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Original Article

Lung function predicts lung cancer risk in smokers: a tool for targeting screening programs

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ABSTRACT

The relationship between smoking, lung cancer and airflow obstruction is recognized but it is unclear whether the presence of minimal lung function damage constitutes an independent risk factor for the development of lung cancer.

In order to identify those individuals at higher risk of lung cancer on the basis of functional impairment, we evaluated baseline pulmonary function tests of 3,806 heavy smokers undergoing annual chest CT screening, and compared the Forced Expiratory Volume in 1 second % predicted (FEV1PP) of 57 lung cancer cases and that of 3,749 subjects without cancer.

We obtained odds ratios (OR) of lung cancer and the corresponding 95% confidence intervals (CI) by unconditional logistic regression, adjusting for age, sex, study, and smoking variables. As compared to subjects with FEV1PP ≥ 90%, the OR of lung cancer was 2.45 (95% CI: 1.39-4.33) for subjects with FEV1PP < 90% and 2.90 (95% CI: 1.34-6.27) for subjects with FEV1PP < 70%.

These data show that even a relatively small reduction in FEV1PP is a significant predictor of increased lung cancer risk. Testing screening for lung cancer using airflow obstruction with FEV1PP less than 90% is a strategy worth future consideration.

Keywords: lung cancer risk, lung damage, lung function, spiral CT screening

Abbreviations

AIRC: Italian Association for Cancer Research

CI: confidence intervals

COPD: Chronic Obstructive Pulmonary Disease

FEV1PP: Forced Expiratory Volume in 1 second % predicted

MILD: Multicentric Italian Lung Detection

OR: odds ratios

Introduction

The relationship between smoking, lung cancer and airflow obstruction is well recognized [1]. However, it is unclear whether the presence of airflow obstruction constitutes a significant risk factor for development of lung cancer, independently from smoking [2].

Several studies have suggested that airway obstruction, based on Forced Expiratory Volume in 1 second (FEV1) reduction, increases lung cancer risk [3-5]. In particular airflow obstruction can be considered as a surrogate marker of carcinogenic exposure of the airways to cigarette smoke. Therefore, it is reasonable to investigate whether the individual predisposition to lung cancer, as well as the clinical and pathological features of cancer arising in smokers, differ according to the degree of respiratory failure [6-8].

The aim of the study is to identify in a population of heavy smokers, recruited in prospective screening trials with annual spiral CT, those individuals with higher lung cancer risk on the basis of functional damage, and to establish whether a cut-off value of lung obstruction can be assumed as a discriminating parameter for early detection lung cancer trials.

Materials and Methods

We examined 3,806 subjects enrolled in early detection lung cancer trial between June 2000 and April 2008. Data were collected from two Italian cohort studies that found a total of 57 cases of lung cancer screened during the observation period. The first pilot study [9] detected 36 cases of lung cancer during the five years of follow-up, and the second randomised study named Multicentric Italian Lung Detection (MILD) project detected 21 cases of lung cancer during the first two years of follow-up. Both trials included subjects aged 50–75 years, current or former smokers (having quit <10 years before the inclusion) of ≥20 pack-years with no history of cancer within the prior 5 years. In the MILD trial, individuals were randomized in two groups: a control group which undergoes a program of primary prevention with pulmonary function test evaluation and blood sample collection, and an early detection group where periodic spiral CT is associated with primary

prevention, pulmonary function evaluation and blood sample collection. The early detection group is further randomized in two arms: yearly low-dose CT vs. CT every 2 years.

The population of volunteers was recruited among respondents to advertisements and articles published in the lay press and from television broadcasts. All volunteers were assessed for their eligibility and asked to sign a consent form, including a detailed information sheet, to participate in the study. The trials were approved by the Institutional Review Board and by the Ethics Committees of the centres taking part in the project.

Participants were asked in advance to allow a couple of hours for completion of the questionnaire, physical examination, blood sampling, lung function test and spiral CT. The questionnaire included a detailed information on smoking history and the presence of respiratory symptoms and previous treatment of selected diseases including cancer, physician-diagnosed chronic bronchitis, emphysema or asthma. We considered participants to be current smokers if they reported the use of cigarettes, cigars, or pipes at the time of the survey, and to be former smokers if they reported any previous use of cigarettes, cigars, or pipes, but no use in the last year. Information about attempts and assistance to stop smoking was also reported.

Forced vital capacity (FVC) and FEV1 were measured at baseline in all study participants by using an electronic spirometer that utilizes a brass Fleisch type pneumotachometer connected to a computer for the analysis of data according to the recommendations of the American Thoracic Society and the European Respiratory Society of 2005 [10]. For each session a three liters syringe was used to calibrate spirometer equipment. We calculated the percentage of FEV1 on the predicted value (FEV1PP) and we assessed the risk of lung cancer for 3 different levels of FEV1PP: <70%, 70%-89%, and ≥90%. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging, we considered COPD subjects those with a FEV1/FVC ratio <70% [11]. Furthermore, in order to adjust for potential age-related modifying effect, we used different FEV1/FVC ratio thresholds [12-14] in subsequent age groups, i. e. <75% below age 60 years, <70% at age 60-69 years, and < 65% at age 70 years and over.

Analysis

We compared the 57 lung cancer patients with 3749 subjects without cancer. We computed the odds ratios (OR) of lung cancer, as estimators of relative risks [with the corresponding 95% confidence intervals (CI)] for several variables related to functional lung damage, by unconditional multiple logistic regression equations [15], including terms for gender, age, and study. Further adjustment for smoking status (current or former smokers), number of cigarettes, and duration of smoking habits was also applied. Since the effect of dose and duration is substantially different in the process of lung carcinogenesis [16] we adjusted the dose and duration separately. To better understand the relation between FEV1PP and the risk of lung cancer, we applied receiver operating characteristic (ROC) curves to find the best sensitivity and specificity cut-off value of FEV1PP. We also considered different standardization of FEV1 and we made a comparison between FEV1PP, FEV1/height^2 and FEV1/height^3 as suggested by Miller et al. [17]. We performed sub-group analyses, separating individuals by sex, smoking status, TNM stage and cancer histology. We assessed the significance of the interactions for the combined effect of FEV1PP with sex and smoking status by comparing the difference between the deviances of the models with and without the term of interest to the $\chi 2$ distribution with 1 degree of freedom. Attributable risk was calculated according to Bruzzi et al. [18].

Results

Table 1 shows the distribution of 57 lung cancer cases and 3749 controls according to selected demographic and lifestyle characteristics. Most cases and controls were men (78.9% vs. 68.1%), but cases were older (22.8% vs. 13.9% being 65 years old or older). Cases and controls did not differ by smoking status (82.5% vs 74.7% of former smokers), but cases reported higher consumption of cigarettes (57.9% vs. 26.6% reporting 30 or more cigarettes per day), and longer duration of smoking (66.7% vs. 40.9% reporting 40 years or more). As a consequence, the number of pack

years was much higher among cases than controls (73.7% vs. 30.7% reporting 45 or more pack years).

Table 2 shows the distribution of cases and controls according to Chronic Obstructive Pulmonary Disease (COPD) status and levels of FEV1PP, and the corresponding ORs. After adjustment for age, sex, study, and smoking variables, the OR of lung cancer was 1.23 (95% CI: 0.68-2.25) for COPD subjects as compared to non COPD subjects, when considering the cut-off level of 70% for the FEV1/FVC ratio, and the risk estimate did not materially change when we considered age-group specific cut-off levels of the FEV1/FVC ratio (OR=1.46). The OR of lung cancer was 2.45 (95% CI: 1.39-4.33) for subjects with FEV1PP <90 as compared to subjects with FEV1PP ≥90. The risk increased with a finer stratification of the levels of the FEV1PP, and the OR was 2.90 (95% CI: 1.34-6.27) for FEV1PP <70 as compared to FEV1PP ≥90. After stratification according to FEV1PP and COPD status, the OR was 2.56 (95% CI: 1.29-5.07) for COPD subjects with FEV1PP <90 and 2.36 (95% CI: 1.23-4.52) for non COPD subjects with FEV1PP <90 as compared to ones with FEV1PP ≥90. When we adopted different thresholds in subsequent age groups, the results were not materially modified and the ORs were 2.67 and 2.15, respectively.

Figure 1 shows the ROC curve plotting the accuracy of FEV1PP in predicting lung cancer. A cut-off level of 90% of FEV1PP corresponded to a sensitivity of 63.2% (95% CI: 50.6%-75.7%) and a specificity of 70.5% (95% CI: 69.0%-71.9%). A cut-off level of 85% of FEV1PP corresponded to a sensitivity of 52.6% (95% CI: 39.7%-65.6%) and a specificity of 79.1% (95% CI: 77.8%-80.4%), and a cut-off level of 95% of FEV1PP corresponded to a sensitivity of 73.7% (95% CI: 63.3%-85.1%) and a specificity of 59.0% (95% CI: 57.5%-60.6%), thus providing a worse compromise between sensitivity and specificity. The area under the curve was 0.70 using FEV1PP, and was 0.68 using both FEV1/height^2 and FEV1/height^3.

Table 3 shows the OR of lung cancer stratified for sex and smoking status, and according to stage and histology. The risk of lung cancer for FEV1PP <90% was higher among women than men, and among former than current smokers, but the interactions between FEV1PP and sex or smoking

status were non statistically significant. When considering the odd ratios according to TNM stage, the risk of lung cancer was similar for stage I lung cancer (OR=2.23) and for stage II, III or IV (OR=2.45). However, the risk of lung cancer for FEV1PP <90% was significantly different according to histology, the OR being 1.46 (95% CI: 0.75- 2.84) for adenocarcinomas and 12.29 (95% CI: 2.75-55.05) for squamous cancer and other cell types.

Discussion

The present report provides definite evidence and more accurate quantification than previously available [3-8] that lung function impairment represents a significant risk of developing lung cancer. In particular, it shows that a reduction of as little as 10% of FEV1PP, is associated with an almost 3 fold greater lung cancer risk. The corresponding attributable risk of lung cancer was 37.3% (95% CI: 15.1%-59.6%). Despite the fact that functional alterations indicative of COPD was not associated with lung cancer risk), the present findings provided a strong evidence that minimal and moderate functional impairment confers an increased risk of lung cancer, and a high attributable risk. This excess of risk was observed even in subjects not reporting functional alterations indicative of COPD.

The FEV1 index is a measure of airflow impairment that varies with age, height and sex. The standardization of FEV1PP has been adopted to adjust for these covariates and other kinds of standardization have also been proposed [17]. In our data, FEV1/heigh^2 and FEV1/heigh^3 gave similar risk estimates, but showed lower values in terms of the estimated area under the ROC curve. Moreover, the variation of FEV1/FVC ratio, with the adoption of different threshold for subsequent age groups, did not modify the results.

Several studies reviewed epidemiologic evidence on the relationship between inflammatory pulmonary diseases, such as asthma and chronic obstructive diseases, and the risk of lung cancer. Research relating asthma and cancer did not reveal a consistent pattern of association, while the relationship between smoking, airflow obstruction, and lung cancer is well recognized [19-24].

Cigarette smoking is the leading cause of lung cancer and is also the main cause of lung function impairment. Diseases characterized by airflow obstruction are associated with an increased risk of lung cancer. The results of our study are in agreement with those from a meta-analysis of population based prospective studies with at least 5,000 participants, adjusting for smoking status [25]. Wasswa-Kintu et al. reported that the reduction of lung function was an independent risk factor for lung cancer even for small differences in FEV1PP, and the association was stronger for women than for men. The pooled relative risk for FEV1PP in the first quintile (<~70%) as compared to the fifth quintile (≥100%) was 2.23 in men and 3.97 in women, but even relatively small decrements of FEV1PP (<~90%) increased the risk of lung cancer, the pooled relative risk being 1.30 in men and 2.64 in women [25].

Subsequent studies confirmed this association. In a cohort study from Sweden based on 834 incident cases of lung cancer, Purdue et al. described the presence of obstructive lung disease as a significant predictor of incident lung cancer, and reported relative risks of 1.5 and 2.2, respectively for mild and moderate/severe COPD [26]. In a case-control study based on 24 lung cancer cases Kishi et al. reported that airflow obstruction, but not emphysema extent on CT, was associated with higher risk for lung cancer [2]. In a prospective study on a lung cancer screening population, de Torres et al. found that the presence of emphysema, but not obstruction was associated with increased frequency of lung cancer [27]. However, a study based on 99 cases of lung cancer reported a two fold increased in risk of lung cancer for subjects with mild, moderate or severe airflow obstruction (GOLD I-GOLD IV) as compared to those without airflow obstruction, and showed that both emphysema and airflow obstruction were related to lung cancer risk [28]. Thereby, data in the literature are still controversial, and further studies are required to clarify the relative importance of emphysema vs bronchial obstruction in lung cancer carcinogenesis.

Our study population is larger (3869 subjects) as compared to Wilson et al. (3638 subjects) [28], Kishi et al. (1520 subjects) [2], and de Torres et al. (1166 subjects) [27] and includes a higher number of cases (57 cases) compared to Kishi et al. (24 cases) and de Torres et al. (23 cases). [2,

27]. Our results underline the importance of baseline pulmonary function tests in lung cancer screening trials, indicating that even a modest reduction of FEV1PP in smokers without COPD is predictive of an increased risk of lung cancer. Although our study is not comparable with previous ones that analyzed the emphysema extent on CT, our preliminary findings, using a dedicated software on 16-slice CT images, suggest that emphysema is not an independent risk factor for lung cancer [29].

The decrement in the levels of the FEV1PP has been also associated with the risk of cancer at other sites than the lung in an epidemiological study from Japan based on 34 cancer cases that reported a relative risk of 2.32 for COPD patients as compared to patients with benign respiratory disease.[30]

There are several possible explanations for the relationship between pulmonary function and lung cancer. In fact, it is well recognized that the extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the accelerated decline in FEV1. Airflow obstruction in smokers can be considered as a surrogate marker of significant carcinogenic exposure of the airways to cigarette smoke, as its effects persist even after separate and accurate allowance for dose and duration of smoking. Airflow limitation may be due to carcinogenic damage at a cellular level in susceptible subjects. Molecules of the stress response and cell death can activate the same receptors triggered by pathogens and contribute to tissue inflammation. Chronic inflammation, characterized by accumulation of inflammatory mucous exudates in the lumens, causes remodelling and thickening of bronchiolar wall associated with impaired tissue repair, whose imbalance might provide several growth factors fostering the growth of sporadically transformed cells. The individual response to inflammatory stimuli, polymorphism in Toll like receptor and interferon regulatory factor genes, as well as of other inflammatory genes, might help to explain some individual variation in inflammation-cancer transition [31-36].

The sub-group analysis by histological types showed a major difference in lung cancer risk, and confirmed previous reports suggesting a stronger association of lung function impairment with squamous cell carcinoma than with adenocarcinoma [37].

The present study indicates therefore the role of lung function tests, a non invasive, low cost and very fast examinations, to identify optimal candidates for early detection trials. Pulmonary function tests and assessment of FEV1 should be considered when constructing strategies for lung cancer screening, in order to improve selection criteria. In fact, the frequency of benign lesions with last generation multi-slice CT is at least 50 times higher than lung cancer detection rate (<1% per year) [38-40]. As a consequence, a very large numbers of subjects have to be recruited in early lung cancer detection programs, with a high chance of false positive results, elevated costs and potential morbidity for the screened population.

In conclusion, defining reliable criteria for the assessment of a higher individual risk of lung cancer in heavy smokers might improve future prevention strategies, early detection approaches, and clinical management of such a lethal disease. Airflow obstruction as surrogate marker for carcinogenic damage of the airways may be better than pack years alone in predicting risk and can be used to select subjects for screening programmes. Moreover, the recognition of minimal lung function impairment, in individuals with otherwise normal CT scan features, could motivate smoking cessation with potential benefit in the overall mortality and public health care.

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Table 1 – Distribution of 57 cases of lung cancer and 3749 controls according to selected characteristics

Characteristics	Cases N (%)	Controls N (%)
Study		
Pilot study	36 (63.2)	834 (22.2)
MILD study	21 (36.8)	2915 (77.8)
Sex		
Men	45 (78.9)	2554 (68.1)
Women	12 (21.1)	1195 (31.9)
Age (years)		
<55	11 (19.3)	1295 (34.5)
55-64	33 (57.9)	1934 (51.6)
≥65	13 (22.8)	520 (13.9)
Smoking status		
Current smokers	47 (82.5)	2798 (74.7)
Former smokers	10 (17.5)	949 (25.3)
Number of cigarettes		
<20	5 (8.8)	877 (23.4)
20-24	15 (26.3)	1580 (42.1)
25-29	4 (7.0)	293 (7.8)
≥30	33 (57.9)	999 (26.6)
Duration of smoking (years)		
<30	2 (3.5)	569 (15.2)
30-34	8 (14.0)	845 (22.6)
35-39	9 (15.8)	801 (21.4)
≥40	38 (66.7)	1532 (40.9)
Pack years of smoking		
<35	6 (10.5)	1568 (41.9)
35-44	9 (15.8)	1025 (27.4)
≥45	42 (73.7)	1151 (30.7)

Table 2 – Distribution of 57 cases of lung cancer and 3749 controls according to lung function measures and corresponding odds ratio (OR) with 95% confidence interval (CI)

Characteristics	Cases N (%)	Controls N (%)	OR (95%CI)[1]	OR (95%CI)[2]
COPD[3,4]				
Negative	39 (69.6)	2910 (77.6)	1.00	1.00
Positive	17 (30.4)	839 (22.4)	1.48 (0.82-2.67)	1.23 (0.68-2.25)
COPD[4,5]				
Negative	30 (53.6)	2390 (63.8)	1.00	1.00
Positive	26 (46.4)	1359 (36.2)	1.68 (0.99-2.88)	1.46 (0.85-2.52)
FEV1PP				
≥90	21 (36.8)	2640 (70.5)	1.00	1.00
<90	36 (63.2)	1107 (29.5)	2.94 (1.67-5.16)	2.45 (1.39-4.33)
FEV1PP				
≥90	21 (36.8)	2640 (70.5)	1.00	1.00
70-89	24 (42.1)	849 (22.7)	2.72 (1.48-4.97)	2.29 (1.24-4.23)
<70	12 (21.1)	258 (6.9)	3.64 (1.70-7.81)	2.90 (1.34-6.27)
chi-trend (p-value)			*14.5 (0.0001)*	*9.45 (0.0021)*
FEV1PP and COPD[3,4]				
FEV1PP ≥90	21 (36.8)	2640 (70.5)	1.00	1.00
FEV1PP <90 and COPD Negative	19 (33.3)	582 (15.5)	2.75 (1.44-5.25)	2.36 (1.23-4.52)
FEV1PP <90 and COPD Positive	17 (29.8)	525 (14.0)	3.19 (1.63-6.23)	2.56 (1.29-5.07)
chi-trend (p-value)			*13.4 (0.0003)*	*8.4 (0.0037)*
FEV1PP and COPD[4,5]				
FEV1PP ≥90	21 (36.8)	2640 (70.5)	1.00	1.00
FEV1PP <90 and COPD Negative	14 (24.6)	450 (12.0)	2.51 (1.24-5.09)	2.15 (1.05-4.40)
FEV1PP <90 and COPD Positive	22 (38.6)	657 (17.5)	3.28 (1.77-6.09)	2.67 (1.42-5.01)
chi-trend (p-value)			*14.8 (0.0001)*	*9.6 (0.0019)*

[1]Obtained from unconditional logistic regression after adjustment for age, sex, and study.

[2]Obtained from unconditional logistic regression after adjustment for age, sex, study, smoking status, duration of smoking and number of cigarettes.

[3] COPD cases had FEV1/FVC index <70% for all subjects.

[4]The sum does not add up to the total because of missing values.

[5] COPD cases had FEV1/FVC index index<75% for subjects of age <60 years, <70% for subjects of age 60-69 years and <65% for subjects of age 70 years or older.

FEV1PP: Forced Expiratory Volume in 1 second % predicted. COPD: Chronic Obstructive Pulmonary Disease.

Table 3 – Distribution of 57 cases of lung cancer and 3749 controls for Forced Expiratory Volume in 1 second % predicted (FEV1PP) levels and corresponding odds ratio (OR) with 95% confidence interval (CI) in strata of sex and smoking status and according to type of cancer for TNM classification and histology.

	FEV1PP				
	≥90		<90		
	Cases: Controls	OR	Cases: Controls	OR (95%CI)[1]	OR (95%CI)[2]
Sex[3]					
Men	17:1766	1	28:786	2.73 (1.45-5.13)	2.24 (1.17-4.28)
Women	4:874	1	8:321	4.04 (1.18-13.77)	4.51 (1.25-16.26)
Smoking status[3,4]					
Current smokers	18:1943	1	29:853	2.57 (1.39-4.76)	2.20 (1.18-4.12)
Former smokers	3:695	1	7:254	5.77 (1.43-23.2)	4.55 (1.11-18.7)
TNM classification[4,5]					
Stage I	15:2640	1	21:1107	2.54 (1.28-5.05)	2.23 (1.11-4.47)
Stage II-III-IV	6:2640	1	13:1107	3.49 (1.28-9.53)	2.45 (0.88-6.84)
Histology[4,5]					
Adenocarcinoma	19:2640	1	20:1107	1.79 (0.928-3.44)	1.46 (0.75- 2.84)
Others	2:2640	1	16:1107	14.60 (3.29-64.75)	12.29 (2.75-55.05)

[1]Obtained from unconditional logistic regression after adjustment for age, sex, and study.

[2]Obtained from unconditional logistic regression after adjustment for age, sex, study, smoking status, duration of smoking and number of cigarettes.

[3]Not significant interaction of FEV1PP with sex, neither with smoking status.

[4]The sum does not add up to the total because of missing values.

[5]The difference in risk for FEV1PP was not significant between stages of TNM classification (p=0.78) and it was significant by histology (p=0.002).

Figure 1 - Receiver operating characteristic curve showing the cut-off level of Forced Expiratory Volume in 1 second (FEV_1)% predicted with the best sensitivity and specificity for estimation of the odds ratio of lung cancer.