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Associations between history of chronic lung disease and non—small cell lung carcinoma in Maryland: variations by sex and race

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Abstract

Purpose: Lung cancer is a multifactorial malignancy for which some risk factors, such as chronic lung diseases, their interactions with smoking, and how they differ by race and sex, are not fully understood. We investigated the associations between chronic inflammatory lung disease and nonesmall cell lung carcinoma (NSCLC) and how sex and race may affect such associations.

Methods: Using logistic regression, we analyzed 1660 lung cancer cases and 1959 population controls and estimated adjusted odds ratios (AORs) and 95% confidence intervals (CIs).

Results: Chronic lung disease was significantly associated with higher odds of having NSCLC in never (AOR=1.99; 95% CI =1.19–3.34),former (AOR = 1.68; 95% CI = 1.29–2.20), and current smokers(AOR= 2.40; 95% CI = 1.62–3.57), after adjustment for relevant covariates. For each 5-year increment in chronic lung disease duration, the risk of lung cancer increased only among females (AOR = 1.07; 95% CI = 1.02–1.13). Females, but not males, with asthma were at risk for NSCLC (AOR= 2.08; 95% CI = 1.40–3.10).

Conclusions: This study provides support for chronic lung in$_{fl}$ammation as a potential contributing factor to lung cancer risk and possible sex difference in the inflammatory events underlying disease mechanisms.

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Keywords

Chronic lung disease; Non-small cell lung carcinoma (NSCLC); Chronic obstructive; pulmonary disease (COPD); Asthma; Inflammation

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide and in the United States [1–3]. There are two predominant types: small cell lung carcinoma and non-small cell lung carcinoma (NSCLC); the latter is the most common type (85%−90% of all cases) [4]. Differences in incidence and mortality exist by race and sex. In the United States, age-adjusted incidence and mortality rates of lung cancer are significantly higher in black than in white men, but comparable between black and white women [3,5,6]. Cigarette smoking is a well-established risk factor for developing lung cancer [7]; however, approximately 25% of all lung cancer cases are not attributable to smoking [8,9], and 10%−15% of these cancer deaths occur in never smokers [10]. Other established risk factors for lung cancer, including environmental tobacco smoke (ETS), radon gas, occupational exposures to carcinogens, air pollution, and genetic susceptibility [11,12], failed to explain all of its incidence, particularly in never smokers [9,10].

Lung cancer in never smokers occurs disproportionately in women [13,14], has better response to targeted therapy [15], and its incidence is higher in non-whites [16]. These unique characteristics suggest that it may be a different disease from smoking-related lung cancer [9,15]. One potential risk factor is chronic inflammation, which can lead to DNA damage, mutations, and ultimately cell growth and proliferation [17], especially among never smokers [18–22]. Both prospective and retrospective studies have found a positive association between chronic obstructive pulmonary disease (COPD) and lung cancer risk in never smokers [18,19,23,24], whereas others found positive associations with other lung diseases such as asthma, tuberculosis, and pneumonia [18]. Many of these studies did not explore sex- and/or race-specific associations, and some studies had small sample size or did not carefully examine the potential interplay of chronic lung diseases and tobacco exposures.

To address these gaps in knowledge, we analyzed data from the Maryland lung cancer study. We assessed the associations between NSCLC risk and history of chronic lung disease (defined as history of chronic bronchitis, COPD, emphysema, or asthma) and its duration (i.e., time since the participants' diagnoses), and how sex and race affect such associations, in the presence or absence of smoking.

Methods

Study design

The parent study is an on-going case-control study designed principally to investigate potential genetic mechanisms underlying variations in NSCLC by sex and race in Maryland [25–28]. The institutional review boards of the University of Maryland, the National Cancer Institute, the Johns Hopkins University School of Medicine, Sinai Hospital, MedStar Research Institute, and Georgetown University, as well as the Research Ethics Committee of

Bon Secours Health System, approved the parent study. The present study is based on analyses of a precollected de-identified data set.

Selection of cases and controls

Selection of cases and controls has been previously described [25,26]. Cases, with histologically confirmed NSCLC, were recruited from the aforementioned hospitals in the Metropolitan Baltimore area and interviewed within 180 days of their cancer diagnosis. Eligibility criteria included (1) Caucasian (white) or African American (black); (2) U.S. born; (3) residing in Baltimore city, adjacent counties, or Eastern Shore of Maryland; (4) speaking English well enough to be interviewed; (5) noninstitutionalized; (6) not diagnosed with HIV or hepatitis B or C; (7) not on antibiotics or immunosuppressive drugs including steroids; (8) no history of prior cancer before lung cancer; and (9) never been interviewed as a control for the study [25–28]. In addition, cases who had already received chemotherapy and/or radiation therapy were not considered for the study.

Population-based controls were recruited via telephone from the same Maryland counties of residence as cases, using screening information from the Department of Motor Vehicles, to match cases by age, gender, and race. Controls were required to meet the eligibility criteria outlined above (1–8 only). Because the original study was designed primarily to investigate potential genetic mechanisms underlying variations in NSCLC race, black controls were oversampled. In addition, owing to the requirements of the mutagen sensitivity analysis that was undertaken in the early years of the study, participants using steroids were excluded. Once the assay results were completed, the investigators decided to drop this criterion; starting in 2004, cases and controls who used steroid medications were included.

Study questionnaire and measures

After completing a written informed consent, cases and population-based controls were interviewed using a standardized questionnaire that included questions on sociodemographic characteristics, medical history, family history of lung disease and cancer, smoking and ETS exposure history, occupational history, and use of medications [25–28]. All information, including medical history, was self-reported by participants or their designated proxies (for cases only).

We defined history of chronic lung disease as ever having been told by their health-care provider that they had chronic bronchitis, emphysema, COPD, or asthma. We also calculated the duration of such disease(s) as the difference between participants' age at cancer diagnosis (or study enrollment for controls) and age (years) at diagnosis of chronic lung disease in years.

Sociodemographic characteristics included age, sex, race (white or black), marital status, education, household income, and alcohol use. Family history addressed (1) chronic lung disease, (2) any cancer, or (3) lung cancer in first-degree relatives. Participants were considered "never cigarette smokers" (smoking fewer than 100 cigarettes in their lifetime), "former smokers" (not smoking within the past year), or "current smokers". Former and current smokers reported their age at smoking initiation and number of packs smoked per day, which was used to create a pack-years variable. ETS exposure included passive

smoking in childhood, adulthood, and workplace(s). Participants' jobs held for the longest time were coded using the U.S. Department of Labor's Dictionary of Occupational Titles [29] and categorized as professional/technical/managerial, clerical/sales/services, and miscellaneous that included all other jobs.

Statistical analyses

Cases and controls were compared using Student's t tests and c^2 tests for continuous and categorical variables, respectively. We used logistic regression to estimate unadjusted and adjusted odds ratios (AORs) with 95% confidence intervals (CIs) for the associations between either history of chronic lung disease or its mean duration and NSCLC risk. Age, year of diagnosis (or interview for controls, to account for any cohort effects), and a dichotomous variable indicator of whether the data were collected before 2004 (year stopped excluding steroid medication use, to minimize selection bias) were included in the baseline model. In addition to the predictor, smoking status (well-established lung cancer risk) and pack-years (set to zero in never smokers), followed by sex, race, and other sociodemographic and family history variables that were significantly associated with case-control status, were introduced in the model, using a stepwise approach; each of these covariates was kept in the model if it remained significantly associated with the outcome or modified the regression coefficient of the main effect by greater than or equal to 10%. The presence of effect modification was examined by adding the main predictor, one covariate, and their interaction term to the model.

Considering that COPD can result from smoking and thus be potentially in the causal pathway between smoking and lung cancer, it was important to stratify by smoking status and analyze the never smoker group. Hence, we built separate multivariable regression models stratified by either sex or race, before and after stratification by smoking status.

As secondary analyses, we assessed the associations between NSCLC risk and history of either asthma or COPD (chronic bronchitis, emphysema, or COPD), before and after stratification by either race or sex, within the smoking strata.

All statistical analyses were conducted using SAS, version 9.3 (SAS Institute Inc, Cary, NC), and significance level was set as twotailed $P < 0.05$.

Results

Between 1998 and 2015,10,380 lung cancer cases were screened, and 2415 (23.3%) met the eligibility criteria and completed screening. Approximately 68% agreed to participate, leading to 1660 enrolled NSCLC cases. Of eligible controls, 90% agreed to participate, resulting in 1959 population-based controls. Descriptive analysis of the data set revealed small numbers for history of asbestosis (n = 117) and tuberculosis (n = 106) and a large missing number (n = 2133) for pneumonia. Therefore, histories of these conditions were not included in the analyses.

Table 1 shows that cases, more than controls, were white, female, not married, less educated, employed in clerical/sales/service jobs, and had lower household incomes. More cases than

controls reported ever smoking cigarettes (91.5% vs. 56.7%), being current smokers (40.4% vs.13.5%) (Table2), initiating smoking at an earlier age (16.6 vs. 17.7 years), smoking a greater number of pack-years (43.8 vs. 23.7), quitting for fewer years (among former smokers 15.0 vs. 26.1), and being exposed to ETS at home and at work (all $P < 0.05$).

Almost 40% of cases reported a history of chronic lung disease, compared with only 16.7% of controls (Table 3); and its duration was significantly longer among cases (6.1 years) than controls (4.6 years). Cases, more than controls, reported family histories of any cancer (83.3% vs. 77.0%) and lung cancer (38.3% vs. 22.2%).

We compared former smokers who had quit smoking for 20 years and above with never smokers and found them significantly different with respect to multiple sociodemographic variables (data not shown). Therefore, we used never, former, and current smokers as separate groups in all analyses.

Participants with chronic lung disease had higher risk for NSCLC compared with those without it (unadjusted OR = 3.24; 95% CI = 2.78–3.78). Race, sex, education, marital status, smoking, ETS exposure, occupation, and family history of lung cancer or any cancer were significantly associated with NSCLC risk. For ETS, exposures in adulthood and at work were included in the final model; childhood exposure became statistically not significant in the fully adjusted model, and its inclusion did not modify the main estimate. These covariates, except for occupation (which strongly correlated with education), were included in the multivariable regression models before and after stratification (Tables 4 and 5).

The associations between chronic lung disease and NSCLC remained elevated in the overall sample (AOR = 1.87; 95% CI = 1.54–2.28), as well as in different smoking strata, including the never smokers' (AOR = 1.99; 95% CI = 1.19–3.34), even after adjustment for several covariates (Table 4). Interaction terms between chronic lung disease and smoking status in the overall model were not statistically significant ($P > 0.05$); nor were they after stratification by either sex or race (Table 4). The AORs of the associations between chronic lung disease and NSCLC were significantly elevated and similar for both sexes and both races. Regardless of their sex, never smokers with chronic lung disease had elevated AORs for NSCLC (2.05 [0.77–5.50] and 2.18 [1.16–4.11], for males and females, respectively), albeit not statistically significant for the former. However, such high risk was significant among both former and current smokers (Table 4). White participants, who were either former or current smokers, had significantly high odds of having NSCLC, whereas among blacks, only current smokers had significantly elevated risk (Table 4).

Similar models were built with duration of chronic lung disease as a predictor (data not shown). Interactions terms between duration and sex ($P = 0.001$), but not smoking status ($P > 0.05$), were statistically significant. For each 5-year increment in chronic lung disease duration, the odds of having NSCLC was higher by 7% (AOR = 1.07; 95% CI = 1.02–1.13) among females but lower by 6% among males (AOR = 0.94; 95% CI = 0.89–0.99).

Analyses of history of asthma revealed statistically significant association (unadjusted OR = 1.46; 95% CI = 1.17–1.81) with NSCLC risk. In the fully adjusted overall regression model, the association remained statistically significant (AOR = 1.42; 95% CI = 1.07–1.88) (Table

5). The interaction term for asthma and sex was statistically significant (P = 0.002). After stratification by either sex or race, history of asthma was associated with statistically significant high NSCLC risk among females and among white participants (Table 5). Such associations remained significant only in former smoker strata (AOR = 2.53; 95% CI = 1.42–4.50, and AOR = 1.66; 95% CI = 1.03–2.68, for female and white, respectively); female never smokers had high NSCLC risk that was borderline significant (AOR = 2.13; 95% CI = 0.97–4.71).

History of COPD was also significantly associated with NSCLC risk (unadjusted OR = 4.66; 95% CI = 3.92–5.55) and remained in the fully adjusted overall model (AOR = 2.19; 95% CI = 1.76–2.72), and in both race and sex strata (Table 5). The interaction term for COPD and race was borderline significant (P = 0.06). After stratification by smoking status, in the overall model of never smokers, the NSCLC risk remained significantly high (AOR = 2.45; 95% CI = 1.31–4.59); such elevated risk persisted after stratification by either race or sex but became not statistically significant in whites (AOR = 2.04; 95% CI = 0.91–4.56) and in males (AOR = 2.82; 95% CI = 0.83–9.58). The AORs (95% CI) for black never smokers or females were 3.14 (1.13–8.74) and 2.83 (1.31–6.10), respectively.

Discussion

We found significantly higher risk of NSCLC in never smokers who had a history of chronic lung disease, asthma, or COPD as compared with those without such history; and for each 5-year increment in chronic lung disease duration, the odds of having NSCLC was significantly higher among females (7%) but lower among males (6%). Women with history of either asthma or COPD were more than men at risk for NSCLC.

Our findings are consistent with those previously reported, although the chronic lung diseases addressed varied among studies [19,30,31]. Association between asthma and lung cancer risk was reported by some investigators [23,32,33], but not by others [19,21,30,34,35] who reported associations with chronic bronchitis [34] and/or emphysema [21,30,35]. We defined chronic lung disease as having had a diagnosis of COPD, chronic bronchitis, emphysema, or asthma, all of which result in chronic inflammation of the respiratory system, although COPD and asthma are clinically different entities.

Furthermore, prior studies with similar findings to ours in never smokers combined never and former smokers because of small numbers of never smokers [21,23]. In our study, we found that former smokers who had quit smoking for 20 years and above were different from never smokers, and hence we did not combine former and never smokers.

Unlike prior studies [35,36], we found a significant association between asthma and NSCLC risk in women, but not in men; and to a lesser extent in white, but not black participants (Table 5)-associations that remained statistically significant only in former smokers. The very small numbers of never smokers in the different strata would help explain the wide CIs and lack of statistical significance. On the other hand, history of COPD was significantly associated with high NSCLC risk across all the strata (Table 5)and remained as such in never smokers who were only women or black participants.

Sex differences in lung cancer risk associated with chronic lung disease were previously reported. Across individual cohort and case-control studies, chronic bronchitis, emphysema, and/or asthma were associated with an increased NSCLC risk in men only [33], women only [32], both sexes [21], or neither sex [37]. In a pooled analysis of 13 case-control studies, men with chronic bronchitis and emphysema had a 33%e50% higher NSCLC risk, whereas women with asthma had a 25% lower risk [35]. We found that history of either asthma or COPD in never smokers contributed to NSCLC risk more in women than men. Dissimilarities between our results and previous studies can be partially attributed to our study population, which included a large number of black participants. The latter may have key differences in smoking habits, history of chronic lung disease, and other risk factors, including genetics [25,28], that affect their likelihood of developing NSCLC. Prior studies included mostly homogenous populations.

Despite these conflicting results, it is plausible that the process by which chronic inflammation leads to the development of malignancy differs between male and female. Indeed, chronic inflammatory events of lung diseases and their subsequent clinical outcomes were reported to be more severe in females than in males [38]. Inflammation that is partially mediated by cytokines could ultimately result in tumor growth [17]; and inflammatory proteins were shown to be associated with lung cancer diagnosis [39,40]. Moreover, racial differences in inflammatory processes were postulated to contribute to racial disparity in lung cancer [41].

Another possibility for the sex difference in the association between chronic lung disease duration and lung cancer risk is the fact that duration represents the time elapsed between when healthcare providers informed participants of their lung disease and NSCLC diagnosis or interview date. Women are more likely than men to visit their health-care providers [42] and thus receive an earlier diagnosis of COPD or asthma.

Our study has some limitations. As a case-control study that relies on self-reported information by participants, it is subject to recall bias, which may result in differential misclassification of exposures. Given the likelihood that participants were unaware of the associations under study, any underreporting or overreporting would likely be similar between cases and controls, resulting in nondifferential misclassification and biasing the OR toward the null. Finally, the study did not collect information on radon exposure, which is the second leading cause of lung cancer in North America; however, the controls were selected from the same counties of the cases and thus could have similar radon exposure.

Nonetheless, this study of histologically confirmed NSCLC cases and population-based controls in the state of Maryland had a large sample of never smokers and detailed pertinent information, and oversampled black men and women, all of which allowed us to investigate NSCLC risk among never smokers and how it differs by sex and race.

Conclusion

This study provides support for an inflammatory process as a potential contributing factor to NSCLC risk, regardless of smoking status, and for possible sex difference in the

inflammatory events underlying disease mechanisms. Additional investigations are needed to confirm the observed relationships and elucidate the role of the inflammatory processes in the development of NSCLC. Should the results confirm the postulated mechanism, one might consider anti-inflammatory drugs as potential preventive therapy for lung cancer.

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Table 1

Sociodemographic characteristics of non–small cell lung carcinoma cases and population controls

Characteristic	Population controls (*n* =1959)	Lung cancer cases (*n* = 1660)	*P*-valu
Age at interview, in years, mean (SE)	65.9 (0.19)	65.6 (0.26)	.3
Race, *n* (%)			
White	1137 (58.1)	1141 (68.8)	<.0001
Black	821 (41.9)	517 (31.2)	
Missing	1	2	
Sex, *n* (%)			
Male	1247 (63.7)	871 (52.5)	<.0001
Female	712 (36.3)	789 (47.5)	
Marital status, s(%)			
Married or living as married	1400(71.5)	911 (55.0)	<.0001
Single, never married	135 (6.9)	117(7.1)	
Divorced, separated, or widowed	423 (21.6)	630 (38.0)	
Missing	1	2	
Education, *n* (%)			
Less than high school	133 (7.0)	405 (25.1)	<.0001
High school or GED	402 (21.3)	521 (32.3)	
More than high school	1353 (71.7)	687 (42.6)	
Missing	71	47	
Household income, *n* (%)			
<$30,000	360 (21.1)	708 (48.0)	<.0001
$30,000–<$60,000	460 (26.9)	377 (25.6)	
$60,000–$90,000	394 (23.0)	190(12.9)	
>$90,000	496 (29.0)	200 (13.6)	
Missing	249	185	
Longest held occupation, *n* (%)			
Professional/technical/managerial	1087 (55.5)	606 (36.5)	<.0001
Clerical/sales/service	506 (25.8)	562 (33.9)	
Miscellaneous *	366(18.7)	492 (29.6)	
Ever drank alcohol, *n* (%)			
Yes	1470 (75.0)	1286(77.5)	.08
No	489 (25%)	373 (22.5)	
Missing	0	1	

Abbreviations: GED = general equivalency degree; SE = standard error.

* Miscellaneous occupations included agriculture/fishery/forestry, processing operations, machine trades occupations, benchwork occupations, structural work occupations, and other miscellaneous occupations.

Table 2

Smoking variables in non–small cell lung carcinoma cases and population controls

Smoking variable	Population controls (*n* = 1959)	Lung cancer cases (*n* = 1660)	*P*-value
Ever smoked *n* (%)	1111 (56.7)	1518 (91.4)	<.0001
Cigarette smoker, *n* (%)			
Never	848 (43.3)	142 (8.6)	<.0001
Former	847 (43.2)	848 (51.1)	
Current	264 (13.5)	670 (40.4)	
Age at initiation, in years, mean (SE) *	17.7 (0.16)	16.6(0.11)	<.0001
Missing	6	9	
Sum of years smoked, mean (SE) *	23.9 (0.44)	34.3 (0.40)	<.0001
Missing	8	11	
Pack-years smoked, mean (SE) *	23.7 (0.66)	43.8 (0.73)	<.0001
Missing	9	10	
Years since quitting, mean (SE) †	26.1 (0.46)	15.0 (0.45)	<.0001
Missing	1	4	
ETS exposure in childhood, *n* (%)	1422 (72.6)	1333 (80.4)	<.0001
Missing	0	2	
ETS exposure in adulthood, *n* (%)	694 (35.4)	1076 (64.9)	<.0001
Missing	0	1	
ETS exposure at work, *n* (%)	947 (48.5)	1084 (65.4)	<.0001
Missing	6	3	

Abbreviations: ETS = environmental tobacco smoke; SE = standard error.

* Denominator included ever smokers only.

† Denominator included former smokers only.

Table 3

Medical and family histories of non–small cell lung carcinoma cases and population controls

Variable	Population controls (*n* = 1959)	Lung cancer cases (*n* = 1660)	*P*-value
Chronic lung disease[*], *n* (%)	328 (16.7)	654 (39.5)	<.0001
Missing	0	3	
Chronic bronchitis, *n* (%)	162 (8.3)	354 (21.4)	<.0001
Missing	0	2	
COP[†], *n* (%)	210(10.7)	595 (35.9)	<.0001
Missing	1	3	
Emphysema, *n* (%)	62 (3.2)	382 (23.0)	<.0001
Missing	0	2	
Asthma, *n* (%)	167 (8.5)	198 (11.9)	.001
Missing	0	2	
Duration of chronic lung disease, mean (SE)	4.6 (0.30)	6.1 (0.33)	.001
Missing	6	26	
Family history of any cancer, *n* (%)	1504 (77.0)	1378 (83.3)	<.0001
Missing	5	6	
Family history of lung cancer, *n* (%)	434 (22.2)	634 (38.3)	<.0001
Missing	5	6	
Family history of chronic lung disease[‡], *n* (%)	371 (37.1)	450 (34.6)	.2
Missing	138	90	

Abbreviations: COPD = chronic obstructive pulmonary disease; SE = standard error.

[*]Chronic lung disease defined as having history of chronic bronchitis, emphysema, COPD, or asthma.

[†]COPD encompasses chronic bronchitis, emphysema, or COPD.

[‡]Denominator included participants who were enrolled in the study from 1998 to 2011 (1391 lung cancer cases and 1139 population controls).

Table 4

Adjusted associations between history of chronic lung diseases and non–small cell lung carcinoma risk, overall and after stratification by either race or sex, before and after stratification by smoking status

History of chronic lung diseases	Adjusted odds ratios and (95% confidence intervals)				
	Overall (*n* = 3619)	White (*n* = 2278)	Black (*n* = 1338)	Male (*n* = 2118)	Female (*n* = 1501)
In Study sample*	1.87 (1.54, 2.28)	1.89 (1.48, 2.43)	1.97 (1.40, 2.78)	1.77 (1.34, 2.34)	2.05 (1.54, 2.73)
Never smokers†	1.99 (1.19, 3.34)	1.87 (0.98, 3.58)	2.04(0.85, 4.91)	2.05 (0.77, 5.50)	2.18(1.16, 4.11)
Former smokers†	1.68 (1.29, 2.20)	1.82 (1.32, 2.51)	1.61 (0.97, 2.67)	1.48(1.03, 2.13)	2.10(1.40, 3.16)
Current smokers†	2.40 (1.62, 3.57)	2.16 (1.29, 3.60)	2.86 (1.50, 5.46)	2.22 (1.31,3.77)	2.29 (1.24, 4.23)

In the overall model of the study sample, interaction terms for chronic lung diseases × smoking status, chronic lung diseases × race, or chronic lung diseases × sex were not statistically significant (*P*-values >0.05).

*Adjustment included year of interview, year steroid stopped as exclusion, age at interview, smoking status (never, former, and current) and pack-years, marital status, environmental tobacco smoke exposure in adulthood and at work, family history of lung cancer, sex and race (for the overall model), or either sex or race for the stratified ones.

†Adjustment included all the above except smoking status.

Table 5

Adjusted associations between history of either asthma or COPD (chronic bronchitis, emphysema, or COPD) and non—small cell lung carcinoma risk, overall and after stratification by either race or sex

Predictor variable	Adjusted odds ratios and (95% confidence intervals)*				
	Overall (*n* = 3619)	White (*n* = 2278)	Black (*n* = 1338)	Male (*n* = 2118)	Female (*n* = 1501)
History of asthma	1.42 (1.07, 1.88)	1.61 (1.11, 2.34)	1.12 (0.70, 1.78)	0.94 (0.61, 1.44)	2.08 (1.40, 3.10)
History of COPD	2.19(1.76, 2.72)	2.04 (1.57, 2.67)	2.83 (1.92, 4.16)	2.28 (1.67, 3.10)	2.10 (1.54, 2.86)

In the overall model, interaction terms for asthma × smoking status, COPD × smoking status, or asthma × race were not statistically significant ($P > 0.05$), whereas asthma × sex was statistically significant ($P = 0.002$), and COPD × race was borderline ($P = 0.06$

*Adjustment included year of interview, year steroid stopped as exclusion, age at interview, smoking status (never, former, and current) and pack-years, marital status, environmental tobacco smoke exposure in adulthood and at work, family history of lung cancer, sex and race (for the overall model), or either sex or race for the stratified ones.