

# Changing Trends in Incidence of Lung Cancer by Histological Type in Montenegro

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## SUMMARY

**Introduction** Lung cancer is one of the most common malignant neoplasms, as well as the most common cause of death cancer. Most lung cancers are squamous cell carcinomas, small cell carcinomas or adenocarcinomas.

**Objective** Examining changes in trends of lung cancer incidence in Montenegro by histological type during a 15-year period, from 1997 to 2011.

**Methods** During the study period, histopathological confirmation was obtained for all primary lung cancer cases in the only hospital for lung diseases in the country. Based on the data from medical records, patients were classified by time period, sex, age groups and smoking history. Descriptive method was used.

**Results** Ratio between incidences of adenocarcinoma and squamous cell carcinoma changes in males, with a significant increase in the incidence rate of adenocarcinoma and drop in the rate of squamous cell carcinoma ( $p < 0.001$ ). In addition, statistically significant ( $p < 0.05$ ) decrease in the incidence of NSCLC (non-small cell lung cancer) and an increase in the incidence of SCLC (small cell lung cancer) was found. A statistically significant increase in linear trend in the incidence of small cell carcinoma was noted in females ( $p < 0.005$ ).

**Conclusion** Incidence rates of adenocarcinoma and small cell carcinoma have increased during the study period.

**Keywords:** cancer; histological types; trends

## INTRODUCTION

Cancer is the second leading cause of death in economically developed countries [1]. Its global health burden is increasing due to aging and growth of the world population which is catalyzed by behaviors that represent a risk factor of cancer development. GLOBOCAN 2008 estimated that about 12.7 million cancer cases and 7.6 million cancer deaths occurred in 2008 [2]. Fifty-six percent of these cases and 64% of deaths took place in the economically developed countries [1, 2, 3]. Lung cancer incidence differs by geographic area, sex and age, being less common in developing countries, especially in Africa and South America [4]. Leaving apart the skin, lung is the most commonly affected organ by cancer in men; it comprises 17% of the total new cancer cases, and it accounts for 23% of the total cancer deaths [2]. The epidemic of lung cancer among women came after that among men, with rates rising steeply from the 1960s to the present [5, 6].

Breast carcinoma is the most commonly diagnosed type of cancer and the leading cause of cancer-related death among women, comprising 23% of the total cancer cases and 14% of the cancer deaths. Colorectal cancer is the second most frequently diagnosed cancer in women, while it is the third most frequently diagnosed cancer in men. Prostate cancer is the second most commonly diagnosed cancer and it is the

sixth leading cause of cancer-related death in men [2].

Lung cancer is classified into two subgroups: small-cell lung cancer (SCLC) and non small-cell lung cancer (NSCLC). Histological identification and tumor staging are immensely important in achieving optimal management of lung cancer. In the initial decades of the 20th century when the smoking-caused epidemic of lung cancer occurred, squamous cell carcinoma was the most frequent type of lung cancer that was observed in the population at risk, while the next most frequent type was small cell carcinoma [4].

Trends in incidence have varied by type in relation to exposures to other lung carcinogens and differences in smoking patterns [5-8].

## OBJECTIVE

This study aims at examining the trends in incidence of lung cancer by histological types in Montenegro from 1997 to 2011.

## METHODS

Study group comprised patients with the histopathological confirmation of primary lung cancer who were hospitalized in the Special Hospital for Lung Diseases "Brezovik" from

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**Table 1.** Number of new cases, crude and standardized incidence rates per 100,000 population in Montenegro in the period from 1997 to 2011

Year	Male			Female			All		
	Cases	Crude rate	Standard rate*	Cases	Crude rate	Standard rate*	Cases	Crude rate	Standard rate*
1997	151	49.5	35.7	22	6.9	4.5	173	27.9	18.6
1998	152	49.8	35.7	24	7.6	4.6	176	28.3	18.6
1999	166	54.3	38.8	27	8.5	5.7	193	31.1	20.5
2000	134	41.1	31.7	34	10.3	6.2	168	25.6	17.1
2001	139	42.4	35.2	28	8.4	5.9	167	25.3	19.1
2002	167	54.7	44.0	33	10.5	7.0	200	32.8	24.4
2003	149	48.8	37.4	27	8.6	5.8	176	28.4	20.6
2004	150	49.0	38.6	42	13.3	9.8	192	30.9	22.9
2005	160	52.1	38.6	38	12.0	7.2	198	31.7	21.4
2006	137	44.6	31.9	33	10.4	6.6	170	27.2	17.9
2007	149	48.4	34.2	40	12.5	7.3	189	30.1	19.3
2008	138	44.6	31.8	37	11.6	7.8	175	27.8	18.5
2009	143	46.0	32.5	35	10.9	7.0	178	28.2	18.6
2010	127	41.4	27.9	39	9.2	5.8	156	25.1	15.9
2011	132	43.1	28.8	31	9.8	5.7	163	26.2	16.0
Average	146	41.6	34.8	32	10.0	6.4	178	28.4	19.2

\* Segi's world population used as a standard.

1997 to 2011. Montenegro has one hospital for lung diseases, so all medical data concerning this study have been found there. Based on the data from medical records, patients were classified by the following characteristics: time period, sex, age group and smoking status. Ex-smokers were included in the group of smokers. Descriptive epidemiological method was used. Montenegro had a population of 620,145 in 1993 and 625,266 in 2011.

There were 1,000 more males than females. Registry personnel extracted information from the medical records department and pathological laboratory. All lung cancer patients were residents of Montenegro. Data that were extracted for each case included gender, histological subtype of cancer, age when diagnosis was established and date of diagnosis. Cases were grouped into the following histological subtypes based on morphological characteristics of the tumor: squamous cell carcinoma, adenocarcinoma, and other carcinomas including small cell and large cell carcinoma. Incidence rates were reported separately for males and females. Incidence rates were age- and sex-standardized by direct method based on the Segi's world population (from 0 to 44, from 45 to 54, from 55 to 64 years and people that are 65 years of age and older) [9].

Rates were calculated for both sexes separately for squamous cell carcinoma, adenocarcinoma and small cell carcinoma.

The linear regression was performed in the analysis of the incidence trends.

## RESULTS

During the study period, two types of lung cancer were established in patients, SCLC (24%) and NSCLC (76%). Two most important types of NSCLC-squamous cell carcinoma and adenocarcinoma, accounted for approximately 78% and 22% of all NSCLC cases, respectively.

In the period 1997–2011, a total of 2,675 new lung cancer cases were diagnosed (2,194 males and 481 females). The most frequent histopathological type in males was

squamous cell carcinoma (62.6%) followed by SCLC (22.6%), and then adenocarcinoma (14.8). In women, the most common type of cancer was squamous cell carcinoma (43.6%), followed by SCLC (29.8%) and adenocarcinoma (26.6%) and SCLC (29.8%).

Average crude incidence rate in the population was 28.4 per 100,000 p/y. The incidence peaked in 2002 (32.8 per 100,000 p/y) and thereafter the rates began to fall. Standardized incidence rates ranged from 15.9 per 100,000 p/y in 2010 to 24.4 per 100,000 p/y in 2002.

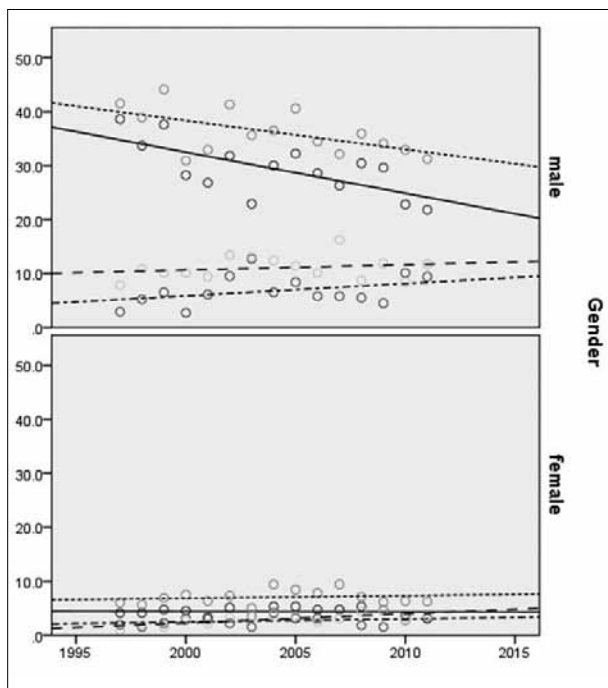
Average crude incidence rate in males was 41.6 per 100,000 p/y with its peak in 2002 (54.7 per 100,000 p/y). Standardized incidence rates in males ranged from 27.9 (2010) to 44 (2002) per 100,000 p/y and average standardized incidence rate was 34.8 per 100,000 p/y.

Average crude incidence rate in females was 10.0 per 100,000 p/y. Standardized incidence rates in the female population ranged between 4.5 (1997) and 9.8 (2004) per 100,000 p/y. Average standardized incidence rate was 6.4 per 100,000 p/y (Table 1).

Ratio between males and females was 5:1 in 1997 and fell to 4.5:1 in 2011.

In males, linear trend shows a significant decrease in the incidence ( $p < 0.01$ ) (SQL=1552.46-0.760\*Year;  $R^2=0.466$ ;  $t=-3.365$ ;  $p=0.005$ ) of squamous cell carcinoma. Incidence rate was the highest in 1997, at 38.6 per 100,000 p/y and thereafter began to fall (Graph 1). In 2011, the incidence of squamous cell carcinoma was 21.8 per 100,000 p/y. In females, incidence of squamous cell carcinoma ranged from 4.1 in 1997 to 5.3 per 100,000 p/y in 2003 and 2004. In 2011, the incidence was 3.1 per 100,000 p/y. During the study period, change in linear trend was not statistically significant ( $p > 0.05$ ) (SQL=17.250-0.006\*Year;  $R^2=0.001$ ;  $t=-0.132$ ;  $p=0.897$ ) (Graph 1).

In males and females, linear trend shows an increase in the incidences of adenocarcinoma, but it is not significant ( $p > 0.05$ ) (Males: ADL=-447.705+0.227\*Year;  $R^2=0.135$ ;  $t=1.426$ ;  $p=0.178$ ) (Females: ADL=-108.282+0.055\*Year;  $R^2=0.065$ ;  $t=0.953$ ;  $p=0.358$ ) (Graph 1). In males, the incidence of adenocarcinoma ranged from 2.9 per 100,000 p/y

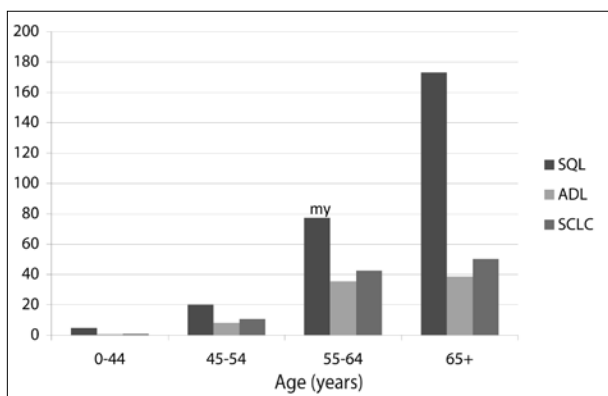


**Graph 1.** Linear trend in the incidence rates per 100,000 p/y for males and females of SQL, ADL and SCLC in the period from 1997 to 2011

(...) – non small cell carcinoma (NSCLC)  
 (---) – small cell lung carcinoma (SCLC)  
 (—) – squamous cell carcinoma of lung (SQL)  
 (---) – adenocarcinoma of lung (ADL)

in 1997 to 12.7 in 2003. In 2011, the incidence rate was 9.4 per 100,000 p/y. In females, in 2001 adenocarcinoma was the most predominant histological type of lung carcinoma (3.3 per 100,000 p/y; ratio SQL:ADL=0.9). Incidence rates ranged from 1.9 in 1997 to 4.7 in 2007.

Incidence of small cell carcinoma in males has increased, but not significantly ( $p > 0.05$ ) (linear trend:  $SCLC = -192.230 + 0.101 \cdot \text{Year}$ ;  $R^2 = 0.042$ ;  $t = 0.759$ ;  $p = 0.462$ ). Incidence of small cell carcinoma ranged from 7.8 per 100,000 p/y in 1997 to 11.7 per 100,000 p/y in 2011, peaking in 2007 (16.2 per 100,000 p/y). In females, linear trend shows a significant increase of small cell carcinoma ( $p < 0.005$ ) ( $SCLC = -336.322 + 0.169 \cdot \text{Year}$ ;  $R^2 = 0.540$ ;  $t = 3.909$ ;  $p = 0.002$ ) (Graph 1). Incidence of small cell carcinoma ranged from 0.9 per 100,000 p/y in 1997 to 3.5 per 100,000 p/y in 2011, peaking in 2009 (4.6 per 100,000 p/y).



**Graph 2.** Average age-standardized incidence rates for males in the period from 1997 to 2011

During the study period, ratio between the incidences of adenocarcinoma and squamous cell carcinoma changed in males, with a significant increase in the incidence rate of adenocarcinoma and a drop in the rate of squamous cell carcinoma ( $p < 0.001$ ) ( $t = -3.5721$ ) (Graph 1). Ratio between the incidences of squamous cell carcinoma and adenocarcinoma in males varied from 13.0 in 1997 to 2.3 in 2011.

Linear trends of squamous cell carcinoma and adenocarcinoma did not show a significant difference in females ( $p > 0.05$ ) ( $t = -0.8146$ ) (Graph 1). Ratio between the incidences of squamous cell carcinoma and adenocarcinoma ranged from 2.1 in 1997 to 1.0 in 2011.

During the study period ratio between the incidences of NSCLC and SCLC changed in males, with a significant decrease in the incidence rate of NSCLC and an increasing drop in the rate of SCLC ( $p < 0.05$ ) (linear trend:  $NSCC = 1104.755 - 0.533 \cdot \text{Year}$ ;  $R^2 = 0.572$ ;  $t = -2.517$ ;  $p = 0.026$ ) ( $SCLC = -192.230 + 0.101 \cdot \text{Year}$ ;  $R^2 = 0.206$ ;  $t = 0.759$ ;  $p = 0.462$ ;  $t = -2.533$ ) (Graph 1). During the study period ratio NSCLC / SCLC in males ranged from 5.0 in 1997 to 2.6 in 2011.

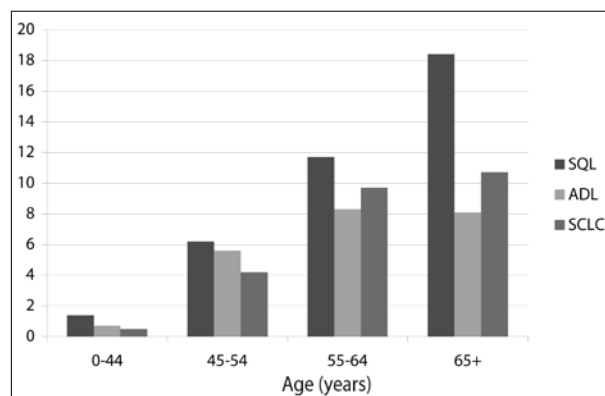
It was found that difference between trends of NSCLC and SCLC in females was not statistically significant ( $p > 0.05$ ) (linear trend:  $NSCC = -91.033 + 0.049 \cdot \text{Year}$ ;  $R^2 = 0.028$ ;  $t = 0.613$ ;  $p = 0.550$ ;  $SCLC = -336.322 + 0.169 \cdot \text{Year}$ ;  $R^2 = 0.735$ ;  $t = 3.909$ ;  $p = 0.002$ ;  $t = -1.325$ ) (Graph 1). Ratio between the incidence rates of NSCLC\* and SCLC\* changed from 6.6 in 1997 to 1.1 in 2003 and 1.8 in 2011.

Age-standardized incidence rates rose steeply for people aged 45 to 54, peaking in the oldest age group (Graphs 2 and 3). In men, lung cancer was most frequently diagnosed in the group 65+ years (51%, 1,128 persons), followed by 55-64 (34.5%, 756 persons) and 45-54 (11.6%, 225 persons).

In females, lung cancer was also most frequently diagnosed in the group 65+ years (41%, 197 persons), followed by 55-64 (38%, 185 persons) and 45-54 (17%, 84 persons).

The smokers to nonsmokers ratios in both males and females were high for squamous cell carcinoma (9.1:1; 3:1) ( $p < 0.001$ ) and SCLC (15.5:1; 8:1) ( $p < 0.001$ ). For adenocarcinoma, these ratios were 5.6:1 and 1.5:1 ( $p < 0.05$ ) in males and females, respectively.

In Montenegro, the incidence of lung cancer ranged from 27.9 per 100,000 per year (p/y) in 1997 to 26.2 per 100,000 p/y in 2011. The rate peaked at 32.8 per 100,000 p/y in 2002. Average number of new cases per year was 178.



**Graph 3.** Average age-standardized incidence rates for females in the period from 1997 to 2011

## DISCUSSION

In a number of developed countries, histological characteristics of lung cancer have changed in the past few decades so that the frequency of adenocarcinoma has risen while squamous cell carcinoma has become less frequent [8, 10]. Small cell carcinoma rates decreased less rapidly [5]. In Europe, squamous cell carcinoma remains the most predominant cell type of lung cancer but substantial increase in the adenocarcinoma frequency has occurred over time [10].

During the study period, lung cancer was the most commonly diagnosed cancer in men in Montenegro. The incidence of lung cancer has continued to fall in men from 54.7 per 100,000 p/y in 2002 to 43.1 per 100,000 p/y in 2011. The most frequent type of cancer in Montenegrin women was breast cancer. Estimated incidence of breast cancer in 2012 was 75.9/100,000 p/y [11].

Incidence range of lung cancer in women was between 6.9 per 100,000 p/y in 1997 and 12.5 per 100,000 p/y in 2007 and 9.8 per 100,000 p/y in 2011 (Table 1). In course of the study period, the histological types of lung cancer have also changed. These changes, as presented in the Results, are consistent with the results published by Devessa et al. [5] in 2005.

The increase in incidence of adenocarcinoma is not likely explained by changes brought about in classification system of lung cancer. As found by Campobasso et al. [12], the largest changes resulted from the reclassification of many large cell carcinomas to adenocarcinomas. Poorly differentiated adenocarcinomas and large cell carcinomas may overlap. The accuracy of histological diagnosis is dependent on the specimen size received by a pathologist. The introduction of flexible bronchoscope resulted in the increased use of sputum cytology [13] and fine-needle aspiration biopsy [14], and all have resulted in smaller biopsies. These diagnostic tools may have resulted in an increase in the number of positive diagnoses of lung cancer, while sacrificing accurate histological typing.

Approximately 85% of all cases of lung cancer occur in people that are smoking, or smoked at some point in their lives. A predominant cause of lung cancer is exposure to tobacco smoke, with active smoking being the biggest contributor, while passive smoking is also an identified contributor to the lung cancer burden. Cigarette smoking is identified as the major cause of all histological types of lung cancer. The risk of developing lung cancer is related to the following factors: number of cigarettes smoked, age at which the individual started smoking and duration of smoking [15]. Between exposure to tobacco smoke and development of lung cancer there is normally a long latent period. The relative risk of dying from cancer in smokers is 11-20 times higher than in nonsmokers [16].

Our results are consistent with results of Freedman's et al. study, where the strongest association with cigarette smoking has been demonstrated for squamous cell carcinoma and small cell carcinoma, whilst adenocarcinoma has not been as strongly correlated to smoking [17]. Rates

of all lung cancer types among women and adenocarcinoma among men have continued to rise in the past few decades in spite of declining cigarette use in many Western countries and shift to filtered/low-tar cigarettes [5]. Changes in cigarette design could have changed the location and histological distribution of lung cancers [18, 19, 20]. Rise in the incidence of adenocarcinoma has been mainly due to the dissemination of low-tar filter cigarettes which enabled the smoke to be inhaled deeper in the respiratory tract compared to earlier unfiltered cigarettes and release of higher concentrations of tobacco-specific carcinogens [21, 22]. Skuladottir et al. hypothesized that filter cigarettes remove large particles in cigarette smoke, thus reducing the deposition of these particles in the central airway where squamous cell carcinoma occurs, therefore exposing the peripheral part of the lung to carcinogenic smoke where adenocarcinoma develops more frequently [23].

There is a question if an increase of adenocarcinoma incidence in Montenegro could be explained only by changes in cigarette design though a shift to filtered and low-tar cigarettes was not much apparent in the last few decades; it took place over a period of 4-5 decades, what is still relevant for considering exposure. There would still be a remote theoretical possibility that changes in the incidence of histological types of lung cancers may indicate changes in the exposure to causal factors.

Factors such as occupational exposures to asbestos, radon and nitrogen oxide have been found to increase the risk of lung cancer [24, 25]. The most common type of lung cancer seen in asbestos and "scar"-related cancers is adenocarcinoma [24].

Out of the total number of lung cancers in the US, proportion of SCLC decreased from 17.26% in 1986 to 12.95% in 2002 [26, 27]. This decrease in incidence can most probably be explained by successful anti-smoking campaign that took place. However, in Montenegro, the incidence of SCLC has increased during the study period; it may most likely be explained by limited success of anti-smoking campaign in this country which began only in the previous decade. Furthermore, in this study, the association between cigarette smoking and histological type of lung cancer was different. In the smoking population, the most frequent histological type of lung cancers are small cell carcinomas and squamous cell carcinomas. SCLC mostly affects smokers and ex-smokers [27, 28]. Correlation between SCLC and smoking is very strong as it affects mostly patients with a clear smoking history.

Lung cancer is strongly related to age. In Montenegro, the peak incidence of all types of lung cancer in males and in females was in the seventh decade (Graphs 2 and 3).

## CONCLUSION

During the study period, the incidence rates of adenocarcinoma and small cell carcinoma have increased over time but squamous cell carcinoma remains the predominant type of lung cancer in Montenegro.

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## Патохистолошки трендови промене инциденција карцинома плућа у Црној Гори

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### КРАТАК САДРЖАЈ

**Увод** Карцином плућа је једна од најчешћих неоплазми и истовремено најчешћи узрочник смрти од свих малигних болести. Највећи део карцинома плућа се патохистолошки класификује у сквамоцелуларни карцином, микроцелуларни (ситноћелијски) карцином и аденокарцином.

**Циљ рада** Циљ истраживања је био да се проучи тренд промена инциденција карцинома плућа према патохистолошком типу током петнаестогодишњег периода (1997–2011) у Црној Гори.

**Методе рада** Током трајања студије патохистолошка потврда за све примарне карциноме плућа добијена је из једине болнице за плућне болести у држави. На основу података из медицинске документације, болесници су класификовани према временском периоду, полу, старосним групама и пушачкој историји. У овој студији је коришћена дескриптивна метода.

**Резултати** Код мушкараца се однос инциденција у оболевању од аденокарцинома и сквамоцелуларног карцинома мења, тако да је у посматраном периоду забележен значајни тренд пораста инциденције аденокарцинома, а смањења инциденције сквамоцелуларног карцинома ( $p < 0,001$ ). Такође, уочено је статистички значајно ( $p < 0,05$ ) смањење инциденције ситноћелијског карцинома и пораст инциденције ситноћелијског карцинома. Код жена је забележено статистички значајно повећање линеарног тренда инциденције ситноћелијског карцинома ( $p < 0,05$ ).

**Закључак** Према је током трајања студије уочено повећање стопа инциденција аденокарцинома и ситноћелијског карцинома, сквамоцелуларни карцином ипак остаје најчешћи вид плућног карцинома у Црној Гори.

**Кључне речи:** карцином; хистолошки типови; трендови

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