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COPD and lung cancer incidence in the Women's Health Initiative Observational Study: A brief report

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Abstract

Objectives: Lung cancer is the leading cause of cancer mortality in both men and women in the United States. COPD is associated with lung cancer independently of cigarette smoking, but remains understudied in women. Utilizing data from the Women's Health Initiative Observational

Declarations of interest: none

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Study (WHI-OS), this report investigates the association between COPD and development of lung cancer, with a focus on ethnicity and cancer subtype.

Materials and Methods: The WHI-OS, part of the larger Women's Health Initiative (WHI), is comprised of postmenopausal women between ages 50 and 79 years old at enrollment. Self-administered questionnaires were utilized to gather baseline demographic, socioeconomic, and behavioral information from participants. For this analysis, COPD status was determined at study entry (baseline) and on annual survey (incident). Information on the primary outcome of interest, diagnosis of lung cancer, was also collected annually.

Results and Conclusion: Of the 92,789 women examined, 1,536 developed lung cancer. Overall, women with COPD were 1.64 times more likely to develop lung cancer than those without COPD, after adjusting for smoking status and intensity, ethnicity, education, body mass index, and income (HR=1.64, 95% CI: 1.43, 1.89). The relationship between COPD and lung cancer was not found to be significantly different between ethnic groups (p-value=0.697). The associations between COPD and lung cancer was similar across subtypes (HR range 1.31–2.16), after adjusting for smoking status and intensity. COPD increases risk of lung cancer in women, thus they may benefit from more intensive surveillance compared to similar women without COPD.

Keywords

COPD; emphysema; lung cancer; smoking; ethnic difference

Introduction

Lung cancer is the leading cause of cancer mortality in both men and women in the United States, with an estimated 154,050 deaths expected to occur in 2018 [1]. Cigarette smoking has been linked to the development of lung cancer and chronic obstructive pulmonary disease (COPD) [2] and COPD has been found to be independently associated with an increased risk of developing lung cancer. A pooled analysis of 17 epidemiologic studies reported a 2.4-fold increase in risk of lung cancer associated with emphysema ($OR_{meta}=2.44$, 95% CI: 1.64, 3.62), and a 1.5-fold association with chronic bronchitis ($OR_{meta}=1.47$, 95% CI: 1.29–1.68) after adjusting for smoking history; however, estimates were not provided separately for men and women [3]. The mechanism driving these associations may be chronic inflammation causing cellular damage while promoting cell proliferation, which provides an environment suitable for oncogenic processes to occur [4]. This is also supported by evidence suggesting that never smokers with emphysema are at higher risk for lung cancer [5]. Interestingly, women may be more susceptible to developing COPD compared to men due to smoking [6].

The association between COPD and lung cancer risk remains less studied in women compared to men. Utilizing data from the Women's Health Initiative Observational Study (WHI-OS), we investigated the relationship between COPD and lung cancer, by ethnicity and histologic subtype.

Materials and Methods

The WHI-OS is comprised of 93,676 postmenopausal women between ages 50 and 79 years old at enrollment. Greater detail regarding the study population is described in Hays et al [7]. The study protocols all received institutional approval and all women provided written informed consent. Initial enrollment started on January 1, 1993 and ended December 31, 1998. Longitudinal follow up continued through December 31, 2015. Self-administered questionnaires were utilized to gather baseline demographic, socioeconomic, and behavioral information from participants.

For this analysis, self-reported, baseline COPD status was determined by the medical history form through the question, “Has a doctor told you that you have emphysema or chronic bronchitis?” Incident COPD was defined as individuals reporting no COPD at baseline, followed by indicating “yes” to the same question on an annual questionnaire. The primary outcome of interest, incident lung cancer, was also collected annually. These self-reports, or reports by next-of-kin, were verified by WHI physician adjudicators through review of medical and pathology records. Details regarding the cancer (i.e., histology) were coded using the International Classification of Diseases for Oncology 3rd Edition.

Demographic characteristics, including smoking status and intensity at baseline, were summarized based on the participant’s COPD status (no COPD, baseline COPD, incident COPD only). Cox proportional hazards models using participant age as the underlying time scale were used to assess the relationship between COPD status and time to the development of lung cancer, adjusting for smoking status and intensity, ethnicity, education, income, and body mass index (BMI). As women developed COPD at different times throughout follow-up, COPD status (yes/no) was evaluated as a time-varying covariate. Separate Cox models for each subtype were also considered; due to small numbers these models were adjusted for smoking status and intensity only. All analyses were performed using SAS/STAT software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC).

Results

After excluding those with self-reported lung cancer at baseline (n=219), those without follow-up time (n=469), and those without COPD information at baseline (n=190) the total study population was 92,798. The median follow-up time was approximately 12.6 years (range: 1 day to 16 years). Of these women, 1,536 developed lung cancer during the follow-up period which included 1,239 (1%) from the no COPD group (n=84,212), 150 (4%) from the baseline COPD group (n=3,430) and 147 (3%) from the incident COPD group (n=5,156). Other characteristics of the study population are included in Table 1.

As shown in Table 2, women with COPD were 1.64 times more likely to develop lung cancer than those without COPD, after adjusting for smoking status and intensity, ethnicity, education, BMI, and income (hazard ratio (HR)=1.64, 95% confidence interval (CI) 1.43–1.89). There were no statistically significant interactions between COPD and these adjustment variables (data not shown). In particular, the interaction between COPD and ethnicity was not significant (p-value=0.697), suggesting that the relationship between

COPD and lung cancer was not modified by ethnicity. Therefore, separate results by ethnicity are not presented and results from the overall model are shown instead. Table 2 also examined the association between COPD and subtypes of lung cancer. Of the 1,536 lung cancers, the majority were adenocarcinomas (41.9%, n=643). Overall, the association between COPD and lung cancer was similar across subtypes, ranging from HR=1.31 (for adenocarcinomas) to 2.16 (for other subtypes) after adjusting for smoking status and intensity.

Discussion

In this analysis, women who reported to have baseline or incident COPD were 1.64 times more likely to develop lung cancer than those who reported no history of COPD, after adjusting for smoking status and intensity, ethnicity, education, BMI, and income. This is consistent with previous findings of COPD being independently associated with an increased risk of developing lung cancer in a pooled analysis of both men and women [3].

In a study evaluating the prevalence of COPD in women compared to men at the time of lung cancer diagnosis, fewer women were noted to have spirometric evidence of airflow obstruction compared to men (OR 0.44, 95% CI 0.26–0.77; p=0.002) [8]. This lower risk for COPD in women was sustained after adjusting for age and smoking status, suggesting that the prevalence of COPD in lung cancer patients may differ between women and men. Furthermore, in a study that assessed the severity of emphysema by measuring lung attenuation on CT, men and women had a similar amount of emphysema overall; however, women in this study had smoked a substantially lower number of pack years [6] suggesting that women may be more susceptible to developing emphysema or COPD than men with higher pack years of smoking. With respect to previous work examining the effects of sex, COPD and lung cancer risk by subtype, individuals with COPD have higher rates of small cell and squamous cell carcinomas, and those without COPD are more likely to have adenocarcinoma of the lung [9, 10]. Women are more likely to have adenocarcinomas, but in recent years, their rates of squamous cell carcinomas have also been increasing [11]. Examining the combined effects of sex and COPD may provide insight to the biological mechanisms that drive development of particular histologic subtypes of lung cancer.

In our analysis, we observed a non-significant association between COPD and higher risk of lung cancer in African American women compared to white women. A population-based case-control study of 114 African Americans with lung cancer conducted previously showed that the incidence of COPD was high in this population with an overall 94% of men and 78% of women with lung cancer also had a diagnosis of COPD [12]. In another study which prospectively enrolled 585 COPD patients, African American women were found to be most susceptible to tobacco smoke compared to white women based on the susceptibility index which was calculated by $(\% \text{ predicted FEV1} - 100)/\text{pack-years}$ which represents the loss of lung function per pack-year smoked [13]. On the other hand, in a population-based study in metropolitan Detroit, lung cancer risk in women with a self-reported history of COPD was noted to be elevated among white women (OR=1.85; 95% CI 1.21–2.81), but not among African American women (OR=1.11, 95% CI 0.49–2.49) [12]. These differences based on

ethnicity raised the concern for delay in diagnosis, underreporting and/or under diagnosis of COPD among African American women compared to white women.

Finally, the association between COPD and lung cancer was similar across subtypes. This is consistent with previous reports from the WHI which showed that ever smokers had significantly increased risk for all lung cancer subtypes, particularly small-cell and squamous cell carcinoma [14, 15]. This analysis is the first to use WHI data to examine COPD and risk of lung cancer.

One of the limitations of this study is the possibility of misclassification of COPD status due to the diagnosis being self-reported. Also, data regarding the duration of COPD, as well as its severity were not captured, thereby resulting in a heterogeneous group of those who reported COPD. In addition, smoking status and intensity were captured at baseline and during the annual surveys. Analyses incorporating the longitudinal changes in smoking habits did not change the overall findings (data not shown). Residual confounding may also influence the estimate of the association between COPD and lung cancer; however, our findings are similar to previous reports [3]. Ideally, examining this association in lifetime never smokers would better address this, but an adequate sample size does not exist in the WHI. Overall, the strengths of our study included the prospective cohort design, large sample size and detailed pathological confirmation of lung cancer cases with information on histologic subtypes.

Our results suggest that women with COPD represent a group susceptible to lung cancer who may benefit from more intensive follow-up, including lung cancer screening and tobacco cessation efforts.

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Highlights

- This analysis of 92,000 women included 1,536 who developed lung cancer.
- Women who self-reported COPD were 1.6 times more likely to develop lung cancer.
- The association between COPD and lung cancer was similar across tumor subtypes.

Table 1:

Baseline demographic information for participants in the Women's Health

Characteristic	No COPD (n=84,212)	Baseline COPD (n=3,430)	Incident COPD (n=5,156)	Total (n=92,798)
Age group at screening:				
<50–59	27250 (32%)	819 (24%)	1362 (26%)	29431
60–69	36948 (44%)	1569 (46%)	2334 (45%)	40851
70–79+	20014 (24%)	1042 (30%)	1460 (28%)	22516
Baseline smoking status and intensity:				
Never smoker	43436 (52%)	1182 (34%)	2038 (40%)	46656
Former smoker with 1-<20 pack years	22110 (26%)	643 (19%)	1083 (21%)	23836
Former smoker with 20 - <40 pack years	7133 (8%)	428 (12%)	534 (10%)	8095
Former smoker with 40+ pack years	3993 (5%)	590 (17%)	558 (11%)	5141
Current smoker with 1-<20 pack years	1940 (2%)	108 (3%)	175 (3%)	2223
Current smoker with 20 - <40 pack years	1289 (2%)	135 (4%)	233 (5%)	1657
Current smoker with 40+ pack years	1216 (1%)	223 (7%)	338 (7%)	1777
Missing	3095 (4%)	121 (4%)	197 (4%)	3413
Ethnicity:				
White (not of Hispanic origin)	70261 (83%)	2911 (85%)	4290 (83%)	77462
Black or African-American	6714 (8%)	301 (9%)	476 (9%)	7491
Other*	7001 (8%)	210 (6%)	373 (7%)	7584
Missing	236 (<1%)	8 (<1%)	17 (<1%)	261
BMI:				
<25	34494 (41%)	1275 (37%)	1739 (34%)	37508
25 – 29	28474 (34%)	1020 (30%)	1711 (33%)	31205
30+	20260 (24%)	1103 (32%)	1635 (32%)	22998
Missing	984 (1%)	32 (1%)	71 (1%)	1087
Education:				
None - some HS	4088 (5%)	279 (8%)	333 (6%)	4700
HS diploma/GED	13402 (16%)	613 (18%)	951 (18%)	14966
Vocational, training school, some college or associate degree	30073 (36%)	1417 (41%)	2148 (42%)	33638
College graduate or more	35959 (43%)	1098 (32%)	1685 (33%)	38742
Missing	690 (1%)	23 (1%)	39 (1%)	752
Income:				
< \$35,000	29650 (35%)	1714 (50%)	2437 (47%)	33801
\$35,000 - \$59,999	15754 (19%)	628 (18%)	936 (18%)	17318
\$50,000 - \$75,999	16082 (19%)	502 (15%)	792 (15%)	17376
\$75,000+	16551 (20%)	342 (10%)	630 (12%)	17523
Missing	6175 (7%)	244 (7%)	361 (7%)	6780

Characteristic	No COPD (n=84,212)	Baseline COPD (n=3,430)	Incident COPD (n=5,156)	Total (n=92,798)
Lung cancer:				
No	82973 (99%)	3280 (96%)	5009 (97%)	91262
Yes	1239 (1%)	150 (4%)	147 (3%)	1536

Initiative Observational Study, stratified by COPD status

* American Indian or Alaskan Native, Asian or Pacific Islander, Hispanic/Latino, Other

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Table 2:

Risk of lung cancer among women with and without COPD among participants in the Women's Health Initiative Observational Study

Comparison	Estimated HR ^a	95% CI	
COPD over time: yes vs. no	1.64	(1.43, 1.89)	
Smoking status and intensity: all comparisons vs. Never smokers			
Former smoker with 1-<20 pack years	1.83	(1.52, 2.20)	
Former smoker with 20 - <40 pack years	5.59	(4.65, 6.72)	
Former smoker with 40+ pack years	12.40	(10.44, 14.71)	
Current smoker with 1-<20 pack years	6.58	(4.92, 8.80)	
Current smoker with 20 - <40 pack years	11.57	(8.98, 14.91)	
Current smoker with 40+ pack years	25.30	(20.86, 30.69)	
Ethnicity: all comparisons vs. White			
Black	1.22	(0.97, 1.52)	
Other	0.97	(0.74, 1.26)	
Education: all comparisons vs. None – Some HS			
HS diploma/GED	0.85	(0.64, 1.12)	
Vocational, training school, some college, or associate degree	0.97	(0.75, 1.25)	
College graduate or more	0.89	(0.68, 1.15)	
Income: all comparisons vs. <\$35,000			
\$35,000 - \$49,999	0.96	(0.83, 1.11)	
\$50,000 - \$74,999	0.97	(0.83, 1.13)	
\$75,000+	0.95	(0.80, 1.12)	
BMI: all comparisons vs. 25–29			
<25	1.27	(1.13, 1.44)	
30	0.94	(0.81, 1.10)	
Comparison	Type	Estimated HR ^b	95% CI
COPD over time: yes vs. no	Small cell carcinoma	2.00	(1.34, 3.00)
	Squamous cell carcinoma	1.66	(1.15, 2.40)
	Large cell carcinoma	1.61	(0.76, 3.43)
	Adenocarcinoma	1.31	(1.04, 1.65)
	Other	2.16	(1.55, 2.88)

^a adjusted for combined smoking status and intensity, ethnicity, education, body mass index, and income

^b adjusted for smoking status and intensity only