LUNG CANCER AND THE SMOKING HABIT – CASE CONTROL STUDY

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A b s t r a c t: *The purpose* of the investigation was to determine the existence of the probable causal associations between cigarette smoking and the development and distribution of lung cancer.

Material and methods: The research was conducted as a case-control study. It included 101 patients with lung cancer (investigated group-IG) and the same number of persons without this malignant disease (control group-CG). The members of both groups were interviewed within the period May 2006-May 2007. Risk analyses were done using unconditional logistic regression, which provides results in the form of a crude odds ratio. The odds ratios and their 95% confidence intervals (CI) were computed.

Results: The habit of cigarette smoking was particularly wide-spread among men with lung cancer (68.8%), while in the CG this percentage was 40.3%. In IG, among the females, current smokers and nonsmokers are represented equally. Smokers and ex-smokers have a 4.05 (95%CI 1.78 < OR < 9.19) times significantly higher risk of becoming ill compared to the non-smokers. The risk of becoming ill increases significantly in smokers who smoke > 20 cigarettes per day (c/d) (p < 0.01) and is 9.33 (95%CI 3.56 < OR < 24.48) compared to nonsmokers. The risk of developing lung cancer is 4.55 (95%CI 1.86 < OR < 11.12) times greater in persons smoking > 15 years (y) > 20 c/d, compared to those who smoke < 15 y < 20 c/d.

Conclusion: Our study supports the statement that cigarette smoking is by far the most important risk factor for lung cancer. Concerted control of smoking appears to be an urgent priority in lung cancer prevention, including efforts to prevent adolescents from starting to smoke.

Key words: lung neoplasm, smoking.

Introduction

Cancer is a disease which knows no limits. It is in the second place as a cause of death in the developed countries, and is among the three leading causes of death in adults in the developing countries.

Every year, worldwide, approximately 10 million persons with malign-nant tumours are diagnosed (in all locations), and more than 6 million of them die. If the present trend continues, it is considered that about 10 million people will die from cancer by 2020, and the number of new cases will increase to 15 million per year [1, 2].

According to the American Cancer Association data, it is stated that during the period 1999 to 2006, cancer surpassed cardiovascular diseases as a leading cause of death in persons younger than 85 years. Mortality rates show a continuous decrease in the three locations in men (lung, colon and rectum, and prostate) and breast, colon and rectum cancer in women. Mortality rate from lung cancer is mildly increasing further in women [3].

Of the total of 10 million new cancer cases diagnosed in 2000, lung cancer has been the most frequent, to which 12.5% of the total number belongs [4].

According the evidence presented by the Macedonian Cancer Register, lung cancer has been in the first place among the ten most primary locations in men, while it has been in the sixth place in women during the last decade [5].

A number of epidemiologic studies point out the role of some risk-factors in the development of lung cancer. The most significant of the so-called "lifestyle" risk-factors are cigarette smoking, passive smoking, alcohol consumption and the style nutrition. Of the exogenous factors there is exposure to certain workplace cancerogenes and air pollution, while the endogenous ones are represented by psychosocial and hereditary factors [6, 7].

The purpose of the investigation was to determine the existence of probable causal associations between cigarette-smoking and the development and distribution of lung cancer.

Material and Methods

The investigation was an analytical type of case-control study. It elaborated patient groups with lung cancer (investigated group – IG) and a group of patients without this malignant disease (control group – CG), in which these factors were investigated from the epidemiological aspect which participated in the disease occurrence.

The members of both groups were interviewed within the period May 2006 to May 2007 (12 months). The investigated group consisted of 101 per-

sons with lung cancer. The disease was diagnosed at the Pulmology and Allergology Clinic. The diagnosis of the disease and its final pathohistological verification were made by biopsy material analysis, taken within the procedure of bronchoscopy at the Institute of Radiotherapy and Oncology.

In order to analyse (quantify) the epidemiological risk which some risk-factors involve, it was necessary to determine their presence in a similar or identical group of individuals who did not have the consequence of the influence of these factors, i.e. lung cancer. In order to minimise the bias risk when both groups were compared, it was necessary that the members of both groups be identical or maximally similar in relation to some accepted features (sex, age). With that aim, the matching method was used for member selection of the control group. In this way, 101 members of the CG were found, selected from the population hospitalized at the Clinic of Gastroentherohepatology in the same period when the IG was selected. Investigation data were taken by means of a questionnaire designed for that aim.

Criteria for defining smoking history

The part of the questionnaire referring to the cigarette smoking habit included modified questions from the Questionnaire on Cigarette Usage, recommended by the World Health Organization Tobacco or Health Programme [8].

A current smoker is a person who smokes at least one cigarette daily, for at least three months, a total of about 100 cigarettes and even more during his lifetime, respectively. *A temporary smoker* is a person who smokes, but not every day. *An ex-smoker* is a person who used to smoke, but at the moment has not for at least 6 months. *Non-smokers* are individuals who have never lit a cigarette or have smoked less than 100 cigarettes in their lifetime.

Statistical analysis

Statistical analysis was made by means of the Statistica for Windows programme. Analysis of attributive series was made through a determination of the coefficient of ratios, proportions and rates, while numerical series were analyzed by measure of dispersion. Through calculation of the risk using the Odds ratio (OR), the risk factors having a role in disease development were defined, while the statistical significance of the investigated variables as risk factors for an error level less than 0.05 (p) was defined with the Confidence Intervals (CI).

Results

This investigation was a case-control study. Of the total of 101 IG members, 83 (82.2%) were men, and 18 (17.8%) women. The ratio of registered men: women was 4.6 : 1. The age span of both group members ranged from 41 to 77 years. The IG and the CG of women had 18 interviewees each, aged 45 to 81 years.

The age distribution shows that the greatest percentage of diseased men and women belonged to the age group 60–69 years (35.6% men; 38.9% women) (Table 1).

Table 1 – Табела 1

Distribution of patients and controls according to sex and age
Дистрибуција на испитаниците (пациенти и контроли)
според пол и возраст

AGE (years)	Investigated group		Control group	
	Men	Women	Men	Women
	N %	N %	N %	N %
< 39	2 (2.0)	/	/	/
40–49	7 (6.9)	3 (16.7)	10 (9.9)	3 (16.7)
50–59	27 (26.7)	5 (27.8)	27 (26.7)	4 (22.2)
60–69	36 (35.6)	7 (38.9)	35 (34.6)	8 (44.5)
70–79	11 (28.8)	2 (11.0)	11 (28.8)	2 (11.0)
> 80	/	1 (5.6)	/	1 (5.6)
Total	83 (100)	18 (100)	83 (100)	18 (100)

87% of the diseased persons lived in towns, and 75.1% of the CG members, respectively. The majority in both groups members were of Macedonian nationality (IG-82.4%; CG-83.5%), followed by Albanians (11%) and Romas (3.3%) in the IG, while after the Albanians with 9.9%, came Serbs with 4.4% in the CG.

Knowledge that cigarette smoking represents a significant risk-factor for cancer development is not new. It is a habit which causes not only lung cancer, but cancer in other locations as well: the mouth cavity, larynx, pharynx, oesophagus, bladder, pancreas and stomach.

The habit of cigarette smoking is particularly widespread among men with lung cancer (68.8%), while in CG members this percentage is 40.3%. Ex-smokers from the IG were 25.3%, and 30.8% from the CG. Among the male

members of the IG, three were nonsmokers, while their number in the CG was 21 (27.2%).

Among the female members of the IG, actual smokers and nonsmokers are represented equally, while 50% were nonsmokers among the non-diseased persons.

Where the age when an individual started smoking was in question, the greatest percentage of those diseased (44.1%) started smoking before the age of 15, while among the non-diseased persons the greatest number started smoking later (16–20 years of age – 40%)

More than half of those diseased with lung cancer smoked between 21 and 40 cigarettes daily (c/d) (56.8%). The group of so-called "passionate" smokers (above 40 c/d) comprised 14% of the patients. Only 2% of the IG members smoked less than 10 c/d. In the CG, the greatest number was those who smoked 11–20 c/d (51.4%), while only 2 (5.7%) smoked more than 40 c/d.
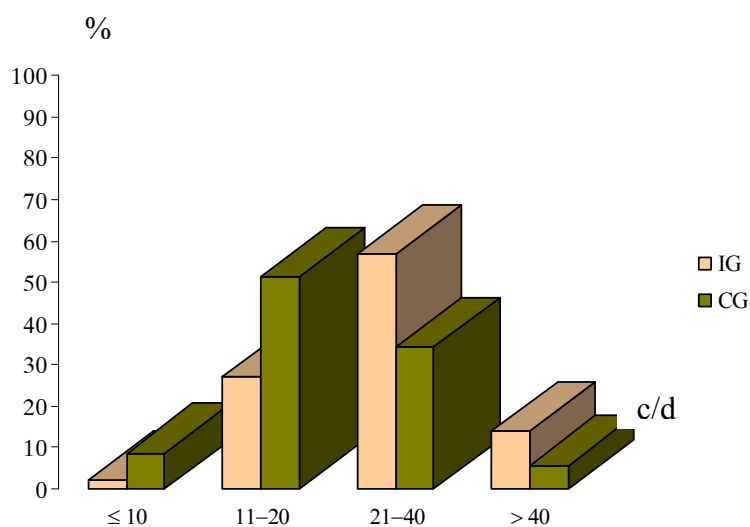

Figure 1 – Distribution according to number of cigarettes smoked daily
(cigarettes per day – c/d)

Слика 1– Дистрибуција според број на дневно испушени цигари
(цигари на ден – ц/ден)

IG – Investigated group
ИГ – Испитувана група
CG – Control group
КГ – Контролна група

The diseased smokers smoked, on average, 29.8 ± 19.9 c/d (min-10; max-60 c/d), while the controls smoked 21.6 ± 8.8 c/d (min-7; max-45 c/d).

The distribution of the interviewees according to length of smoking shows the greatest representation in the period of 31–45 years in both groups (54.23% – IG; 48.6 – CG). In persons with lung cancer, those having a length of smoking above 45 years (25.4%) follow, while in CG that percentage is 14.2%.
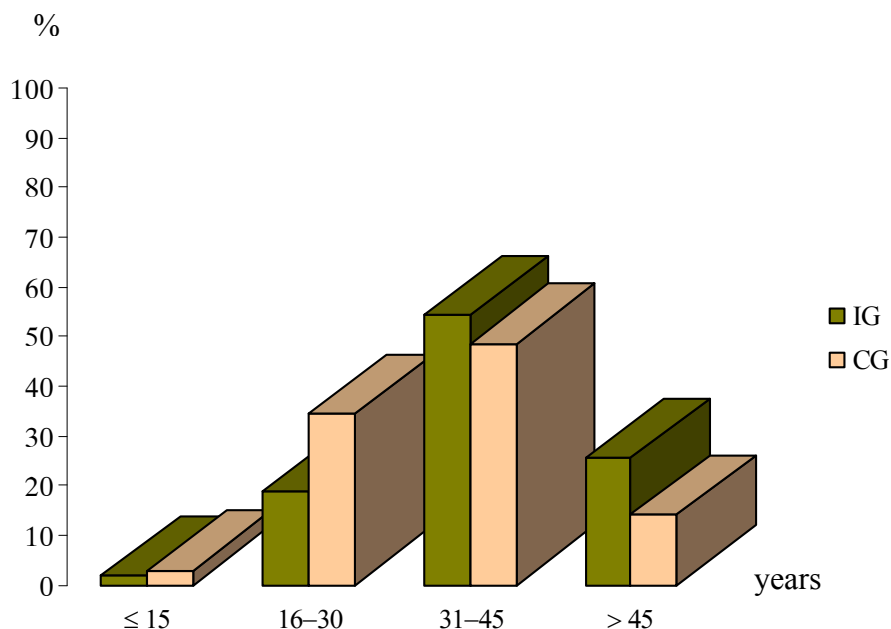

Figure 2 – Distribution according to length of smoking (years)
Слика 2 – Дистрибуција според должина на пушачки стаж (години)

IG – Investigated group
ИГ – Испитувана група
CG – Control group
КГ – Контролна група

Actual smokers in the IG had smoked continuously, on average, 41.1 ± 11 years, while in the CG the average length of time was 34.2 ± 10.3 years.

To the question whether they had tried to stop smoking, the greatest percentage of the diseased (79.7%) answered negatively, while in the CG 57.1% gave a negative answer.

Table 2 – Табела 2

Habit of cigarette smoking and the risk of lung cancer
Навика за йушење циѓари и ризик од йојава на белодробен карцином

Variable	Cases[1]	Controls[2]	Crude OR[3]	95% CI[4]
Smoking habit				
Never smokers	9	28	1.00	
Current and ex-smokers	82	63	4.05	1.78–9.19
Current smokers	59	35	5.24	2.22–12.39
Number of cigarettes per day (c/day)				
Never smokers	9	28	1.00	
Current smokers < 20 c/day	17	21	2.52	0.94–6.75
Current smokers > 20 c/day	42	14	9.33	3.56–24.48
Duration of smoking (years)				
< 15 years < 20 c/day	1	1	1.00	
> 15 years > 20 c/day	58	34	1.71	0.10–28.17
Number of cigarettes per day (c/day) and duration of smoking (years) (combined)				
> 15 years < 20c/day	16	22	1.00	
> 15 years > 20c/day	43	13	4.55	1.86–11.12

[1] IG – Investigated group; [2] CG – Control group; [3] OR – Odds ratio; [4] CI – Confidence interval

[1] ИГ – Испитувана група; [2] КГ – Контролна група; [3] ОР – Однос на доминација; [4] Интервал на доверба

Smokers and ex-smokers have a significantly greater risk of becoming ill. They become ill 4.05 times more frequently (95% CI $1.78 < OR < 9.19$) compared to the non-smokers. If the number of cigarettes smoked is taken into consideration, the risk of becoming ill is 2.52 (95% CI $0.94 < OR < 6.75$) times greater for those who smoke up to 20 c/d compared to the nonsmokers. The risk of becoming ill increases significantly in smokers who smoke above 20 c/d ($p < 0.01$) and is 9.33 (95% CI $3.56 < OR < 24.48$). Smokers who smoke more than 20 c/d have a 3.71 times significantly greater risk of becoming ill (95% CI $1.54 < OR < 8.94$) compared to those who smoke up to 20 c/d. The risk of becoming ill in smokers who have smoked for more than 15 years is almost twice as great (95% CI $0.10 < OR < 28.17$) compared to those who have smoked for less than 15 years. On the other hand, the risk of developing lung cancer is 4.55 (95% CI $1.86 < OR < 11.12$) times greater in persons smoking more than 20 c/g for over 15 years, compared to those who have smoked up to 20 c/d for less than 15 years.

Discussion

Many epidemiological studies define lung cancer as a disease which primarily develops in the male sex. It is supposed that the cause of this is smoking as well as working with work-related cancerogenes. But the last few years have shown an increase of the disease among women, which, to some extent, has been connected with the increased number of women smokers [9, 10]. In 1987, lung cancer replaced breast cancer as a leading cause for cancer death in women in the USA. This disease was responsible for the death of about 67,000 women, which accounted 25% of the deaths caused by cancer in 2000 [11]. Lung cancer in women, in the USA, has been responsible for the same number of deaths as breast cancer and gynecological cancers taken together. The cause is the smoking habit. Despite everything that is known about the harmful effects of smoking, 1 in 8 women smoke in the USA. It is considered that women are more sensitive to the harmful effects of smoking than men. The cause of that is: biological difference between the sexes, manifested by increased CYP1A1 expression, impaired possibility of DNK capacity reparation, and the increased incidence of K-ras genetic mutation in women. It is supposed that estrogens most probably have a role in tumour genesis [12]. Similar knowledge comes from Ben-Zaken Cohen S. *et al.* [13]. According to them, estrogen and components similar to it have a role in the regulation of cytochrome P450 (CYP) enzyme expression in the lungs and liver, being involved in the metabolism of some components present in cigarette smoke. An important xenobiotic substrate for CYPs in cigarette smoke is a polycyclic aromatic hydro carbonate which, in its natural form, is relatively harmful in small doses, but when activated under the action of CYP enzymes, becomes a very toxic substance for the lungs. The disease ratio between men and women is different from one country to another: Iceland 1.2 : 1; Singapore 3.3 : 1; Belgium 10.9 : 1, Denmark 3.1 : 1; France 9.5 : 1; Greece 7 : 1; Italy 8.6 : 1; Luxemburg 7.8 : 1; Netherlands 10.5 : 1; Spain 8 : 1; Britain 3.5 : 1 [14].

Of a total of 101 IG members included in the case-control study, 83 (82.2%) are men and 18 (17.8%) women. The ratio of men to women was 4.6 : 1.

Each cancer is a consequence of some consequent mutation of genetic material in a normal cell. The risk of the disease grows with ageing of the organism, so the incidence of the cancer logarithm is in linear relation to the logarithm of age. This means that the possibility of cancer occurrence is in a direct proportion to the age. Ak *et al*. [15] made an investigation aiming to research the clinico-pathologic characteristics of lung cancer in patients younger than 50. The results showed that 12.5% of the total number of diseased people were younger than 50 years. More than 90% of them were smokers.

Results from our own investigation showed that 11.9% of the diseased (9 men and 3 women) were younger than 50.

Cancer is a disease of ageing and the main cause for morbidity and mortality. More than 50% of all cancers occur at above 65 years of age. According to the National Supervision Institute and Cancer Epidemiology in the USA, the median age of patients who died from the most frequent cancer tumours (lung, colorectal, lymphoma, leukemia, pancreas, stomach) appearing in both genders and in all races ranges from 71 to 77 years. It is considered that the cause of this is demographic changes in the USA population as well as increased possibilities for treatment of some types of cancer [16].

A performed case-control study pointed out that among the diseased persons, there were 13 patients older than 70 (12.9%).

There is a difference in disease incidence from lung cancer between the urban and rural environments. In addition to the significance of urbanization as a pollution factor, the Italian evidence indicates that the incidence rate of lung cancer in this country registered an increase from 1954 in both genders, although only 29% of men and 2.1% of women were smokers. The increase in incidence was followed in urban areas, where the number of vehicles has increased 10 times over the last 20 years [17]. Our own investigation showed that 87% of the diseased persons live in towns, and 75.1% members of the CG.

Prospective epidemiological studies worldwide have proved the association between the cigarette smoking habit and lung cancer, and indicate that, in comparison to nonsmokers, smokers have an approximately 9 to 10 times greater risk of developing lung cancer [18]. According to evidence presented by Gomez Raposo C. *et al*. 18,000 new cases of lung cancer are recorded each year in Spain. About 80–90 % of the cases of both sexes have been due to cigarette smoking. Cigarette smoke contains above 300 chemical substances, 40 of them potent cancerogenes. Length of smoking, the number of cigarettes smoked, passive smoking, genetic predisposition as well as many workplace and cangerogenic substances present in the human environment play a very important role [19]. Pesut D and Basara HZ gave evidence that almost half of the population in Serbia smoke cigarettes. They analysed the incidence rate and the trend of lung cancer development in Serbia during the period 1994 to 2003. Diseased people were divided into three categories: smokers, ex-smokers and nonsmokers. Percentile representation of some categories among the diseased persons was: smokers – 70.3%; ex-smokers – 17%; and nonsmokers – 12.6%. An increased trend of lung cancer was registered in women in all three categories, but much more so among smokers [20].

Our own study showed that the percentage of the diseased male actual smokers – 68.8% – was high. Ex-smokers were 25.3%, and only three persons had never smoked cigarettes. Among the women, actual smokers and nonsmokers were represented equally, with 42.9% each.

Results presented by Gupta *et al*. [21], showed that 89% of men and 33% of women who became sick were cigarette smokers. The risk of disease

development is as high as 5 times greater (OR = 5.0 95% CI 3.11–8.04) in men, and 2.47 (95% CI 0.79–7.75) times greater in women, compared to nonsmokers. Smoking, according to them, remains a major risk-factor for the development of lung cancer, while other factors play a significant role in women. A performed case-control study showed that the greatest percentage of the diseased persons had smoked for 31 to 45 years (54.2%). They are followed by those with a length of smoking above 45 years (25.4%), a percentage which is not negligible. According to the study by Flanders W *et al.*, the length of the smoking is a more important factor than the number of cigarettes smoked daily by men in the USA. New investigations point to identical results in women [22].

Conclusion

In conclusion, our results support the statements that cigarette smoking is by far the most important cause of the on-going epidemic of lung cancer in Macedonia. The dominant role of active smoking among lung cancer factors has generally been recognized. The daily number of cigarettes and duration of smoking were significantly associated with lung cancer risk. The risk is higher if a person starts to smoke earlier.

All this indicates the importance of taking measures to point out the harmful effects of smoking, with the aim of preventing young people from starting this harmful habit.

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Р е з и м е

КАРЦИНОМ НА БЕЛИ ДРОБОВИ И НАВИКАТА ЗА ПУШЕЊЕ ЦИГАРИ – CASE-CONTROL СТУДИЈА

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Цел на студијата е да се согледаат евентуални каузални асоцијации меѓу навиката за пушење цигари и настанувањето и дистрибуцијата на белодробниот карцином.

Истражувањето претставува case-control студија. Во неа се вклучени 101 пациент заболен од белодробен карцином (испитувана група – ИГ) и идентичен број лица без малигно заболување (контролна група – КГ). Членовите на двете групи се анкетирани во периодот мај 2006 – мај 2007 година. Зголемениот ризик од појава на заболување е пресметан со стапки на предимство (Odds ratio – OR), а со интервали на доверба е дефинирана статистичката значајност на испитуваните варијабли како фактори на ризик.

Навиката за пушење цигари е посебно присутна кај мажите заболени од белодробен карцином (68,8%), додека кај КГ тој процент изнесува 40,3%. Во ИГ кај жените, актуелните пушачи и непушачите се еднакво присутни. Актуелните и поранешни пушачи имаат 4,05 (95%CI, 1,78–9,19) пати сигнификантно поголем ризик да заболат во однос на непушачите. Ризикот за заболување е сигнификантно повисок кај пушачи кои пушат > 20 цигари/ден (ц/д) (p < 0,01) и изнесува 9,33 (95%CI, 3,56–24,48), споредено со непушачите. Ризикот од појава на белодробен карцином е 4,55 (95%CI, 1,86–11,12) пати повисок кај лица, кои > 15 години пушат > 20 ц/д, споредено со оние кои пушат < 15 години < 20 ц/д.

Реализираната студија го потврдува веќе етаблираното сознание дека пушењето е еден од главните ризик фактори за појава на карцином на бели дробови. Главниот акцент во превенцијата треба да се насочи кон запознавање на младите со штетните ефекти од пушењето, со цел да се спречат во започнување со оваа навика.

Клучни зборови: неоплазма на бели дробови, пушење.

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