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PULMONARY CANCER AMONG NON SMOKERS - RISK FACTORS

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Abstract: *Lung cancer remains the largest cause of cancer deaths worldwide and the overall 5-yr survival rate is only 15%. Approximately 85%–90% of all lung cancer deaths in the United States are caused by active cigarette smoking. The complex plurifactorial determinism of lung cancer, the intertwining and mutual conditioning of the risk factors, acting either directly (carcinogenic) or indirectly as favouring the effect of the former (cocarcinogenic), demonstrates the need to know the causes and mechanisms of carcinogenesis. The detection and remediation of the factors leading to the malignant transformation of the healthy tissue is the main way to prevent lung cancer. With lung cancer persisting as the leading cause of cancer mortality' research into the epidemiology of lung cancer in never smokers should be an important public health priority*

Key words: *lung cancer, risk factor, nonsmoker.*

1. Introduction

Lung cancer is the major cancer killer worldwide, and 5-yr survival is extremely poor (≤15%), accentuating the need for more effective therapeutic strategies.

However, in the United States, lung cancer remains the leading cause of cancer death, killing more patients than breast, colon, and prostate cancers combined. [5]

Although cigarette smoking accounts for the great majority of lung cancer cases, there are many who smoke but who do not develop this disease. [12] Approximately 85%–90% of all lung cancer deaths in the United States are caused by active cigarette smoking. The remaining 10%–15% represent between 17000 and 26000 deaths annually, a number that would rank among the six to eight most common fatal cancers in the United States if considered as a separate category. [8] In recent years, it is increasingly recognized that factors not related to direct cigarette smoking, such as passive smoking, toxicity from vaporized cooking oil, indoor fossil fuel combustion, and so forth, might also contribute to lung cancer development, particularly in women. [11]

The incidence of lung cancer has steadily declined in men (2.4%/yr) and has reached a plateau in women. Despite this apparent improvement, it is estimated that 171,900 individuals received a diagnosis of lung cancer, resulting in 157,200 deaths in the United States in 2003. The vast majority of lung cancer cases are attributed to smoking. [9]

Information on lung cancer risk among lifelong non-smokers is needed to understand racial and sex disparities in incidence and mortality, to determine whether lung cancer occurrence has changed over time because of factors other

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than active smoking and to quantify the risks associated with smoking. Such information also helps to inform ongoing scientific debates, such as whether women are more susceptible to lung cancer than men in the presence or absence of current cigarette smoking and whether factors other than active smoking contribute to the disparity in lung cancer risk between African Americans and whites. [8] Several studies have suggested that chronic bronchitis and emphysema may increase the risk of lung cancer. Most of the lung cancer cases in published studies occurred in current or former cigarette smokers; thus, the observed associations may be biased by residual confounding from smoking. [12] The role of second-hand smoke has received considerable exploration, as have other environmental toxins and some genetic polymorphisms. A viral aetiology has even been proposed, with some literature supporting a potential role of human papillomavirus in lung cancer development, as well as pathologic similarities between bronchioloalveolar carcinoma and the retrovirus-induced ovine pulmonary adenocarcinoma. [5] Investigation of lung cancer and diet continues, using both observational and experimental approaches, and concern remains over the risk of indoor and outdoor pollutants, including, for example, radon and diesel emissions. [1] The cause of lung cancer in never-smokers remains controversial, but no conclusive cause for most cases has been identified.

2. Work hypothesis

The complex plurifactorial determinism of lung cancer, the intertwining and mutual conditioning of the risk factors, acting either directly (carcinogenic) or indirectly as favouring the effect of the former (co carcinogenic), demonstrates the need to know the causes and mechanisms of carcinogenesis. The detection and remediation of the factors leading to the malignant transformation of the healthy tissue is the main way to prevent lung cancer**.**

3. Material and methods

We carried out the statistical analysis of the results obtained by studying a group of 100 patients diagnosed with lung cancer, in the Clinic of Pneumology, Cluj-Napoca, between 1996-2000. The following aspects have been pursued: the age and the gender of the patients, the origin of the patients, risk factors for lung cancer - LC (non smoking).

In correlation with the histological type, their pathological personal history and heredo-colaterale antecedents with risk of developing lung cancer, aiming at the existence of a basis of genetic predisposition to cancer. The patients underwent the following investigations: clinical examination, complete blood and biochemical tests chest X-rays, EKG, abdominal ultrasound, hepatic scintigraphy, chest CT, fibrobronchoscopy with brushing, bronchial and transbronchial biopsies, chest ultrasounds. We analyzed patient age, place of origin, status time elapsed from the onset of symptoms to diagnosis, radiographic and CT finding, results of biopsy at fibrobronchoscopy.

4. Results

The relation between the gender patient and the apparition of pulmonary cancer: we observed the predominance of male 84%. Perrot found that women were more likely to be never-smokers compared to men (27% vs. 2%, $p < 0.001$), women had a superior survival (hazard ratio, 0.72; $p = 0.009$) independent of age, presence of symptoms, smoking habits, histology or stage of disease. [9]

Within countries, lung cancer incidence

among men invariably exceeds that in women, by well more than 100% in most nations. [1]

Lung cancer**,** like many other solid tumours, is a typical disease of the elderly patient. More than 50% of all patients with NSCLC are aged >65 yrs and about one-third of all patients are aged >70 yrs when the disease is diagnosed (ERS pre-operative evaluation).

Age average ranged between 36 – 79 years, with a peak of 36% for the 50-59age groups and 33% for the 60-69 age groups.

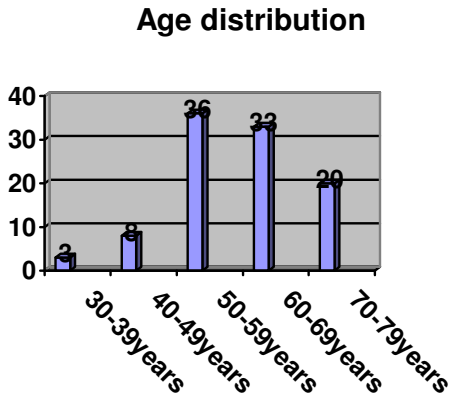

Fig. 1. *Age distribution*

A higher proportion of cases diagnosed with lung cancer is noted in the urban area (58%). Generally, lung cancer occurs more frequently in urban areas which are highly polluted with carcinogenic substances.

Regarding the relationship between pulmonary cancer and professional toxins we are able to say that industrial pollution plays an important role in the development of pulmonary carcinogenesis through chemical substances, toxic gases, imitative dust, radioactive substances and other oncogenic potential related toxins. Because, generally, these kinds of work places are taken by men, the share of pulmonary cancer due to work conditions is lower in women than in men.

Investigations of occupational groups, often heavily exposed over a long time to workplace agents, have provided substantial understanding of the carcinogenicity of a number of chemicals and physical agents. Lung cancer has been observed to be associated with many workplace exposures. [1, 3]

Occupation of our patients were in table 1.

Table 1

Profession	Patients	Percent
Worker, miner	8	8%
Intellectual	4	4%
Office worker	6	6%
Without occupation	11	11%
Retired	71	71%
Total case	100	100%

Lung cancer is more likely to occur in the poor and less educated a pattern that is observed in many countries worldwide. [1]

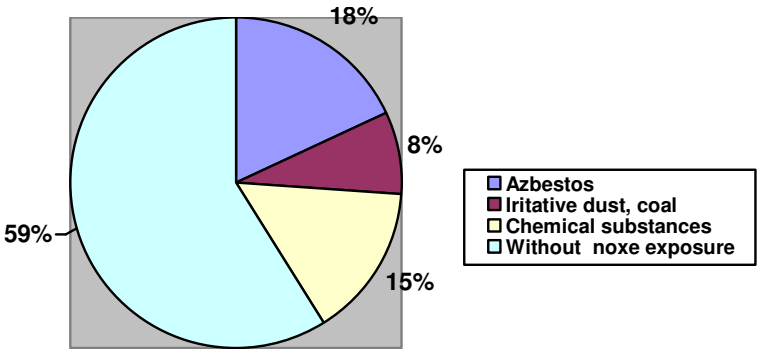

Fig. 2. *Noxious exposure*

Genetic susceptibility to lung cancer has long been postulated. There are much data showing a familial aggregation of cancers, including lung cancer. One of the first evidence of the presence of a genetic factor is the high frequency of cancer history in the family in 30-40% of the persons with lung cancer or other malignnancies, even if they are non-smokers. We noticed the association of multiple intrafamilial neoplasia in 17% of the cases. The risk factors for non-smokers are not fully understood, but known risks include: passive smoking, gender: according to Centres for Disease Control and Prevention, among non-smokers, women are more likely to develop cancer than men, with no definite explanation for the time being; diet: fats and alcohol abuse; radon: this colourless, odourless gas that enters the houses through the soil and it is the main cause of lung cancer among non-smokers, according to the Environmental Protection Agency. (4,6) Family history of other types of cancers suggests that there is a predisposition of developing cellular anomalies which have oncogenic potential (only 4% had lung cancer, the other had other malignancies).

The results of a linkage analysis based on 52 extended pedigrees indicated that a locus on chromosome 6q23–25 was associated with a major susceptibility to lung cancer. [1] Molecular epidemiology studies, in particular of the *TP53*, *KRAS* and *EGFR* genes, demonstrate strikingly different mutation patterns and frequencies between lung cancers in never-smokers and smokers [2].

The personal pathological antecedents were associated with risk for the development of lung cancer. We observed the association of pulmonary neoplasia with respiratory diseases in 26%.

COPD and lung cancer are both related to smoking and the incidence rate of lung cancer in smokers with COPD is two- to five-fold higher compared to smokers without COPD [10]. In our group we have 12% patients with COPD.

We observed the predominant symptoms were shortness of breath for 77 patients, cough in 56 cases, followed by weight loss 60cases, thoracic pain 49 cases, haemoptysis 28 patients, appetite loss 31 cases and other symptoms in smaller percentage (fever 23 patients, hoarseness 8 cases) and 2 cases without respiratory clinical symptoms.

There are a number of sources of delay in the referral process for a patient with lung cancer**,** and clinical guidelines have been developed to improve medical practice. Sources of delay include the patient, the family doctor and the referral specialist.

The time interval from the onset of symptoms to first reporting to a physician was a major prognostic factor reflected in the advanced stage of the disease at diagnosis.

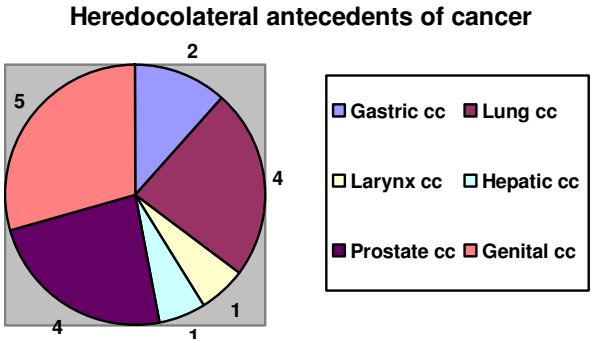

Fig 3. *The heredo-colaterale antecedents of lung cancer*

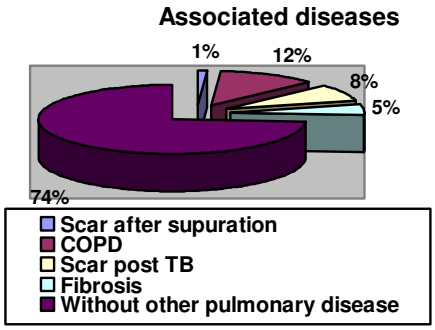

Fig. 4. *Associated diseases*

While many lung cancers are diagnosed on chest radiographs after the patient presents with symptoms, the standard poster anterior radiograph is of limited use for staging**.** The predominant forms of lung cancer were peripheral radiological (55%). Lung cancer consists of a number of histological subtypes that are preferentially located in different parts of the tracheobronchial tree *i.e.* Central bronchial cancers tend to be squamous or small cell carcinoma types and peripheral lung cancers tend to be adenocarcinoma and neuroendocrine cell types. Squamous cell carcinoma still accounts for 40–50% of lung cancers in males and 20–30% in females. [7] Although smoking-related carcinogens act on both proximal and distal airways, inducing all the major forms of lung cancer, cancers arising in never-smokers target the distal airways and favour ADC histology. [2]

In recent years, adenocarcinoma has replaced squamous cell carcinoma as the predominant histological subtype of lung cancer in the United States, a trend that may be due to the introduction of filter tip and lower tar and nicotine cigarettes. [1]

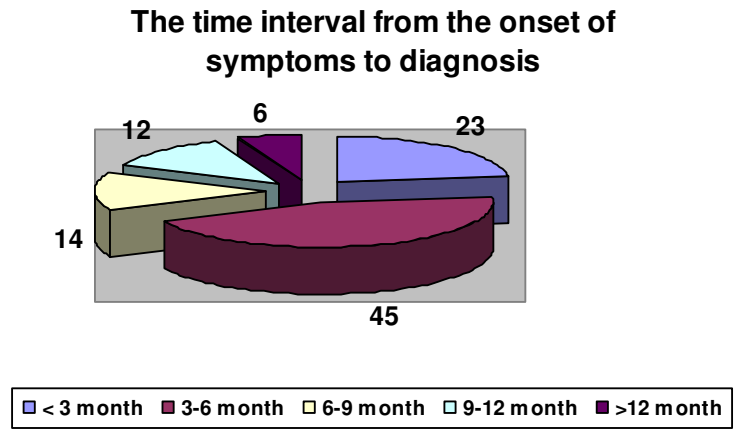

Fig. 5. *The time interval from the onset of symptoms to first reporting to a physician*

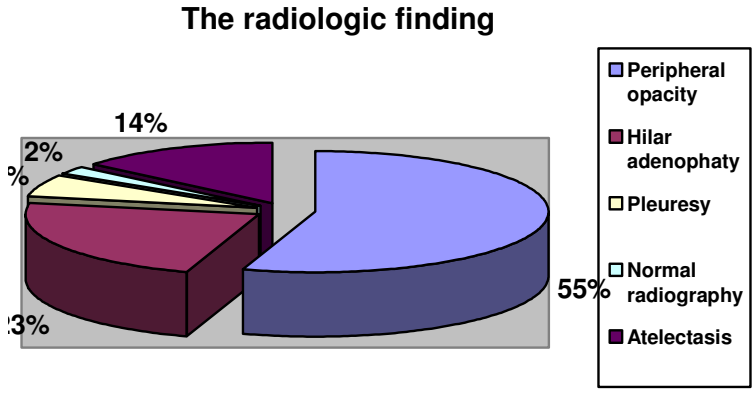

Fig. 6. *The Radiologic findings*

In general, lung cancer 5-yr-survival rates are <15%, because the disease is often diagnosed in an advanced stage. (7)

Stage of disease at presentation is one of the most important prognostic determinants in lung cancer. Most patients present with regional-stage or distant-stage disease for which long-term survival rates remain poor. [1] Our patients were early diagnosis only in small percent (12% stage I, 18% stage II). Stage IV (51%) and stage III (18%) represent the majority of patients. Metastases to the adrenal glands, liver, brain, bones, and lymph nodes may be present in patients with lung cancer at diagnosis. However, the decision to perform extra thoracic imaging to detect metastasis is not uniform. We have liver metastasis (34 cases), brain metastasis (6 patients), bones dissemination (9 cases), and skin metastases (3 patients).

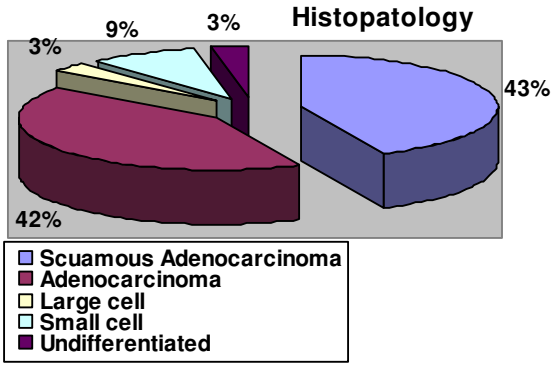

Fig. 7. *Histopathology*

In 10 cases patients had multiple metastases (16, 13%).

5. Conclusion

Despite the emergence of clinical and epidemiologic studies focused on identifying biologic and genetic differences between smoking- and non–smoking-associated lung cancers and risk factors for non–smoking-associated lung cancer, it remains uncertain whether the incidence of lung cancer in never smokers is increasing (25% of lung cancer cases worldwide are not attributable to tobacco smoking, resulting in lung cancer in never-smokers being the seventh leading cause of cancer deaths in the world).

Despite the fact that the first cause of lung cancer risk is, indeed, tobacco consumption, epidemiological studies have shown a 2.5-fold increased risk attributable to family history of lung cancer, implying a major susceptibility locus at 6q23–25. [2]

There are major clinical differences between lung cancers arising in never-smokers and smokers, and their response to targeted therapies. These facts strongly suggest that lung cancer arising in never-smokers is a disease distinct from the more common tobacco-related forms of lung cancer.

With lung cancer persisting as the leading cause of cancer mortality research into the epidemiology of lung cancer in never smokers should be an important public health priority.

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