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DOI: 10.2478/rjom-2024-0003

Original papers

Occupational domains and age at onset of lung cancer diagnosis

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Abstract

Introduction: Occupational cancer is a major public health issue and continuous efforts are developed all around the world to find better solutions to decrease this prevalence. This is important in particular for the persons diagnosed earlier, as they might have different prognosis and health-related quality of life.
Objectives: The main objective of the study is to present the prevalence of the early diagnosed lung cancer in different activity domains and possible factors associated to a younger age recognition.
Methods: This is a secondary analysis of data collected during the ROMCAN project (reference/acknowledgements). From the whole data-base we have received only anonymized data concerning lung cancer. Age, gender, level of education, occupational domain, smoking, personal medical history, family history of cancer was included in the analysis. Based on the distribution of age in the whole sample, we considered the early diagnosis any diagnosis before 56 years of old; the others were considered the control group. Among the demographic factors only education seems to be of influence ($\chi 2=31.24$, $p< 0.001$). Family history was more prevalent in the earlier diagnosed group ($OR=1.4$, $p=0.009$). In terms of occupational domains, the highest prevalence at younger age was in the leather industry (57.14%), trade services (42.22%), extractive industry (34.62%) wood and furniture (34.48%) domains.
Conclusions: Occupational exposure to carcinogens contributes to the early development of lung cancer but other elements (smoking, socio-economic level, comorbidities), have also a significant role. Based on these results, awareness related to lung cancer in extractive, leather, wood manufactures and trade should be re-in forced.

Keywords: *lung cancer, early diagnosis, occupational domains*

Introduction

Cancer is the second leading cause of death after cardiovascular diseases, with major effects on health and social protection systems. Current evidence shows that 40% of cancers might be prevented if all scientific knowledge would be implemented in real life actions [1].

Worldwide, lung cancer ranks second in total number of diagnosed cases of cancer, being the most common in men and the third in frequency in women [2]. The increase in incidence in the last century, especially in women, gives it a priority position in public health. The statistics in Romania overlap with the European ones as this type of cancer represents the most common cancer in men, and is in the fourth place in terms of frequency in women [3].

The transformation of the normal cell into a tumor cell, follows, in general, several steps: the initiation phase, characterized by a direct or indirect genotoxic action of the carcinogens, followed by the promotion stage which leads to the uncontrolled multiplication of the malignant cell. The type and speed of these changes depend genetic, gender, age, race and behavioral factors contributing to the defense mechanisms against the development of cancer. Therefore, the extent and form of the carcinogenic response has a large inter-individual variation.

For that matter, like any form of cancer, the etiology of lung cancer is multifactorial. Smoking has long been considered the most common cause of lung cancer. However, some studies - Samet et al., showed that even by eliminating smoking, the incidence of lung cancer did not decrease as much as we would have expected. Current incidence still places it in the top 10 worldwide among all forms of cancer [4].

In the last decade, the incidence of lung cancer diagnosed in advanced stages is continuously decreasing; thus, the diagnosis of localized forms raised from 17% in 2004 to 28% in 2018, which led to an increase in the 3-year survival rate from diagnosis from 21% to 31% [5]. This is due to the improvement in medical practice, particularly regarding screening and treatment. United States Preventive Services Task Force recommends, from 2021, reducing the age for the annual examination by low-dose computed tomography (LDCT) from 55 to 50 years and the number of packages/year from 30 to 20. The recommendation includes adults between 50 - 80 years old, smokers. Screening programs do not include people who have been abstinent for 15 years or whose health conditions prevent lung excision surgery [6]. Occupational exposure to carcinogens is not explicitly included, but should be considered in such screenings. A research report from the UK in 2012, estimates a total, both men and women, of the fraction attributable to occupational exposure in lung cancer of 14.47% (95% CI = 13.0 – 17.2) [7]. The potential synergism between smoking and some occupational carcinogens should also be considered [8]. Frost et al. pointed out that smokers and those who quit smoking and work in environments with asbestos exposure have an increased risk of lung cancer compared to non-smokers, who work in the same environment [9].

While the majority of cancers still occurs after the 6th decade of age [10], patients diagnosed earlier than 45 years old have worse survival rate [11]. Therefore, we conducted an analysis to evaluate if occupational exposure has any influence in the earlier age of diagnosis of lung cancer.

Material and methods

The analysis presented in this article is a secondary processing of data collected in the ROMCAN project, a research study which included only hospitalized patients with primary lung cancer. The hypothesis of the current analysis was that the occupational exposure characteristic of some fields of activity causes cancer at a younger age.

A number of 1473 consecutive hospitalized patients who signed an informed consent were included. For these patients, the following data were recorded: age at diagnosis, gender, occupation, smoking status (including maximum and minimum number of cigarettes smoked/day, age of smoking initiation and age of smoking cessation), body mass index at 20 years, 2 years before diagnosis and current, the family history of cancer. Among the personal medical history, the followings were selected for this analysis: personal history of cancer, lung infections, including tuberculosis and bronchial asthma.

The statistical analysis was performed with an SPSS software program (StatPlus: mac, AnalysisSoft Inc. – statistical analysis program for macOS. Version v8). The dependent variable was the age of onset of lung cancer. The independent variable was the occupation and the field of activity, and the predictive variables were demographic data: gender, level of education and classification as a smoker, non-smoker. Testing the link between these variables was done with regression analysis. The relationship between the nominal variables was calculated using the χ^2 test. The threshold of statistical significance was set at a probability of 95%, respectively at a value of $p<0.05$.

TThe age of the patients ranged between 28 and 80 years. The sample was divided into two categories based on the age at which lung cancer was diagnosed. The study group (early onset of cancer) was represented by patients with an age in the 25% percentile. Based on the studied sample, the 25% percentile was calculated at 56 years. Therefore, the patients under the age of 56 formed the study group and the patients aged ≥ 56 years at the time of diagnosis were included in the control group.

Initially, the coding was done on the fields of activity: agriculture, extractive industry, manufacturing industry, production and supply of electricity, heat, gas, hot water and air conditioning, construction, trade, transport and storage, services (hotels and restaurants, information and communications,

Table 1. Demographic data

	Total	Study group	Control group	p
Age (average ± SD)	1473	327	1146	
Gender				0.23
Women (no, %)	325 (22.06%)	90 (27.69%)	235 (72.31%)	
Men (no%)	1148 (77.94%)	281 (24.48%)	867 (75.52%)	
Level of education**				<0.0001
Primary school	63 (4.27%)	5 (0.33%)	58 (3.93%)	
Secondary school	188 (12.76%)	28 (1.9%)	160 (10.88%)	
Lyceum without graduated exam or apprentice school	540 (36.66%)	133 (9.03%)	407 (27.63%)	
Lyceum with bachelor diploma	212 (14.39%)	66 (4.48%)	146 (9.9%)	
Post lyceum school	195 (13.24%)	29 (1.99%)	166 (11.27%)	
Faculty	275 (18.67%)	64 (4.34%)	211 (14.32%)	
Smoking				
Smokers or former smokers (no, %)	1200 (82.3%)	268 (22.33%)	932 (77.67%)	0.82
Non-smokers (no, %)	258	56	202	
Family history for cancer* (no, %)	325 (22.06%)	102 (26.49%)	283 (73.51%)	0.01
Personal medical history				
Lung infections (no, %)	324 (22.08%)	60 (19.73%)	264 (80.27%)	0.26
Tuberculosis (no, %)	92 (6.25%)	21 (22.83%)	71 (77.17%)	0.85
Bronchial asthma (no%)	20 (1.36%)	4 (20%)	16 (80%)	0.82
Other neoplazia (no, %) *	132 (8.99%)	19 (14.39%)	113 (85.61%)	0.02

*p<0.05; **p<0.01.

professional and scientific activities, administrative and support services, public administration and defense, education, health and social assistance, other service activities, activities of private households). The relatively small number of cases in the field of extractive industry and the field of production and supply of electricity, thermal energy, gas, hot water and air conditioning imposed the cumulation with the processing industry in a wider category, called - industrial activities.

For each field of activity, the number of study participants included in the two age categories was identified. The differences in age of cancer diagnosis according to the domain of activity was tested. Then the analysis of the whole sample was stratified according to the subgroups of smokers and comorbidities considered as favoring tumor development.

The occupational categories with high number of cases were compared to the number of cases estimated in the total sample. For comparability, their ranking was done by dividing the excess in prevalence by the total number of participants in the respective occupational domain.

Results

The general data of the two groups of patients included in this analysis are shown in Table 1. Regarding smoking, former smokers were included as non-smokers if they stopped smoking at least 5 years before the lung cancer diagnosis; some missing data to calculate this smoking status were excluded.

As seen from Table 1, the number of women was lower than that of men and this structure was also maintained in the distribution by age groups ($\chi2=1.39$, $p=0.23$). Regarding the level of education, most cases in the study group were registered among people with high school education without graduated exam or vocational school (40.92% of the study group), followed by those with high school education completed with baccalaureate (20.31% of the study group) and those with university degrees (19.69% of the study group). In the control group, most cases were also registered among people with high school education without graduated exam or vocational school (35.45% of the control group), followed by people with university education (18.38% of the control group) and those with post-secondary education (14.46% of the control group). The difference in the distribution of cases according to the level of education was statistically significant ($\chi2=31.24$, $p< 0.001$).

The relationship between BMI at 20 years and BMI 2 years before diagnosis did not correlate with age of lung cancer diagnosis (Table 2).

Table 2. Correlation between BMI and age at diagnosis

Variable	OR	LCL	UCL
BMI at 20 years old	0.97	0.94	1.01
BMI 2 years before the diagnosis	0.98	0.95	1.001

Among the comorbidities, only diabetes and the presence of another neoplasia in the personal pathological history were statistically significantly more frequent among patients in the control group ($\chi2=27.82$, $p< 0.001$ and $\chi2=4.98$, $p= 0.02$, respectively.

Pulmonary infections, pulmonary tuberculosis and asthma had similar distribution in the two groups. In contrast, a family history of cancer was more frequent in the study group and the difference was statistically significant ($\chi2=5.95$, $p=0.01$). The Fisher test indicated an OR=1.4 ($p=0.009$) for family history of neoplasia.

Regarding smoking status, there was no statistically significant difference between the groups ($\chi2=0.05$, $p=0.83$). The age of onset of smoking had no influence on the age of onset of lung cancer (OR=0.99, LCL = 0.96, UCL=1.01, $p=0.33$), but the number of pack-years negatively influenced the age of onset of lung cancer (OR=1.01, LCL=1.009, UCL=1.02, $p<0.001$).

The distribution of the age of diagnosis on the activity domain was significantly different ($\chi2= 40.3$, $p= 0.001$).

The number of cases in the study group was 325, representing 22.09% of the total sample. Larger percentages (higher to lower) were recorded in: leather processing industry, trade, extractive industry, furniture and woodworking industry, recreational industry, security and protection services, construction, food industry, power generation, military, transport, medical services, welders and metallurgical and non-metallic materials industry and medical services (Table 3).

Table 3. Distribution by activity domain

Occupational domain	Total	Study group (N, %)	Control group (N, %)
Agriculture	153	27 (17.65%)	126 (82.35%)
Industry	515	110 (21.36%)	405 (78.64%)
Extractive	26	9 (34.62%)	17 (65.38%)
Food industry	24	6 (25%)	18 (75%)
Textile industry	36	4 (11.11%)	32 (88.89%)
Leather products industry	7	4 (57.14%)	3 (42.86%)
Woodworking and furniture	29	10 (34.48%)	19 (65.52%)
Paper and printing industry	4	1 (25%)	3 (75%)
Manufacture of chemical substances and products	17	3 (17.65%)	14 (82.35%)
Metallurgical industry + products from non-metallic materials	133	29 (21.8%)	104 (78.2%)
Metal construction industry (welders)	54	12 (22.22%)	42 (77.78%)
Manufacture of motor vehicles + manufacture of other means of transport + other industrial activities (electricians, locksmiths)	161	26 (16.15%)	135 (83.85%)
Production of electricity, heat, gas, hot water and air conditioning	24	6 (25%)	18 (75%)
Construction	152	40 (26.32%)	112 (73.68%)
Trade	45	19 (42.22%)	26 (57.78%)
Transport and storage	149	35 (23.49%)	114 (76.51%)
Hotels and restaurants	21	2 (9.52%)	19 (90.48%)
Information and Communications	31	5 (16.13%)	26 (83.87%)
Administrative services	175	34 (19.43%)	141 (80.57%)
Security and protection services	37	10 (27.03%)	27 (72.97%)
Defense	28	7 (25%)	21 (75%)
Education	58	7 (12.07%)	51 (87.93%)
Medical services	45	10 (22.22%)	35 (77.78%)
Recreational and cultural activities + other service activities + activities of private households	62	19 (17.65%)	43 (82.35%)

Discussion

This study highlights several domains of activity with early age of lung cancer diagnosed, among which leather products industry, trade, extractive industry, wood and furniture had the highest rates. Many of these economic activities were evaluated and classified by IARC based on their carcinogenic effects on lung tissue.

IARC group I include industrial processes and occupations such as: aluminum (Soderberg process), silicon carbide (Acherson process), coke making, coal gasification and distillation, underground hematite mining and iron and steel production, rubber industry activities, painters, dyers and welders. The occupational exposure to arsenic, beryllium, cadmium, chromium, nickel and their compounds, to ethers, free crystalline silicon dioxide and asbestos, diesel exhaust emissions, soot and emissions from industrial coal combustion are also included. Also included in group I carcinogens are some physical agents, such as X and gamma radiation and exposure to radioactive products such as plutonium and radon. IARC group II includes industrial activities related to the manufacture of glass, the manufacture of carbon electrodes, from printing, exposure to bitumen (most frequently from emissions during asphalting works), to acid vapors tars, benzene, alpha chlorinated toluene, hydrazine, silicon carbide, divalent antimony, cobalt and tungsten. An occupation with a very high risk of exposure is the production, packaging and distribution of organophosphorus insecticides (diazinon) or other non-arsenic insecticides.

The results of this analysis generally overlap with the results of other studies related to lung cancer and areas of activity with a high risk of exposure. However, we have a limitation in the clear identification of carcinogens in each field of activity and another limitation due to the low number of study participants in some fields.

Increased exposure to carcinogens in the leather and leather products industry may be related to inhalation of leather dust, contact with chromium, arsenic and/or vapors of chemicals used (organic solvents, benzene, formaldehyde, toluene, acetone). IARC has included many substances which are frequently used for this activity in the group I list. Studies published mainly before 2000, showed an increased risk of lung cancer compared to other forms of cancer [13-15]. An up-to-dated review form 2003, by Stern et al. did not confirm these findings [16], reflecting the tendency of better protection and also of changes in technology to reduce the utilization of the most aggressive carcinogens.

The values obtained in the wood, woodworking and furniture industries should be analyzed more carefully, even if in other countries, such as Canada, the HR in this type of activity was lower than expected [17]. However, a more detailed analysis showed an increased risk in those with very high exposure [18], which might be the exposure pattern in workers included in our study. By now, wood dust exposure was considered with low medium evidence for a causal relation with lung cancer, compared to the much stronger one with nasopharyngeal or ethmoidal sinus cancer [19] and the effects of other carcinogens present in these workplaces was underlined. An area with higher reported prevalence was the wood cut activity (sawmills) [20], probably because of a much smaller wood dust particles produced that are no more retained in the upper respiratory tract and can reach the lung.

Trade is a very heterogenous domain in terms of occupational exposure. It covers different activities, different goods, smaller and larger companies with various protective policies. In a large, national, Korean study the standard incidence rate was significantly higher than expected only in women [21].

For food industry, transport, extractive industry, production of electricity, thermal energy, gas, hot water and air conditioning, metal construction industry, metallurgical industry and products from non-metallic materials, medical services, the values obtained are not surprising. Most of these types of industry are included or related to IARC group I carcinogens. Many studies [21-24] demonstrated an elevated prevalence of lung cancer, as this study has also showed. Therefore, they should be considered for lung cancer post exposure surveillance.

The values obtained in the domain of printing is difficult to interpret, due to the low number of participants. This type of industry is more commonly associated with other types of cancer. A study on a much larger cohort showed that the incidence of lung cancer is much lower than the bladder, liver and pancreatic cancer [25].

The correlation between the early lung cancer diagnosis and the number of packs-year was not a surprising result; the increase in risk was not very high, but still statistically significant. The high rate of smoking in the two groups probably explain why the additional risk was not very high. Smoking (either active or passive) is a well-known IARC Group I carcinogens; cigarette smoke contains over 7000 chemicals, several hundreds of which are toxic, of which about 70 are carcinogenic. The risk of developing lung cancer is 15 to 30 times higher in smokers than in non-smokers, directly related to the number of packs/year. There is no safety zone for passive smoking, and exposure at home or at work increases the risk of lung cancer by 25-30% [26]. There are several reports underlying that smoking is more frequent in construction, industrial, vehicle mechanics and repairers' workers [27-29]. For these workers, smoking might have an additive or synergic effect with the occupational carcinogens. In our sample, smoking was not more prevalent in any occupational domain, therefore it did not seem to influence the differences recorded by activity domains.

Concerning the medical history, the prevalence of lung cancer risk was increased in workers with personal or family history of cancer and with diabetes.

In a recently published systematic review, the family history of cancer was present in 2 to 46.8% of lung cancer cases [30]. Several germline mutations (*ATM*, *BRCA2*, and *TP53*) [31] were recorded but only in few of these studies. However, in a dedicated retrospective study of 7,788 persons with germ line genetic testing, genetic modifications were found in a similar proportion in lung (14.9%) and other forms of cancers (14.3%) [32]. Even more suggestive for a possible environmental-genetic interaction, in the above-mentioned study, the presence of these mutations was not related to the familial or to the personal history of cancer.

There are some contradictory findings in the relation between diabetes and lung cancer. In our study, the association might be biased by age, as diabetes increases with increasing in age in modern societies. Beside this bias, some studies did not find an increased risk [33], while a meta-analysis found just for women an 18% increased risk [34]. Concerning the evolution of cancer in diabetic population, a 2016 meta-analysis showed a poorer prognosis in patients with non-small cell lung cancer [35].

Limitations

These results are based on a secondary analysis of data collected during the ROMCAN project. Data of occupational exposure were collected retrospectively, between 2014 and 2017 and the current exposure might have been changed. However, the long latency of occupational cancer makes this exposure relevant for the current evaluation of patients with lung cancer.

We considered in this study the date of diagnosis, although it is well established that it depends on many factors and does not reflect the onset of the disease. Access to medical care, early recognition of symptoms might be a barrier which can explain the interference of education, in the early diagnosis. However, as untreated symptomatic lung cancer evolves rather quickly it is very unlikely that this will change with more than 1 year the results. A limitation of more concern is that the sample was recruited in the largest institutes of lung disease and oncology of Bucharest, not in the general population, with the possible bias derived from this recruitment.

This is a cross sectional analysis by domains of activity and it is not meant to infer causation. The benefit of such an analysis is to raise the awareness about several activities in which the prevalence is higher and should initiate a more in-depth risk assessment in order to find the specific hazards and the solutions for workers' protection.

Conclusion

Occupational exposure to carcinogens contributes to the early development of lung cancer but other elements (smoking, socio-economic level, comorbidities), have also a significant role. Based on these results, medical surveillance in leather, wood manufactures, extractive industry and trade should be re-in forced.

Acknowledgements

The authors are grateful to the team of the ROMCAN project (GA 7SEE/2014, financed by the Romanian-EEA Research Programme 2012-2017), who designed, collected and processed data on the epidemiology of different cancers at international level. In particular, we thank to the researchers involved in the Romanian branch of the project, led by the University of Medicine and Pharmacy of Bucharest, who had allowed us to access part of Romanian data.

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