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LUNG CANCER - RISK FACTORS AND PREVENTION STRATEGIES - OVERVIEW OF THE LITERATURE

Jakub Rybak[1]✉, Barbara Magiera[2], Karol Magiera[1], Martyna Grabowska-Szczurek[3], Alicja Grabarczyk[4], Piotr Bator[1], Michał Razik[1], Patrycja Rozwadowska[1], Karol Wielgus[5]

[1]Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[2]Prof. K. Gibiński University Clinical Center of the Medical University of Silesia in Katowice, Poland
[3]The Hospital of the Bonifratres of St. John Grand in Cracow, Poland
[4]Students' Scientific Society, Department of Gynecology and Obstetrics in Katowice, Medical University of Silesia, Katowice, Poland
[5]Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

✉ ***rybakjak@gmail.com***

ABSTRACT

Introduction and purpose: Lung cancer is the second most common cancer worldwide. The aim of this study is to analyze the key modifiable and non-modifiable risk factors associated with the development of lung cancer and to discuss existing prevention strategies.

Materials and methods: A literature review was conducted using the "PubMed" database with the keywords "lung cancer", "lung cancer risk factors", "lung cancer prevention".

Results: Lung cancer risk factors can be divided into two groups: modifiable and non-modifiable. Modifiable risk factors include: smoking, radon, diet, chronic lung diseases, asbestos and diesel fumes. Non-modifiable risk factors include: age, race, genetic factors and gender. In primary prevention of lung cancer it is important to reduce exposure to risk factors, especially cigarette smoke. Screening using low-dose computed tomography plays a major role in secondary prevention.

Conclusion: Lung cancer is one of the most frequent malignant tumors. Over the years, enormous progress has been made in the fight against lung cancer. Despite a large reduction in smoking prevalence, cigarette smoking remains the most important risk factor of lung cancer. Several other factors have been identified, with e.g. asbestosis exposure and air pollutants being among top-5 risk factors with the highest impact. Effective methods of primary and secondary prevention such as health campaigns and screening tests have led to a reduction in the incidence of lung cancer. Smoking cessation and low-dose chest CT screening were proven to be the most effective in the lung cancer prevention. However, lung cancer remains the most common cause of death in cancer patients so further research and effective and practical public health policy are crucial in decreasing incidence and mortality.

Keywords: lung cancer, lung cancer risk factors, lung cancer prevention

INTRODUCTION

Lung cancer is the second most common cancer worldwide. It is the most common cancer in men and the second most common cancer in women [1]. More than 22,000 people die from this cancer annually in Poland, which makes it the most common cause of death in cancer patients [2]. It is estimated that lung cancer-related mortality will increase in the coming years, probably as a result of an aging population [3]. Lung cancer is associated with a low survival rate, due to its long asymptomatic course that allows it to remain undetected until it is in an advanced stage [4]. The aim of this review is to provide an in-depth analysis of the risk factors associated with lung cancer, dividing it into modifiable and non-modifiable risk factors, and to discuss prevention methods that may contribute to reducing the incidence and mortality associated with this disease.

MATERIALS AND METHODS

A review of the literature available in the "PubMed" database and books was conducted. The search was performed by using the following keywords: „ lung cancer”; „lung cancer risk factors”; „lung cancer prevention”. By systematizing and verifying the content, 64 most reliable sources were selected and the work was based on them.

RESULTS AND DISCUSSION

MODIFIABLE RISK FACTORS

Smoking. Cigarette smoking is the most common cause of lung cancer development [5]. It is estimated that 80-90% of lung cancer cases are caused by smoking. [6]. As a result of the Surgeon General's Report of 1964 on Smoking and Health, the number of people who smoked in the U.S. decreased and, consequently, the incidence of lung cancer decreased significantly [7]. Cigarette smoke contains as many as 55 substances considered carcinogenic by the International Agency for Research on Cancer, including polycyclic aromatic hydrocarbons and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Their activation leads to the formation of DNA adducts, gene methylation, changes in the DNA sequence, amplification or deletion of a DNA segment and numerical aberrations of chromosome [8]. The relative risk of lung cancer among smokers is increased by 10 to 30 times and depends on the number of cigarettes smoked per day and the duration of smoking. Some studies have shown a stronger effect of smoking duration than the number of cigarettes smoked per day [9]. It has also been shown that cigarette smokers can reduce the risk of developing lung cancer by smoking cessation at any age [10]. Cigar and pipe smoking have also been linked to an increased risk of lung cancer [11,12].

Passive smoking. Considering the strong link between smoking and lung cancer, the issue of secondhand smoke has been extensively studied. Öberg et al. examined the effects of tobacco exposure in 192 countries on six continents and found that 40% of children and 33–35% of nonsmokers were exposed to secondhand smoke. In 2004, 603,000 deaths worldwide were attributable to secondhand smoke, with 21,400 cases caused by the development of lung cancer as a result of secondhand smoke [13]. An analysis of the International Agency for Research on Cancer (IARC) estimated that the risk of developing lung cancer is increased by 35% in men and 25% in women exposed to secondhand smoke compared with men and women who were not passive smokers. [14]. An updated IARC meta-analysis of 19 studies showed a 20% increased risk of lung cancer in women who were passive smokers [15].

E-cigarettes. The most controversial products potentially increasing lung cancer risk are electronic nicotine delivery systems (ENDS), including e-cigarettes, e-pens, e-pipes, and e-cigars [16]. Although the components of e-cigarette vapor differ from those found in traditional tobacco cigarettes, available data suggest that formaldehyde, acetaldehyde, and reactive oxygen species are present in sufficient concentrations to cause damage to the respiratory tract and lung epithelium. Aerosols created by smoking e-cigarettes may contain polycyclic aromatic hydrocarbons, nitrosamines and trace metals, and their involvement in cancer is unclear [17]. It has also been shown that the use of e-cigarettes is associated with a higher risk of later initiation of cigarette smoking [18]. There is no clear evidence regarding the safety of e-cigarettes in general or compared to tobacco smoking. A statement by the Forum of International Respiratory Societies suggests that the use of tobacco products should be restricted or banned until more convincing evidence is available. [19].

Radon. Radon is a radioactive gas emerging as a product of the decay of radium [20]. GIt is probably the second most common cause of lung cancer after smoking. Radon in indoor spaces usually comes from soil and building materials [21]. The results of three cohort studies conducted in Europe, North America and China showed that chronic exposure to radon contributes to the occurrence of lung cancer, and the relative risk of lung cancer at radon concentrations greater than 100 Bq/m3 was 8%, 11% and 13%, respectively. [22,23,24]. Approximately 20,000 lung cancer deaths in the United States each year are related to radon

[21].

Diet. Diet may have an impact on the risk of lung cancer. Dietary products whose consumption is associated with an increased risk of developing cancer include: red meat, dairy products, saturated fats and lipids. A meta-analysis found a 24% increased risk of lung cancer with high red meat consumption among never-smokers and current nonsmokers. A pooled analysis of 10 prospective cohort studies found that high intakes of total fat and saturated fat were associated with an increased risk of lung cancer, with the risk being greater in smokers. High intake of polyunsaturated fats was associated with a reduced risk of lung cancer [25]. Other foods that have an adverse effect on lung cancer include foods containing nitrosodimethylamine and nitrites, which are found in salted and smoked meat products [26].

Chronic lung diseases. Chronic lung diseases are associated with an increased risk of lung cancer, with the strongest association with chronic obstructive pulmonary disease (COPD). One study found that the incidence of COPD in newly diagnosed lung cancer patients was 6 times higher than in a matched group of smokers without lung cancer [27]. Additional research has shown that factors such as increasing airway obstruction, older age, lower body mass index, and lung diffusion capacity of carbon monoxide less than 80 may be associated with a lung cancer diagnosis [28]. Moreover, the advancement of emphysema on CT scan has been shown to be an independent risk factor for lung cancer [29]. A large retrospective study of patients with COPD found that the risk of lung cancer was lower among patients taking high doses of inhaled corticosteroids compared with those taking lower doses or no corticosteroids at all [30]. The meta-analysis also found an increased risk of lung cancer in never smokers with a history of chronic bronchitis, tuberculosis or pneumonia [31,32]. It has been proven that the incidence of lung cancer in patients with interstitial fibrosis is significantly increased. The risk of developing lung cancer in the setting of idiopathic pulmonary fibrosis is higher in older male smokers and significantly higher in people who have both idiopathic interstitial fibrosis and emphysema [33]. Other fibrosis-related diseases, including asbestosis and scleroderma lung disease, are also associated with an increased risk of lung cancer [34].

Air pollution. Air pollution is a significant factor in the development of lung cancer. Long-term exposure to air polluted by factories and car exhaust fumes, kitchen fumes or formaldehyde significantly increases the risk of lung cancer [35]. Epidemiological studies suggest that air pollution, especially exposure to Particulate Matter, is associated with an increased risk of lung cancer and mortality, regardless of cigarette smoking. [36]. Early studies involving urban and rural comparisons found that there was an "urban factor" that was associated with a 10-40% increase in lung cancer deaths [34,37]. Carcinogens generated by the combustion of fossil fuels include polycyclic aromatic hydrocarbons and metals such as arsenic, nickel and chromium. [38]. Studies have also shown that nitrogen monoxide, nitrogen oxide and nitrogen dioxide are the main carcinogens found in vehicle exhaust [35]. A study by Liaw et al. revealed that there is a dose-response relationship between nitric oxide levels and lung adenocarcinoma [39].

Occupational exposure. It is estimated that approximately 10% of lung cancer deaths in men and 5% in women worldwide are attributable to exposure to occupational carcinogens, namely asbestos, arsenic, beryllium, cadmium, chromium, nickel, silica and diesel fumes [40]. Asbestos exposure is one of the best-known occupational causes of lung cancer. Those most at risk are workers in asbestos mining and milling, shipbuilding, textiles, insulation, and car repair [41]. The risk of developing lung cancer is dose-dependent but varies depending on the type of exposure to asbestos fibers and is higher for workers exposed to amphibole fibers than for workers exposed to chrysotile fibers [42]. It has also been revealed that the relationship between asbestos exposure and cigarette smoking in terms of the risk of developing lung cancer is additive and multiplicative. The relative risk of developing lung cancer increases 6-fold when exposed to asbestos alone, 11-fold when exposed to cigarettes alone, and up to 59-fold when exposed to both factors [43]. The relationship between exposure to diesel exhaust fumes and the risk of lung cancer has also been studied in transport workers and miners. As part of the SYNERGY project, a pooled analysis of 11 case-control studies conducted in Europe and Canada, including 13,304 cases, found that cumulative exposure to diesel fuel was associated with an increased risk of lung cancer [44]. Similar results were obtained in studies conducted in the US trucking and non-metallic mining industries. Other occupations where an increased incidence of lung cancer has been observed include coal mining, asphalt paving, chimney sweeping and painting, although the risk appears to be lower than for exposure to asbestos and diesel exhaust [12].

NON-MODIFIABLE RISK FACTORS

Gender. Lung cancer incidence and mortality are consistently lower in women compared to men, but the gender gap is narrowing due to a more rapid decline in both values in men [34]. In women, lung cancer is usually diagnosed at a younger age, women are more likely to be non-smokers, and are more likely to be diagnosed with adenocarcinoma [45]. In women, the prognosis of lung cancer is better at all stages of the disease than in men [46].

Genetic factors. Genetic factors leading to increased susceptibility to lung cancer haven’t been studied well. Forty years ago, Tokuhata and Lilienfeld provided the first evidence of a familial occurrence of lung

cancer. They also showed that familial aggregation occurred regardless of tobacco use history. [47]. Studies have shown that the risk of lung cancer in first-degree relatives of probands was 1.88 times higher compared to the families of controls [48]. Additionally, genome-wide association studies have identified several new genes predisposing to the development of lung cancer, including genes located on chromosomes 5p15.33, 6p21, 15q24-25.1, 6q23-25 and 13q31.3 [49].

Age. Lung cancer most often occurs in men and women over the age of 70 [50]. The median age at diagnosis of lung cancer is 70 years, and the median age at death from lung cancer is 72 years [51]. Lung cancer has become the most common cause of cancer death in men over 40 years of age and women aged 60 years and older [50]. Lung cancer mortality increases with age, up to the age of 80–85 [34,51]. A recent study found a higher incidence of lung cancer among young, white women compared to men aged 30-49. In this case, the patterns of higher lung cancer incidence among men than among women were reversed and cannot be fully explained by differences in smoking behavior. Further research is needed to identify the reasons for the increased incidence of lung cancer among young women. [52].

Race. Lung cancer incidence and mortality are highest in African American males and lowest in Latino females [51]. According to data from 2008–2014, the rate of localized cancers at diagnosis was lower in African Americans compared to Caucasians (13% vs. 17%), and the prognosis was worse at all stages [50]. The higher mortality rate associated with lung cancer by race is likely multifactorial and includes smoking prevalence, treatment modalities, access to health insurance, and screening [34,53].

RISK FACTORS OF LUNG CANCER	
Modifiable	**Non-modifiable**
Smoking	Gender
Passive smoking	Genetic factors
E-cigarettes	Age
Radon	Race
Diet	
Chronic lung diseases	
Air pollution	
Occupational exposure	

Fig. 1 Risk factors of lung cancer divided into modifiable and non-modifiable

PRIMARY PREVENTION

The basic strategy for primary prevention of lung cancer is to reduce exposure to risk factors, especially cigarette smoke. Studies show that life expectancy in smokers is reduced by at least 10 years compared to people who have never smoked. Smoking cessation before the age of 40 reduces the risk of smoking-related death by 90%. Smoking cessation has also been shown to be beneficial regardless of the smoker's age [54]. Health promotion activities are particularly important in the primary prevention of lung cancer. Due to effective educational activities and limiting the sale of tobacco products, the number of people smoking cigarettes is decreasing [55, 56]. According to the results of the Multicenter Nationwide Population Health Survey (WOBASZ), the prevalence of tobacco smoking in Poland in 2003-2014 decreased by 9% among men and 4% among women [57].

Diet is also important in the primary prevention of lung cancer. A study conducted in 2021 on 416,588 participants revealed that a diet characterized by a high intake of fruits, vegetables and dietary fiber, as well as a low consumption of red meat, is associated with a lower risk of lung cancer [58]. Studies have also been conducted on the impact of beta-carotene, vitamin E and vitamin A supplementation on the development of lung cancer. In the ATBC (α-Tocopherol β-Carotene) study, 29,133 male smokers between 50 and 69 years of age were randomly assigned to one of four groups: α-tocopherol, β-carotene, both agents, or placebo. The study showed that the incidence of lung cancer in the study group was 18% higher than in the placebo group [59].

The CARET (β-carotene, the β-Carotene and Retinol Efficacy Trial) intervention was conducted on 14,254 participants at high risk of lung cancer. The subjects were randomly assigned to a group receiving a β-carotene preparation combined with vitamin A or a placebo. The CARET trial was stopped 21 months

before its scheduled end due to clear evidence of no benefit and substantial evidence of possible harm. In the active intervention group, there were 28% more cases of lung cancer and 17% more deaths compared to the placebo group [60].

There are many more substances that have the potential to reduce the risk of lung cancer. These include, among others, acetylsalicylic acid, isotretinoin, selenium, prostacyclin analogues, non-steroidal anti-inflammatory drugs, myo-inositol, metformin, pioglitazone. However, there are no clear research results indicating a beneficial preventive effect of these agents [61].

SECONDARY PREVENTION

Screening for lung cancer is particularly important due to its long asymptomatic course that allows it to remain undetected until it is in an advanced stage.

In the National Lung Screening Trial (NLST), conducted on a sample of 53,454 people, participants underwent an X-ray or low-dose computed tomography examination every year for 3 years. The study showed a decrease in lung cancer mortality by 20% and overall mortality by 6.7% [62].

The results of a randomized prospective NELSON study, which included 15,789 people, were published in 2020. In the active intervention group, the protocol included low-dose computed tomography at enrollment and then after 1, 3 and 5.5 years. No screening tests were performed in the placebo group. The study revealed that mortality in the study group was 24% lower than in the control group. Over 58% of detected lung cancers were stage I cancers [63].

The results of these studies contributed to increasing public awareness of the risk of lung cancer and the benefits of low-dose computed tomography in the prevention of lung cancer.

Currently, in Poland there is a screening program for detecting lung cancer based on low-dose computed tomography examinations. The program applies to people at high risk of developing lung cancer [64].

CONCLUSION

Lung cancer is one of the most frequent malignant tumors. Studies revealed that modifiable risk factors such as tobacco use, passive smoking, radon exposure, air pollution, occupational exposure, diet with high contain of red meat and low in fruits and vegetables are responsible for the increasing lung cancer incidence. These findings can help us in preventing lung cancer in the future. Over the years, enormous progress has been made in the fight against lung cancer. Despite a large reduction in smoking prevalence, tobacco use still remains the most important risk factor of lung cancer. Effective methods of primary and secondary prevention such as health campaigns and screening tests have also led to a reduction in the incidence of lung cancer. However, lung cancer remains the most common cause of death in cancer patients so further research, effective and practical public health policy are crucial in decreasing lung cancer incidence and mortality.

AUTHORS CONTRIBUTION

Conceptualization: J.R., B.M.; methodology: J.R., B.M.; software: J.R., B.M., K.M., M.G.-S., A.G.; formal analysis: J.R., B.M., K.M., M.G.-S., A.G., P.R., M.R., P.B., K.W.; investigation: J.R., B.M., K.M., M.G.-S., A.G., P.R., M.R., P.B., K.W. resources: J.R., B.M., K.M., M.G.-S., A.G., P.R., M.R., P.B., K.W.; data curation: J.R., B.M., K.M., M.G.-S., A.G.; writing - rough preparation: J.R., B.M., K.M., M.G.-S., A.G. writing - review and editing: J.R., B.M., K.M., M.G.-S., A.G., P.R., M.R., P.B., K.W.; visualization: J.R., B.M.; supervision: J.R., B.M. project administration: J.R., B.M., K.M.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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