

CASE-CONTROL STUDY

Tobacco use and the risk of lung cancer in Macedonia

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Abstract: *Introduction:* Lung cancer (LC) is one of the most common diseases in the world. Smoking is the most important “lifestyle” risk-factor attributed to the development of LC.

Objective: The aim of the study was to determine the existence of a causal association between cigarette smoking and the development and distribution of LC.

Material and methods: The case-control study was conducted in 91 patients with LC (investigated group-IG) and the same number of persons without malignant disease (control group-CG). Both groups were interviewed between 14 July 2005 and 14 July 2006. Risk analyses were done using unconditional logistic regression, which provided results in the form of crude odds ratio. The odds ratios and their 95 % confidence intervals (CI) were computed.

Results: Cigarette smoking is wide spread among men with LC (68 %), while in CG this percent is 40.3 %. In IG, among females, current smokers and nonsmokers are represented equally. More than a half of the LC patients smoke between 21–40 c/d (56.8 %). Smokers and ex-smokers have 4.05 (95 % CI 1.78<OR<9.19) times significantly higher risk to become ill compared to the non-smokers. The risk for becoming ill is 9.33 (95 % CI 3.56<OR<24.48) times higher in smokers who smoke >20 c/d (p<0.01) compared to nonsmokers. The risk for developing LC is 4.55 (95 % CI 1.86<OR<11.12) times higher in persons smoking >15 years >20 c/g, compared to those who smoke <15 years <20 c/d.

Conclusion: Our study supports the statement that cigarette smoking is by far the most important risk factor for LC. Concerted control of smoking appears to be an important priority in LC prevention, including efforts to prevent adolescents from starting to smoke at an early age (Tab. 2, Fig. 2, Ref. 22). Full Text (Free, PDF) www.bmj.sk. Key words: lung neoplasm, age, smoking.

Cancer is a disease without limits. It is on the second place as a death cause in developed countries and among the three leading death causes in adults in developing countries.

Every year, worldwide, approximately 10 million persons have been diagnosed with malignant tumors (in every locations), and more than 6 million of these people die. If the present trend continues, it is considered that about 10 million people will die from cancer up to 2020, and the number of new cases will increase to 15 million per year (1, 2).

According to the American Cancer Association, during the period 1999 to 2006, cancer surpasses the 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 further mildly increasing in women (3).

From the 10 million of new cancer cases diagnosed in 2000, lung cancer has been the most frequent, representing 12.5 % of the total number (4).

According to the evidence presented by the Macedonian Cancer Register, lung cancer is on the first place among the ten most primary locations in men, while it is on the sixth place in women during the last decade (5).

A number of epidemiologic studies point out the role of some risk factors for the development of lung cancer. The most significant of the so called “lifestyle” risk factors are the smoking cigarette, passive smoking, alcohol consumption and the way of nutrition, then, regarding the exogenous factors, it is an exposition to some professional cancer promoting factors and air pollution, while the endogenous factors are represented by psychosocial and hereditary factors (6, 7).

Objective of the study is to determine the existence of the causal association between the cigarette smoking and development and distribution of the lung cancer.

Material and methods

This study is an analytical type of a case-control study. It elaborated patient groups, suffering from lung cancer (investigated group – IG) and group of patients without malignant disease (control group – CG), in which these contributing factors were investigated from the epidemiological aspect.

Both group members were interviewed within the period from 14 July 2005 to 14 July 2006 (12 months). Investigated group

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Tab. 1. Distribution of the patients and controls according to sex and age.

| Age (years) | Investigated group | | Control group | |
|-------------|--------------------|------------|---------------|------------|
| | Men | Women | Men | Women |
| <39 | 2 (2.6 %) | – | – | – |
| 40–49 | 7 (9.1 %) | 3 (21.5 %) | 9 (11.7 %) | 2 (14.3 %) |
| 50–59 | 25 (32.5 %) | 4 (28.6 %) | 25 (32.5 %) | 3 (21.5 %) |
| 60–69 | 33 (42.8 %) | 5 (35.7 %) | 33 (42.8 %) | 7 (50 %) |
| 70–79 | 10 (13 %) | 1 (7.1 %) | 10 (13 %) | 1 (7.1 %) |
| >80 | – | 1 (7.1 %) | – | 1 (7.1 %) |
| Total | 77 (100 %) | 14 (100 %) | 77 (100 %) | 14 (100 %) |

consisted of 91 persons from the whole territory of Macedonia, suffering from lung cancer. Disease was diagnosed at the Clinic of Pulmology and Allergology. The diagnosis and its final pathohistological verification was made by biopsy, taken within the procedure of bronchoscopy at the Institute of Radiotherapy and Oncology.

In order to analyze (quantify) the epidemiological risk, which some risk-factors convey, it was necessary to determine their presence in similar or identical group of individuals, who do not have the consequence of these factors, i.e. the lung cancer. In order to minimize the bias risk when both groups were compared, it was necessary for the member of both groups to be identical or maximally similar in relation to some accepted features (sex, age). For that aim, matching method was used for the member selection of the control group. In that way, 91 members of the CG were found, selected from the population hospitalized at the Clinic of Rheumatology in the same period when IG was selected. Study data were collected by means of questionnaire designed for that aim.

Criteria for defining smoking history

The part of the questionnaire referring to cigarette smoking habit, included modified questions from the Questionnaire for cigarette usage, recommended by World Health Organization Tobacco or Health Programme (8).

Current smoker is a person who smokes at least one cigarette daily, at least for three months, a total of about 100 cigarettes and even more during his lifetime, respectively. *Temporary smoker* is a person who smokes but not every day. *Ex-smoker* is a person who used to smoke, but in the moment does not, for at least 6 months. *Non-smokers* are individuals who never lighted cigarette or smoked less than 100 cigarettes in their lifetime.

Statistical methods

Statistical analysis was made using the program Statistica for Windows. An analysis of attributive series was made through coefficient of ratios, proportions and rates, while numerical series were analyzed by dispersion. Through calculation of the risk with the Odds ratio (OR), the risk factors were defined, having a role in disease development, while statistical significance of the

studied variables as risk factors for the error level less than 0.05 (p) was defined with the Confidence Intervals (CI).

Results

This study represents a case-control study. Of the total 91 IG members, 77 (84.6 %) were men and 14 (15.4 %) were women. Ratio of registered men to women was 5.5:1. Men’s mean age, suffering from lung cancer, was 60.2±9.3 years, and that of the CG members was 60.4±8.9 years. The age interval of both group members (men) ranged from 38 to 77 years. IG and CG of women had 14 interviewees each, aged 45 to 81 years. Mean age of the women with lung cancer was 58.9±10.1 years and without lung cancer 59.1±9.6 years.

The age distribution shows that the greatest percent of men and women with lung cancer belonged to the age group 60–69 years (42.8 % men; 35.7 % women) (Tab. 1).

67 % of the affected persons and 71.4 % of the CG members lived in town. Majority in both groups are of Macedonian nationality (IG-82.4 % ; CG-83.5 %), followed by Albanians (11 %) and Romas (3.3 %) in the IG, while in the CG Albanians were represented with 9.9 %, followed by Serbs with 4.4 %.

The 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: mouth cavity, larynx, pharynx, oesophagus, bladder, pancreas, stomach.

The habit of cigarette smoking is especially spread among men diseased from lung cancer (68.8 %), while in CG members this percent is 40.3 %. Ex-smokers from the IG were 25.3 %, and 30.8 % from the CG, respectively. Among the male members of the IG, three were nonsmokers, while their number in the CG was 21 (27.2 %).

In IG, among the female members, actual smokers and non-smokers were represented equally, while 50 % were nonsmokers among the non-affected subjects.

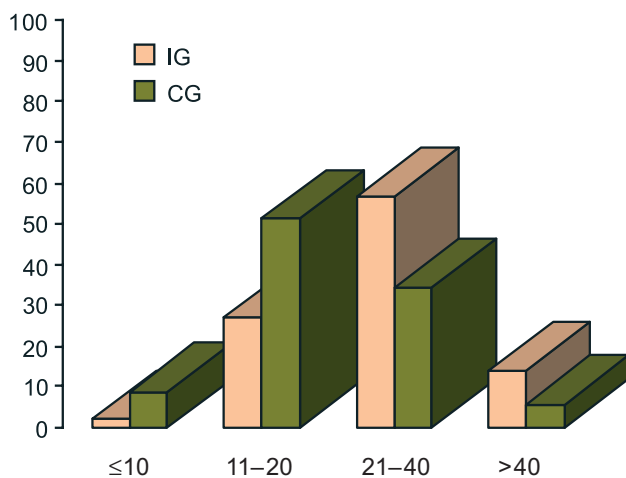


Fig. 1. Distribution according to the number of daily smoked cigarettes.

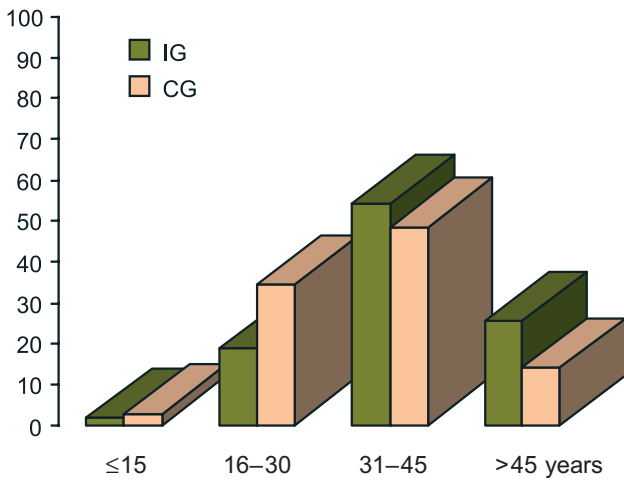


Fig. 2. Distribution according to the length of smoking.

When the starting with smoking was in question, the greatest percent of the affected (44.1 %) started smoking up to the age of 15 years, while in unaffected persons the greatest number started smoking later (16–20 years of age – 40 %).

More than a half of the patients with lung cancer smoke between 21 to 40 cigarettes daily (c/d) (56.8 %). The group of the so called “passionate” smokers (above 40 c/d) made 14 % of the patients. Only 2 % of the IG members smoked less than 10 c/d. In CG, the greatest portion represented those who smoke 11–20 c/d (51.4 %), while only 2 (5.7 %) smoked more than 40 c/d (Fig. 1).

The actual affected smokers smoked, in 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).

Distribution of the interviewees according to length of smoking showed 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 length of smoking above 45 years (25.4 %) follow, while in CG that percent is 14.2 % (Fig. 2).

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

On the question if they tried to stop smoking, the greatest percent of the affected subjects (79.7 %) answered negatively, while in CG negative answer gave 57.1 % (Tab. 2).

Smokers and ex-smokers had a significantly higher risk to become 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 were taken into consideration, the risk to become ill was 2.52 (95 % CI 0.94<OR<6.75) times greater for those who smoked up to 20 c/d, compared to the nonsmokers. The risk for becoming ill increased significantly in smokers who smoked above 20 c/d (p<0.01) and was 9.33 (95 % CI 3.56<OR<24.48). Smokers who smoked more than 20 c/d had 3.71 times significantly higher risk to become ill (95 % CI 1.54<OR<8.94) compared to those who smoked up to 20 c/d.

The risk for becoming ill in smokers who smoked longer than 15 years was almost twice higher (95 % CI 0.10<OR<28.17) compared to those who smoked shorter than 15 years. On the other hand, the risk for developing lung cancer was 4.55 (95 % CI 1.86<OR<11.12) times higher in persons smoking above 15 years more than 20 c/g, compared to those who smoked shorter than 15 years up to 20 c/d.

Discussion

Many epidemiological studies define the lung cancer as a disease, which primarily develops in male gender. It is supposed that the cause is smoking as well as the work with professional cancer promoting factors. But, the last several years noted an increase of the affected women, which, to some extent, has been connected with the increased number of women smokers (9, 10). In 1987, lung cancer replaced the breast cancer as a leading cause for cancer death in women in USA. This disease was responsible for about 67000 dead women, which represented 25 % of the death cases, caused by cancer in 2000 (11). Lung cancer in women, in USA, has been responsible for identical number of death cases as the breast cancer and gynecological cancers altogether. The cause is the smoking habit. Beside everything that is known about harmful effects of smoking, 1/8 of women smoke in USA. It is supposed that women are more sensitive to harmful effects of smoking compared to men. The cause is biological difference between both genders, manifesting with an increased CYP1A1 expression, impaired possibility for DNK capacity reparation, as well as the increased incidence of K-ras genetic mutation in women. It is supposed that estrogens have most probably a role in tumor genesis (12). Similar knowledge stated Ben-Zaken Cohen et al (13). According to them, estrogen and components similar to it have a role in the regulation of cytochrome P450 (CYP) enzymes expression in lung and liver, being involved in

Tab. 2. Active cigarette smoking and the risk of lung cancer.

| Variable | Cases ¹ | Controls ² | Crude ³ | OR 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 (/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 | 1 | 1 | 1.00 | |
| ≥15 | 58 | 34 | 1.71 | 0.10–28.17 |
| Number of cigarettes per day (c/day) and duration of smoking (years) (combined) | | | | |
| <15 years <20 c/day | 16 | 22 | 1.00 | |
| >15 years >20 c/day | 43 | 13 | 4.55 | 1.86–11.12 |

metabolism of some components present in cigarette smoke. Important xenobiotic substrate for CYPs in cigarette smoke is a polycyclic aromatic hydrocarbonate, which, in its natural form, has been relatively harmful in small doses, but when activated under the action of CYP enzymes, becomes a very toxic substance for the lung.

The disease ratio between men and women is different from country to country: 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).

From a total 91 IG members, included into the case-control study, 77 (84.6 %) were men and 14 (15.4 %) were women. Men and women ratio was 5.5:1.

Each cancer has been a result of some consequent mutation of genetic material in normal cell. The risk of the disease grows with ageing of organism, so the incidence of cancer logarithm is in linear relation to the logarithm of the age. It means that the possibility for cancer occurrence is in direct proportion with the age. Shirish et al (15) made a study on the clinic-pathologic characteristic of lung cancer in patients younger than 50 years. Results showed that 12.5 % were younger than 50 years from the total number of affected people. More than 90 % of them were smokers.

Results from our own study showed that 13.2 % of the affected subjects (9 men and 3 women) were younger than 50 years.

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

The performed case-control study pointed that there were 11 patients older than 70 years (12.1 %) among affected subjects.

There is a difference in disease incidence from lung cancer among the urban and rural environments. In addition to the meaning of urbanization as a pollution factor, as the Taiwan evidence indicates. The incidence rate of lung cancer in this country increased from 1954 in both genders, although only 29 % of men and 2.1 % of women were smokers. Increase in incidence was noted in urban areas, where the number of the vehicles increased 10-times for the last 20 years (17).

Our own study showed that 67 % of the affected persons and 71.4 % members of the CG lived in towns.

Prospective epidemiological studies worldwide prove the association between the cigarette smoking habit and lung cancer and indicate that compared to nonsmokers, the smokers have approximately 9 to 10 times greater risk to develop lung cancer (18). According to evidence presented by Gomez Raposo et al new 18000 cases of lung cancer are recorded each year in Spain. About 80–90 % of the cases of both genders have been due to cigarette smoking. Cigarette smoke contains above 300 chemi-

cal substances, 40 of them are potent cancer promoting substances. The length of smoking, the number of cigarettes smoked, passive smoking, genetic predisposition as well as many professional and cancer promoting substances present in human environment have a very important role (19). Pesut D and Basara HZ gave an evidence that almost half of the population in Serbia smoke cigarettes. They analyzed the incidence rate and the trend of lung cancer development in Serbia during the period 1994 to 2003. Affected people were divided into three categories: smokers, ex-smokers and nonsmokers. The percentage of some categories among the affected persons was following: smokers – 70.3 %; ex-smokers – 17 %; and nonsmokers – 12.6 %. An increased trend of lung cancer was recorded in women in all three categories, but much more in smokers (20).

Our own study showed that the percentage of the affected male's actual smokers – 68.8 % was high. Ex-smokers were 25.3 %, and only three persons never smoked cigarettes. In 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 the disease development is as high as 5 times (OR=5.0 95 % CI 3.11–8.04) in men, and 2.47 (95 % CI 0.79–7.75) times higher in women, respectively, compared to nonsmokers. Smoking, according to them, remains a major risk-factor for the development of lung cancer, while other factors have a significant role in women. The performed case-control study showed that the greatest percentage of the affected persons smoked 31 to 45 years (54.2 %). They were followed by those with the length of smoking above 45 years (25.4 %), percentage which should not be negligible. According to Flanders W et al, the length of smoking is more important factor than the number of cigarettes smoked daily by men in USA. New investigations point to the identical results in women.

All this indicate the importance of taking measures for highlighting the harmful effects of smoking, with the aim to prevent the youth from starting with this harmful habit (22).

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Received June 11, 2007.

Accepted January 22, 2009.