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ORIGINAL RESEARCH

Prevalence of chronic obstructive pulmonary disease in asymptomatic smokers

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Background: Physicians do not routinely recommend smokers to undergo spirometry unless they are symptomatic.

Objective: To test the hypothesis that there are a significant number of asymptomatic smokers with chronic obstructive pulmonary disease (COPD), we estimated the prevalence of COPD in a group of asymptomatic smokers.

Methods: Two thousand nine hundred and sixty-one smokers with a cumulative consumption history of at least 10 pack-years, either smokers with symptoms or smokers without symptoms (WOS) were invited to perform a spirometry and complete a symptom questionnaire.

Results: Six hundred and thirty-seven (21.5%) smokers had no symptoms, whereas 2,324 (78.5%) had at least one symptom. The prevalence of COPD in subjects WOS was 1.5% when considering the whole group of smokers (45/2,961) and 7% when considering only the group WOS (45/637). From 329 smokers with COPD, 13.7% were WOS. Subjects WOS were younger, had better lung function and lower cumulative consumption of cigarettes, estimated as both cigarettes per day and pack-years. According to severity of airflow limitation, 69% vs 87% of subjects were classified as Global Initiative for Chronic Obstructive Lung Disease stages I–II in the WOS and smokers with symptoms groups, respectively ($P<0.001$). A multivariate analysis showed that forced expiratory volume in 1 second (mL) was the only predictive factor for COPD in asymptomatic smokers.

Conclusion: Prevalence of COPD in asymptomatic smokers is 1.5%. This number of asymptomatic smokers may be excluded from the benefit of an "early" intervention, not just pharmacological but also from smoking cessation counseling. The higher forced expiratory volume in 1 second may contribute to prevent early diagnosis.

Keywords: COPD, asymptomatic smokers, early diagnosis

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by a poorly reversible limitation in airflow, is predicted to be the third most frequent cause of death worldwide by 2020.[1] Therefore, early diagnosis of COPD is relevant both to prevent disease progression as well as to treat it. The diagnosis and risk of death in patients with COPD is usually estimated with the use of the forced expiratory volume in 1 second (FEV_1). However, physicians do not routinely recommend smokers to undergo spirometry,[2,3] unless they are symptomatic, particularly with dyspnea. An important and unknown number of patients with COPD seek medical help for the first time, either during a physician's office visit or during an emergency room event in the face of an exacerbation. Because it is feasible that the disease initiation was not on the day of the exacerbation, one may assume that those patients were asymptomatic.[4]

The large majority of information on early diagnosis of COPD results from case-finding studies, which is based on the presence of chronic respiratory symptoms.

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Information resulting from screening studies that aim to apply spirometry to all smokers without considering the presence of symptoms is scarce. Zielinski et al[5] tested >100,000 smokers and found among the prevalent cases (20.3%) of COPD that almost 64% of subjects had respiratory symptoms, mainly cough. Recently, we found in a screening study that, among the 13.3% of smokers who had COPD, up to 56% had symptoms.[6] Both studies suggest the existence of a number of smokers without symptoms (WOS) having COPD whose actual prevalence is unknown. These data are relevant because of the increased COPD subdiagnosis.[7]

Therefore, to test the hypothesis that there are a significant number of asymptomatic smokers with COPD, we estimated the prevalence of COPD in a group of smokers in whom spirometry and a questionnaire on symptoms were carried out.

Methods

This study included 2,961 smokers from a database of subjects enrolled in a continuing program of early detection of COPD.[6] The study was performed in the COPD and Smoking Cessation Clinic of the National Institute of Respiratory Diseases (INER) in Mexico City. INER is a public tertiary care center devoted to medical care, teaching and research focusing on respiratory diseases. The original project was approved by the ethics committee of the INER (Comité de Ciencia y Bioética en Investigación, approval number C08-05).

Financial considerations for spirometry, technicians, and medical care during the study were supported by a grant from the research programs of the INER.

Subjects and recruitment strategies

Smokers, either with symptoms (WS) (cough, phlegm, wheezing, and shortness of breath) or WOS, were invited to be included for spirometry at no cost during the COPD Day campaigns using mass media advertisements. They were classified as WS or WOS if they had even one symptom or no symptoms at all, respectively. Additionally, all smokers attending our smoking cessation program were also invited for spirometry. The details of both recruitment strategies are described elsewhere.[5] Those smokers who were aware of having some type of respiratory disease were excluded from this study. As part of the early diagnosis program, tests such as spirometry and a questionnaire regarding respiratory symptoms were completed. All subjects read and signed the "patient information consent form".

Participants were required to be current or former smokers with a cumulative consumption history of at least 10 pack-years. Additionally, subjects fulfilled the following criteria: 1) have a valid pre- and postbronchodilator spirometry; 2) complete a symptom questionnaire; 3) no self-report of previous diagnosis of asthma or other pulmonary diseases such as bronchiectasis; and 4) no self-report of a history of exposure to wood smoke or biomass.

Questionnaire

A brief questionnaire containing 28 items, including age, sex, smoking status, presence of cough, phlegm, wheezing, and shortness of breath, was completed by all participants. Shortness of breath was determined by answering yes or no to the statement "I experience shortness of breath when walking fast on level ground or walking up a slight hill", which corresponds to the modified Medical Research Council (dyspnea scale) grade 1.[8] In order to appropriately complete the questionnaire and assist smokers, a facilitator was available at all times.

Spirometry

Subjects were submitted to both pre- and postbronchodilator spirometry following the procedures recommended by the American Thoracic Society and the European Respiratory Society[9] with a dry rolling-seal volume spirometer (Sensormedics, Yorba Linda, CA, USA). Data were expressed as percent of predicted value using Mexican values of reference equations of Pérez-Padilla et al.[10] COPD was defined in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[11] using a fixed FEV_1/forced vital capacity ratio (<0.70) in long-term smokers who were >40 years of age. Severity of airway obstruction was quantified in accordance with GOLD guidelines.[12]

Statistical analysis

General characteristics were described using mean and standard deviations or median and interquartile range accordingly with variables distribution. Comparisons between groups were done using Student's *t*-test or chi-square test for comparisons between proportions.

In order to determine the predicting factors associated with COPD in asymptomatic subjects, variables such as age, height, weight, sex, pack-years, and tobacco smoking status were estimated using models of uni- and multivariate logistic regression analysis. Cronbach's alpha that was used to estimate the generalizability of the four included items to determine symptoms was 0.71.

Results

Table 1 shows general characteristics according to symptoms in smokers. From the total group of smokers, 21.50% (637) of subjects had no symptoms, whereas 78.50% (2,324) had at least one symptom. Subjects WOS were younger, had better lung function, and lower cumulative consumption of cigarettes, both estimated as cigarettes per day and pack-years. From the total group, 11.11% (329/2,961) of smokers had COPD. The prevalence of COPD in subjects WOS was 1.5% when considering the whole group of smokers (45/2,961) and 7% when considering only the group WOS (45/637). These prevalences were lower when the lower limit of normal was used to estimate the prevalence (10.01%, 1.2%, and 5.65%, respectively).

Table 2 shows differences in COPD according to symptoms. From 329 smokers with COPD, 13.7% were WOS and 86.3% WS. Subjects WOS were younger, had better lung function, and median lower cumulative consumption of cigarettes (pack-years). According to the severity of airway limitation, 69% vs 87% of subjects were classified as GOLD stages I–II in the WOS and WS groups, respectively ($P<0.000$), whereas no differences were found between groups for stages III and IV.

Both in the uni- and multivariate regression analysis, FEV_1 (mL) was shown to be a predictive variable for COPD in asymptomatic smokers (Tables 3 and 4).

Discussion

This group of asymptomatic smokers with COPD represents ~1.5% from a sample of 2,961 apparently healthy smokers who were screened and 13.7% (329) of those who had COPD (Table 2). By using the lower limit of normal, the number of asymptomatic smokers with COPD decreased from 1.5% to 1.2%.

An interesting finding of this work is the fact that 69% of asymptomatic smokers with COPD were in GOLD stages I and II. This observation may be relevant, considering that recent emerging evidence suggests that subjects in the mild stages of COPD are those with the greatest FEV_1 decline. Casanova et al[13] found that, in subjects with moderate disease (stage II), the mean loss of FEV_1 is higher than in stages III and IV (−112, −78 and −61 mL/year, respectively). Furthermore, these authors found that FEV_1 was significantly higher in decliners with slope change than in subjects without significant slope change (1,540±0.60 mL vs 1,390±0.54 mL, respectively $P=0.005$). In another study,

Table 1 Demographic data of smokers according to the presence of symptoms

n (%)	WOS 637 (21.50)	WS 2,324 (78.50)	*P*-value
Male, n (%)	306 (49.90)	1,160 (49.91)	0.401
Age, m (SD)	49.63 (11.33)	51.92 (10.48)	0.000
Height cm, m (SD)	163.04 (9.06)	163.06 (9.46)	0.972
Weight kg, m (SD)	71.01 (14.28)	71.29 (14.83)	0.776
FEV_1 post-BD mL, m (SD)	2.97 (0.76)	2.80 (0.83)	0.000
FEV_1 post % predicted, mean (SD)	98.98 (16.55)	94.49 (19.48)	0.000
FEV_1/FVC post %, m (SD)	81.03 (7.63)	79.10 (10.24)	0.000
FVC post mL, m (SD)	3.66 (0.89)	3.53 (0.94)	0.000
FVC post % predicted, m (SD)	99.90 (15.36)	97.25 (16.05)	0.000
Smoking status			
Former smoker, n (%)	120 (18.84)	452 (19.45)	0.377
Current smoker, n (%)	517 (81.16)	1,872 (80.55)	0.377
Years of smoking, m (SD)	27.53 (11.12)	28.79 (11.31)	0.019
Cigarettes/day, m (SD)	14.53 (9.88)	15.85 (10.60)	0.009
Pack-years, median (IQR)	17.00 (8–28)	19.50 (10–33)	0.012
Respiratory symptoms			
Cough, n (%)	0	1,249 (53.74)	–
Phlegm, n (%)	0	1,417 (60.97)	–
Wheezing, n (%)	0	137 (5.89)	–
Dyspnea, n (%)	0	1,611 (69.32)	–
At least one symptom, n (%)	0	2,324 (100)	–
COPD prevalence according to fixed GOLD ratio	45 (7.06)	284 (12.22)	0.000
COPD prevalence according to LLN	36 (5.65)	264 (11.35)	0.000

Note: Data is presented as either n (%), mean ± SD, or median IQR, χ^2 test, Student's *t*-test, Mann–Whitney test were used as appropriate.

Abbreviations: BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IQR, interquartile range; LLN, lower limit of normal; m, mean; SD, standard deviation; WOS, smokers without symptoms; WS, smokers with symptoms.

Table 2 Demographic data of COPD patients according to the presence of symptoms

n (%)	Total 329 (100)	WOS 45 (13.7)	WS 284 (86.3)	*P*-value
Male, n (%)	195 (59.30)	25 (55.55)	170 (59.85)	0.585
Age, m (SD)	59.47±10.19	56.91 (9.78)	59.86 (10.22)	0.070
Height cm, m (SD)	164.19±9.46	166.09 (8.97)	163.79 (9.54)	0.212
Weight kg, m (SD)	70.53±16.08	67.95 (14.77)	71.01 (16.33)	0.415
FEV_1 post-BD mL, m (SD)	1,969±810	2.20 (0.75)	1.93 (0.81)	0.036
FEV_1 post-BD % predicted, m (SD)	68.92±26.95	78.52 (22.59)	67.42 (22.39)	0.002
FEV_1/FVC post-BD, m (SD)	58.84±11.00	63.59 (11.45)	58.09 (11.55)	0.003
FVC post-BD mL, m (SD)	3,248±1,050	3.48 (1.01)	3.21 (1.05)	0.099
FVC post % predicted, m (SD)	89.26±20.97	94.25 (22.35)	88.46 (20.68)	0.093
Smoking status	Total			
Former smoker, n (%)	64 (19.45)	7 (15.56)	57 (20.07)	0.353
Current smoker, n (%)	265 (80.55)	38 (84.44)	227 (79.93)	0.353
Years smoking, m (SD)	37.83 (11.91)	36.04 (10.67)	38.10 (12.09)	0.305
Cigarettes/day, m (SD)	20.13 (13.12)	16.92 (12.04)	20.60 (13.23)	0.102
Pack-years, median (IQR)	34.75 (18.71–51.00)	23 (13.25–37.00)	36.75 (20.00–53.00)	0.013
Respiratory symptoms				
Cough, n (%)	165 (50.15)	–	165 (58.09)	–
Phlegm, n (%)	168 (52.66)	–	168 (59.15)	–
Wheezing, n (%)	137 (42.94)	–	137 (48.23)	–
Dyspnea, n (%)	224 (70.21)	–	224 (78.87)	–
COPD severity (GOLD)				
I–II, n (%)	279 (84.80)	31 (68.88)	248 (87.32)	0.000
III–IV, n (%)	50 (15.20)	14 (31.12)	36 (12.68)	0.296

Note: Data is presented as either n (%), mean ± SD, or median IQR, χ^2 test, Student's *t*-test, Mann–Whitney test were used as appropriate.
Abbreviations: BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; IQR, interquartile range; m, mean; SD, standard deviation; WOS, smokers without symptoms; WS, smokers with symptoms.

Ramírez-Venegas et al[14] found a significantly higher number of rapid decliners in subjects with mild and moderate stages (GOLD II) in comparison to those with the lower FEV_1 (GOLD stages III and IV). Additionally, in an analysis of the Framingham offspring cohort, Kohansal et al[15] found that, in the asymptomatic subject with diagnosis of COPD (as in this study), the rate of FEV_1 decline was increased in comparison to healthy continuous smokers and healthy never-smokers. Another important point to be considered is that COPD is associated with a substantial burden on the health care systems, mainly attributable to the occurrence of exacerbations.[16]

Table 3 Factors associated with COPD in asymptomatic subjects (univariate analysis)

Variable	OR	95% CI	*P*-value
Sex*	0.838	0.444–1.580	0.585
Current smoker	1.534	0.061–3.812	0.356
Cigarettes/day	0.975	0.945–1.005	0.103
FEV_1, mL	1.485	1.021–2.159	0.038
Age, years	1.002	0.976–1.029	0.833
Pack-years	0.988	0.974–1.002	0.101
Height, cm	1.025	0.985–1.067	0.213
Weight, kg	0.987	0.957–0.017	0.413

Note: *Reference category: female.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; OR, odds ratio.

The majority of asymptomatic subjects described in this work, although classified as GOLD stages I and II according to the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study,[17] are susceptible as well to exacerbations, irrespective of disease severity. An additional and appealing finding consistently reported by Ohar et al[18] relating to potential costs of the disease is that 10% of asymptomatic subjects with COPD from this study had important airflow limitations (GOLD stages III and IV). In this group of patients, the frequency,[17] recurrence rates, and health care utilization are significantly higher.

Asymptomatic smokers with COPD have been previously described in small groups of subjects with emphysema using magnetic resonance imaging of the lungs.[19] In another study, 29/75 smokers had emphysema and significantly higher mean

Table 4 Factors associated with COPD in asymptomatic subjects (multivariate analysis)

Variables	OR	95% CI	*P*-value
FEV_1, mL	2.05	1.22–3.40	0.006
Sex 1= male	0.64	0.29–1.42	0.259
Smoking index, pack-years	0.99	0.97–1.00	0.099

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; OR, odds ratio.

values of functional residual capacity, residual volume, and total lung capacity than smokers without emphysema.[20] When these subjects (GOLD stage I) become symptomatic, end-expiratory lung volume during exercise is greater and breathing pattern more shallow and rapid.[21] Results from O'Donnell et al[22] show that if these smokers (GOLD stage I) are treated with bronchodilators, modest but consistent improvements are observed in airway function, lung volume, and exercise dyspnea. In another study, it was found that out of 1,269 smokers with COPD (44% from their original sample of smokers), 14.3% had no symptoms.[18] Of these smokers, only 2.5% had received a diagnosis of COPD, suggesting that the lack of symptoms is a risk factor for undiagnosed COPD. Consistent with this finding, data from the Proyecto LatinoAmericano de Investigación en Obstrucción Pulmonar study[23] showed that the absence of respiratory symptoms increases the likelihood of undiagnosed COPD. Accordingly, our results showed that the higher level of FEV_1 predicted COPD in asymptomatic smokers, suggesting that being asymptomatic as well as having better lung function prevents early suspicion and diagnosis of COPD.[24]

Do symptoms predict COPD in smokers? Symptoms are frequent in smokers. In the current study, 78.5% of 2,961 subjects had at least one symptom and, of these, 284 (8.18%) had COPD. However, it appears that symptoms are poor predictors of the presence of COPD in smokers at risk.[18] Therefore, given the low added sensitivity to smoking history and age, an alternative approach to early diagnosis is needed.

Establishing an early diagnosis of COPD is important both for advanced as well as for mild cases of the disease. There are several reasons for this: first, exacerbations are frequent in all stages of the disease[17] and are associated with an accelerated rate of decline in FEV_1[25] and worsening of quality of life.[26] Second, pharmacological intervention in moderate disease reduces the rate of decline of FEV_1[27,28] and mortality, even after adjustments according to GOLD stages.[29] Likewise, pharmacological treatment may reduce exacerbations by the same mechanisms through which bronchodilators prevent exacerbations in severe stages of the disease.[30] Nevertheless, the US Preventive Services Task Force review from 2008[31] concluded that the efficiency of treatment has been established only in symptomatic patients. Therefore, the benefits in this population are speculative. In this sense, it is noteworthy to observe that the post hoc data from the Understanding Potential Long-term Impacts on Function with Tiotropium study showing that treatment provides clinical efficacy by improving the health status and decreasing time to first and severe exacerbations[27] have been described in patients with $FEV_1 \geq 60\%$ predicted (GOLD stage II).[32]

Most of the identified asymptomatic subjects from this study with COPD had FEV_1 within the "normal" range. Whether these subjects will progress to develop symptomatic and clinically significant airflow disease largely remains unknown.[15] Nevertheless, according to Price et al,[33] the perception of symptoms may be different or dismissed in some individuals despite being limited in terms of their daily activities and health-related quality of life.[34] In this sense, the frequent and consistent finding of undiagnosed COPD[35] is the responsibility of both patients and physicians. On the one hand, an important number of smokers do not seek medical help prior to symptom onset[36] and, on the other hand, a minority of respiratory physicians indicates the use of spirometry to smokers.[37]

Conclusion

In summary, growing clinical positions state the need for "early and earlier"[33] diagnosis of COPD to prevent late consequences of the disease. Most of these are based on case-finding strategies where symptoms and history of heavy tobacco smoking are the main indicators for spirometry. Our results suggest that a number of asymptomatic smokers may be excluded from the benefit of an "early" intervention, not just pharmacological but also from smoking cessation counseling. Therefore, screening all heavy smokers aged >40 years with a history of ≥20 pack-years, WS or WOS, with spirometry, may help to resolve the universal issue of underdiagnosed COPD. However, our results should be interpreted with caution when considering the recent US Preventive Services Task Force review[31] stating some inconveniences of the screening programs on COPD such as the effects of overdiagnosis, the possibility of unnecessary treatment, and potential side effects of the spirometric maneuver.[31] An additional limitation of this work is that the questionnaire did not search for passive smoking and the possible effects on prevalence of COPD in asymptomatic smokers.

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Disclosure

The authors report no conflicts of interest in this work.

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