, were determined through self-report.

finding, along with research that previously identified an association of SA-NSCLCs with adenocarcinomas (1), led to subset analyses of adenocarcinomas in order to identify possible histology-specific associations. Adenocarcinoma cases and controls were similar to the full sample for demographics and clinical characteristics (Table 4). In univariate analyses, self-reported history of emphysema (OR = 5.56, 95% CI = 1.83 to 16.87) and female sex-positive family history of lung cancer interaction (OR = 3.83, 95% CI = 1.02 to 15.78) were statistically significantly associated with SA-NSCLC.

A final multivariable logistic regression model for adenocarcinomas, along with bootstrap bias–corrected estimates, is presented in Table 5. Sex and family history of lung cancer had a statistically significant multiplicative interactive association with SA-NSCLC (bias-corrected $OR_{interaction}$ = 6.55, 95% CI = 1.06 to 50.80). The interaction term statistically significantly improved the full adenocarcinoma model, when compared with the nested model without the term (LRT: $P = .018$). The odds ratios excluding the interaction term for female sex (OR = 1.44) and positive family history of lung cancer (OR = 1.45) indicate that the expected multiplicative combination of odds ratio for females with a family history of lung cancer is 2.09 (joint effect = 1.44*1.45 = 2.09). In those with adenocarcinomas, this study identified statistically significant positive multiplicative interaction for females with a

Table 5. Final and bootstrap bias–corrected multivariable logistic regression estimates of associations with SA-NSCLC among individuals with adenocarcinomas (n = 142)*

	Final model	Bias-corrected model
Variable	OR (95% CI), *P*	OR (95% CI), *P*
Emphysema diagnosis (yes vs no)	5.85 (1.82 to 18.82), .003	5.15 (1.63 to 23.00), .007
Sex (female vs male)	0.86 (0.34 to 2.16), .752	0.88 (0.35 to 2.21), .763
FHLC (yes vs no)	0.56 (0.19 to 1.65), .296	0.59 (0.11 to 1.59), .359
Sex*FHLC interaction	7.47 (1.34 to 41.71), .022	6.55 (1.06 to 50.80), .042

*CI = confidence interval; FHLC = family history of lung cancer; OR = odds ratio; SA-NSCLC = small aggressive non–small cell lung cancer.

family history of lung cancer compared with males without, with an adjusted odds ratio for the joint effect of 3.62 (95% CI = 1.06 to 12.34). We further evaluated this interaction among SCLC, and the associations did not approach statistical significance ($P_{interaction}$ = .68). Due to small numbers of SCLC cases (n = 23) and controls (n = 20) and wide confidence intervals, these findings should be interpreted cautiously.

The previously reported association of SA-NSCLC with younger age at diagnosis was not observed in the current study, and the association with ibuprofen use could not be validated as ibuprofen use was not measured in NLST (1). Age at diagnosis showed a suggestive inverse trend with SA-NSCLC risk, but these effects were attenuated when models were adjusted for sex and histology, as adenocarcinomas and females were both associated with younger age at diagnosis (data not shown). Associations for screening arm with sex or family history of lung cancer were not observed (data not shown), suggesting that confounding by trial arm is unlikely. Exploratory analyses identified an association between SA-NSCLC and emphysema in the final multivariable model (OR = 5.15, 95% CI = 1.63 to 23.00).

Discussion

Females with a family history of lung cancer in a first-degree relative are at statistically significantly increased risk of having small aggressive lung adenocarcinomas. This result validates findings from a previous study in a separate population (1) and provides a basis for future research on the role of female hormones in lung carcinogenesis and clinical progression, particularly in those with a family history of lung cancer. Further research is needed to elucidate the genetic, epigenetic, and environmental mechanisms contributing to increased familial risk. A history of emphysema may also lead to early disease progression and metastases indicative of relevant tobacco-related lung damage. All participants were heavy current or former smokers, so the comparisons of other potential risk factors were all done in a population with a history of tobacco exposure.

The primary control group used to address the study objectives included patients with tumors that were T2 to T3, N0 to N2, and M0. Less aggressive T1 tumors were excluded from the control group to avoid potential misclassification, as these tumors still have the potential to spread to distant lymph nodes and metastasize, and thus could be early SA-NSCLC. Similarly, large aggressive tumors (>30 mm, T4/N3/M1) were excluded as they could have been SA-NSCLCs that had the opportunity for the primary tumor to grow in size and were identified later in disease course. As such, the control group only contains tumors that have not gone through the SA-NSCLC disease course.

Although the NLST participants were more white, more educated, and more likely to be former smokers than the general US population (16,17), in large part, the findings of the current study reflect biological processes and are expected to be generalizable beyond the NLST cohort. Computed tomography imaging can detect smaller lung nodules than CXR (18), but in this study more SA-NSCLCs were detected by CXR. Random sampling variation may account for this difference.

Despite evidence suggesting that adenocarcinomas are more likely to have early metastases (19,20), including a recent study that identified an adenocarcinoma subtype with an aggressive phenotype in early stage (21), they generally have been shown to have similar or slightly better prognosis than other histologies (20,22,23). Our previous study found a similar association of SA-NSCLCs with adenocarcinomas when compared with other NSCLC histologies (1). Adenocarcinomas are disproportionately higher in females than males, despite being the most common lung cancer subtype for both sexes (20,24,25). In this study, SA-NSCLCs were found to be significantly associated with adenocarcinomas. The sex–family history interaction persisted within adenocarcinoma, suggesting that this finding is not confounded by early metastases being more common in adenocarcinomas, which are more common in women, those with a family history of lung cancer, and younger individuals (24–26).

The link between female factors, such as sex hormones, and heritable genetic variations in causing lung cancer is not clear, but there is cause for speculation. Compared with somatic gene mutations, less is known of inherited gene mutations in the development of lung cancer. KRAS gene mutations are the most frequently occurring mutated oncogenes in lung adenocarcinomas (27). A germline single nucleotide polymorphism (rs61764370) in the 3'-untranslated region of the KRAS oncogene, termed the KRAS variant, has been identified as an inherited mutation that may play a role in cancer risk and altered tumor biology (28). Carriers of this gene variant tend to develop highly aggressive cancers (28,29). A relationship between hormonal exposure and breast cancer risk in women with the KRAS variant has been observed, and it suggests a possible interaction between this variant and female sex hormones for increasing breast cancer risk, and may predict aggressive tumor biology (28,29). A similar relationship may exist in lung cancer. No association was observed for overall familial or sporadic breast cancer risk and the variant (28). Results from two case–control studies identified 1.4- and 2.3-fold increases in the risk of NSCLC for below-median smokers (<40 and <41 pack-years, respectively) with the KRAS risk allele, but no overall association among heavier smokers (30). A meta-analysis found no association between the KRAS variant (rs61764370) and overall risk of ovarian, breast, or colorectal cancer (31). These pooled findings did not account for potential interaction with hormonal exposures. Future molecular epidemiologic studies may investigate germline genetic variants associated with a family history of SA-NSCLC and how these variants interact with the female hormone environment. Existing tissue microarrays and DNA cores assembled for the PLCO and NLST could be used for these and other similar purposes.

In univariate and multivariable analyses, SA-NSCLCs were associated with history of emphysema. Lung comorbidities have been linked to an increased risk of developing lung cancer

(32); however, the current study implicates lung disease as playing a role in early lung cancer progression. Chronic obstructive pulmonary diseases, such as emphysema, are pathologically characterized by activation of inflammatory processes of the lung (33–36). The proposed mechanisms by which an inflammatory response could contribute to carcinogenesis include increased genetic mutations, anti-apoptotic signaling, and increased angiogenesis (32). Increased angiogenesis is considered a required precursor for tumor growth, and for tumor cells to enter the blood stream and metastasize (37,38). Avascular tumors have limited capacity for growth and metastases (37). Inflammation can activate cell populations that release angiogenic factors (39). Increased levels of proangiogenic factors may allow for increased vascularization of tumors, increasing growth and metastatic potential (37,38). Lung comorbidity, in particular emphysema, is an important factor to consider in a population with extensive history of tobacco use.

The metastatic potential of NSCLC has been consistently linked with tumor size (2,3,40–43). This is likely because the factors that promote tumor growth also increase metastatic potential (39). Little is known about possible lower boundaries of size for a tumor to develop a profile necessary to become metastatic or locally invasive. Research has suggested that the angiogenesis required for a solid tumor to become metastatic occurs by the time a tumor is 1 to 2 mm (42). Nodules as small as 1 mm were detected in the NLST, though no NSCLCs were this small. The frequency of metastases increased substantially at or beyond 10 mm tumor sizes, and for those lung tumors that met the criteria of being SA-NSCLC, the smallest was 8 mm. Ten mm may represent an approximate lower bound for SA-NSCLC development. Lung tumors 3 cm or smaller in size, with limited invasion of surrounding tissue (T1), are further subclassified as T1a if the tumor is 2 cm or smaller in the long axis (TNM–AJCC, 7th ed.) (44). If 10 mm is an approximate lower boundary for tumors to become regionally aggressive and/or metastasize, future studies may consider revising the T1 subclassification to better reflect tumor biology.

A limitation of the current study is its small sample size, which was a consequence of the case–case study design. The conclusions drawn from this study may need to be replicated with a larger sample size. On the other hand, the nested case–case study took place in a large, semirepresentative, defined cohort, with carefully measured outcome and predictor variables. Recall bias was eliminated by prospective data collection, and selection biases were minimized by sampling all eligible cases and controls from within the same cohort.

In summary, this study validates the finding that in a population with an extensive smoking history, women with a family history of lung cancer are at elevated risk of small aggressive lung adenocarcinomas, suggesting that heritable factors may interact with sex-specific factors in the early progression of adenocarcinomas. In addition, SA-NSCLC is associated with a history of emphysema. Knowledge of the gene-sex interaction and biology of SA-NSCLC might lead to a better understanding of carcinogenesis and cancer progression, as well as identification of high-risk populations that might benefit from screening or increased clinical monitoring, and may lead to effective chemoprevention and improved therapeutics.

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