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EPIDEMIOLOGICAL ANALYSIS OF LUNG CARCINOMA IN THE CENTRAL DALMATIA REGION: RESULTS OF TWENTY-YEAR FOLLOW-UP

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SUMMARY – A several-fold increase in the incidence of lung cancer during the last 20 years has been obvious in the central Dalmatia region. It has been on a constant increase in both men and women. A 2.4-fold increase has been recorded in male, and 4.2-fold in female population. The majority of patients are long-time cigarette smokers. Thirty years ago this habit was characteristic for men, while today the number of female smokers has been on an increase (the percentage of female patients cigarette smokers increased from 17.8% to 47.3%). Most patients are older than 65 and together with those over 60 years of age they make over 42% of lung carcinoma patients. The increased incidence of adenocarcinoma not directly connected with cigarette smoking, on the account of a decrease in the incidence of squamous cell carcinoma of the lung has been confirmed. The highest increase was recorded during the postwar years (by as much as 32% in 2000), which could be attributed to severe psychical traumas and other hardships related to the war and life in the postwar period. The increase in the incidence of squamous cell carcinoma in women (from 17.5% to 20.4%) could probably be attributed to the increase in the number of female smokers. The decrease in the incidence of small cell anaplastic lung carcinoma was evenly distributed in both sexes (from 27% to 22.6%). Comparison of data obtained for one part of Croatia (coastal region) with global data suggests a similar epidemiological pattern to exist in the south and southeast Europe (south Italy, Spain, Greece).

Introduction

The first description of lung cancer appeared in the 15th century, after a mine in Schneelberg, Germany, had been opened, and it was referred to as "mountain sickness". Numerous authors considered lung cancer as sarcomas.

Only 90 years ago (in 1912), Adler wrote the first monograph on lung cancer, he apologized for writing about such a rare disease, and expressed his doubt whether it should have been written about at all (cited from ref. 1)[1]. It was in the very next year that some authors, Weller being one of them, found 89 cases of bronchial and lung cancer worldwide[2]. During the last 50 years, lung cancer has convincingly taken primacy among the causes of death from malignant diseases in male population worldwide, while a considerable increase has been recorded in women[6,12,14,21,23].

Lung cancer is posing an ever increasing medical and social problem due to its increasing morbidity and mortality. Treatment results are not encouraging, and the treatment is a painstaking and expensive process. Annual mortality rate could be regarded as annual morbidity rate

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since the annual rate of persons affected by the disease almost equals the number of deaths[1,3,7,8]. In the risk groups of population, the disease has been assuming characteristics of an epidemic, so permanent follow-up of its incidence and spread is imperative if the epidemiological data are to be used to fight this disease and cancer in general[3].

It is beyond doubt that one of the basic etiologic factors of lung cancer is cigarette smoking, i.e. tobacco smoke. Auerbach confirmed this in tests on dogs[4]. The risk of bronchial and lung cancer grows proportionally with the daily consumption of cigarettes and years of smoking. According to Kubik's study, the smokers between 60 and 64 years of age who smoked 200,000 cigarettes during their life suffer from this disease 50 times, and those who smoked under 200,000 cigarettes suffer 10 times more often than the non-smokers[5].

The risk in smokers who quit smoking decreases to reach the non-smoker risk level only after 15 years. Passive smokers are also exposed to a higher risk of lung cancer. The Japanese author Hirayami maintains that the incidence of lung cancer in smokers' wives is 2.8 times higher than in non-smokers' wives[6,22].

Other inhalation factors can also contribute to the incidence of lung cancer, the best known being asbestos, uranium, tar, nickel, cobalt, chromium, arsenic, radioactive radiation, vinyl-chloride, and other detrimental carcinogenic factors from the living and particularly working environment. The psychophysical condition of the body contributes to the incidence of malignant diseases, including lung cancer.

Patients and Methods

The analyzed patients were treated at the Department for Pulmonary Diseases, Split Clinical Hospital, as outpatients or inpatients during the last 12 years, and their results were compared with the data previously collected and processed (1981-1983) in a master's thesis. The areas covered by the study were: the City of Split, Kaštela, Solin, Trogir, Sinj, Omiš, Makarska, Metković, Ploče, Vrgorac and the islands of Brač, Šolta, Hvar, Vis, Čiovo and Drvenik, partly the island of Korčula, and Drniš and Knin town areas. This area mostly corresponds to the present borders of the Split-Dalmatia County, a major part of the Dubrovnik-Neretva County (Ploče and Metković, island of Korčula), and a part of the Šibenik-Knin County (greater area of Drniš and Knin). During the war and several years after the war, the share of refugees and population from the neighboring Bosnia and Herzegovina (particularly of those from west Bosnia and Herzegovina) was large. They are presented separately in the total number of patients.

The 20-year period was divided into three study periods: pre-war period 1981-1983; war period 1991–1993; and postwar period 1999-2001.

The data obtained were statistically analyzed by Student's t-test and Mann-Whitney U test.

Results

During the first study period (20 years ago), 352 persons were affected by lung cancer in three years. Out of 352 patients, 321 (91.2%) were male and 31 (8.8%) female. The male/female ratio was 10.4:1. The majority of patients were 60-64 years of age (18%) (58/321). The incidence of affected men in this group was 292 (292/100,000 male of this age). The majority of women, 21% (7/31) fell ill between 55-59 years of age, yielding an incidence of 24 patients *per* 100,000 women of that age.

Only 0.8% (3/352) patients fell ill at the age of 40, but as many as 4.5% (16/352) at the age of 40-44. The incidence at the then City of Split territory (including Kaštela and Solin municipalities) was 62.5/100,000 inhabitants.

In 96% of cases, the patients contacted their doctors because of health problems or disease symptoms they felt. In 3.6% of patients, the disease was detected accidentally.

Approximately 80.5% (284/352) of patients were smokers, i.e. 86.5% (278/321) of male and only 17.4% (6/31) of female patients.

Squamous cell carcinoma was the most common type of lung cancer detected in 43% (139/321) of patients, i.e. 46% of male and 17.8% of female patients. The next form was small cell anaplastic cancer in 27.5% (97/352), equally present in male and female patients. The most common type of lung cancer in women was adenocarcinoma in 51% (16/31), which in male patients was on the third place with 20.2% (65/321). Undifferentiated and other cancer forms were found in 8.2% of patients.

During the second three-year study period, 682 patients were treated for lung cancer: 590 (85.3 %) male and 88 (14.7%) female. The male/female ratio was 7.1:1.

Squamous cell lung carcinoma was still on the lead with 45.4% (311/682) of patients, i.e. 52% (311/590) of male and 22.6% (20/88) of female patients. In women, adenocarcinoma was on the first place with 51.1% (45/88),

and small cell anaplastic carcinoma on the second place with 26% (23/88) of patients.

During the third, postwar study period, 1017 patients suffering from lung cancer were treated, 1011 of them being evaluated: 889 (87.8%) male and 122 (12.2%) female. The male/female ratio was 7.3:1 ($p<0.01$). The mean age was 63.0 years ($x=63.40 \pm 10.2$) for male and 65.5 years ($c=65.51 \pm 1.4$; $p<0.04$) for female patients.

Figure 1 shows the disease incidence rate for 5-year age groups. Bronchial and lung cancer are extremely rare before 40 years of age, so we found only 18 (1.8%) affected persons. In the next five-year age group (40-45), the incidence increased to 37 (3.7%), and in the 46-50 age group to 82 (8.1%). During the fifth decade of life, the number of affected grew from 1.8% in the <40 age group to 12.8% in the 40-50 age group. The highest incidence of 429 patients or 42.35% of all patients was recorded in the 61-70 age group.

Squamous cell cancer is still a lung cancer with the highest incidence in man, and was found in 41% (367/889) of cases, being most frequently diagnosed in the 66-70 age group with 24.1% (n=96) and 6l-65 age group with 18.6% (n=74) of patients. The second place was held by adenocarcinoma with 271 (30.5%) patients. Small cell anaplastic lung cancer was on the third place with 21.7% (n=193) of cases, most frequently diagnosed in the 6l-65 age group (21.3%). In women, adenocarcinoma had the highest incidence of 51.6% (63/122), followed by small cell anaplastic cancer with 22% (27/122) and squamous cell cancer with 20.4% (25/122) of patients. Adenocarcinoma was most frequently found in the 66-75 age group (41.6% of female patients), squamous cell carcinoma in the 56-65 age group with 22%, and small cell anaplastic cancer in the 66-70 age group with 28.7% of patients.

A history of smoking for more than 20 years was recorded in 917 (80.8%) patients, 85.3% (759/889) of male and 47.5% (58/122) of female.

Discussion

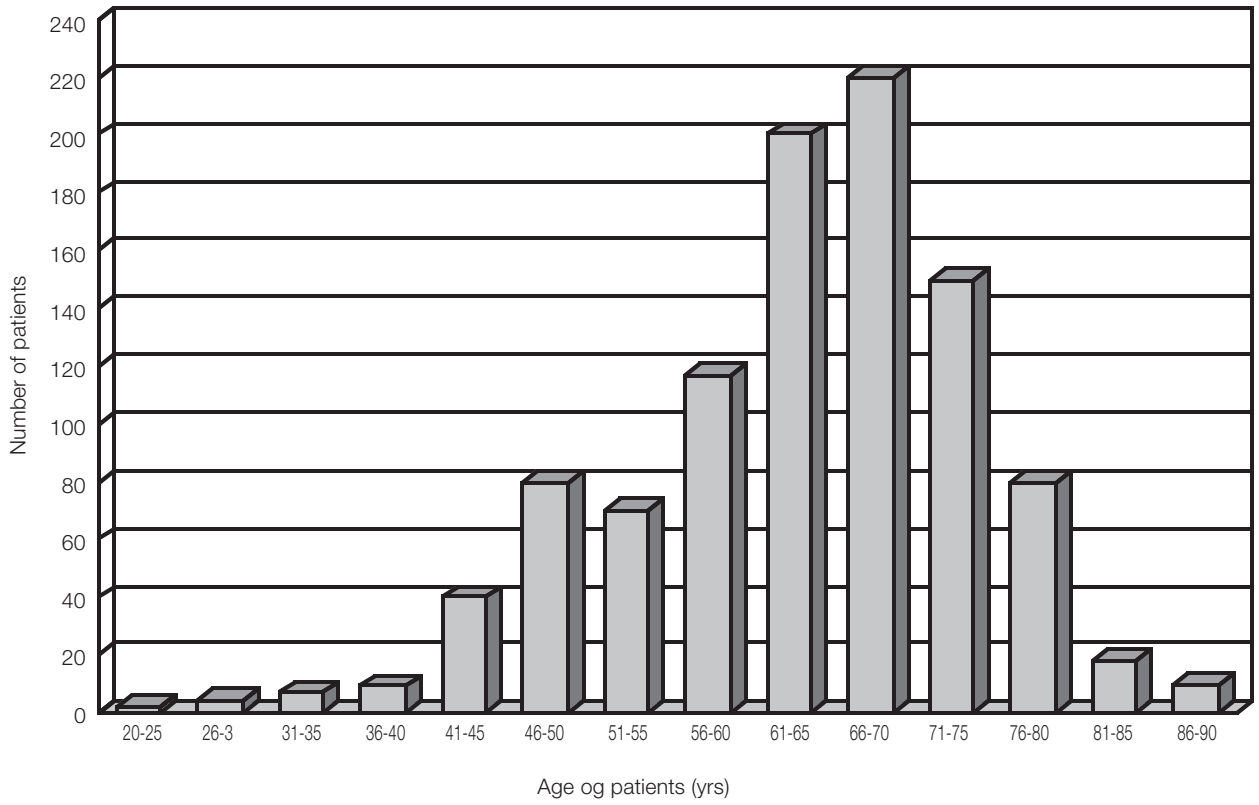
Lung cancer is one of the rare diseases that have spread during the last century at a pace incomparable in history: less than 90 odd years have passed from the first description in the literature, and it has already imposed itself during the last fifty years as a large and unresolvable medical and social problem worldwide[9,10,12,15]. Comparison of results obtained 20 years ago and those collected for the last three years leads to a conclusion that we are facing a quickly spreading disease in Croatia. Smoking is without doubt the major cause of lung cancer. Twenty years ago, 80.5% of patients were smokers, whereof 86.5% of male and only 17.6% of female, as reported by Miše *et al.*[1,7,8]. Certainly, smokers are most commonly affected by squamous cell carcinoma (92% of cases). A most recent study showed no decrease in smokers (84.7% of total number); however, the number of female patients who were smokers increased from 17.6% to 47%. Zelicort *et* a*l.* also report on an increase in women smokers who fell ill from lung cancer to 56% in France from 1985 to 1995[9]. The American and European authors also correlate smoking with lung cancer: Williams reports that 85%-90% of lung cancer patients in America are smokers[10], and Sobue's data for Japan show 90%[17], and Buiatti's for Italy 80%-85% of smokers[18] as lung cancer patients. Our data correspond with the global data by approximately 85%. However, some authors like Wynder[19] and Francheschi[12] write about a decreasing number of smokers in the USA, Denmark and north Italy since 1990, and a small decrease in lung cancer incidence in men but not in women. On the contrary, lung cancer in women is on an increase, particularly in south and southeast Europe. The data recorded for our region correspond with the global trends.

Lung cancer is a disease affecting male population from the high-risk group that include men over 45 years of age, those who smoke more that 20 cigarettes a day for more than 20 years, and persons exposed to detrimental carcinogenic substances. This can be confirmed by analysis of lung cancer incidence according to age groups (Fig. 1), which shows that it is extremely rare before 40 years of age (1.8%), and rare before 45 years of age (4.5%). Total number of persons affected before 50 years of age in our study was 11.8%, and Ramalingam *et al.* report on 9% of patients younger than 50[15]. Early lung cancer diagnosis is a problem, since patients mostly contact their doctors late, once they have already developed clinical and subjective problems. This calls for a national multi-level multidisciplinary strategy for lung cancer prevention, similar to the one implemented in Japan[17].

Twenty years ago, most patients were aged 61-65, whereas lately this has changed to 65-70 years of age, with most (42.3%) of patients in the seventh decade of life. In Moscow, over 50% of female patients with lung cancer are over 70 years of age[23].

Twenty years ago, 91.2% of patients were male and only 8.8% female. The male/female ratio was significantly unfavorable for men because only one woman was recorded *per* more than 10 affected men (10.4:1; $p<0.0002$)[7].

Fig. 1. Age distribution of lung carcinoma patients



However, this ratio has changed during the last decade with 87.9% of male and 12.1% female patients and the male/female ratio of 7.3:1 ($p<0.001$) (Fig. 2). There is a noticeable increase in the incidence of lung cancer in female patients. In other countries, it has been 3-5:1 for years[6,16,23]. In Croatia, this number has increased mainly due to the increase in the number of female smokers. Negri reports on an increase in lung cancer in women in south Europe by 24%, and in east Europe by 32%, as the result of an increased number of female smokers[20,23].

Comparison of the results obtained 20 years ago with those for the last three years shows an increase in the incidence of lung cancer in men and even more in women, both in Croatia and worldwide: by 2.4 times in male and 4.1 times in female population (Fig. 3).

Recently, changes have been recorded in the distribution of different types of lung cancer, with squamous cell carcinoma remaining in the leading position but with a slightly decreasing trend (from 45% to 43.4%) ($p<0.34$). A significant increase in the incidence of adenocarcinoma was noticed (from 20.3% to 30.5%; $p<0.0005$), which was

Fig. 2. Lung carcinoma types in males, periods 1 and 2

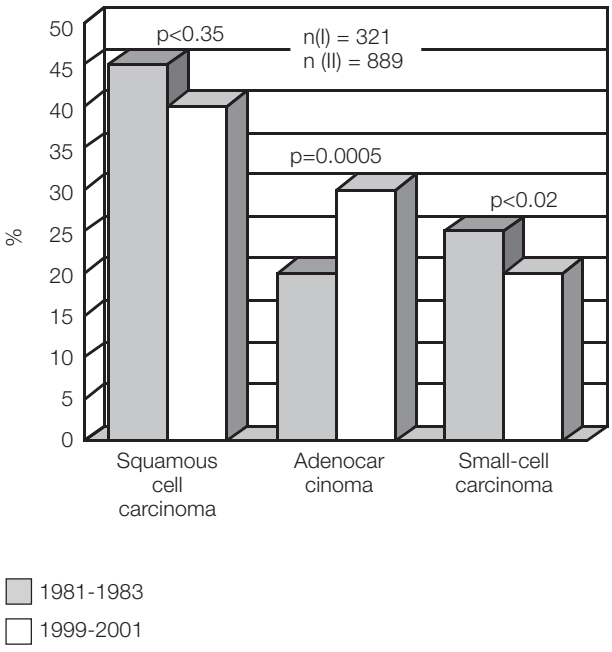
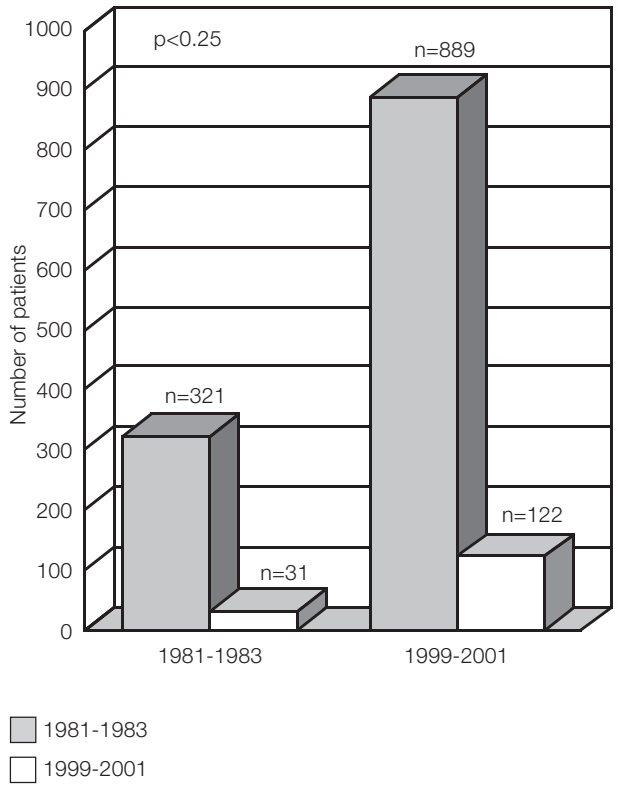


Fig. 3. Sex distribution of lung carcinoma in periods 1 and 2



due to the increase in the rate of adenocarcinoma in men since the number of affected women practically remained unchanged (51%). Small cell anaplastic carcinoma was on a significant decrease (from 27% to about 21%; p<0.01). There was an increase in the rate of squamous cell carcinoma in women (from 17.8% to 20.4%; p<0.03). Many authors report on a significant increase in lung adenocarcinoma in general, and in smokers as well, on the account of a decrease in the squamous cell carcinoma morbidity[11,14,17,19,20,22]. This has been attributed to the new design and technology in the manufacture of filter cigarettes, so called "light or low-yield" cigarettes with finer nicotine particles that penetrate deeper into the lungs and reach the periphery in higher quantities. The substance N-nitrosamine from nicotine may be inducing lung adenocarcinoma. Other provocation factors could also be added, such as specific living conditions in the analyzed area (region) during the last 10 years, caused by war and postwar events, and enormous psychical stress. This could be a provocation factor that contributed to the increase in the incidence of adenocarcinoma in male population. It should not be neglected that the diagnosis of small peripheral pulmonary lesions have improved over the last 20 years since the CT guided fine-needle aspiration biopsy of lungs has come into use. All these factors could be the cause of increase in the incidence of lung adenocarcinoma. Other types of lung carcinoma were rare, most often undifferentiated carcinoma (7%-8.9%).

During the war years of 1992 and 1993, a slight decrease in the morbidity compared to 1991 was noticed in our region, which was probably a consequence of large migration and immigration of the population caused by war, which entailed an increased admission of patients, refugees and displaced persons from the neighboring Bosnia and Herzegovina to the Department.

In the west European countries and United States of America, a decrease in the lung cancer morbidity rate has been consistently recorded, particularly due to intensive antismoking campaigns and ban on the use of asbestos and its products introduced in USA introduced 30 years ago[18,21], whereas some European countries have only recently placed ban on asbestos processing. However, the Croatian asbestos industry is still operating, although asbestos is being imported.

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Sažetak

EPIDEMIOLOŠKA ANALIZA RAKA PLUĆA U PODRUČJU SREDNJE DALMACIJE
(20-godišnji rezultati)

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Porast raka pluća zadnjih 20 godina ošit je i u našem području, i to višestruko. Širi se iz godine u godinu, kako u muškaraca tako i u žena. Bilježi se porast u muškaraca za 2,4 puta, a u žena čak za 4,2 puta. Najveći broj oboljelih su bili dugogodišnji pušači. Ova navika bila je još prije 30-tak godina značajka muškaraca, a sada sve više i žena (porast bolesnica koje su pušile od 17,8% na 47,3%). Najveći broj oboljelih je iznad 65. godine života, a zajedno s brojem onih iznad 60. godine života čine preko 42% oboljelih. Dokazana je povećana učestalost adenokarcinoma, koji nije bio u izravnoj vezi s pušenjem, na račun pada broja učestalosti planocelularnog raka pluća. Najveći porast nalazi se u poratnim godinama (2000. g. čak 32%), a za taj porast mogli bismo kriviti teške psihičke traume i ostale životne nedaće u ratu i nakon njega. Porast planocelualrnog raka u žena (sa 17,5% na 20,4%) je vjerojatno zbog većeg broja žena koje su pušile. Bilježi se pad mikrocelularnog anaplastičnog raka pluća, koji je podjednako zastupljen u oba spola (s 27% na 22,6%) oboljelih. Uspoređujući iznesene podatke iz jednoga dijela Hrvatske (priobalnog područja) s podacima iz svijeta možemo zaključiti da su epidemiološki podaci slični onima iz područja južne i jugoistočne Europe (južne Italije, Španjolske, Grčke).