

THE UNIVERSITY OF MEDICINE AND PHARMACY  
CRAIOVA

**DOCTORAL DEGREE**  
**THE EPIDEMIOLOGY OF COPD IN THE NON-SMOKER**

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## I.GENERAL INFORMATION ABOUT COPD

### 1. COPD and the never-smoker

COPD is currently the 5<sup>th</sup> cause of mortality and morbidity in the industrialized countries. It's social and economic costs are substantial. On a personal level, COPD means a chronic suffering of the patient while on an larger, economic scale, it means very high costs resulting from treatment and disability. In the EU, COPD represents the main respiratory cause of mortality and morbidity and is responsible for 8% of deaths caused by respiratory diseases(1). Even so, these figures are probably underestimated, because in a danish study, only 21% of the COPD patients with GOLD stage IV disease had COPD listed as the cause of death, and only 45% of them had any sort of mention regarding COPD in their death certificate.(2)

In Romania, a series of clinical trials started in the early seventies, shows that the incidence of COPD has been increasing steadily so far. A more recent trial, by Stefan Dutu et al., conducted in 1996, showed a prevalence of obstructive lung disease of about 9.9%. In 1998, the prevalence of COPD was estimated at about 4.6% in the rural male population and 2.3% for the female population. The mortality due to COPD was estimated to be about 20 per 100.000 male deaths and 5 per 100.000 female deaths.

Although COPD is mainly caused by cigarette smoking, only 15% of the smokers ever develop the disease, thus suggesting that may be other risk factors for the disease(3). Epidemiological studies have shown that between 5-12% of COPD patients have never smoked and there is evidence of an increase of this proportion with patient's age (4). Never smokers with COPD are usually female and have low income (5).

Lower respiratory tract infections(LRTIs) are usually regarded as a risk factor for COPD. Knowing that lungs continue to develop throughout the childhood period, it is plausible to think that infections of the lower respiratory tract that happen in childhood may produce permanent lung damage or defects in lung development.

Children that are exposed to cigarette smoke from their parents, especially their mothers, have an increased risk for LRTIs and asthma, as their lung volumes and respiratory flow are decreased. An association between exposure to cigarette smoke from the mother and the reduction of FEV1 in adulthood has been reported and does not seem to be influenced by the patient's smoking status.

The association between COPD and atmospheric pollution is clear (6) and biologically plausible(7). Many studies have confirmed an excess of cardiopulmonary deaths registered with an measurable increase in atmospheric pollution (8).

Occupational exposure to various respiratory irritants was considered as a risk factor for COPD in many recent studies but their results were inconclusive. Nevertheless,

in the last few years, there seems to be a consensus regarding occupational exposure to dust as a risk factor for COPD (9), (10). In longitudinal studies of occupational exposure, a more marked decline of FEV1 was associated with exposure to gases and vapors, with values of about 7-8ml/year (11),(12)

In the NHANES III study, Behrendt (13) identified some of the occupations associated with an increased prevalence of COPD, such as plastic manufactures, textile workers, rubber and leatherworking industry, food industry, auto repairs and some beauty services (14). In this study, the proportion of COPD patients was 19% for the entire cohort and 31% for the ever-smoker sub-group. An increase of COPD prevalence was also observed for occupations associated with exhaust fumes exposure and many other fumes and vapors(15)

The use of biomass for heating and cooking is associated with a decrease of the lung function. Slight to moderate decreases of the FEV1 and the FEV1/FVC ratio have been observed in many longitudinal studies for the patients that were exposed to indoor biomass smoke(16). Other case-controlled studies have shown that people exposed to biomass smoke have an increased risk of developing obstructive lung disease, with a significant reduction of the FEV1 and the FEV1/FVC ratio.

Social and economic status has been proven to correlate significantly with lung function even after adjusting for the smoking status, occupational exposure and ethnic origin(17). The magnitude of this effect, although variable, is situated at about 300ml of FEV1 in men and 200ml of FEV1 in women. Because of this aspect, low social and economic status must be regarded as an important risk factor for COPD (18)

Another risk factor, independent of the smoking status, is the alpha-1 antitrypsin deficiency. AAT deficiency is the only known genetic risk factor for COPD and is responsible for about 1% of the COPD cases in the US. AAT is an protease inhibitor produced by the liver whose main action is to inhibit the lung neutrophil-elastase. Severe AAT deficiency leads to premature emphysema at an average age of 53 for non-smokers and 40 for smokers.

Diet is a potentially modifiable risk factor for the deterioration of lung function. Available studies suggest that an increased dietary intake of antioxidants, especially vitamin C, protects the lung in COPD (19) although antioxidant vitamin supplements do not seem to have the same effect.

## 2. Epidemiology of COPD in the world

The prevalence of COPD in the world population is largely unknown. Estimates vary between 7-19%. The most recent study suggest a global prevalence of 10.1%(10). In men, the prevalence is 11.8% while in women it is only 8.5%. These values vary greatly in different parts of the world. Capetown, South Africa, has the highest reported

prevalence of COPD in the world – 22.2% for men and 16.7% for women. On the opposite, Hannover, Germany, has the lowest reported prevalence – only 8.6% for men and 3.5% for women. High as these figure may seem, they are probably underestimates of the real values. Another notable trend is that of the incidence of COPD in women, which is rising, and is predicted to equal that of men.

Rate of mortality by COPD is also varied throughout the world. The extremes are Romania, with 400 per 100.000 deaths of men aged between 65-74 and Japan with less than 100 deaths per 100.000 inhabitants. In the US, COPD is the 4<sup>th</sup> reported cause of mortality.

Y. Zhou, in his article called “COPD in Chinese nonsmokers” analyses the non-smoker subgroup of the CESCOPD(Chinese epidemiological Survey of COPD) study has found a 5.6% prevalence of COPD (21) while Behrendt found a 6.6% prevalence of the disease in never-smokers.

Together with the increase in morbidity and mortality due to COPD, a dramatic increase in the costs of the disease has been observed. In 2002, the US has spent 32.1 billion dollars for the management of COPD. 18 billion dollars represented the direct costs of the disease – diagnosis and treatment of COPD and its exacerbations. 14.1 billion dollars were spent on indirect costs of the disease.

### 3. Epidemiology of COPD in Romania

In Romania, COPD was largely ignored by public health officials for a long period of time. Because of its rather inexact definition and its difficult diagnosis for the pulmonologist that did not have an spirometer in their office, COPD remained underdiagnosed and undertreated. Epidemiological data about COPD are scarce, as researchers have only recently started to investigate the disease.

The oldest epidemiology study concerning obstructive lung disorders in Romania was conducted by Stefan Dutu et al. in 1996 on 3002 people. This study showed a prevalence of COPD of only 2.06%, of chronic bronchitis – 10.06% and obstructive lung disorders of 9.99%. While interpreting these figures, we should take into account the differences between the definition of the disease in 1996 and now.

In 1998, another study showed a prevalence of COPD of 2.3% in women and 4.6% in men. The increase of prevalence from the previous study probably reflects the improvement of diagnosis (22). The mortality due to COPD is four times bigger in men than women.

A study published in 2011 (23) on 1214 subjects has revealed a number of 560 of “potentially ill” patients. These patients are frequently men, living in an urban environment, with a high degree of education. A remarkable finding is that 34.29% of them are never-

smokers. Data regarding smoking status from this clinical trial shows higher figures than those offered by public institutions – 44.1% of the male subjects and 22.6% of the female subjects were smokers. The prevalence of chronic bronchitis was 8.15%, higher than the European average reported by Halbert's meta-analysis (24) of 6.4%.

An analysis made in 2004 showed that COPD is the second most expensive disease caused by smoking, after the cerebrovascular diseases (25). Most of the costs are related to COPD exacerbations which lead to hospitalization. The average length of hospitalization in Romania is 17 days, higher than that observed in countries like the US(6days) or Spain(11 days), with patients hospitalized in disease stages I and II when, theoretically, the disease should be managed in out-patient settings. The average cost of a hospitalization is 700 euros, below other European figures.

## II PERSONAL CONTRIBUTION

### 4. Study rationale

Blaming only smoking for the development of COPD may overlook important data about the disease that may be observed when looking at patients that have never smoked. The analysis of other risk factors than smoking, in its absence, may lead to the discovery of novel ways of epidemiological or therapeutic intervention.

The main objective of this study is to determine the clinical and epidemiological differences between COPD patients that are currently non-smokers but have a smoking history in the past and those that have never smoked. The secondary objective of the study is to evaluate the impact of the bronchodilator therapy on the evolution of disease for the period of observation.

### 5. Materials and methods

I have chosen to conduct an prospective, observational study, with a 6 month duration, on non-smokers with COPD that have been seen by a pulmonologist in the Pulmonology Outpatient in Ramnicu Valcea, between 2007-2010. Patients with a COPD diagnosis were included and a post-bronchodilation spirometry was done to confirm the diagnosis and ensure a baseline of the lung function. A CAT questionnaire was administered and the patients were called for subsequent visits after 3 and 6 months. At the 6 months visit, another spirometry was performed and the CAT questionnaire was administered again to determine the evolution of the disease in this period.

The patients that were included in the study were stratified by their smoking status in 2 groups – one of never smokers, composed of 169 patients, and one of former smokers, with a history of at least 100 cigarettes that had quit smoking at least 6 months before the first visit.

## 6. Results and discussions

The median age of the 398 patients was 67, with a standard deviation of 9.032 years. The oldest patient included was 88 years old. The average age of non-smokers was 69 while that of ex-smokers was 65.84.

A vast predominance of the male patient was observed. 274 of all patients, representing 68.8%, were male. 27.9% of former smokers are female (n=64) while 35.5% of never-smokers were women.

Most studied patients lived in rural areas – 62.1% (n=105) of never-smokers and 59.8% (n=137) of former smokers.

The sex ratio favors male patients. In the former smoker subgroup we observed a male to female ratio of 2.3:1 in rural settings and 3.1:1 in urban settings. The difference was smaller in the never smokers group: 1.7:1 for men living in urban areas and 1.9:1 for men living in rural areas.

The educational level of the subjects was rather low, with only 7% (n=28) went through college while almost half – 49.2% (n=196) – had only primary school. This is concordance with data observed throughout the world.

Comorbidities have been reported for 53% of the ex-smokers, and are mostly cardiovascular diseases (32.3% of the patients). Never smokers had co-morbidities in 63.9% of the cases, with the cardiovascular system being affected in 50.9% of patients.

Most cases were diagnosed in GOLD stages II (44%) and III (36%). Even though a relatively small percentage of the patients had very severe disease – 7% of patients were in stage IV – we should not be very optimistic because the number of patients diagnosed in the early stage of the disease is also small – 13% diagnosed in stage I.

Occupational exposure to respiratory irritants was found in both subgroups in equal percentages – 60%, representing 101 never-smokers and 137 ex-smokers. For the never-smokers, occupational exposure was associated with more severe disease. 14% of the never-smokers with occupational exposure had stage IV disease.

Never-smoker women had more frequent exposure to biomass smoke than ex-smokers – 38.2% (n=44) vs 30.9% (n=48). About 25% of the women studied and 35% of the men had central heating and no exposure to biomass smoke.

Regarding median FEV1 values, we observed a higher value in women – of 55.36% of predicted values by NHANES III formulae – than in men – median value of 51.9% of predicted. Men are diagnosed with smaller values of FEV1 than women. Also,

never smokers are diagnosed at a value of the FEV1 that's 7% smaller than that of former smokers.

At the 6 months visit, an improvement of the lung function was seen in all patients enrolled in the study. The improvement ranged from 6.82% for ex-smoker women in urban areas to 10.42% in former smokers in rural areas.

The median value of the CAT score at the time of the diagnosis was 17.21 points for never-smokers and 15.03 points for former smokers. Women have a smaller value of the CAT score, of about 14 points, regardless of their smoking status. Men have a higher CAT score value if they have never smoked – 18.63 points – than those that have previously smoked – 16.2 points.

Most of the patients were treated with a combination of inhaled long acting beta-agonist(LABA) and corticosteroid(ICS) in the highest dosage available (54%). Another 16% were on the same kind of treatment, but on medium dosage of inhaled corticosteroid. 19% of the patients had an antimuscarinic agent added to the LABA+ICS combination. Only 11% of the patients were receiving only antimuscarinic agents as treatment.

## 7. Conclusions

- Valcea county is a good choice for the analysis of the epidemiology of COPD in non-smokers, due to its geographic, demographic social and occupational heterogeneity. Results obtained here can easily be extrapolated to the entire country.
- Because the median age of never-smokers was larger than that of former smokers, we can say that the disease may develop later if the patient does not have a smoking history.
- Unlike ex-smokers, never smokers are older when they live in a rural area. Smoking on the other hand seems to level the ages of people with COPD, regardless of their living environment.
- Sex ratio clearly favors the male sex, both for never smokers and ex-smokers. However, if we eliminate smoking from the equation, we might see an equalizing of tis ratio.
- 62% of the never-smokers and 59.8% of the former smokers lived in rural areas, percentages that are above the regions average of 55% rural population. Only 23.9%of the women lived in urban environments. Access to healthcare in rural areas is usually worse than in the urban ones.
- Heating and cooking with biomass products was found in 68% of the never smokers and 67.6% of the former smokers. Although conditions for exposure to biomass smoke may be found in most of the patients, exposure levels are hard to describe.

- Women have a greater risk of exposure to biomass smoke than men, regardless of their smoking status. The risk is higher for those that have never smoked.
- The educational level of the studied patients was low. This may be a very accurate indicator of their low social and economic status.

#### 8. Recommendations

Amongst physicians, especially those treating diseases that may be related to the lung, the existence of COPD must be underlined. They should see it as a disease that is easy to diagnose and has efficient treatment.

The lack of a relevant smoking history usually leads the diagnosis, wrongfully, to other diseases with similar symptoms, such as asthma. Even diagnostic procedures, when not coupled with a high suspicion degree, may lead to the same erroneous direction. A wrong diagnosis may lead to a wrong therapeutic strategy, thus decreasing its efficacy and the patient's quality of life. This is why I consider necessary to increase the awareness for COPD in the never-smoker.

In this study I have described the demographic profile of the non-smokers with COPD in a small, controlled, area. This profile may be used in future screening campaigns.

The cultural differences between peoples may lead to decreased efficacy of quality of life questionnaires. This is why I consider that a questionnaire designed after psychometric principles tailored to suit the Romanian people may be better than the global approach of questionnaires created in foreign countries.

Inhaler drugs for COPD are usually expensive. When we see that the patients that have the disease also have a low socio-economic status, we can assume that many patients simply cannot afford the therapy. This leads to a worsening of the disease, with an increase in disability adjusted life years and frequent hospitalizations. These in turn lead to a dramatic increase in the costs of the disease. This is why I consider that setting lower, affordable prices for the patients that need them may lead to a reduction of the costs of the disease in the long term, even though the costs may rise in the short term.

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