Declining FEV₁ and Chronic Productive Cough in Cigarette Smokers: A 25-Year Prospective Study of Lung Cancer Incidence in Tecumseh, Michigan

Syed Shafiqul Islam and David Schottenfeld

Abstract
A community-based study has been reviewed to assess whether impaired forced expiratory volume in 1 s (FEV₁) and/or the symptoms of chronic cough and sputum production predict the incidence of lung cancer, after controlling for age, sex, cigarette smoking history, and the dietary intake of carotenoids and retinoids. A cohort of 2099 women and 1857 men, 25 years of age or older, were first examined from 1962 to 1965. As of 1987, there were 60 validated lung cancers diagnosed in men (1.83 per 1000 person-years) and 17 in women (0.39 per 1000 person-years). The incidence density of lung cancer in current smokers at baseline, when compared with never smokers, was increased 5.34 (95% confidence interval, 1.74, 16.38) times in women and 4.11 (95% confidence interval, 1.63, 10.34) times in men. The risk of lung cancer increased in women and men in relation to the average daily intensity of exposure in current smokers and the duration of smoking history (<20 years, ≥20 years) in current and ex-smokers. When stratified by cigarette smoking intensity, subjects with chronic cough and phlegm experienced a future risk of lung cancer that was more than 3 times higher than that in the nonsymptomatic subgroup. Among the smoking women and men at entry, those in the lowest quartile of the percent predicted FEV₁, after controlling for the average number of cigarettes smoked per day, experienced a risk of lung cancer that was 2.7 times that of subjects in the highest quartile. With each 10% decrease in percent predicted FEV₁, the risk of lung cancer increased 1.17 times (0.96, 1.42), after controlling for age, sex, and cigarette smoking intensity at baseline. The average annual decline in FEV₁ as estimated between 1962 and 1965 and 1967 and 1969 was a significant independent predictor of future lung cancer incidence after controlling for cigarette smoking history; the slope of the regression line indicated that with each decline in FEV₁ of 100 ml/year, lung cancer incidence density increased 1.16 per 1000 person-years (95% confidence interval, 0.30, 2.01). Controlling for potential confounding by quartile distribution of calorie-adjusted dietary intake of vitamin A, beta-carotene, cholesterol, and fat did not weaken or alter the fundamental relationship with impaired pulmonary function. Rapidly declining ventilatory function in conjunction with persistent symptoms of chronic bronchitis in current smokers is predictive of the increased risk of lung cancer and correlates with cumulative levels of exposure to cigarette smoke. In addition to the consideration of individual dosimetry, the biological implications of chronic obstructive airways disease in conjunction with pulmonary inflammatory and proteolytic parenchymal disease as antecedent events in the natural history of lung cancer may be hypothesized to be related to altered bronchopulmonary clearance mechanisms and the biochemical mediators of an inflammatory or reparative response.

Introduction
Cigarette smoking may result in chronic bronchitis and/or emphysema (COPD) and/or lung cancer. In the early 1960s, Passey (1) hypothesized that it was the irritating properties of tobacco smoke, resulting in chronic bronchitis and inflammatory destruction of lung tissue, that was of pathogenic significance in the causal pathway of lung cancer, rather than any direct action by volatile and particulate carcinogens in tobacco smoke. The experiments of Kuschner, however, suggested an alternative explanation, i.e., that bronchial and bronchiolar inflammation, accompanied by reactive proliferation, squamous metaplasia, and dysplasia in basal epithelial cells, provided a cocarcinogenic mechanism for neoplastic cell transformation upon exposure to polycyclic aromatic hydrocarbons (2). Rimmer-on (3) determined the lung cancer incidence in relation to cigarette smoking history and symptoms of chronic bronchitis (cough with sputum production) in men participating in a chest radiographic screening program. The 5-year cumulative age-adjusted lung cancer incidence in smokers with symptoms (9.09 per 1000) exceeded that in smokers without symptoms (5.22 per 1000), from which we may infer a relative risk of 1.74 (0.94, 3.22). In the Philadelphia Pulmonary Neoplasm Research Project, the cumulative probability of developing lung cancer over an interval of 10 years in men over age 45 years who were smoking one or more packs of cigarettes per day was 6.23% in those with a

The abbreviations used are: COPD, chronic obstructive pulmonary disease; TCHS, Tecumseh Community Health Study; FEV₁, forced expiratory volume in 1 s; %FEV₁, percent predicted FEV₁; CI, confidence interval; FVC, forced vital capacity.

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chronic cough, compared to 2.51% in those without a cough (P < 0.05) (4).

Although cigarette smoking is the predominant cause of COPD, with an estimated attributable risk fraction exceeding 80% in smoking individuals, perhaps only 10—15% of current smokers will eventually develop clinically significant sequelae of productive cough, exertional dyspnea, and cardiovascular disease. Individual variability in the expression of risk may be demonstrated by the accelerated rate of age-specific decline in measured expired airflow. The structural and functional correlates of COPD include: chronic mucus hypersecretion accompanied by enlargement and hyperplasia of tracheobronchial mucus glands; inflammation and narrowing of small bronchial and bronchiolar segments with progressive limitation and increased resistance in expiratory airflow; and abnormal dilatation and proteolytic destruction of terminal bronchioles and alveolar ducts and sacs which may be associated with impaired pulmonary gas exchange and reduced lung elastic recoil (5).

The community-based historical cohort study that is to be described will evaluate whether obstructive airway disease is an independent predictor of lung cancer risk.

Materials and Methods
The Tecumseh Community Health Study began in 1959 as a comprehensive study of health and disease in a semi-rural community located 45 miles southwest of Detroit, Michigan. The population was relatively stable and almost entirely Caucasian. A population census was conducted in 1957, which enumerated 9794 persons, among whom 8641 (88%) participated in the first round of examinations in 1959—1960 (TCHS I). The second round of examinations (TCHS II) took place between 1962 and 1965 and involved 9226 subjects. Apart from routine demographic and socioeconomic information, a medical history interview was conducted which included questions about respiratory and cardiovascular symptoms and conditions. Participants were then asked to attend a special clinic where they were examined by physicians and received various laboratory procedures, including physical and anthropometric measurements, x-rays of the chest and hands, resting and exercise electrocardiograms, tests of ventilatory lung function, hematological and biochemical testing, and urine analysis. The third round of examinations (TCHS III) took place between 1967 and 1969, and subsequently a chronic respiratory disease survey was conducted between 1978 and 1979.

All individuals, aged 25 years and older (n = 4318) who had participated in TCHS II (1962—1965) were eligible for the longitudinal COPD study. Subjects were excluded if they reported a history of any cancer prevalent at baseline, except for nonmelanoma skin cancers, or if they developed cancer within 1 year of entering the study. At each examination cycle, a history of any cancer was obtained and then verified.

A retrospective cohort design was used to evaluate the incidence density of primary lung cancer. After the exclusion of preexisting cancers (n = 175), other than nonmelanoma skin cancers, 4143 individuals aged 25 years and older were eligible for the longitudinal study that encompassed follow-up until December, 1987. Vital status could not be determined for 187 participants who were considered lost to follow-up. This resulted in a final sample of 3956 subjects, 2099 females and 1857 males for whom complete follow-up data were available. The cohort was considered fixed with no new entries.

All surviving participants of TCHS II (1962—1965) were invited to take part in TCHS III (1967—1969) and in the special chronic respiratory disease survey (1978—1979). The incidence of lung cancer was determined in a comprehensive cancer survey of the participants and/or their next of kin, which was conducted from 1986 to 1987. Members of the cohort who had moved out of the Tecumseh community received a mailed questionnaire or were interviewed by telephone. The next of kin was contacted if the subject was known to be deceased. Death certificates were obtained for more than 99% of the decedents. The cancer survey was conducted in approximately 95% of the TCHS II participants. When the diagnosis of cancer was reported on the mailed questionnaire or death certificate, permission was obtained to request an abstracted copy of each hospital record which was reviewed to provide the date of diagnosis, histopathological classification, and other sources of diagnostic information for each registered cancer.

The date of diagnosis of lung cancer was determined from the hospital record, and the person-years were calculated from the date of initial observation in 1962—1965 to either the: (a) date of diagnosis of lung cancer; (b) date of death; (c) last known date of contact; or (d) end of follow-up (December 31, 1987).

All but four of the reported 81 lung cancer cases were verified histopathologically. Of the 77 histopathologically confirmed lung cancer cases, 11 required additional clinical documentation before they were classified as primary neoplasms of the bronchus and lung. Neither clinical records nor histopathology records were available for four reported lung cancer cases that were excluded from the analysis. Information on morphology, or cell type, was available and reviewed for 75 of the confirmed cases. The cell type at diagnosis in males was squamous cell (17), adenocarcinoma (14), small cell (13), and other carcinomas, including large cell, undifferentiated, or not otherwise specified (16); in females, the cell type consisted of squamous cell (8), adenocarcinoma (6), and other (3).

At TCHS II, a wedge spirometer (Med Science Electronics, Model 170) and a two-channel recorder were used to measure ventilatory lung function. All measures, including FEV1, the volume of air exhaled during the first second of the FVC, were recorded. All measurements were expressed in liters and corrected to body temperature and ambient air pressure, saturated with water vapor. Ninety-four percent of the participating cohort provided satisfactory pulmonary function testing. Several linear regression models were tested, separately for females and males, in deriving the optimal predictive equation for FEV1, independent of cigarette smoking history. The most parsimonious model incorporated age and standing height which accounted for 48—49% of the variation (coefficients of determination) in women and men, respectively. Gender-specific regression equations for the predicted FEV1 were derived on the basis of the subcohort of individuals who had never smoked and did not have chronic respiratory symptoms or skeletal or other structural thoracic deformities at time of entry: FEV1 = a + b (height) + c (age). The %PFEV1 was calculated by dividing the observed maximum
FEV₁ by the predicted FEV₁, and multiplying the ratio by 100. The observed FEV₁ was also expressed as a percentage of the observed FVC; both ratios diminish with increasing severity of obstructive disease of the proximal tracheobronchial and distal small airways, the latter of 2 or 3 mm or less in diameter.

Cigarette smoking history was measured at each examination cycle in terms of average number of cigarettes smoked per day. Smoking cessation was described with respect to the categories: current; former; and never smokers. The potential risk of environmental tobacco smoke will not be addressed in this report.

Respiratory symptoms of cough, phlegm, and/or shortness of breath were evaluated at each examination cycle. The duration of cough and/or the production of phlegm of less than 3 months was compared with symptoms lasting 3 months or longer in the previous 1 year. The FEV₁ in males and females was significantly correlated with various ventilatory lung functions such as the FVC, and the maximum mid-expiratory flow rate at 25–75% of the total forced expired volume. The analysis of airflow obstruction was based upon the covariates, %PFEV₁, and average annual decline of FEV₁. Initially, the %PFEV₁ distribution was dichotomized using the conventional cut-point, >70% and ≤70%. In addition, the %PFEV₁ distribution for the TCHS II cohort was stratified into quartiles, with the best functional cohort was stratified into quartiles, with the best functional.

Statistical Analysis. The initial analysis reviewed the demographic structure and distribution of exposure variables in the cohort. The 5-year age- and gender-specific person-years matrix enabled the calculation of age-standardized lung cancer incidence rates in male and female subjects. A correlation matrix of exposure and demographic variables identified potential confounders that then required testing by Mantel-Haenszel stratification analysis and multivariate regression analysis. Kaplan-Meier survival curves and log rank statistics were employed using SAS PROC LIFETEST for investigating lung cancer incidence in relation to the various strata of age, sex, cigarette smoking intensity, and pulmonary ventilatory function. The Cox proportional hazards method was used to examine the significance of each regression coefficient while simultaneously considering: age; sex; cough and sputum production; occupational exposures to dusts and fibers; cigarette smoking, either as a categorical (never, current, ex-smoker) or continuous (number of cigarettes per day in current smokers) covariate; %PFEV₁; declining FEV₁ (ml/year); and dietary intake of vitamin A, beta-carotene, and total fat. The Cox model explored potential interactions among the covariates, in particular cigarette smoking and pulmonary function.

Results

Over the 25-year interval of followup, the age-adjusted lung cancer incidence rate (per 1000 person-years) in the cohort of males (1.83) was 4.69 times (95% CI = 2.74, 8.04) that observed in the females (0.39) (Table 1). The cumulative incidence or lung cancer incidence proportion during the 25-year period of observation was 3.2% in the males and 0.8% in the females. At baseline (1962–1965), 55% of the males were current cigarette smokers and 21% were former smokers; among the females, 34% were current smokers and 7% were former smokers. Among those who had ever smoked at baseline, 65% of the males and 40% of the females had smoked for 20 or more years. In the 1965 survey of adults conducted by the United States Bureau of the Census, the prevalence of current smokers was 53% in males and 34% in females, and of former smokers it was 21% in males and 8% in females. In a cross-sectional survey of surviving cohort participants from 1978 to 1979, the prevalence of current smokers was 38% in males and 30% in females.

In assessing the completeness of reporting of lung cancer incidence in the Tecumseh cohort, we compared the observed number of lung cancer cases with that expected,
using the Connecticut tumor registry as the referent population. The Standardized Incidence Ratio and 95% confidence interval for lung cancer was 0.79 (0.50, 1.17) in females and 1.17 (0.94, 1.43) in males. Of 60 incident lung cancer cases in males, 55 (92%) occurred in ever smokers. When compared with never smokers, the age-adjusted incidence rate ratio was increased 4-fold in current smokers and 2-fold in former smokers. Of 17 incident lung cancer cases in females, 13 (76%) occurred in ever smokers, and the incidence in current smokers at baseline was increased more than 5 times that in never smokers; there were no lung cancers recorded in the females who were former smokers at baseline, after only 3116 person-years of observation. The relative risk of lung cancer was increased significantly in relation to the average intensity and history of duration of smoking (Table 2). The \( \chi^2 \) test for linear trend by level of daily intensity of cigarette smoking was, in the males, 8.03 \((P = 0.005)\) and, in the females, 3.30 \((P = 0.069)\).

The prevalence of chronic recurring cough and phlegm was significantly associated with current cigarette smoking at entry (odds ratio, 3.74). Chronic respiratory symptoms of cough and phlegm were independent risk factors for lung cancer, after controlling for the number of cigarettes smoked per day (Table 3). Within the cohort subgroup who smoked 20–39 cigarettes per day, the incidence rate ratio for those with symptoms was 3.60 (95% CI = 1.23, 10.52) when compared with the subgroup without symptoms; for the subgroup who smoked 40 or more cigarettes per day, the rate ratio was 3.16 (95% CI = 0.79, 12.64). Shortness of breath was not an independent predictor of lung cancer risk, after adjusting for cough and phlegm, cigarette smoking history, age, and sex.

In assessing the risk factor of impaired expiratory airflow, the initial analysis dichotomized %PFEV\(_1\) into \( \leq 70\% \) and \( >70\% \), and compared lung cancer incidence density in the subcohort of never smokers with that of ever smokers (Table 4). In the subcohort of never smokers with impaired expiratory airflow (%PFEV \( \leq 70\% \)), there were two lung cancer cases (1.45 per 1000 person-years) and the risk of lung cancer was increased significantly when compared with that in the subcohort of never smokers with %PFEV \( >70\% \) \([rate ratio = 6.30 (1.31, 30.33)]\). The combined risk factors of smoking and impaired expiratory airflow increased the incidence density of lung cancer 13 times (95% CI = 4.92, 33.99) that recorded in the subcohort with relatively better pulmo-
Table 4  Lung cancer incidence rate per 1000 person-years in relation to baseline ventilatory lung function and cigarette smoking status

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>P-Yrs*</th>
<th>No.</th>
<th>Rate</th>
<th>Rate ratio</th>
<th>P-Yrs</th>
<th>No.</th>
<th>Rate</th>
<th>Rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoker</td>
<td>1,379</td>
<td>2</td>
<td>1.45</td>
<td>6.30</td>
<td>30,102</td>
<td>7</td>
<td>0.23</td>
<td>1.00*</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>3,342</td>
<td>10</td>
<td>2.99</td>
<td>13.00</td>
<td>39,640</td>
<td>56</td>
<td>1.41</td>
<td>6.13</td>
</tr>
</tbody>
</table>

* P-Yrs, person-years.

Table 5  Association of estimated average decline in FEV1 (ml/year) in 1962–1965 and 1967–1969 with subsequent lung cancer incidence per 1000 person-years, stratified by history of cigarette smoking at entry

<table>
<thead>
<tr>
<th>Smoking status (cigarettes/day)</th>
<th>Average annual decline in FEV1 (ml/year)</th>
<th>&lt;100</th>
<th>≥100*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>Incidence per 1000 P-Yrs</td>
<td>0.34</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>Rate ratio</td>
<td>1.0</td>
<td>4.12</td>
</tr>
<tr>
<td>20–39</td>
<td>Incidence per 1000 P-Yrs</td>
<td>1.10</td>
<td>2.08</td>
</tr>
<tr>
<td></td>
<td>Rate ratio</td>
<td>3.24</td>
<td>6.12</td>
</tr>
<tr>
<td>≥40</td>
<td>Incidence per 1000 P-Yrs</td>
<td>3.80</td>
<td>10.05</td>
</tr>
<tr>
<td></td>
<td>Rate ratio</td>
<td>11.18</td>
<td>29.56</td>
</tr>
</tbody>
</table>

* P-Yrs, person-years.

cohort. There were no apparent interactions between tobacco smoking and pulmonary function risk factors when incorporated into the Cox model (Table 6). In a Cox model which was not presented, the covariates of age and sex were combined with the number of cigarettes per day in current smokers entered as a continuous variable. The negative B coefficient for each unit percent increase in FEV1 (%PFEV1) was −0.0132 (SE = 0.0072). We may infer from the regression model that with each 10% decrease in percent predicted FEV1, in current smokers, the risk of lung cancer increased 1.17 times (0.96, 1.42), after controlling for age, sex, and cigarette smoking intensity.

In a subset of the original cohort members, food frequency questionnaires were administered in 1967–1969 to 1284 (69%) males and 1380 (66%) females. Comparison of those who participated in the dietary survey with those who did not (33%) did not reveal systematic differences in smoking and pulmonary function characteristics. After controlling for cigarette smoking intensity, age, and sex, the quartile distribution of the level of intake of total fat, saturated fat, or cholesterol was not associated with the level of lung cancer incidence density. The level of intake of each of these macronutrients was not associated with age-sex-tobacco-standardized measures of pulmonary ventilatory function.
<table>
<thead>
<tr>
<th>Authors (Yr)</th>
<th>Sources of exposed and nonexposed</th>
<th>P-Yrs* and interval (yrs) of follow-up</th>
<th>Index of risk</th>
<th>Age, smoking-adjusted relative risk (95% CI)</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peto et al. (1983) (8)</td>
<td>2718 British men identified in random surveys conducted 1954–1961, 25–64 years of age</td>
<td>20–25 years of follow-up</td>
<td>Maximal value for FEV₁ = Standing height³ chronic phlegm production by questionnaire</td>
<td>When index of airway obstruction exceeded 2 SD below average (108 men) risk of lung cancer mortality increased, 1.3.</td>
<td>Mucus hypersecretion was not predictive of COPD mortality, but was correlated with lung cancer mortality.</td>
</tr>
<tr>
<td>Skillrud et al. (1986) (9)</td>
<td>93 men, 20 women, 45–59 years of age from rural area of S.E. Minnesota; 123 controls treated for fractures, dental extractions. Matched on age, sex, occupation, smoking history</td>
<td>1973–1974 until 1984</td>
<td>% predicted FEV₁ ≤70% compared with FEV₁ ≥85%</td>
<td>10-year cumulative probability in men: 0.108 + 0.025 = 4.32 (0.93, 19.99)</td>
<td>No lung cancer cases in women</td>
</tr>
<tr>
<td>Tockman et al. (1987) (14)</td>
<td>Screening and early detection for lung cancer clinical trial at Johns Hopkins: 3,728 white males, 45 yrs and older, who smoked at least 1 pack of cigarettes/day Intermittent positive pressure breathing trial, 667 white males, 30–74 yr of age, with COPD</td>
<td>Lung cancer screening: 4436 P-Yrs or less than 2 yrs IPPB trial: 2001 P-Yrs or 3 yrs followed</td>
<td>FEV₁ greater than 60% of predicted value compared with less than or equal to 60%. FEV₁/FVC ≤60% chronic cough and shortness of breath</td>
<td>Lung cancer screening trial: 2.72 (0.98, 7.55) IPPB trial: 4.85</td>
<td>Presence of symptoms of chronic cough or shortness of breath did not contribute significantly to lung cancer risk after adjustment for FEV₁ % predicted.</td>
</tr>
<tr>
<td>Tenkanen et al. (1987) (10, 11)</td>
<td>3 urban and 3 rural areas in Finland, 4,452 men, selected by sampling birth cohorts, 1898–1902; 1903–1907, 1908–1917, from electoral lists</td>
<td>Follow-up period 1964–1980</td>
<td>Phlegm, all day for at least 3 months each year Shortness of breath, when walking Wheezing</td>
<td>Phlegm = 1.9 (P &lt; .001) Shortness of breath = 1.6 (0.05 &lt; P &lt; 0.10) (controlling for other symptoms, smoking, age) Severe wheezing alone was not associated with significant increase in risk of lung cancer.</td>
<td>Significant lung cancer risk was associated with severe level of phlegm production, even after controlling for smoking, shortness of breath, and wheezing.</td>
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<tr>
<td>Study</td>
<td>Description</td>
<td>Follow-up Details</td>
<td>FEV₁ and FEV₆ Details</td>
<td>Proportional Hazards Model</td>
<td>Other Notes</td>
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<tr>
<td>Kuller et al.</td>
<td>Cigarette smoking males (n = 8,194) participating in the Multiple Risk Factor</td>
<td>Average follow-up, 10.5 yrs (1973–1984). However, the</td>
<td>FEV₁ levels distributed into quintiles. For example, lowest quintile included ≤2670 ml</td>
<td>FEV₁ (lowest) = FEV₁ (highest) = 3.57 (94, 12.5)</td>
<td>Production of phlegm for greater than 3 months in a year was a significant predictor of lung cancer, after adjusting for age, smoking, and FEV₆. There was no relation between baseline shortness of breath and subsequent lung cancer mortality.</td>
</tr>
<tr>
<td>(1990) (15)</td>
<td>Intervention Trial. Of the above, 6,075 (75%) had satisfactory pulmonary     highest quintile, ≥1749 ml allow for 7.5 yrs of follow-up</td>
<td>quintiles. For example, lowest quintile included ≤2670 ml highest quintile, ≥1749 ml</td>
<td>reduction in risk with increase in FEV₁ of 1000 ml.</td>
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<td>function measurements; aged 35–57 yrs at entry</td>
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<tr>
<td>Lange et al.</td>
<td>Population-based sample of 7,573 women and 6,373 men who were participants in</td>
<td>Average follow-up period of about 10 years</td>
<td>% predicted FEV₁, FEV₁/FVC%, chronic phlegm (3 months each year for more than 1 y)</td>
<td>Cox regression model controlling for age, sex, cigarette smoking</td>
<td>Regression coefficients did not differ between women and men. Among subjects who reported chronic phlegm at enrollment, only 54% reported it on reexamination 5 years later.</td>
</tr>
<tr>
<td>(1990) (7)</td>
<td>the Copenhagen City Heart Study</td>
<td></td>
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<tr>
<td>Ventebo et al.</td>
<td>Random sample (6.6%) of all men, 46–69 yrs of age, living in city in Denmark,</td>
<td>1974–1985, 12,134 P-Yrs Cancer incidence was based on</td>
<td>Chronic phlegm (lasting at least 3 months), cough, or shortness of breath.</td>
<td></td>
<td>Dyspnea was significant predictor of COPD and overall mortality.</td>
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<tr>
<td>(1991) (12)</td>
<td>1973; n = 876</td>
<td>the Danish Cancer Registry</td>
<td>FEV₁/FVC, under the expected FEV₁ given the height</td>
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<td>Chronic bronchitis (defined as cough and phlegm lasting three months or more for at least 2 years).</td>
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<td>Nomura et al.</td>
<td>6,317 Japanese-American men residing on Hawaiian island of Oahu, who were 45–68</td>
<td>19-year follow-up survey subsequent to examination in 1965–1968</td>
<td>% predicted FEV₁ quartile distribution.</td>
<td>Lowest quartile % predicted FEV₁ = 2.1 (1.3, 3.5) (&lt;84.5%)</td>
<td>Only 2 percent of the cohort had % predicted FEV₁ of less than 60%. The data suggested that subjects with % predicted FEV₁ below 94.5%, after controlling for age and smoking, were at increased risk of lung cancer (95% CI, 1.3–4.1)</td>
</tr>
<tr>
<td>(1991) (13)</td>
<td>yrs of age at entry.</td>
<td></td>
<td>Highest quartile category (&gt;103.5%) was baseline in estimating relative risk.</td>
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*P-Yrs, person-years.*
Declining FEV₁ and Chronic Productive Cough

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Cigarette Smoke
Duration, Intensity, Depth of Inhalation, Genetic Susceptibility

Obstruction of tracheobronchial and broncholar airways:
- Mucus hypersecretion
- Impaired mucociliary clearance
- Deposition and retention of particulates
- Increased airway reactivity ("asthmatic bronchitis")

Inflammatory injury of lung parenchyma:
- Release of proteolytic enzymes
- Production of oxygen radicals
- Macrophage secretion of polypeptide growth factors

Molecular genetic events:
- c-myc amplification
- k-ras point mutation
- c-erb-2 altered transcription, loss of tumor suppressor genes (Rb, p53, 3p deletion)
- Genotoxic initiators (e.g., n-nitrosamines, polycyclic aromatic hydrocarbons)
- Co-carcinogens (e.g., catechols)
- Promoters (e.g., aldehydes, peroxides)

Biochemical autocrine tumor growth factors:
- Insulin-like growth factor
- Neuroendocrine peptides
- Transforming growth factor -α

LUNG CANCER

Discussion
The Tecumseh community-based cohort study enabled an evaluation in women as well as in men of the independent significance of chronic recurring symptoms of cough and phlegm, in association with baseline impaired and longitudinally declining FEV₁ in predicting lung cancer incidence density; the relevance of these relationships was assessed while controlling for age, cigarette smoking history, and dietary intake of calorie-adjusted total fat, cholesterol, vitamin A, and beta-carotene. In the population-based study conducted by Lange et al. (7), the elevated Cox regression coefficients for chronic phlegm, and percent predicted FEV₁ and FEV₁/FVC were similar in women and men. Other cohort studies have controlled for age and smoking on the basis of surveys of healthy working men in urban or rural areas (8–13), male participants in a lung cancer screening trial or clinic patients receiving treatment for COPD (14), and male participants at increased risk for coronary heart disease in a randomized Multiple Risk Factor Intervention Trial (15) (Table 7). Although baseline health status, degree of abnormality in ventilatory function and length of followup interval varied considerably in its distribution in the various cohorts, there was notable consistency in the ranges of estimations of relative risk for the same indices of airflow obstruction.

In the cohort subgroup who were smoking at entry, about 14% experienced a markedly accelerated rate of decline in FEV₁ (≥100 ml/year) after age 25 years, which was at least 3 to 4 times the expected average rate of decline in never smokers (25–35 ml/year) (16); both the baseline level of percent predicted FEV₁ and the rate of decline in FEV₁ were independent predictors of lung cancer incidence. In the subgroup characterized by smoking two or more packs of cigarettes per day accompanied by a decline in FEV₁ of 100 ml/year or greater, their long-term risk of lung cancer was almost 30 times that in the subgroup who had smoked less than 1 pack per day and had experienced a lesser rate of decline in FEV₁. In addition to the cumulative level of exposure to cigarette smoke, i.e., the exposure level derived from the product of average intensity and duration, susceptibility to the toxic effects of smoking and the pathological sequelae of COPD and/or lung cancer would appear to be correlated with the accelerated rate of decline in FEV₁ with age.

Cigarette smokers manifest a substantially increased rate of loss in age-height-standardized FEV₁ and FVC relative to never and former smokers. The rate of decline is correlated with baseline pulmonary function and the current daily intensity of exposure and increased airway reactivity to tobacco smoke (17–26). Fletcher et al. (27) in an 8-year longitudinal study reported that the mean annual loss in FEV₁ was 36 ml for never smokers, 45 ml for up to 15 cigarettes per day, and 54 ml for 15 or more cigarettes per day (27). Those who stop smoking cease to lose FEV₁ at an accelerated rate, with the benefits of cessation enhanced among the youngest smokers who have experienced the shortest mean duration and pack-years of exposure (28–30).

The attributable fraction is the estimated proportion of exposed cases that is due to the risk factor. In the context of the incidence densities or hazard rates derived in the Tecumseh population, the attributable fraction in the exposed lung cancer cases was: male current smokers, 75.9%; female current smokers, 81.6%; and with combined exposures, i.e., impaired FEV₁ and ever active smokers, 92.3%. Of potential significance is the increased lung cancer incidence density observed in the never smokers with markedly

Fig. 1. Enhancement of the causal pathway of cigarette smoke and lung cancer by the association with chronic obstructive pulmonary disease.
impaired ventilatory function. However, the increased rate ratio, 6.30 (1.31, 30.33), was based on only two cases and fewer than 1500 person-years of observation. Van Den Eeden and Friedman (31) in their study of members of the Northern California Kaiser Permanante Medical Care Program did not observe any trend or variation in lung cancer incidence among never smokers by quintile of FEV1.

Chronic cigarette smoking retards mucociliary clearance of foreign particulates and respiratory tract secretions, evokes an inflammatory response (i.e., alveolar macrophages and neutrophils) accompanied by fibrosis and thickening in the membranous and respiratory bronchioles, and causes mucus gland hypertrophy, hyperplasia and dysplasia in the proximal airways. The defensive role of pulmonary macrophages can be compromised by cigarette smoke and, furthermore, subverted to release excessive amounts of lysosomal proteases that cause structural damage in the lung. Excessive phagocytosis and oxidases of nitrogen generated by tobacco combustion elevate tissue levels of reactive oxygen-free radical species that degrade mucus glycoproteins and render lung tissue more susceptible to proteolytic injury (32–38).

The manifestations of COPD signal the extent of bronchopulmonary structural and functional damage arising from the interaction of sustained exposure to toxic products of tobacco combustion and host susceptibility. In this context, COPD is both a biomarker of dosimetry and tissue susceptibility. A more controversial interpretation would be that of how COPD impacts the development of lung cancer. A conceptual model is proposed that incorporates the potential cocarcinogenic effects of chronic obstructive pulmonary disease in the causal pathway of cigarette smoke and lung cancer (Fig. 1). Cocarcinogenesis implies an augmentation of neoplastic transformation brought about by nongenotoxic factors or mechanisms operating in conjunction with an initiating agent. The molecular events in the natural history of lung cancer comprise multiple genetic mutations that are determinants of neoplastic transformation and tumor progression, and the elaboration of autocrine growth factors that influence the clonal behavior and morphological features of neoplastic cells (39–41). Chronic inflammation in the distal small airways is an important cause of obstructive symptoms and provides the dynamic setting for oxidative stress and the formation of free radicals that augment the likelihood of DNA structural and transcriptional errors.

Increased proliferation kinetics and the interaction of hydroxyl radicals with DNA augment the likelihood of DNA formation that is determinants of neoplastic transformation and tumor progression, and the elaboration of autocrine growth factors that influence the clonal behavior and morphological features of neoplastic cells (39–41). Chronic inflammation in the distal small airways is an important cause of obstructive symptoms and provides the dynamic setting for oxidative stress and the formation of free radicals that augment the likelihood of DNA structural and transcriptional errors.

The collective results of at least 10 cohort studies currently provide a compelling scientific rationale for targeting preventive interventions (e.g., smoking cessation, introduction of a chemopreventive agent (45), and use of candidate biomarkers for screening and early detection (46) in a susceptible subgroup of cigarette smokers.

References
Declining FEV1 and Chronic Productive Cough


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