Risk factors in the etiology of lung cancer

MONICA GORON*, MAN MILENA**, COSMINA BONDOR**OANA ARGHIR***
*Spitalul de pneumoftiziologie Baia Mare,**UMF Iuliu Hatieganu Cluj , ***UMF Constanta
Caraiman 3 Street Cluj Napoca
ROMANIA
manmilenaadina@yahoo.com

Abstract: - The complex plurifactorial determinism of lung cancer demonstrates the need to know the causes and mechanisms of carcinogenesis. We carried out the statistical analysis of 116 patients diagnosed with lung cancer, in the Clinic of Pneumology, Cluj-Napoca, between 1999-2005. We analyzed the age and the gender of the patients, the origin of the patients, risk factors for lung cancer - LC (especially smoking and toxic environment at work) in correlation with the histological type, their pathological personal history and heredocolateral antecedents with risk of developing lung cancer correlated with the histological type and patients’ characteristics, aiming at the existence of a basis of genetic predisposition to cancer in the patients taking part in the study Despite the progress recorded in translating the mechanisms of carcinogenesis and diagnostic imaging, lung cancer cure rates are still low. The key intervention in reducing LC is prophylaxis: quiting smoking

Key-Words: - lung cancer, etiology, risk factor, smoking

1 Introduction
The complex plurifactorial determinism of lung cancer, the intertwining and mutual conditioning of the risk factors, acting either directly (carcinogenic) or indirectly as favoring 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 This made our interest move towards the main objective of the study: the analysis of the results obtained by investigating risk factors and their relationship with lung cancer occurrence, the histological type.

2 Problem Formulation
We carried out the statistical analysis of the results obtained by studying a group of 116 patients diagnosed with lung cancer, in the Clinic of Pneumology, Cluj-Napoca, between 1999-2005. 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 (especially smoking and toxic environment at work) in correlation with the histological type, their pathological personal history and heredocolateral antecedents with risk of developing lung cancer correlated with the histological type and patients’ characteristics, aiming at the existence of a basis of genetic predisposition to cancer in the patients taking part in the study in both groups.

3 Problem Solution
63.36% of males with LC have smoked 20-40 cigarettes/day, regardless of their provenance: 60% smokers in rural areas and 65.15% smokers in urban areas. Among females, 33.33% have smoked 20-40 cigarettes/day, 33.33% in rural areas and 40% smoked in urban areas, irrespective of their provenance - the same as among males, 55.55% are nonsmokers, urban > rural. Also, overall, we found a much larger number of smokers who developed LC in urban areas than in rural areas. We noted most cases in great smokers 20-40 cigarettes/day, with the following distribution urban/rural = 45/22 = 2.04, as well as in those who smoked between 40-60 cigarettes/day with a double number of cases urban/rural and a
small number of smoker cases < 20 cigarettes/day, equally distributed in the urban/rural areas = 1, regardless of gender. The estimation of the correlation coefficient \( r = 0.0344 \), shows that there is no correlation between "number of packages/ years and tumor dimension".

A large percentage of cases, 15.51% were classified as being of undetermined histological type for different reasons: negative bronchial endoscopy for peripheral tumors, inconclusive bronchial biopsy, refusal to bronchial biopsy, contraindication to bronchial endoscopy due to associated diseases. We observed a broad distribution of the epidermoid carcinoma histological type 38.18%, followed by small cell carcinoma 17.27%, adenocarcinoma 10%, and large cell carcinoma 8.18%.5.45% combined carcinoma and 4.54% non small cell carcinoma. The estimation of the correlation coefficient \( r = 0.95 \), shows that there is a strong connection between "male and alcohol consumption and lung cancer occurrence". Moreover, \( r = 0.32 \) indicates that there is little correlation between alcohol consumption and lung cancer when it comes to females.

There have been 40 cases of confirmed LC when exposed to occupational noxa \((40/116)\), representing 34.48% of the cases, a large number being assigned to exposure to chemical agents 32.5%, followed by exposure to \( \text{Ni, Cr, Ti, Si, Cu, Pb, Au, Zn} \) 25%. The exposure to noxa usually comes together with smoking and alcohol total separation being impossible. We also noted a large number of cases arising in the context of exposure to sawdust 10% of cancer cases and exposure. Of the 97 smokers, 24 (24.74%) quit smoking for a longer period of time (between 1 month - 46 years).

The personal pathological antecedents with risk for the development of lung cancer and other associated diseases in correlation with the histological type and patients' characteristics. We observed the association of pulmonary neoplasia - epidermoid carcinoma in particular - with cardiovascular diseases 36.2%, respiratory diseases 31.03% and digestive diseases 29.31%, the connection being smoking and alcohol consumption in over 80%. Diabetes mellitus was observed in association with small cell carcinoma at a rate of 21.05% and in 6.034%. Moreover, the second neoplasia was associated in 3 cases (2.72%),

**Heredocolateral antecedents HA favouring lung cancer and other malignancies, aiming at the existence of a basis of genetic predisposition for cancer.**

The coexistence of heredocolateral antecedents of lung cancer was found in 10.9% of those with HA of lung cancer, followed by large cell carcinoma 25%, small cell carcinoma and undetermined carcinoma in equal proportions 16.66% In all cell types found in this combination in group I, there was a predominant paternal genetic heritage 41.66% The average age of the patients with this combination was 57.6 years old. **Other genetic susceptibility related to HCA of other neoplasia with different location than the lung, we have also found a predominance of the epidermoid carcinoma 40% \((4/10)\) in male smokers from the urban area 70% \((7/10)\), followed by small cell carcinoma 30% \((3/10)\), and in equal proportions non-small cell carcinoma, adenocarcinoma and carcinoma of undetermined origin 10% \((1/10)\). We noticed an associated multiple intrafamilial neoplasia in 40% of the cases. Predominant genetic heritage in this group also comes from the father in 50% \((5/10)\) of the cases, where multiple neoplasia coexist among close relatives brother/sister in 70% \((7/10)\) of the cases (average age was identical, 57.6 year)

**4 Discussion** The group analysis results in a correlation between "male and lung cancer occurrence" with no difference by gender according to age groups. The largest proportion of patients was around 50-70 years old \(\sim 66-70%\). Marius Nasta Institute study in Bucharest in 1999-2001 reveals the most affected age groups in smokers: 39% 65-74 years old and
26% 55-64 years old (1). General data of age groups show an increased risk of LC along with the age, reaching a variable maximum at the age of 65-74 years old (2). A higher proportion of cases diagnosed with lung cancer is noted in the urban area in both groups, both in women and men. Generally, LC occurs more frequently in urban areas which are highly polluted with cancerogenic substances (2).

Regarding the risk factors for lung cancer, the correlation coefficient between "male smoker and all patients in our group" is \( r = 0.99 \), showing that there is a strong correlation between male and smoker and cancer. Related to women, \( r = 0.69 \), showing that there is a relative correlation between smoking and cancer when it comes to women. The correlation coefficient \( r = 0.50 \) between "cancer occurrence and no smoking" is lower than the correlation coefficient between "smoking and cancer occurrence". Lung cancer is the first tobacco-related disease.

Simultaneously and later on, after many epidemiological surveys, particularly in the U.S. (Wynder and Graham), United Kingdom (Doll and Hill), but also in other northern and western European countries (Hammond and Horn), a direct dose-effect correlation could be established between the extent and intensity of smoking on one hand and the presence and growth of lung cancer on the other hand, showing that the risk of lung cancer is 30-60 times higher in smokers than in non-smokers, or 217/100,000 in smokers compared to 3.4/100,000 in non-smokers (2,3). Regarding the number of cigarettes smoked a day and the number of packs a year both women and men have mostly smoked around 20-40 cigarettes/day, respectively 20-40 packs/year.

The dopamine receptor polymorphism confers a different individual susceptibility regarding nicotine addiction. The fact that not all heavy smokers develop lung cancer led to the hypothesis of an interindividual variation on the metabolic pathways of carcinogens, resulting from a genetic polymorphism (4). As a result of recent years genetic studies, we could establish a direct connection between tobacco and LC (5). The distribution of the histopathological types of confirmed bronchopulmonary carcinomas was similar to that in the literature with regard to squamous cell carcinoma and small cell carcinoma, but with a lower percentage of adenocarcinomas in the studied group, which is likely due to subdiagnosis (2,6).

In a Finnish study on 440,000 people, of which 602 patients with lung cancer, this was histologically confirmed in 63% of the cases and, furthermore, cytologically in 23% and unconfirmed in 14% (7). The correlation coefficient \( r = 0.95 \), indicates that there is a strong connection between "male and alcohol consumption and lung cancer occurrence" and little correlation \( r = 0.32 \) for females. The risk factors for non-smokers are not fully understood, but the known risks include: fats and alcohol abuse. Alcohol abuse may increase the risk of disease development (8).

In terms of exposure to noxa, there were 36.36% of the cases of confirmed cancer, a large number being assigned to exposure to chemicals 32.5%, followed by exposure to Ni, Cr, Ti, Si, Cu, Pb, Au, Zn 25%. Epidemiological studies and experimental animal models have shown that hazardous emissions: asbestos, chromium, nickel, arsenic, iron oxide, polycyclic aromatic hydrocarbons, haloethers, are certified carcinogens conferring an increased risk of LC as ionizing radiation (2,3,5). When it comes to the carcinogenic risk assessment at the workplace, it is important to estimate and eventually exclude the role of smoking, which interacts with these factors. The incidence rate of LC is greatly increased with regard to the association of smoking with increased exposure to carcinogens at the workplace (3). Accidental or occupational exposure to radiation increases the risk of lung cancer both in smokers and non-smokers (4). The cumulative risk of lung cancer in smokers exposed to asbestos is up to 90 times higher than in the population which is not exposed to these two risk factors (2,3,4).

Smokers dominate all the histological types of cancer, with 92.85% of the cases of epidermoid carcinoma, 84.21% small cell carcinoma, and 100% large cell carcinoma. Researchers at Memorial Sloan Kettering Cancer Center in collaboration with Fred Hutchinson Cancer Research have developed and tested a risk assessment tool for smokers developing lung cancer in the following 10...
years based on the person’s age, sex, smoking history. Knowledge of risk may help clinicians and patients in making decisions on health such as participating in screening programs. Researchers have shown that among long-term smokers older than 50, the risk of developing lung cancer can vary. However, the risk of lung cancer for a person who has never smoked is typically lower than the lowest percentage calculated for this tool. Quitting smoking does not only reduce the risk of lung cancer, but also the risk of many other health problems related to smoking. This tool can assess: • age: 50-75 • smoking history: 10-60 cigarettes/day for 25-55 years old • current situation: current smoker, ex-smokers who quit smoking 20 years ago or a few years ago. (9,10) In what concerns ex-smokers who developed lung neoplasia, we saw that the earlier the patient quit smoking the later did he develop pulmonary neoplasia and survived longer. Those who abandoned smoking earlier (more than 30 years ago) developed neoplasia later and, in most cases, were simultaneously exposed to noxa and/or alcohol. In conclusion, those who have abandoned smoking a long time before the occurrence of neoplasia, have survived longer, living more than 70 years of age, and cancer has developed in conditions of exposure to other carcinogenic factors (2,3,4) The coexistence of heredocolateral lung cancer antecedents was found in 10.9% of the cases in our group, out of which 10% were associated with smoking as a risk factor, only one case (0.9%) had no other risk factor, a non-smoker woman. Given the genetic susceptibility correlated with the histopathological type, a predominance of the epidermoid type was found, 41.66% out of those with HCA of LC, followed by large cell carcinoma 25%, equal proportions of small cell carcinoma and carcinoma of undetermined origin 16.66% . 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 malignancies, even if they are non-smokers (3,4). We noticed the association of multiple intrafamilial neoplasia in 40% of the cases, all men, where smoking as a risk factor was associated with the genetic load. (11). The risk factors for non-smokers are not fully understood, but known risks include(4): passive smoking, gender: according to Centers 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 colorless, odorless 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. Epidemiological studies and experimental animal models have shown that hazardous emissions: asbestos, chromium, nickel, arsenic, iron oxide, polycyclic aromatic hydrocarbons, halothers, are certified carcinogens with an increased risk of LC as ionizing radiation (11,12,13). Asbestos, responsible for producing the pleural mesothelioma (true "occupational disease") is also involved in determining lung cancer (12-15% in patients with asbestosis), particularly with peripheral occurrence and at the level of the lower lobes(12,14). The risk of carcinomas increases in non-smokers by 3-4 times (12,14). The risk of carcinoma in smokers also increases by up to 90 times(12,13,14). Each of the industrial types of asbestos causes all histological types of lung cancer(13). As histological type in the relationship with asbestos, cubic-cylindrical cell carcinomas are predominant (adenocarcinomas) with mortality rate more than double (64/100.000) than in the rest of the population (31/100.000)(12). It is estimated that the removal of asbestos exposure at the workplace could reduce the incidence of LC by 23%. Even brief exposure is sufficient to determine LC if the asbestos concentration is high enough. There is a synergistic effect of exposure to asbestos and smoking, but non-smokers’ exposure to asbestos also presents a significantly increased risk of developing LC by 1,5-30 times higher than in the people who were not exposed(13).Other occupational factors with definite carcinogenic role have been identified in epidemiological studies, after excluding the role of smoking: arsenic, cadmium, chromium, hematite and chemicals such as: chloromethyl-ether, formaldehyde, etc. (13). Occupational
pollutants contribute with 5-10% to the etiology of lung cancer in men and women of different races and cultures (13). Other authors believe that occupational exposure to cancerogenic noxa in males is even higher 30% (Pastorino, 1984) (12). Radon is a natural radioactive gas with omnipresent distribution: in the atmosphere and in the natural materials of the biosphere, being the product of the radioactive decay of uranium-238 (238 U), which is found in the earth's crust and in the biosphere, and of the direct decomposition of radium 226 (226 Ra), which exists in substantial concentrations in the soil and in rocks and in some building materials (13). If ventilation is reduced, radon accumulates in the atmosphere thus creating a high risk in mines and homes (14). Occupational exposure to radon: occupational internal radiation due to radon (Rn) and its derivatives (X-rays) in uranium mines, involves a wide carcinogenic risk according to the seriousness of the exposure, assessed through the cumulative dose of exposure to radon in WLM units (working-level-months) „monthly level at work”(13.12), defined as exposure to approximately 100pCi/radon/liter of air/170 hours (13) Exposure to radiation in uranium mines is proven to increase the incidence of LC up to 10-30 times, after a latency period of 15 years (11.12). The role of air pollution. In addition to smoking, the pollution typical for the major conurbations is also accused with regard to "inhalation carcinogenesis", especially the smoke resulting from incomplete combustion (industrial or domestic heating), the exhaust gases as well as other pollutants containing HAP or other carcinogenic substances (Anastasatu, 1978). An increase in benzopiren with 1 mcg/1000 m³ would increase lung cancer with 5% (Carnow, 1973) (11.12). The role of other chemical carcinogens. Other carcinogenic or cocarcinogenic risk factors are less frequently taken into account. These includes a number of chemical agents: besides the above-mentioned hydrocarbons, coal tars, mustard gas, some anesthetics (chloroethyl-ether), arsenic (from insecticides and pesticides), spray for vines, glass fibers, polyvinyl chloride, some drugs (cyclophosphamide, mileran), oil, coal, creosote, anthracene, haloethers, some mineral oils (isopropyl), SiO₂ metal powder, beryllium, aluminum, cadmium, copper, iron, lead, etc.. Their effect associates with that of smoking, as in the case of asbestos (12,14).There are data showing a familial aggregation of cancers, including lung cancer (14). According to a study conducted in Connecticut - U.S.A.on 30,000 people with respiratory tract cancers (1935-1985), 44% of the cases reported the occurrence of a second cancer after lung cancer: respiratory tree, oral cavity, bladder and kidney. After 10 years of observation, the risk of a second neoplastic location stayed high at 50%. More frequently, the association between lung cancer and cancers from HEENT medical area (larynx, nasopharyngitis) has been pointed out (13).Three arguments suggest the intervention of a genetic component (13): ● increased risk of cancer in the offsprings of individuals with LC, which includes neoplastic location in other anatomical areas, including the respiratory tract (Lynch and col) ● familial predisposition to respiratory diseases in smokers and their increased risk for LC ● 10 times higher risk of LC in people who have an intensive metabolic capacity to metabolise debrisoquine, found in individuals both exposed and unexposed to carcinogens (15). The genetic factors may contribute to the risk of LC because the metabolism of chemical carcinogens (xenobiotics) is made by genetically controlled detoxification enzyme systems (3). The studies have shown that LC tumor cells accumulate numerous genetic lesions, including the activation of dominant oncogenes and the inactivation of recessive suppressor genes (14). For oncogenes, the changes consist in punctiform mutations: K-ras in adenocarcinomas; amplification, rearrangement and/or loss of transcriptional control: c-myc in non small carcinomas; c-, N-and L-myc in small cell carcinomas; gene overexpression: Bcl-2, Her2/neu, EGRF or telomerase gene (14). According to the current etiopathogenic conception, developing lung cancer is the resultant of all the above-mentioned factors, where smoking has a proportion of 85-90%. Exposure to industrial carcinogens adds an extra ~ 5% and ionizing radiation another ~ 1%.
The association of carcinogens, including smoking, always implies a higher risk of disease than any factor alone. It is possible that the cancerogenic impact of the above-mentioned factors be exercised only on the background of a genetic susceptibility, yet difficult to be accurately defined. Even though it appears to be local, the disease has a complex local and general determinism and once installed, it affects the entire body (12).

Despite the progress recorded in translating the mechanisms of carcinogenesis and diagnostic imaging, lung cancer cure rates are still low. The key intervention in reducing LC is prophylaxis. Quiting smoking is a challenging goal due to nicotine addiction (16). If we do not take categorical measures to reduce smoking, LC incidence will increase dramatically within the next 20-30 years. It is estimated that 2-3 million people will die annually by 2025 (13).

Therefore, primary prevention is very important and education in schools is vital, this being the critical period when smoking addiction occurs (16).

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