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Lung Cancer in Non-smokers in Czech Republic: Data from LUCAS Lung Cancer Clinical Registry

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Abstract. *Background/Aim: LUCAS is a clinical lung cancer registry (ClinicalTrials.gov identifier is NCT04228237), prospectively collecting data from newly diagnosed lung cancer patients in seven pneumooncology centers in the Czech Republic, since June 1, 2018. The aim of the study was to assess the stage of the disease at the time of diagnosis, percentage of morphological types, survival, percentage of driving mutations, eligibility for radical surgery, and percentage of patients who undergo radical surgery, in the non-smoking population in comparison with smokers and former smokers. Patients and Methods: The total number of patients in the registry at the time of the analysis was 2,743. Only 2,439 patients with complete records (smoking status, stage, and type of tumor) were included in this study. Results: The analysis indicated that non-smokers are diagnosed at a later stage of the disease but they have a better survival rate than smokers. Fewer smokers with stage III disease who are eligible for radical surgery will undergo surgery compared to non-smokers with the same clinical stage. Driving mutations are more common in non-smokers, even after adjustment for the more frequent occurrence of adenocarcinoma in the group of non-smokers. Conclusion: The data from LUCAS registry are consistent with already known facts, suggesting that the LUCAS registry is a useful clinical tool.*

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Lung cancer is one of the most common cancers. According to the World Health Organisation (WHO) data from 2020, compared to the other types of cancer, lung cancer shows the 2nd highest incidence in the overall population, the highest incidence among male patients (1,435,943 new cases) and the

3rd highest incidence among female patients (770,828 new cases). It is the leading cause of cancer-related death in men (1,188,679) and second most frequent in women (607,465) worldwide resulting in a total of 1,796.144 lung cancer related deaths in the year 2020 (1). Approximately 10-15% of all lung cancer cases are non-smokers (2).

In the Czech Republic, lung cancer is the 4th most frequently diagnosed type of cancer in the overall population. There were 4,243 new cases of lung cancer amongst men (incidence 81.5/100,000) and 2,350 in women (incidence 62.3/100,000) in the year 2017. In the same year, 3,639 cases of lung cancer related deaths were reported in men (mortality 69.9/100,000) and 1,824 in women (mortality 51.6/100,000). Compared to other European countries, the Czech Republic ranks 26th in both incidence and mortality (3).

Lung cancer is mostly associated with tobacco smoking, however, there is a group of lung cancer patients without history of tobacco use. According to the WHO non-smoker is any subject who has smoked fewer than 100 cigarettes in his/her lifetime or who has not smoked more than 1 cigarette per day over a period of 6 months (4).

The most important risk factor for the development of lung cancer in non-smokers is long-term radon exposure. Radon is a naturally occurring decay product of radium. Miners in uranium mines are exposed to radon, but domestic exposure is also possible, especially in buildings with poor foundations. During radon exposure, development of all histological types of lung cancer is possible, but adenocarcinoma is the most common (5).

Furthermore, particulate matter in the air is a proven human carcinogen. In addition to the exhaust gases, traffic makes a significant contribution to the solid air particles also by releasing particles from the use of car brakes. These are mainly Fe, Cu, Ba and Pb (6, 7).

The first reports on the harmful effects of passive smoking and its association with lung cancer dates back to 1981 (8). In 2002 an article was published stating a direct relationship between the intensity of passive exposure to smoking at home or at work and the risk of developing lung cancer (9).

Furthermore, exposure to asbestos, silicon, arsenic, pesticides, and solvents, whether at home or at work, is associated with an increased risk of lung cancer. In 2000, a European study, which included 650 non-smokers and 1,542 control subjects was published. It was shown that 28% of non-smoking men and 9% of non-smoking women were exposed to carcinogens in the working environment. In Asia, the possible causes of lung cancer in non-smokers are also household pollutants – oil fumes and smoke from burning coal during cooking (9, 10).

Chronic diseases, such as chronic bronchitis, interstitial pulmonary fibrosis, pneumonia, or tuberculosis can also increase the risk of lung cancer. Repeated remodelling of tissues damaged by the inflammatory process leads to a higher risk of DNA damage, mutations, and carcinogenesis. Due to the inflammatory process, antiapoptotic signals also propagate and neoangiogenesis occurs (11).

Moreover, the predominance of women among non-smokers with lung cancer may suggest an influence of hormones. Oestrogen receptors are present in both lung and lung tumor tissue and are expressed at higher levels in women, non-smokers, and some types of adenocarcinomas. Activation of these receptors leads to the expression of genes involved in cell proliferation. The influence of hormone replacement therapy, early menopause, pregnancy, and number of births is unclear (12, 13).

There are epidemiological data suggesting a higher familial risk for lung cancer development, regardless of tobacco smoking (12, 14). There is a possible influence of polymorphisms in DNA repair genes (15) and genes encoding enzymes important for carcinogen metabolism (16). The risk of lung cancer development is higher in patients with inherited p53 mutation (17).

A significant portion of non-small cell lung cancer (NSCLC) is linked to certain driving mutations. Many of these mutations are more likely to be found in non-smokers. In current practice, mutations in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*) and *ROS-1* rearrangements are commonly sought in newly diagnosed non-squamous NSCLC. These mutations enable tumor cells to resist apoptosis and stimulate growth and spread of the disease (18).

Patients and Methods

The source of the data used in this article is the national lung cancer registry LUng CAncer focuS (LUCAS). LUCAS is a joint project of the Czech Pneumological and Phthisiological Society, and the Czech medical society. The project prospectively monitors patients with lung cancer diagnosed in seven Czech pneumooncology centers. The project was launched on June 1, 2018.

LUCAS records basic parameters and performance status of all newly diagnosed patients with lung cancer. Morphological, immunohistochemical, immunochemical and molecular genetic characteristics of lung cancer cases are recorded in the registry. Data about treatment, including combinations and sequences, are also recorded. The course of the disease is assessed according to clinical and laboratory results.

The aim of the LUCAS project is to assess real clinical practice and care for patients with lung cancer in pneumooncology centers in the Czech Republic.

All the data and results published in this article were processed in cooperation with the Institute of Biostatistics and Analyses. Cox regression model was used to evaluate the influence of tobacco smoking on the survival of the patients. Kaplan–Meier curves were used to illustrate the survival of the patients. The Pearson Chi-Square test was used to calculate statistical significance. Data were

Table I. *Basic characteristics of the analysed population.*

Parameter	Total (n=2,439)	Smoker (n=1,309)	Former smoker (n=831)	Non-smoker (n=299)
Gender - n (%)				
Female	921 (37.8%)	482 (36.8%)	233 (28.0%)	206 (68.9%)
Male	1,518 (62.2%)	827 (63.2%)	598 (72.0%)	93 (31.1%)
Age at the time of the diagnosis				
n	2,439	1,309	831	299
Mean value (SD)	68.7 (8.62)	66.9 (8.05)	71.4 (7.57)	68.8 (11.40)
Median	69	68	72	71
Min-Max	24-99	24-87	41-93	34-99
PS - n (%)				
0	557 (23.6%)	287 (22.6%)	178 (22.2%)	92 (31.6%)
1	1,314 (55.6%)	714 (56.1%)	457 (57.1%)	143 (49.1%)
2	380 (16.1%)	212 (16.7%)	127 (15.9%)	41 (14.1%)
3	113 (4.8%)	59 (4.6%)	39 (4.9%)	15 (5.2%)
Not evaluated	75	37	30	8
Stage - n (%)				
I	215 (8.8%)	118 (9.0%)	71 (8.5%)	26 (8.7%)
II	202 (8.3%)	96 (7.3%)	80 (9.6%)	26 (8.7%)
III	692 (28.4%)	390 (29.8%)	255 (30.7%)	47 (15.7%)
IV	1,330 (54.5%)	705 (53.9%)	425 (51.1%)	200 (66.9%)
Morphology – n (%)				
Adenocarcinoma[1]	1,071 (43.9%)	512 (39.1%)	328 (39.5%)	231 (77.3%)
Squamous	720 (29.5%)	412 (31.5%)	277 (33.3%)	31 (10.4%)
SCLC	425 (17.4%)	271 (20.7%)	142 (17.1%)	12 (4.0%)
NOS	101 (4.1%)	53 (4.0%)	37 (4.5%)	11 (3.7%)
Other[2]	122 (5.0%)	61 (4.7%)	47 (5.7%)	14 (4.7%)

[1]Adenocarcinomas and adenosquamous carcinomas merged; [2]The group "Other" includes neuroendocrine and large cell carcinomas.

Table II. *General overview of driving mutations in non-small cell lung cancer patients.*

Parameter	Total (n=2,014)	Smoker (n=1,038)	Former smoker (n=689)	Non-smoker (n=287)
Mutations - n (%)				
No mutation	1,804 (89.6%)	984 (94.8%)	627 (91.0%)	193 (67.2%)
ALK positive[1]	39 (1.9%)	8 (0.8%)	9 (1.3 %)	22 (7.7%)
EGFR positive[1]	134 (6.7%)	28 (2.7%)	38 (5.5 %)	68 (23.7%)
Other mutations[2]	37 (1.8%)	18 (1.7%)	15 (2.2%)	4 (1.4%)
KRAS+	18 (0.9%)	8 (0.8%)	10 (1.5%)	0
BRAF+	8 (0.4%)	4 (0.4%)	3 (0.4%)	1 (0.3%)
MET+	4 (0.2%)	4 (0.4%)	0	0
ROS-1+	4 (0.2%)	1 (0.1%)	1 (0.1%)	2 (0.7%)
RET+	2 (0.1%)	1 (0.1%)	0	1 (0.3%)
NRAS+	1 (<0.1%)	0	1 (0.1%)	0

[1]Patients with positive mutations ALK or EGFR in combination with ROS-1+ or MET+ are included in the *EGFR* or *ALK* positive group. [2]Specific other mutations are listed below, percentage in relation to the total number of patients.

adequately adjusted for the influence of age and stage of the disease. We aimed to assess certain parameters in the non-smoking population in comparison with smokers and former smokers. Specifically, the stage of the disease at the time of diagnosis, percentage of morphological types, survival, percentage of driving mutations, eligibility for radical surgery, and percentage of patients who undergo radical surgery.

Results

General characteristics of the analysed population. The overall population was further divided into subgroups of smokers (1,309, 53.7%), former smokers (831, 34.1%) and non-smokers (299, 12.3%). Within the non-smoking group,

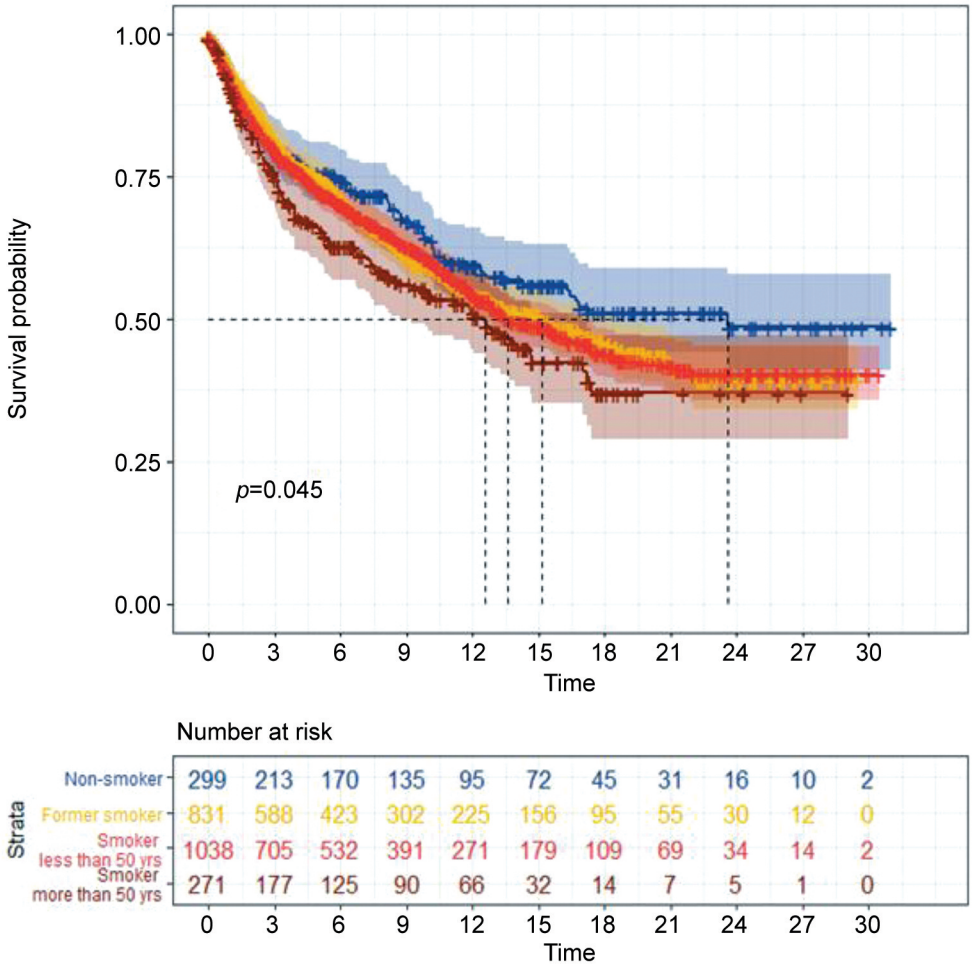

Figure 1. *Differences in overall survival: non-smokers vs. former smokers and smokers. Smokers were further divided into patients smoking for more than 50 years and those for less than 50 years. Overall survival correlates with tobacco smoking load.*

although without statistical significance (*p*-value for gender, stage, and morphology <0.001), the highest percentage were women with stage IV disease at the time of diagnosis, and adenocarcinomas, whereas the lowest percentage were small cell lung cancer (SCLC) and squamous carcinomas, which is consistent with other cohorts (19). There was a switch from 7th to 8th TNM during the data collection, therefore only stages I to IV were used, without further division (Table I).

Within the group of 2,014 NSCL patients, divided into smokers (1,038), former smokers (689), and non-smokers (287), the non-smoking subgroup had the highest representation of *ALK* (7.7%) and *EGFR* (23.7%) mutations. The number of patients in the group of other mutations was too small and the differences were therefore statistically insignificant (Table II).

Influence of tobacco smoking on the overall survival (OS). Cox regression model was used to evaluate the influence of tobacco smoking on the OS of the patients. The non-smoking group was used as a reference. The smoking group was further divided into patients smoking for more and less than 50 years. The Kaplan–Meier curve showed OS differences between non-smokers, former smokers, smokers smoking for less than 50 years, and smokers smoking for more than 50 years. As expected, the group with the highest smoking load

Table III. *Risk of death adjusted for age and stage of the disease.*

Risk of death	n	Hazard ratio (95%CI)	*p*-Value
Non-smoker (reference)	299	1	
Former smoker	831	1.27 (1.02-1.57)	**0.029**
Smoker – less than 50 years	1,038	1.42 (1.15-1.75)	**0.001**
Smoker – more than 50 years	271	1.54 (1.19-2.00)	**0.001**

CI: Confidence interval. Bold *p*-Values indicate statistical significance.

Table IV. *Morphology in non-smokers vs. smokers/former smokers.*

Morphology	Smokers and former smokers (n=2,140)	Non-smokers (n=299)	*p*-Value
Adenocarcinoma[1]	39.3% (n=840)	77.3% (n=231)	**<0.001**
NOS	4.2% (n=90)	3.7% (n=11)	
SCLC	19.3% (n=413)	4.0% (n=12)	
Squamous	32.2% (n=689)	10.4% (n=31)	
Other[2]	5.0% (n=108)	4.7% (n=14)	

The Chi-squared test was used to calculate statistical significance. Bold *p*-Value indicates statistical significance. NOS: Non-otherwise specified; SCLC: small-cell lung cancer. [1]Adenocarcinomas and adenosquamous carcinomas merged. [2]The group "Other" includes neuroendocrine and large cell carcinomas.

Table V. *EGFR mutations in non-small cell lung cancer patients.*

EGFR positivity	Smokers and former smokers (n=1,727)	Non-smokers (n=287)	*p*-Value
EGFR positive[1]	3.8% (n=66)	23.7% (n=68)	**<0.001**
EGFR negative	96.2% (n=1,661)	76.3% (n=219)	

The Chi-squared test was used to calculate statistical significance. Bold *p*-Value indicates statistical significance. [1]Patients with positive mutations ALK or EGFR in combination with ROS-1+ or MET+ are included in the EGFR or ALK positive group.

Table VI. *EGFR positivity in adenocarcinoma/NOS patients.*

EGFR positivity	Smokers and former smokers (n=930)	Non-smokers (n=242)	*p*-Value
EGFR positive[1]	7.1% (n=66)	27.7% (n=67)	**<0.001**
EGFR negative	92.9% (n=864)	72.3% (n=175)	

The Chi-squared test was used to calculate statistical significance. Bold *p*-Value indicates statistical significance. [1]Patients with positive mutations ALK or EGFR in combination with ROS-1+ or MET+ are included in the EGFR or ALK positive group.

Table VII. *Stage of the disease at the time of diagnosis.*

Stage	Smokers and former smokers (n=2,140)	Non-smokers (n=299)	*p*-Value
I	8.8% (n=189)	8.7% (n=26)	**<0.001**
II	8.2% (n=176)	8.7% (n=26)	
III	30.1% (n=645)	15.7% (n=47)	
IV	52.8% (n=1,130)	66.9% (n=200)	

The Chi-squared test was used to calculate statistical significance. Bold *p*-Value indicates statistical significance.

had the worst OS. Also, there was an increasing risk of lung cancer development in former smokers (Figure 1).

There was a statistically significant higher risk of death in the group with the highest load of tobacco smoking, even after adjustment for age and stage of the disease for groups of former smokers, smokers smoking for less than 50 years and smokers smoking for more than 50 years (Table III).

Differences in morphological diagnosis, driving mutations, stages, and radical surgery between groups of non-smokers and smokers/former smokers. As for the morphological types of lung cancer in the groups of non-smokers and smokers merged with former smokers, there was a statistically significantly higher percentage of adenocarcinomas and lower number of squamous carcinomas and SCLC in the non-smoking group (Table IV).

Positivity for *EGFR* mutations in NSCLC patients was significantly higher in the non-smoking group (Table V); the same applies for adenocarcinoma/non-otherwise specified (NOS) patients only (Table VI). There was a significantly higher percentage of stage IV and lower percentage of stage III in the non-smoking group at the time of diagnosis compared with smokers/former smokers (Table VII).

Differences in percentage of a radical surgery treatment in the groups of non-smokers and smokers/former smokers were without any statistical significance in both NSCLC and small cell lung cancer (SCLC) patients. We decided to include SCLC patients just for completeness, because this morphological type of lung cancer is operated very rarely, mostly for the purpose of diagnosis, and radical surgery is incidental (Table VIII).

There was a slightly higher number of non-smoking patients with clinical stage I and II, who underwent radical surgery, in both the overall and NSCLC groups, but without statistical significance (Table IX).

There was a statistically significantly higher number of non-smokers in clinical stage III, who underwent radical surgery. In further division into subgroups, the difference was also present in the NSCLC group, but it was statistically insignificant (Table X).

Discussion

The non-smokers are diagnosed at a later stage of the disease (Table I, Table VII). There was a significantly higher representation of stage IV and lower percentage of stage III in the non-smoking group. There are most likely two reasons behind this phenomenon. First, the non-smokers tend to be less a polymorbid type of patient, as tobacco smoking damages not only respiratory apparatus, but it also increases, *e.g.*, the risk of cardiovascular diseases (20). Smoking is often associated with a generally unhealthy lifestyle (21). Non-smokers are an overall healthier population and therefore lung cancer may take longer time to manifest. The second possible reason may be the

Table VIII. *Radical surgery across all clinical stages*.

	Smokers and former smokers	Non-smokers	*p*-Value
Radical surgery			
N	2,140	299	
Radical surgery	15.8% (n=338)	17.7% (n=53)	0.394
Without radical surgery1	84.2% (n=1,802)	82.3% (n=246)	
Radical surgery in NSCLC patients			
N	1,727	287	
Radical surgery	19;3% (n=333)	18.5% (n=53)	0.745
Without radical surgery1	80.7% (n=1,394)	81.5% (n=234)	
Radical surgery in SCLC patients			
N	413	12	
Radical surgery	1.2% (n=5)	0% (n=0)	>0.999
Without radical surgery[1]	98.8% (n=408)	100% (n=12)	

The Chi-squared test was used to calculate statistical significance. [1]Patients with non-radical surgery or without any surgery are included.

Table IX. *Radical surgery in stage I and II patients*.

	Smokers and former smokers	Non-smokers	*p*-Value
Radical surgery			
N	365	52	
Radical surgery	65.8% (n=240)	75.0% (n=39)	0.185
Without radical surgery[1]	34.2% (n=125)	25.0% (n=13)	
Radical surgery in NSCLC patients			
N	353	52	
Radical surgery	66.6% (n=235)	75.0% (n=39)	0.225
Without radical surgery[1]	33.4% (n=118)	25.0% (n=13)	
Radical surgery in SCLC patients			
N	12	0	
Radical surgery	41.7% (n=5)	-	-
Without radical surgery[1]	58.3% (n=7)	-	

The Chi-squared test was used to calculate statistical significance. [1]Patients with non-radical surgery or without any surgery are included.

Table X. *Radical surgery in stage III patients*.

	Smokers and former smokers	Non-smokers	*p*-Value
Radical surgery			
N	645	47	
Radical surgery	13.6% (n=88)	25.5% (n=12)	**0.025**
Without radical surgery[1]	86.4% (n=557)	74.5% (n=35)	
Radical surgery in NSCLC patients			
N	526	47	
Radical surgery	16.7% (n=88)	25.5% (n=12)	0.128
Without radical surgery[1]	83.3% (n=438)	74.5% (n=35)	
Radical surgery in SCLC patients			
N	119	0	
Radical surgery	0% (n=0)	-	-
Without radical surgery[1]	100% (n=119)	-	

The Chi-squared test was used to calculate statistical significance. Bold *p*-Value indicates statistical significance. [1]Patients with non-radical surgery or without any surgery are included.

insufficient awareness regarding lung cancer among non-smokers not only in the general population, but also among the medical professionals (22). In case of smoking patients, or former smokers with cough, the lung cancer is considered immediately, but the diagnosis may take longer in non-smokers.

Although non-smokers are diagnosed at a later stage of lung cancer, they have a better survival rate than smokers, even after adjustment for the influence of age and clinical stage of the disease (Table III, Figure 1). Similarly to the previous point, this may be due to an overall better condition of the non-smoking population, and also to the more frequent adenocarcinoma morphology and targetable driving mutations. Smokers and former smokers tend very often to suffer from chronic obstructive pulmonary disease (COPD) (23), chronic cardiovascular diseases or even other types of cancers (24, 25). Non-smokers are healthier and more capable to withstand various, often challenging, treatment modalities. As expected, the group with the highest smoking load had the worst results. The data also illustrate the continued risk of lung cancer development even after smoking cessation (26).

Fewer smokers in clinical stage III, eligible for radical surgery, will actually undergo surgery, compared to non-smokers in the same clinical stage (Table VIII, Table IX and Table X). The smoking population is very often burdened with COPD in various stages. Persistent airflow limitation is an integral part of COPD (27). To be able to undergo resection of the required part of the lung parenchyma, the patient must have sufficient reserve, which in many cases of lung cancer patients with COPD is severely compromised (28), and therefore other treatment modalities, *e.g.,* stereotactic radiotherapy, must be considered in these patients instead of the radical surgery.

Driving mutations are more common in non-smokers, even after adjustment for more frequent occurrence of adenocarcinoma in non-smokers (Table I, Table II, Table IV, Table V and Table VI). We hypothesize that this may be due to the different circumstances, under which cancer is developing. More specifically - in the absence of the influence of a potent carcinogen, like tobacco smoking, there is a higher probability that a genetic predisposition (*e.g.*, inherited p53 mutation) is present and facilitates carcinogenesis, independently of the type of lung cancer (17).

Conclusion

The general conclusions derived from the analysis of the LUCAS registry are consistent with already known facts, which suggest that the LUCAS data are a valid source for clinical practice. Analysis of this registry shows that the non-smokers with lung cancer are more frequently women, the percentage of adenocarcinomas is higher and survival is slightly better. The smokers and former smokers are more limited by comorbidities, mainly COPD and cardiovascular diseases, which can prevent them from radical surgery, mainly in clinical stage III of the disease. Smokers and former smokers also have worse survival, despite earlier diagnosis, compared to non-smokers. The non-smokers with lung cancer are diagnosed in later stages of the disease, because they escape screening programs since they lack the main risk factor – tobacco smoking.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Ondrej Venclicek, Jana Skrickova, Kristian Brat: conceived and designed the analysis, wrote the paper. Ondrej Fischer, Libor Havel, Michal Hrnciarik, Miloslav Marel, Petr Opalka, Gabriela Krakorova, Denisa Rozsivalova, Juraj Kultan, Andrea Mullerova, Lydia Zarnayova, Petra Smickova, Martina Vasakova, Zsuzsanna Gyorfy, Michal Jirousek, Daniel Krejci, Jana Krejci, Petr Zuna, Martin Svaton, Kristyna Hrda: collected and contributed the data, critically revised manuscript. Jaroslav Duba, Jana Alahakoon: contributed analysis tools, performed the analysis. Michal Svoboda, Jiri Silar: contributed analysis tools, performed the analysis.

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