CT Screening for Lung Cancer: Importance of Emphysema for Never Smokers and Smokers

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Manuscript type: Original Research

Word count: paper: 2,339, abstract 212

Partially funded by a grant from the Flight Attendants Medical Research Institute, the sponsor had no involvement in any study design, data collection, data analysis and interpretation and manuscript writing.

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Abstract

Purpose: To address the prevalence of lung cancer in high and low-risk people according to their smoking history, age, and CT findings of emphysema.

Methods: We reviewed the baseline low-dose CT scans of 62,124 current, former and never smokers, aged 40-90 to determine the prevalence of lung cancer. We performed logistic regression analysis of the prevalence of lung cancer to determine the odds ratio (OR) for emphysema, conditionally on age, female gender, and ethnicity.

Results: The prevalence of lung cancer was 1.4% (95% CI: 1.3 – 1.6) for current smokers, 1.1% (95% CI: 1.0 – 1.2) for former smokers, and 0.4% (95% CI: 0.3 – 0.6) for never smokers.

Emphysema was identified in 29% (6,684), 21% (5,422), and 1.6% (194) of current, former, and never smokers, respectively. The prevalence of lung cancer among current smokers was 1.1% for those without emphysema vs. 2.3% for those with emphysema (odds ratio [OR] 1.8; 95% confidence interval [CI]: 1.4 – 2.2) and the corresponding difference for former smokers was 0.9% vs. 1.8% (OR: 1.7; 95% CI: 1.3 – 2.2), and for never smokers, it was 0.4% vs. 2.6% (OR: 6.3; 95% CI: 2.4 – 16.9).

Conclusions: Identification of emphysema in low-dose CT scans increases the risk of lung cancer and is important in determining follow-up of current, former, and never smokers.

Keywords: emphysema, lung cancer, smokers, never smokers, CT screening,

Introduction

The number of people who have a CT scan of the chest continues to increase in the United States and throughout the world for many indications, including CT screening for lung cancer. In 2009, it was estimated that in the US alone, almost 10 million CT scans of the chest were performed for lung and cardiac indications (1). It is estimated that over 50% of these people had at least one noncalcified nodule (NCN) identified in the lung parenchyma, raising the possible diagnosis of lung cancer (2). Beyond the identification of NCNs on CT scans, emphysema has been identified as an important risk factor for lung cancer which appears to be independent of the presence of airflow obstruction as measured by pulmonary function tests (3-6).

In light of the high lung cancer fatality rate, the management of findings on CT is of great concern. Different management strategies have been developed with a goal of diagnosing a possible cancer as early as possible while minimizing unnecessary diagnostic tests, invasive procedures, and surgery. These strategies have focused mainly on high-risk smokers in the context of CT screening studies (7-11). The Fleischner Society Guidelines also addressed the recommended workup for NCNs in low-risk individuals, including never smokers (12). These management strategies, however, do not use the information on findings provided by the CT scan other than the presence of NCNs.

In this report we address the prevalence of lung cancer according to the presence of emphysema as identified in the CT scan in both high and low-risk people as defined by their smoking history and age.

Methods

Participants (n = 62,124) enrolled in a program of CT screening for lung cancer in the International Early Lung Cancer Action Program (I-ELCAP) in 2000 - 2013 (13). At the time of enrollment, all were 40 to 90 years of age (median age of 60) and asymptomatic for lung cancer. Consent for the research was obtained from all participants according to HIPAA-compliant protocols that were approved by the IRBs of the participating institutions.

Smoking status: All participants completed a baseline questionnaire that provided information on their smoking status, quantity smoked, and, if they had quit, when. Smokers were defined as participants who had smoked 100 or more cigarettes and were classified as being a current smoker if they had smoked more than 1 cigarette in the month prior to enrollment or quit within 1 year of enrollment (n = 23,415). The remaining smokers were classified as former smokers (n = 26,341). Never smokers (n = 12,368) were defined as having smoked less than 100 cigarettes in their lifetime; some 32% (3,982) may have had occupational exposure to lung carcinogens while the rest had some level of secondhand tobacco smoke exposure (SHTS). Current and former smokers were divided into 3 categories according to the total pack-years of smoking: light, if less than 30 pack-years, moderate if 30-59 pack-years, and heavy if 60 or more pack-years.

Baseline CT scan and diagnosis of lung cancer: Upon enrollment, the baseline low-dose CT scan was obtained according to a common protocol from the lung apices to the bases in a single breath hold at maximum inspiration at 120 kVp and 80 mAs or less (13). No intravenous contrast material was used. The CT images were read by radiologists at the participating institutions who had undergone training at the center. The readings were performed using standard lung settings (width 1500 HU and level -650 HU) and standard mediastinal settings

(width, 350 HU; level, 50 HU). Diagnoses of lung cancer resulting from the baseline CT scan were documented in the web-based management system and had pathologic confirmation.

Emphysema: The absence/presence of emphysema was ascertained from the baseline low-dose CT image and documented (6, 13). Emphysema was considered to be present if discrete areas of decreased attenuation could be identified anywhere in the lung parenchyma, or, if no discrete areas of decreased attenuation could be identified on the CT scan, when the blood vessels were splayed suggesting parenchymal expansion.

Secondhand tobacco smoke exposure score: All participants completed a background questionnaire about secondhand tobacco smoke (SHTS) exposure before age 18 as a child, and after age 18, as an adult at home and at work as previously described in detail (14). The responses determined the *permission status*, *duration of SHTS exposure (years)*, *daily intensity of the SHTS exposure* (packs per day) for each of these life-exposures as a child, and as an adult at home and at work. The permission status was 1.0 if smoking was allowed anywhere, 0.5 if smoking was restricted, or 0 if smoking was not permitted. The exposure duration was the sum of the years that the participant was exposed to SHTS divided by the maximum possible score. The total SHTS exposure score ranged from 0 to 0.70 and the entire range was divided into quartiles. The analysis focused on the two highest SHTS quartiles.

Statistical analysis: The prevalence of diagnosed lung cancers and emphysema was determined overall and for each decade of age. Percentages, median and interquartile range (IQR) were calculated as needed. The Chi-square test was used to compare percentages. The prevalence of lung cancer was addressed as a joint function of potential risk indicators using multivariate logistic regression analysis, adjusting for emphysema, age, sex and Asian ethnicity. All analyses were performed using the SAS (SAS, Cary, NC, Version 9.2) statistical package.

Results

The characteristics of the 62,124 participants at the time of the baseline CT scan are given in Table 1, separately for current, former and never smokers. On average, former smokers were older than current and never smokers (62 vs. 57 vs. 56 years of age, $P < 0.0001$). The median pack-years of smoking was 35 pack-years (IQR: 23-49) for current smokers and 30 (IQR: 19-47) for former smokers. For former smokers, the median years of quitting prior to enrollment was 15 years (IQR: 6-24). Gender and ethnicity were also significantly different between groups.

The prevalence of participants diagnosed with lung cancer as a result of findings on the baseline CT scan was 1.4% (N=333) (95% CI: 1.3 – 1.6) for current smokers, 1.1% (N=283) (95% CI: 1.0 – 1.2) for former smokers, and 0.4% (N=52) (95% CI: 0.3 – 0.6) for never smokers. Between the age of 40 and 50, the prevalence of lung cancer was the same (0.2%) for smokers and never smokers, though the numbers of participants diagnosed with lung cancer were small. After age 50, the prevalence was always higher among smokers than never smokers (Table 2).

For smokers, the prevalence of participants diagnosed with lung cancer increased with increasing cumulative smoking (Table 3). For current smokers, the prevalence was 0.6%, 1.6%, and 2.8% for 1-29, 30-59, and 60+ pack-years, respectively and for former smokers, the prevalence was 0.4%, 1.3%, and 2.4%, respectively. Current smokers with less than 30 pack-years had a prevalence of 0.6%, similar to that for former smokers (0.4%) and never smokers (0.4%), and this remained the same even when adjusted for age.

Emphysema of any extent was identified in 28.5% (6,684), 20.6% (5,422), and 1.6% (194) of current, former, and never smokers. Like lung cancer, the prevalence of emphysema increased with increasing age (Table 2) and among smokers, it increased with increasing pack-years of smoking (Table 3). Unlike lung cancer, however, the prevalence of emphysema for

current and former smokers was much higher than among never smokers at all ages and all levels of smoking (Tables 2 and 3). Even for light smokers (< 30 pack-years), the prevalence of emphysema was 17.5% and 10.9% for current and former smokers, 10- and 6-fold higher, respectively when compared with 1.6% for never smokers (Table 3).

For smokers and never smokers with emphysema, the prevalence of lung cancer was 2.1% (255/12,106) and 2.6% (5/194), not significantly different ($P = 0.61$). The prevalence of lung cancer among current smokers increased from 1.1% for those without emphysema to 2.3% for those with emphysema, among former smokers, the prevalence increased from 0.9% to 1.8%, and for never smokers it increased from 0.4% to 2.6%. Thus, there was a slightly more than 2-fold increase for current and former smokers while there was a 6-fold increase among never smokers. This increase in the prevalence of lung cancer when emphysema was present was confirmed by the multivariate regression analysis (Table 4). The adjusted odds ratios for the presence of emphysema were 1.8 (95% CI: 1.4 – 2.2, $P < 0.0001$) for current smokers, 1.7 (95% CI: 1.3 – 2.2, $P < 0.0001$) for former smokers, 6.3 (95% CI: 2.4-16.9, $P = 0.0003$) for never smokers. To have the same comparison for current, former, and never smokers, pack-years of cigarette smoking was not included in the logistic regression. However when comparing current and former smokers when including pack-years of smoking, the odds ratio for the presence of emphysema remained the same.

In a subset of the cohort whose participants had never smoked cigarettes, detailed information about secondhand tobacco smoke (SHTS) exposure was available on 3,266. Multivariate logistic regression analysis revealed an odds ratio of 13.6 ($P = 0.01$) for the prevalence of emphysema for the two highest quartiles of the SHTS exposure score, even when adjusted to age, gender, Asian ethnicity, and history of asthma. The 3rd and 4th quartile of SHTS

separately were significant ($P=0.01$, and $P=0.02$), but were combined to have more stable estimates.

Discussion

Our study demonstrated an increase in the prevalence of lung cancer among those who also had CT evidence of emphysema, thereby demonstrating the importance of identifying emphysema when interpreting a CT scan of the chest. While this increased risk of lung cancer has been previously reported for smokers (3-6), this is the first such report for never smokers. In never smokers, when emphysema is identified as seen in 1.6% of never smokers in our report, that person has the same prevalence of lung cancer as a smoker. Further, it was shown, in a smaller subcohort of 3,266 never smokers on whom detailed SHTS exposure was documented, that the adjusted odds ratio of emphysema was significantly increased when there was moderate to high SHTS exposure. Although it is unclear whether this increased risk of emphysema reflects some underlying chronic pulmonary condition or additional risk factors that predisposes to it, the finding of emphysema in a never smoker should be interpreted as a marker of increased lung cancer risk.

Smokers, both current and former, had a higher prevalence of lung cancer than never smokers in our study, as expected, as active smoking is the dominant risk factor for lung cancer (15). However, never smokers in our study had the same prevalence of lung cancer as light current and former smokers (< 30 pack-years) (Table 3). For smokers, the adverse effect of smoking on respiratory function has been extensively documented as cigarette smoke was considered to be the single most important risk factor for COPD (15-18). Table 3 clearly illustrates the increase in prevalence of lung cancer and emphysema by increased cumulative

smoking. CT-detected emphysema by itself has been shown to be a strong, independent risk factor for lung cancer in the CT screening studies for lung cancer (3-6).

Further evidence of the association of SHTS and COPD comes from more than 50 additional studies summarized in the 2006 Surgeon General report (19). These studies included ones that carefully considered potential sources of bias and confounding of this association and identified the damage of SHTS on the respiratory health of children. Fewer studies have analyzed its effect on adults, partly due to the challenges in studying chronic diseases that may only become clinically apparent after 20 or more years of exposure. An association of SHTS and COPD was also reported in 4 of the 5 studies reported by Tredaniel et al. (20). Data from 3 national health and nutrition surveys, including the NHANES study, found that among 12,980 never smokers, aged 18-74 years, the prevalence of physician-diagnosed chronic obstructive pulmonary disease (COPD) was 3.7% for men and 5.1% for women (21, 22). These rates are higher than the prevalence of emphysema found in our study, but our study was limited to CT-detected emphysema and not on the other respiratory illnesses included in the definition of COPD. Jordan et al. (23) demonstrated a doubling of risk of COPD (OR 1.98, 95% CI 1.03-3.79) for SHTS exposures over 20 hours per week. A large prospective study, the European Prospective Investigation into lung cancer and nutrition (EPIC) (24), concluded the SHTS is a risk factor for lung cancer and other respiratory diseases, including emphysema, in smokers and never smokers. Further, flight attendants heavily exposed to SHTS, compared to a matched sample from NHANES 2005-2009, had an increased prevalence of chronic bronchitis (11.7 vs. 7.2%, $P = 0.05$), emphysema/COPD (3.2% vs. 0.9%, $P < 0.03$), despite a lower prevalence of other medical illnesses (25). The worldwide effect of SHTS has been summarized in more recent articles (26, 27).

A limitation of our study is that the smoking status was self reported, and this may lead to misclassification of the actual smoking status of the participant, particularly among never smokers. However, our reported prevalence rates of lung cancer and emphysema are in line with many other publications cited above. Our never smoker cohort included individuals who had occupational and SHTS exposure, but our reported rate of emphysema is lower than that reported for COPD in prior studies (20, 22). This is understandable as we reported only the CT finding of emphysema and did not include airway obstruction which is included in the definition of COPD. The possibility of some misclassification of never smokers may be present, however the failure to correct for background exposure to SHTS in most epidemiologic studies (as truly unexposed populations are essentially unavailable) might bias the associations toward the null (28).

Important findings of our report is that the identification of emphysema in low-dose CT scans provides additional information as to the risk of lung cancer and that this increased risk of lung cancer suggests using same frequency of annual repeat CT screening for those with emphysema, regardless of whether the person smoked or was a never smoker.

Acknowledgements

This report has been funded in part by the Flight Attendant Medical Research Institute. The sponsor had no involvement in any study design, data collection, data analysis and interpretation and manuscript writing.

The screenings in the I-ELCAP pooled database has been supported in part by National Institutes of Health R01-CA-63393I and R01-CA-78905; Department of Energy DE-FG02-96SF21260; The City of New York, Department of Health and Mental Hygiene; New York State Office of Science, Technology and Academic Research (NYSTAR); Institute de Salud Carlos III, Spain (PI10/01652, PI07/0792, RD12/0036/0062); American Cancer Society; The Starr Foundation; The New York Community Trust; The Rogers Family Fund; The Foundation for Lung Cancer: Early Detection, Prevention, and Treatment (primary source from an unrestricted gift in 2000-2003 from the Vector Group, the parent company of Liggett Tobacco); Dorothy R. Cohen Foundation, Jacob and Malka Goldfarb Charitable Foundation; Auen/Berger Foundation; Berger Foundation; Mills Peninsula Hospital Foundation, Tenet Healthcare Foundation; Ernest E. Stempel Foundation; Academic Medical Development Corporation; Columbia University Medical Center, Empire Blue Cross and Blue Shield; Eastman-Kodak Corporation; General Electric Corporation; Weill Medical College of Cornell University; Cornell University; New York Presbyterian Hospital; Swedish Hospital; Christiana Care Helen F. Graham Cancer Center; Holy Cross Hospital; Eisenhower Hospital; Jackson Memorial Hospital Health System; Evanston Northwestern Healthcare.

Potential Conflicts of Interest:

- Dr. Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF), are non-exclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents. Dr. Yankelevitz also serves on the scientific advisory board (unpaid) for Give-A-Scan, Lung Cancer Alliance.
- Dr. Henschke is also an inventor of the patents and pending patents owned by Cornell Research Foundation (CRF). As of April 2009, she has divested herself of all royalties and other interests arising from these.
- Others: None

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Table 1. Gender, ethnicity, age and smoking history for current, former, and never smokers.

Table 2. Prevalence of diagnosed lung cancer cases and emphysema by age in 23,415 current smokers, 26,341 former smokers and 12,368 never smokers, all asymptomatic for lung cancer

Table 3. Prevalence of lung cancer and emphysema in current and former smokers by pack-years of smoking

Table 4. Logistic regression analysis of prevalence of lung cancer in relation to the presence of emphysema, conditionally on age, female gender, and Asian ethnicity. Analysis performed separately for current smokers, former smokers, and never smokers.

Table 5. Logistic regression analysis of the prevalence of emphysema in 3,266 asymptomatic never smokers for SHTS adult exposure, conditionally on age, male, Asian ethnicity, and self report of history of asthma.

Table 1. Gender, ethnicity, age and smoking history for current, former, and never smokers.

	Current smokers		Former smokers		Never smokers		P-value
	N=	23415	N=	26341	N=	12368	
Gender							
Male	13377	(57%)	16263	(62%)	6514	(53%)	<.0001
Female	10038	(43%)	10078	(38%)	5854	(47%)	
Ethnicity							
White	18298	(78%)	23532	(89%)	5940	(48%)	<.0001
Asian	2385	(11%)	1368	(5%)	5800	(47%)	
Other	2732	(12%)	1441	(5%)	628	(5%)	
Age							
Median(IQR)	57	(52-63)	62	(57-68)	56	(50-65)	<.0001
Smokers							
Median pack-years (IQR)	35	(23-49)	30	(19-47)			<.0001
Median years quit (IQR)	-		15	(6-24)			

Table 2. Prevalence of diagnosed lung cancer cases and emphysema by age in 23,415 current smokers, 26,341 former smokers and 12,368 never smokers, all asymptomatic for lung cancer

	Age (years)						
Current Smokers	40-50	50-60	60-70	70-80	80-90	Total	
# participants	2,937	10,783	7,823	1,744	128	23,415	
# with lung cancer	9	96	167	56	5	333	
Prevalence of lung cancer	0.3%	0.9%	2.1%	3.2%	3.9%	1.4%	P < 0.0001
#. with emphysema	421	2,629	2,812	768	54	6,684	
Prevalence of emphysema	14.3%	24.4%	35.9%	44.0%	42.2%	28.5%	P < 0.0001
Former smokers							
# participants	1,313	8,137	11,238	4,990	663	26,341	
# with lung cancer	1	48	132	92	10	283	
Prevalence of lung cancer	0.1%	0.6%	1.2%	1.8%	1.5%	1.1%	P < 0.0001
#. with emphysema	107	1,092	2,557	1,453	213	5,422	
Prevalence of emphysema	8.1%	13.4%	22.8%	29.1%	32.1%	20.6%	P < 0.0001
<hr/>							
Never smokers	40-50	50-60	60-70	70-80	80-90	Total	
# participants	2,734	4,791	3,048	1,475	320	12,368	
# with lung cancer	5	18	15	10	4	52	
Prevalence of lung cancer	0.2%	0.4%	0.5%	0.7%	1.3%	0.4%	P = 0.02
#. with emphysema	14	44	50	62	24	194	
Prevalence of emphysema	0.5%	0.9%	1.6%	4.2%	7.5%	1.6%	P < 0.0001

Table 3. Prevalence of lung cancer and emphysema in current and former smokers by pack-years of smoking

Smoking status	Overall prevalence	Pack-years of smoking		
		<30	30-59	60+
Prevalence of lung cancer				
Current	1.4%	0.6%	1.6%	2.8%
Former	1.1%	0.4%	1.3%	2.4%
Prevalence of emphysema				
Current	28.5%	17.5%	32.7%	41.9%
Former	20.6%	10.9%	25.3%	37.5%

Table 4. Logistic regression analysis of prevalence of lung cancer in relation to the presence of emphysema, conditionally on age, female gender, and Asian ethnicity. Analysis performed separately for current smokers, former smokers, and never smokers.

Current Smokers	OR	95% CI	P-value
Emphysema	1.8	(1.4, 2.2)	<.0001
Age in decades	2.0	(1.7, 2.3)	<.0001
Female	1.1	(0.9, 1.4)	0.36
Asian ethnicity	0.8	(0.5, 1.3)	0.40
Former Smokers	OR	95% CI	P-value
Emphysema	1.7	(1.3, 2.2)	<.0001
Age in decades	1.8	(1.5, 2.0)	<.0001
Female	2.0	(1.6, 2.5)	<.0001
Asian ethnicity	0.7	(0.3, 1.5)	0.35
Never smokers	OR	95% CI	P-value
Emphysema	6.3	(2.4, 16.9)	0.0003
Age in decades	1.5	(1.2, 2.0)	0.0018
Female	1.1	(0.6, 2.0)	0.64
Asian ethnicity	2.1	(1.1, 3.9)	0.017

Table 5. Logistic regression analysis of the prevalence of emphysema in 3,266 asymptomatic never smokers for SHTS adult exposure, conditionally on age, male, Asian ethnicity, and self report of history of asthma.

Never smokers	OR	95% CI	P-value
SHTS Quartiles			
1st quartile	Ref		
2nd quartile	4.8	(0.5, 47.2)	0.18
3rd/4th quartile	13.6	(1.7, 106.1)	0.01
Age (in decade)	2.0	(1.3, 3.0)	0.001
Male	1.2	(0.5, 2.9)	0.71
Asian	3.8	(1.5, 9.5)	0.01
Asthma	1.1	(0.2, 4.9)	0.90