

# Association between Risk Factors and the Existence of Lung Malignancies in a Population from the South-West Romania: A Single-Center Study

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**ABSTRACT:** Introduction: Lung cancer, one of the most prominent malignancies of today worldwide, affects mainly men; however, recently women have also been increasingly afflicted by the disease. Our aim was to retrospectively analyze a series of potential risk factors for the disease and their potential to affect both genders. Methods: Our retrospective study relied on anonymized data collected between 2017 and 2020 at a single hospital specialized on lung diseases. After receiving ethical clearance, data pertaining to risk factors as well as statistical aspects of the lot were recorded and analyzed. Results: We found 493 patients (398 men) aged between 31 and 90 years (median 67) who were found with lung tumors and selected a matched cohort of patients with other diseases. We found positive associations between the presence of smoking, COPD, or pollution and the occurrence of lung cancer. Almost all lung cancer patients presented different significant associated diseases. Family history also favored the appearance of lung cancer. Conclusion: Several risk factors remain high in lung tumor patients, and rapid measures to diminish the impact of such factors are needed in order to decrease the overall incidence of this pathology.

**KEYWORDS:** Lung cancer, risk factors, smoking, air pollution, COPD

## Introduction

Lung cancer is still one of the most common malignancies today, not only in Romania but also worldwide, being the leading cause of death in both sexes combined [1-5].

The epidemiology of lung cancer is varied, reaching threatening proportions in recent decades.

Multiple pieces of evidence from various sources have shown that the main risk factor involved in lung carcinogenesis is smoking.

The risk of lung cancer is correlated with the number of cigarettes smoked in a day but also with the accumulated duration of smoking time (packs per day×years of smoking).

Patients with a smoking history of at least 20 to 30 years (1 pack per day for 20-30 years) have a substantially increased risk of developing lung cancer [1].

Other forms of smoking, including the use of shisha and cigars, are also linked to an increased risk of cancer [6,7].

Other risk factors, such as inadequate nutrition, exposure to toxins and chemicals, air pollution, genetic factors, may act independently

or in association with tobacco smoking in the epidemiology of this disease [8-12].

Lung cancer is on the rise largely due to modern habits but also the association with an unhealthy lifestyle, which is becoming more common nowadays.

Although these factors have been identified with a major risk of developing lung cancer, the significance of each seems to vary depending on gender, country or region in a particular country.

Increased air pollution and smoking have been linked to a high incidence of lung cancer mortality.

The main source of indoor air pollution is cooking smoke. Numerous studies have shown the contribution of indoor air pollution, exposure at work (bakeries, metallurgical factories, mines, halls for car construction, sawdust exposure, production of artificial goods, etc.) but also the importance of smoking as major risk factors for the incidence of lung cancer [13].

There are also predisposing factors that either belong to the individual, the genetic predisposition, or acquired through the professional sphere. All factors contribute in general etiological context, which also explains the particularity of the pathology: rapid or

slower evolution, a preferential affectation of a certain territory or resistance to disease, the severity of the disease or the post-therapeutic response. Some eating habits, alcoholism, smoking, low level of education and personal hygiene, associated with other occupational factors, over time will lead to the onset of the disease.

A multitude of other associated diseases (liver, kidney, neuropsychiatric, pulmonary diseases) are conditions that will favor the onset of the disease and they can exacerbate under the influence of occupational diseases.

It is important to know and to be aware of the many risk factors involved in the occurrence of malignant transformation of lung tissue and cancer, because it is the main way in which people can consistently help prevent lung cancer.

Many factors are considered to be important in the occurrence of lung cancer, such as tobacco smoking, passive smoking, occupational exposure, air pollution, indoor pollution, radiation exposure, asbestos, hereditary history, radon, personal history of lung disease, arsenic in drinking water, genetic mutations, but also others with high potential such poor diet in vegetables and fruits, weakened immune system, sedentary lifestyle.

## Material and Methods

We performed a retrospective statistical study of diagnoses on patients who were diagnosed with lung cancer, in the Clinical Hospital for Infectious Diseases and Pneumophthisiology, "Victor Babes", in Craiova, examined between January 2017 and October 2020.

The study was approved by the Ethics Commission of the University of Medicine and Pharmacy of Craiova (42/17 June 2020) and the Ethics Commission of the Clinical Hospital of Infectious Diseases and Pneumophthisiology, "Victor Babes", from Craiova (approval no. 3381/15 March 2021).

The diagnostic codes that we extracted from the medical records were C34.1 (malignant tumor of the upper lobe, bronchi and lungs), C34.2 (malignant tumor of the middle lobe, bronchi and lung tumor), C34.3 (malignant neoplasm of the lower lobe, bronchus or lung), C34.8 (malignant tumor that exceeds the bronchi and lungs), D14.3 (benign tumor located in the bronchi and lungs) D14.4 (benign tumor in the respiratory system, without specifying the location). A matched group of patients with non-

malignant pathology was selected for odds ratio calculations.

The following aspects were registered: age of patients, distribution by gender, environment, risk factors involved in the occurrence of lung cancer and their frequency (especially smoking, the presence or absence of toxic factors at work, air pollution, radiation exposure, asbestos), personal pathological history, but also genetic susceptibility (family history).

In addition, we performed a search for the diagnoses listed above (C34.1, C34.2, C34.3, C34.8, D14.3 and D14.4) in association with Z72.0 (tobacco use, currently).

Anonymized data was stored in Excel (Microsoft Corp, USA) software and processed on-site. Odds ratio was calculated using the statistical package provided by the same software.

## Results

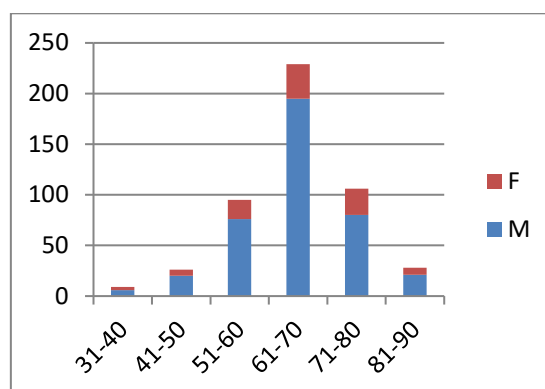
We found 493 patients, (398 men and 95 women) aged between 31 and 90 years.

In women, the minimum age was 34 years and maximum 88 years with a median of 67 years, and men-31 years, 90 years and respectively a median of 65 years.

The distribution of age according to sex is highlighted in Table 1 and Figure 1.

**Table 1. Age distribution according to gender.**

	MEN	WOMEN
<b>Number of patients</b>	<b>398</b>	<b>95</b>
<b>Minimum age</b>	<b>31</b>	<b>34</b>
<b>Median age</b>	<b>65</b>	<b>67</b>
<b>Maximum age</b>	<b>90</b>	<b>88</b>

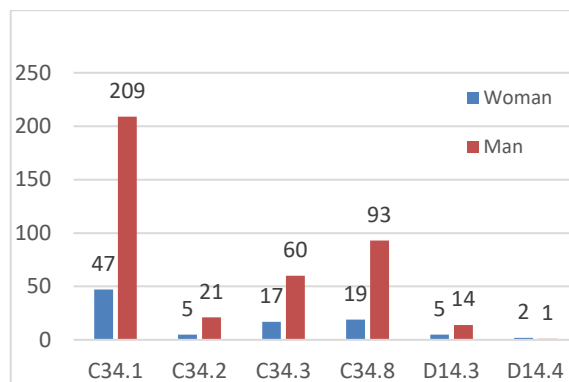


**Figure 1. Age histogram for males and females, composite view.**

The gender distribution associated with the diagnostic codes for lung cancer is shown in Table 2 and Figure 2.

**Table 2. Distribution of diagnostic codes according to gender.**

	WOMEN		MEN		Total	
	N	%	N	%	N	% of total
<b>C34.1</b>	<b>47</b>	<b>18%</b>	<b>209</b>	<b>82%</b>	<b>256</b>	<b>52%</b>
<b>C34.2</b>	<b>5</b>	<b>19%</b>	<b>21</b>	<b>81%</b>	<b>26</b>	<b>5%</b>
<b>C34.3</b>	<b>17</b>	<b>22%</b>	<b>60</b>	<b>78%</b>	<b>77</b>	<b>16%</b>
<b>C34.8</b>	<b>19</b>	<b>17%</b>	<b>93</b>	<b>83%</b>	<b>112</b>	<b>23%</b>
<b>D14.3</b>	<b>5</b>	<b>26%</b>	<b>14</b>	<b>74%</b>	<b>19</b>	<b>4%</b>
<b>D14.4</b>	<b>2</b>	<b>67%</b>	<b>1</b>	<b>33%</b>	<b>3</b>	<b>1%</b>
<b>Total</b>	<b>95</b>	<b>19%</b>	<b>398</b>	<b>81%</b>	<b>493</b>	<b>100%</b>



**Figure 2. Gender distribution per diagnostic.**

The association of lung cancer codes with tobacco use codes (Z72.0) is shown in Table 3.

**Table 3. Association of all diagnostic codes with tobacco use.**

	WOMEN		MEN		Total	
	N	%	N	%	N	% from total
<b>C34.1+Z72.0</b>	<b>8</b>	<b>13%</b>	<b>56</b>	<b>88%</b>	<b>64</b>	<b>66%</b>
<b>C34.2+Z72.0</b>	<b>0</b>	<b>0%</b>	<b>3</b>	<b>100%</b>	<b>3</b>	<b>3%</b>
<b>C34.3+Z72.0</b>	<b>3</b>	<b>23%</b>	<b>10</b>	<b>77%</b>	<b>13</b>	<b>13%</b>
<b>C34.8+Z72.0</b>	<b>0</b>	<b>0%</b>	<b>11</b>	<b>100%</b>	<b>11</b>	<b>11%</b>
<b>D14.3+Z72.0</b>	<b>1</b>	<b>17%</b>	<b>5</b>	<b>83%</b>	<b>6</b>	<b>6%</b>
<b>Total</b>	<b>12</b>	<b>12%</b>	<b>84</b>	<b>88%</b>	<b>97</b>	<b>100%</b>

At the time of examination, among patients with lung cancer, 97 (19.67%) were active smokers, claiming that they smoked between 10-30 cigarettes/day, for a period between 10 and 50 years, while 73 were former smokers, which means that we have a total of 170 (34.48%) patients who smoked at some point in their lives

Of the above, 48 patients came from urban areas and 49 from rural areas (Tables 4 and 5).

**Table 4. Active smokers classified by source of environment.**

+ Z72.0	WOMEN	MEN	TOTAL
<b>URBAN AREA</b>	<b>9</b>	<b>40</b>	<b>48</b>
<b>RURAL AREA</b>	<b>3</b>	<b>45</b>	<b>49</b>
<b>TOTAL</b>	<b>12</b>	<b>85</b>	<b>97</b>

**Table 5. The distribution of patients by source of environment.**

	MEN	WOMEN	TOTAL
<b>Urban areas</b>	<b>168</b>	<b>53</b>	<b>221</b>
<b>Rural areas</b>	<b>230</b>	<b>42</b>	<b>272</b>

In our study, the number of smokers with lung cancer was distributed almost evenly depending on the environment.

There have been a number of confirmed cases of lung cancer that have also been linked to occupational exposure (9.5%), 4.66% were exposed to air pollution and 2 of them were exposed to asbestos.

This exposure to environmental hazards is usually associated with cigarette smoking and alcohol consumption.

Family history also favored the appearance of lung cancer, thus highlighting the susceptibility and importance of genetics.

We found these in a percentage of 2.65%, and in a number of 5 patients, the inheritance came from the father, and in 8 patients, from the mother.

Almost all lung cancer patients presented different significant associated diseases.

Generally, the associated diseases were from the lung area (pneumonia, pleurisy, COPD, pulmonary tuberculosis, pulmonary fibrosis), followed by cardiovascular disorders.

The most common comorbidities were: cardiovascular disorder (275 cases, 33.87%), pneumonia (136 cases, 16.75% of total), secondary anemia (110 cases, 13.55% of total) and COPD that we encountered in 58 cases (7.14% of total).

Of these, 7.64% had associated metastases (Table 6).

**Table 6. The distribution of current comorbidities and personal pathological antecedents distributed by gender.**

	MEN		WOMEN		TOTAL	
	N	%	N	%	N	% of total
Metastases	46	74.19%	16	25.81%	62	7.64%
Pleurisy	26	81.25%	6	18.75%	32	3.94%
Hemoptysis	22	88.00%	3	12.00%	25	3.08%
COPD	55	94.83%	3	5.17%	58	7.14%
Tuberculosis	12	80.00%	3	20.00%	15	1.85%
Cardiovascular disorder	217	78.91%	58	21.09%	275	33.87%
Pneumonia	110	80.88%	26	19.12%	136	16.75%
Diabetes	34	75.56%	11	24.44%	45	5.54%
Secondary anemia	92	83.64%	18	16.36%	110	13.55%
Pulmonary fibrosis	39	72.22%	15	27.78%	54	6.65%
All complications	653	80.42%	159	19.58%	812	100%

A matched retrospective cohort of 493 patients, in both gender and age distribution, was selected in order to study the impact of known risk factors on the risk of malignancy.

We found positive association between the presence of certain risk factors and the occurrence of lung cancer (smoking, COPD, or pollution). Odds ratio were 1.15, 1.65 and 1.23 (Table 7). Out of the 493 patients with lung cancer, 170 were active smokers or former smokers, and 323 were non-smokers.

After comparing the data with the control group, a 1.076 relative risk was recorded, with a positive association between the risk factor and the occurrence of cancer (odd ratio 1.15).

The same analysis was performed for COPD, which showed a 1.45 relative risk and odd ratio 1.66 and pollution (relative risk 1.09 and odd ratio 1.23). Synthetic data is presented in Tables 7, 8 and 9

**Table 7. Odds ratio for smoking and the risk of existing lung malignancy.**

Smoking	Affected	Not affected	Incidence	Relative Risk		Odds Ratio	
Smokers	170	158	0.518	1.076	positive association	0.526	1.159
Non-smokers	323	348	0.481			0.454	

**Table 8. Odds ratio for COPD and the risk of existing lung malignancy in smokers, non-smokers and the entire lot.**

COPD	Affected	Not affected	Incidence	Relative Risk		Odds Ratio	
Smokers	38	86	0.306	1.455	positive association	1.9	1.656
Non-smokers	20	75	0.210			1.146	

**Table 9. Odds ratio for pollution and the risk of existing lung malignancy analyzed by smoking and in the entire lot.**

Pollution	Affected	Not affected	Incidence	Relative Risk		Odds Ratio	
Smokers	20	13	0.606	1.09	positive association	1.333	1.230
Non-smokers	15	12	0.555			1.083	

and in men-31 years, 90 years and respectively a median of 65 years.

The development of lung cancer is associated with old age due to DNA damage that occurs over time and telomere shortening. According to studies conducted so far, the median age of diagnosis of lung cancer is 70 years (for both sexes) [14].

## Discussions

### Age

We found 493 patients, (398 men and 95 women) aged between 31 and 90 years. In women, the minimum age was 34 years and maximum 88 years with a median of 67 years,

About 53% of cases occur in patients aged 55 to 74 years and about 37% are over 75 years [14,15].

Lung cancer has become the leading cause of death in men over the age of 40 and in women over the age of 59 [15].

However, about 10% of cases occur in patients under young age, under 55 years [15].

Young patients have less comorbidities and genetic factors are likely to be a defining factor in the occurrence of cancer in this category of patients.

Our study group presented ages between 31 and 90 years. The average age for women it was 65 years, and for men also 65 years. The average age for the two cumulated categories was 65 years old.

### **Gender**

Statistically, men smoke more tobacco than women and are more likely to develop lung cancer. In recent years, lung cancer is common among women, probably caused by increased tobacco use among them [15].

The data, which can be found in the literature, were also consistent with our results.

There are conflicting data on the possibility of women's susceptibility to lung cancer [16].

There is a higher rate of lung cancer in non-smokers compared to non-smokers [17].

### **Socio-Economic Environment**

There are studies that have shown a correlation between poor socioeconomic status and an increased incidence of lung cancer, associated with other environmental factors, including living environment and occupational exposures [18].

In our study, the higher incidence of this disease was found mainly in rural areas.

Between 2013-2014, a study conducted on the American population shows that the prevalence of exposure to secondhand smoke has been increasing in those with poor living conditions [19,20].

### **Smoking**

The association between smoking and cancer has been intensively studied over the years, providing important evidence to support this relationship [21,22].

It has been shown that the risk increases significantly in those who smoke more than 20 cigarettes a day. The risk of lung cancer is 4.55 times higher in people who smoke more than 15 years and more than 20 cigarettes a day, compared to those who smoke less than 15 years and less than 20 cigarettes a day.

The risk of developing and dying of lung cancer is up to 50 times higher in smokers, compared to non-smokers [23].

Other forms of smoking, including the use of shisha and cigars, are also linked to an increased risk of cancer [24].

The time of smoking should, however, be considered the strongest determining factor in the risk of lung cancer [43].

Former smokers, the sooner they quit smoking, either did not develop the disease or later developed in association with other factors, so they had a higher survival rate [25].

The risk of lung cancer in non-smokers is not fully understood, but the known risks include: secondhand smoke, sex; women are more likely to develop cancer than men without a clear explanation at the moment [25].

Interestingly, most lung cancers found in non-smokers were in women; 10% of men and 20% of women with lung cancer are non-smokers [26].

Secondary smoke contains more than 7,000 chemicals, hundreds of which are toxic and many of which are carcinogenic (70 known carcinogens) [19, 27-29].

Regarding the number of cigarettes smoked per day, both men and women smoked on average around 10-30 cigarettes/day, respectively 10-30 packs/year, for a duration between 10-50 years. Alcohol may also increase the risk of developing the disease [30].

### **Genetics**

Several arguments also suggest the importance of a genetic component:

- increased risk of cancer in relatives of people with lung cancer
- familial predisposition to respiratory tract diseases in smokers and high risk of developing neoplasm [31-33].

Studies have shown that tumor cells have numerous genetic lesions, including activation of dominant oncogenes and inactivation of recessive suppressor genes [31].

Genetic susceptibility may be the most important element for the carcinogenic impact of these risk factors, but it is difficult to define precisely.

About 8% of lung cancer is caused by inherited factors [31].

In relatives of people with lung cancer, the risk is doubled, probably due to gene combinations [32].

The sensitivity and risk of lung cancer has increased in inherited cancer syndromes, being

caused by mutations in the p53 gene line and epidermal growth factor receptor-EGFR [33].

Family aggregation is well documented for multiple cancers, and various studies [34,35] have confirmed an increased incidence of familial lung cancer. It has been shown that people with a family history of lung cancer have a 2 to 3 times higher risk of developing this disease compared to the general population, even after quitting smoking.

Among our patients 13 had first-degree relatives in the family with lung cancer. They were all current smokers or had smoked for a period of time in their lives.

### **Environmental Risk Factors**

Certain occupations (working in bakeries, metallurgical factories, mines) or exposures to substances such as asbestos, uranium, nickel, vinyl chloride, increase the risk of developing lung cancer. High-dose ionizing radiation is carcinogenic [32].

The listed risk factors are found in some of the patients included in the study.

A number of 69 patients confirmed exposure to occupational chemicals and toxins.

Work environments with occupational pollutants, outdoor pollutants or even indoor pollutants are known risk factors for lung cancer, especially among women, who are more prone by the increased time they spend on household chores. These include burning coal in poorly ventilated homes, burning wood and other solid fuels, as well as fumes from cooking at high temperatures using vegetable oils.

The development and appearance of lung cancer is the result of the interaction of a multitude of factors, where smoking has the highest percentage (85-90%). Exposure to industrial carcinogens also adds about ~ 5%.

In multiple epidemiological studies, other occupational hazards have been identified after the role of tobacco was excluded: chromium, arsenic, formaldehyde, etc [36].

The incidence of lung cancer is increased in association with carcinogens in the workplace [36].

Exposure to asbestos increases the risk of developing lung cancer. The latent period before the development of lung cancer is 10-30 years. It is responsible for the onset of pleural mesothelioma [36].

Lung cancer is the most common malignancy in people exposed to asbestos, especially when combined with smoking. Tobacco smoking and asbestos have a synergistic effect on the constitution of lung cancer [38].

Quitting smoking can lead to a gradual reduction in the risk of lung cancer, [1] but may never return to baseline levels [1,37,39,40].

In our group were 2 patients exposed to asbestos in their youth.

With the exception of smoking, there is also what is called "inhalation carcinogenesis", given by the smoke resulting from the combustion of fuel, exhaust fumes [36].

Other risk factors are taken into account less often (coal, insecticide and pesticide substances, fiberglass, some drugs, anthracene, beryllium, aluminum, copper, iron, lead, etc.). Their effect is associated with smoking [36].

### **History of Lung Disease**

Patients with chronic obstructive pulmonary disease have a higher risk of lung cancer [41-43].

It has also been found that patients with a history of pulmonary tuberculosis have an increased risk for lung cancer [44].

In a study involving a large cohort of tuberculosis patients in population of Shanghai, China [45], it was shown that the relative risk of lung cancer in patients with a history of tuberculosis was 1.5 and as after 20 years after the diagnosis of tuberculosis, the risk was 2.0.

It is not clear whether the increased risk is given by chronic inflammation of the lung parenchyma or the action of the bacillus *Mycobacterium tuberculosis*.

In our study were 15 who had concomitant active tuberculosis, being under antibacterial treatment, but there were also patients (6%) who had pulmonary fibrosis, mostly acquired by a history of TB.

### **COPD and Lung Cancer**

Smoking, through its harmful effects, leads to the development of major health problems worldwide, with the appearance of various lung diseases such as COPD and lung cancer. A large number of lung cancer patients also have COPD or vice versa [46].

In a small case-control study [46], Papi A et al showed that airflow obstruction is a risk factor for squamous cell lung cancer, and the symptoms of chronic bronchitis without the presence of COPD is a risk factor (4 times higher) for pulmonary adenocarcinoma.

Another study [47], managed by De Torres JP, showed that the risk of lung cancer was more strongly associated with emphysema diagnosed on computer tomography than with airway obstruction diagnosed by spirometry. This

finding was also confirmed by a US cohort study [48].

COPD is characterized by irreversible airflow obstruction, but is also recognized as a systemic inflammatory imbalance, with numerous pulmonary and extrapulmonary manifestations, including an increased risk of developing lung cancers [49].

Compared to people with normal lung function, lung cancer has a risk of up to five times higher in smokers with obstructed airflow obstruction [50].

A major medical challenge that deserves special attention is the increased incidence of these two diseases, as there is much evidence to indicate a link between them. The role of smoke exposure in the development of many chronic lung diseases and lung cancer has been highlighted over time in numerous studies and reports that have underlined the health consequences of smoking [51].

The overall 5-year survival rates of COPD-lung cancers associated were significantly lower than those of lung cancers without the presence of COPD [48,52,53].

Chronic inflammation of the airway obstruction plays a significant role in the occurrence of lung cancer. It has been suggested in some studies that chronic inflammation of the lower respiratory tract can induce carcinogenesis and that inflammatory mediators promote the production of preneoplastic mutations, resistance to apoptosis, cell proliferation, invasion, metastasis [54-60].

Many people with COPD do not realize that they have an increased risk for developing lung cancer.

A study of 40 people with COPD in 2019 [61] found that a large proportion of patients were unaware that their disease could lead to cancer over time. Although many had changes in symptoms, they associated this with their underlying disease, COPD, rather than thinking about a cancer screening. The symptoms of obstructive pulmonary disease can mask the appearance of lung cancer, so it is much more difficult to get an early diagnosis.

We found that 7.14 % of comorbidities were COPD (58 patients-94.8% women and 5.2% men).

Patients with lung cancer and COPD have a worse prognosis than patients without the association of these two conditions [62-65].

## Conclusions

We performed a three-year retrospective study of 493 patients with lung cancer from a known hospital from Romania.

We found more male patients, aged between 31 and 90 years, with several associated conditions.

These associations were the risk factors that could lead to the development of lung cancer.

Prevention is essential and education in schools is vital, this being the critical period in which smoking addiction occurs.

Despite the progress made in recent decades in identifying the mechanisms of carcinogenesis and diagnostic imaging, the cure rate for lung cancer is still low.

## Acknowledgements

Andreea-Georgiana Gheorghe is a PhD student of the University of Medicine and Pharmacy of Craiova Doctoral School and this research is part of her dissertation thesis.

## Conflicts of interest

The authors declare no conflicts of interests.

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