**World Bulletin of Public Health (WBPH)**
**Available Online at:** https://www.scholarexpress.net
Volume-24, July 2023
**ISSN: 2749-3644**

# HISTOPATHOLOGICAL AND RISK FACTORS OF TISSUE LUNG CANCER IN IRAQ PATIENTS REVIEW ARTICLE

**Sabreen Saleem Abd Alkreem Alsaqi*,**
Dept. of Anatomy, College of Medicine, Univ. of Babylon /Iraq
*(e-mail; med.sabreen.saleem@uobabylon.edu.iq; moaile:07814619859)

**Article history:**
**Received:** May 16th 2023
**Accepted:** June 16th 2023
**Published:** July 18th 2023

**Abstract:**

The most prevalent kind of cancer, lung cancer, claims a significant number of lives every year. In a case when the cells in the body start growing out of control, it might result in cancer. Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma represent the 3 main sub-types of cancer. The most prevalent kind of cancer is adenocarcinoma, which frequently affects long-term smokers. The second most prevalent cancer type is squamous cell carcinoma, which frequently affects those with a history of sun exposure or smoking. The cultural and social environment in Iraq that promotes tobacco use is the cause of the problem. Smoking is one of the leading causes of lung cancer cases and is responsible for 90% of lung cancer fatalities. Another significant environmental risk factor for lung cancer is indoor radon exposure. The chance of developing lung cancer is doubled in the cases where there is a family history of the disease. There is a higher risk when exposed to air pollution, have a history of lung disease, receive high radiation doses, or are near chemical or industrial carcinogens. More than one type of cancer was linked to mutations of TP53 tumor suppressor gene and EGFR oncogene. The EGFR is a trans-membrane tyrosine kinase receptor promoting cell survival and proliferation.

**Keywords:** Lung cancer, Histopathological, and Risk factors

## 1-EXTERNAL FEATURES OF LUNG

The two lungs of a human are found in the chest. Each of them measures roughly 2.9 pounds. Less weight is in the right lung than in the left. 1,2. The right and left lungs are located in their respective hemi-thoracic cavities. They are separated by the heart and the mediastinum. An adult's normal lung weight range is about 300 to 450 grams.
The lung has two primary bronchial buds. Both the right and left buds branch out into two and three secondary bronchial buds, respectively. The primary parts of the lungs were identified, and such structures make up the lungs' lobes. However, the alveoli (small air sacs in the lungs) will not form until later in embryogenesis[4,5]
Increased lung weight means that there is congestion, edema, or inflammation in the lungs. Lung volume, measured when the lungs are inflated with water, ranges from 3.5 to 8.5 liters. [6.]

## 2 - ANATOMY OF LUNG

The left and right bronchi connect the lungs, which have a pyramidal form, to the trachea. The small lobes that make up each lung. The inferior surface of the lungs is where the diaphragm is also situated 7. The right lung is divided to 3 sections, which are: the middle, upper, and lower regions. Inferior and superior parts make up the left lung. Each lung's lobules are divided by an interlobular septum. 8 Due to the fact that the left lung shares space with the heart, which is situated two-thirds of the way along the left side of the body, the left lung is smaller than the right lung. At the root of each lung, there is a depression known as the hilum, and on medial side of left lung, there is an impression known as the Cardiac Impression. Here, the airways and blood arteries that feed the lungs enter the lungs. Lung weight is made up of cells, and there are no glands, no cartilage, and no goblet cells in the left lung. There is a thick, smooth muscle layer and many elastic fibers present, and the bronchi are lined by ciliated pseudostratified columnar cells. These cells contain goblet cells which produce mucous. There are also glands, cartilage, and a smooth muscle layer present,[10]

## 3 LUNG HISTOLOGY

The lower respiratory tract includes the lungs. This is where the air is breathed in and expelled. They are a functional unit that is responsible for the way that the air moves around us, helps to deliver oxygen to our bodies, and removes carbon dioxide from our bloodstream[11]. The smaller airways (bronchial tubes) that end in the lung's bronchial airways that terminate in alveoli are among bronchial airways that branch from trachea. The lung tissue is surrounded by

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Volume-24, July 2023
**ISSN: 2749-3644**

lymphatic vessels, arteries, nerves, and veins [12]. The bronchial cartilage is a layer of tough, fibrous tissue that circles the bronchi (small tubes leading from the mouth and nose to lungs). The cartilage gets smaller and less dense as the bronchi move deeper into the lung. [13] Neuroendocrine cells show neurosecretory-type granules and include calcitonin, serotonin, and gastrin-releasing peptides. Alveoli are made up of 2 different types of the cells: type I squamous cells and The bronchi and trachea are surrounded by hyaline cartilage rings, which make them very stable. The bronchioles, on the other hand, are lined by simple columnar cells. These cells have the presence of Clara. as monocytes through the blood and into the lungs [14,15.]

## Epidemiology

One of the most prevalent cancers is lung cancer, also accounting for most cancer-related fatalities. Lung cancer will claim the lives of approximately 154,050 Americans in 2018. 16. The most prevalent type of lung cancer is non-small cell lung cancer, which has various subtypes. [17]. Lung cancer, which is the most prevalent kind of cancer, is a major health issue. It's especially common in men, and it leads to high numbers of deaths in the world. [18,19]. Here are many reasons why people are living longer, having babies at older ages, and being more healthy now than in the past. This includes things like having more years of life expectancy, being able to get pregnant earlier, and having a healthier diet. [20]

In Iraq, lung cancer is the most prevalent cancer in women as well as men and the second most prevalent cancer overall. People in Kurdistan are more likely to develop lung cancer. 21 Studies examining the prevalence as well as incidence rates of cancer amongst men and women in various Iraqi cities have produced varying results. [22] Lung cancer is a highly prevalent cancer in men in Fallujah city. [23] There are numerous reasons why lung cancer rates can vary from one country to another. However, the rates vary greatly across the country. The second most common cancer-related death cause in the females and the fourth most prevalent cancer overall is lung cancer. [24]

In 2009, African Americans had the highest cancer rates, whereas Hispanics had the lowest rates. [25] Lung cancer is a disease which is common in Iran. It is believed to be caused by smoking, and there is a high incidence rate of it in this country. [26,27] Lung cancer represents a common disease, but it's more common in males compared to females. The incidence of lung cancer starts to increase rapidly after 50 years old but is basically the same for both men and women before that age. But as people get older, the incidence

type II alveolar cells. The major site of gas exchange takes place in type I squamous cells, while type II alveolar cells are mostly responsible for the removal of bacteria and foreign particles from the alveoli. The type III cell alveolar macrophage is also important in this process. Stem cells that may begin in the bone marrow may migrate to other body parts, which include the alveoli. [12]

of lung cancer in the males tends to be higher compared to it in the women. [28]. The third most common cancer in China is colorectal cancer. [29]

In China[30], lung cancer survival rates are 16.1%. In the United States [31], it is 17%. In Europe [32], it is 13%.

## Risk Factors

### 1. Tobacco and smoking:

One of the largest factors of risk for lung cancer is smoking tobacco products. Quitting smoking could help prevent lung cancer because smoking is almost always lung cancer cause. [33] Smoking is one of the most significant causes of lung cancer, albeit it isn't the only one. After someone starts smoking, it could take several years for lung cancer to grow and much longer for it to manifest itself. [34]

Lung cancer is on the rise nowadays, and cigarette smoking is a major contributing factor. Even if you only smoke a little bit, smoking cigars or pipes increases your chance of lung cancer [35,36].

According to studies, the impacts of smoking on various types of lung cancer is different. Smoking cigarettes and starting young is more strongly linked to SCLC than NSCLC. [37]

The neurotransmitters serotonin, dopamine, endorphins, gamma-aminobutyric acid (GABA) and norepinephrine are released into the bloodstream when nicotine, which is the addictive tobacco component, leads to the activation of the nicotinic acetylcholine receptors (nAChRs) in the nervous system. These neurotransmitters have the potential to be addictive in and of themselves, as well as raising the risk of cigarette dependency.[45,46,47]

### 2- Age

As you get older, your risk of developing cancer increases. This is because damage to your DNA can lead to cancer. Actually, both women and men are diagnosed with lung cancer on average at the age of 70.[50]

Lung cancer is mostly brought on by cigarette smoking, which claims more lives in nations with high human development indexes (HDIs). Yet, both male and female lung cancer rates are lower in nations with lower HDIs. [38,39,40] Women who smoke are much less

prevalent than men, and Asian women in particular. The smoking rate among women is, therefore, 2%. [41,42]

The study found that, in 2000, 50% of lung cancers in women were not caused by primary consumption of combustible tobacco, and in 2012, that number had decreased to 42%.[43,44]

Tobacco smoke contains a lot of harmful chemicals. Some of these chemicals can cause cancer. [48]

Nicotine may make it harder for the body to fight cancerous tumors[49]

A third of lung cancer instances occur in adults over 75, while around half of lung cancer cases affect people between the ages of 55 and 74. Men have a higher likelihood to develop lung cancer between the ages of 85 and 89, while the women are most likely to develop lung cancer between the ages of 75 and 79 [51].

### 3-Gender

There are typically more male patients with lung cancer than female ones, though this isn't always the case. [52]

Women are more likely to develop an adenocarcinoma with lepidic characteristics and have more EGFR mutations in their lung cancer cells. [54,55]

### 4-Family History

No matter how much you smoke, having a family history of lung cancer doubles risks developing it.[56,57]

### 6-Occupational exposure

Workplaces can often make people exposed to harmful substances, like carcinogens, more likely to get cancer. Crystalline silica and asbestos are two of the cancer-causing substances found in the air we breathe and in the dust that often accumulates on our floors. People who are exposed to a lot of these things are at higher risks of getting cancer. Miners are especially at risk because they are often exposed to these things while working underground, and people who work at nuclear plants are especially at risk because of their exposure to radioactivity.[61]

Women have been smokers for a longer time than men, but their rates of smoking and dying from smoking-related diseases have lagged behind men's rates. As a result, women are only now beginning to experience a peak in lung cancer incidence. [53]

### 5-Air Pollution

Lung cancer may develop as a result of long-term exposure to air pollution, which can contain high levels of polycyclic aromatic hydrocarbons (PAHs). These chemicals can cause oxidative stress, inflammation, and other problems in the body, which can lead to lung cancer. [58,59]

About 11% of lung cancers can be blamed on air pollution in Europe, which is a lot higher than in other regions of the world.,[60]

### 7-Asbestos

5–10% of occurrences of lung cancer have been estimated to be a result of occupational exposures to the carcinogens. [62] Asbestos is a type of mineral that is found in nature. It can have different subtypes, including amphibole and serpentine. People have been using asbestos in construction for a long time. Chrysotile fibers are particularly associated with developing cancer[63]

### 8-Pollution and Air Quality

Outdoor air quality is important because it helps protect us from harmful chemicals produced by cars and other things that burn. Particulate matter in the air can also be harmful and can cause respiratory problems. [64]

Outdoor air can contain carcinogens, including PAHs (polycyclic aromatic hydrocarbons), sulfur dioxide, and metals trace [65]. When we burn things like coal and wood, we create particles called smog that can get into our lungs. This pollution can make us sick, and it's especially dangerous for young children and the elderly, is a major lung cancer cause. This is especially true in developing countries. [66,67]

### 9- Infection

The lung can get cancer from infection and inflammation. In the past, infections such as tuberculosis caused people to have increased risks of developing lung cancer, even if they did not smoke. There is now a prevalence. There is a lower risk of tuberculosis in the developed world now than there was in the past.[68,69]

### 10-Radon

In today's medical era, epidemiological researches of people who work in mines uranium had helped us understand how radiation from mines uranium can cause lung cancer[70]. Soil is a source of radiation that can cause cancer, and it's the second most common lung cancer cause. [63]

Radon is a gas that is made from uranium decaying. It can be found in the environment in small amounts. The average radon concentration in environment is 0.2 parts per thousand. [71]

### 11- Diet

The diet can contribute to the risks of some cancer types. For example, people who have low levels of antioxidants in their blood lung cancer are more possible to develop. [72]

### 12-Genetic Risk Factors for Lung Cancer

Lung cancer can occur in smokers. However, not everyone who smokes gets it [73,74]. Although those who have family history of lung cancer are more likely to get it, it is not necessarily inherited. [75]

### Pathology

The most prevalent cancer type in the world is lung cancer. Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) represent the 2 main lung cancer types, both of which are extremely dangerous. NSCLC has three primary subtypes, including:

### 1- Squamous Cell Carcinoma (SCC)

Cancer cells that grow in the lungs are called squamous cell carcinomas. The most common type is called central squamous cell carcinoma, which is found in the center of the lung. But there's also a squamous cell carcinoma type that is found on the outside of the

lungs. This type is called peripheral squamous cell carcinoma.[76]

**2- Adenocarcinoma(ADC)**

Lung cancer is a type of cancer that has certain specific features, such as the formation of glands or ducts. It is more common in women and people who are younger than 45 years old, and it tends to occur in people who don't smoke.[77]

Some tumors are graded on a scale from 1 to 4, with one being the least serious and 4 being the most serious Neuroendocrine tumors, which are tumors of the brain or spinal cord, are graded as 3s.

**Lung Cancer Grading**

There isn't one agreed-upon grading system for the majority of lung cancer types, but some kinds, like carcinoid and intermediate-grade atypical carcinoid, are always considered to be high-grade. In the resection specimens, proposals were made to use architectural or nuclear grading approaches to classify lung adenocarcinoma.[79]

**3- Large Cell Carcinoma**

If tumors include indicators that suggest they are likely to spread and grow, they are now classed in the 2015 WHO Classification as non-keratinizing squamous cell carcinoma or solid adenocarcinoma.[80]

**Diagnosis of NSCLC:** If a person has typical symptoms of lung cancer, like coughing up blood or losing weight, their doctor may do some additional tests to investigate the problem. These might include having a sputum test, lung tissue analysis (such as a needle aspirate or a thoracoscopy), bronchoscopy, mediastinoscopy, bronchoalveolar lavage, and imaging tests (CT scans, MRI scan and chest x-ray). If the person has lung cancer, they may also get a PET scan or a bone scan. Scan Lab tests of biopsy and other samples Immunohistochemical tests, Molecular tests) has been shown to be important for the apoptotic functions of the p53 protein.[81]

**Mutation-Based Biomarkers**

**1- Gene p53:** the p53 protein is a gene that helps to control how many different genes are expressed in cells. This can have important consequences, like regulating cell-cycle progression, inducing apoptosis, and controlling development, differentiation, and gene expression. In several instances, cancer cells frequently have p53 gene alterations. One typical modification is changing a proline at the codon location for an arginine 72. This mutation can inactivate p-53 gene and is often found in cancer cells. are several different genetic mutations that can be found in the TP53 gene. Some of these mutations change the amino acid at codon 72 from Arg to Pro. This change results in a different version of the TP53 gen. has been shown to be important for the apoptotic functions of the p53 protein.[82]

**2-Epidermal growth factor receptor (EGFR):**

EGFR gene is situated at location 12 on the short (p) arm of the chromosome 7. This gene is in charge of producing proteins that aid in regulating cell growth. Increased sensitivity to the EGFR tyrosine kinase inhibitors (TKIs), which are medications used for treating cancer, could result from mutations in this gene. Exon 19 has one particular mutation, a short in-frame deletion. The amino acid residues 747–750 are part of this deletion. Exon 21 experiences a clustered mutation, a different kind of mutation. L858R is one of the amino acids affected by this mutation. Up to 90% of all activating EGFR mutations have this mutation.[83]

Cancer is prevalent and on the rise in Iraq, most likely due to a variety of factors, which include sex, age, etc. Cancer prevention and treatment are still insufficient, and tobacco use keeps being the leading lung cancer cause. There are 4:1 more men than women; hence lung cancer is a significant issue everywhere.

**REFERENCES**


l. W. and Mitchell Adam, W.M.(2014). Gray's anatomy for students.3rd edition. Edinburgh: Churchill Livingstone/Elsevier; pp. 167–174.05).

2- Johannes, C., Schittny,(2017);.Development of the lung. Cell and Tissue Research 367(3): 427-444.

3- Betts, J. and Gordon (2013). Anatomy &physiology. pp. 787–846.

4-Hines EA, Sun X(2014). Tissue crosstalk in lung development.J Cell Biochem. Sep; 115(9):1469-77.

5- Morrisey, E.E. and Hogan, B.L.,(2010). Preparing for the first breath: genetic and cellular mechanisms in lung development. Dev. Cell, 18(1); 8–23.

6- Standring, Susan, B. and Neil,R. (2008). Gray's Anatomy: The Anatomical Basis of Clinical Practice (40 ed.). Edinburgh: References Churchill Livingstone/Elsevier. pp. 992–1000. ISBN 978-0-443-06684-9

7- Azlin, A.H., Looi, LM and Cheah,P.L. (2014). Tissue Microarray Immunohistochemical Profiles of p53 and p RB in Hepatocellular Carcinoma and Hepatoblastoma. Asian Pac J Cancer Pre v, 15, 3959-63.

8- Akihiko- Miyanaga, Kumi- Shimizu and Rintaro-Noro (2013). Activity of EGFR-tyrosine kinase and ALK inhibitors for EML4ALK-rearranged non–small–cell lung cancer harbored coexisting EGFR mutation. BioMed Central Ltd. 29 May.

9- Drake Richard L., Vog l. W. and Mitchell Adam, W.M.(2014). Gray's anatomy for students.3rd edition. Edinburgh:Churchill Livingstone/Elsevier; pp. 167–174.

10- Ganter, B.G., Jakob, S.M., Takala, I.(2006) Pulmonary capillary pressure.A review. Minerva Anestesiol;72(1-2):21-36.

11- Ando, K., Oki, E., Saeki, H., Yan, Z., Tsuda, Y., Hidaka, G., Kasagi, Y., Otsu, H., Kawano,H.and Kitao, H. (2015). Discrimination of p53 immunohistochemistry-positive tumors by its staining pattern in gastric cancer. Cancer Med.; 4: 75-83.

12- Pocock, Gillian; Richards(2006). Christopher D. Human physiology: the basis of medicine. (3rd ed.). Oxford: Oxford University Press. pp. 315–318,
13- Pawlina, W (2015). Histology a Tex &Atlas (7th ed.). pp. 670–678. ISBN 974511-874284511-8742.
14- Tamai, S.,(2009): Lung endocrine cells and their pathology. Endocrinol Pathol., 1:171-188.
15- Ahmadi, G., Jiyuan, Tu.,Kiao, I., (2013). Computational fluid and particle dynamics in the human respiratory system (1st ed.). Dordrecht: Springer. pp. 23–24
16-Siegel, R., D. Naishadham, and A. Jemal, (2012). Cancer statistics, 2012, CA Cancer J. Clin. 62(1) 10–12.
17- Travis, W.D., Brambilla, E. and Riely, G.J., (2013). New pathologic classification of lung Cancer: relevance for clinical practice and clinical trials. J Clin Oncol. 10;31(8):992-1001.
18- Muller, P.A. and Vousden, K.H.,(2013). p53 mutations in cancer. Nat Cell Biol.; 15(1):2-8.
19- Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R. (2014). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer;.
20- Torre, L.A., Siegel, R.L., Jemal, A.,(2016). Lung Cancer Statistics. Adv Exp Med Biol;893:1-19.
21-Khoshnaw, Najmaddin, Hazha A. Mohammed, and Dana A. Abdullah(2015). "Patterns of cancer in Kurdistan-results of eight years cancer registration in Sulaymaniyah Province-Kurdistan-Iraq." Asian Pac J Cancer Prev 16: 8525-8531.
22-Ali Abdul Hussein, S. AL-Janabi, Zhoor, H. Naseer and Thuha,A. Hamody,(2017).Epidemiological Study of Cancers in Iraq-Karbala from 2008 to 2015. International Journal of Medical Research & Health Sciences, 6(1): 79-86.
23- Abdulwahab, A. R. Al-Faluji, Salih, H.A., Arkan, A. and Jasem Al-Esawi.(2012). "Incidence of cancer in Fallujah above 10 years ago, with over view of common cancers in 2011." Published DOI:10.4236/ Health..49092
24- Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C., Parkin, D.M. (2010) Esti¬mates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer.;127:2893–2917.
25- Hodkinson, PS & Sethi, T., (2011). Advances in the prevention and treatment of lung cancer. J R Coll Physicians Edinb. Jun;41(2):142-9.
26- Garcia, M., Jemal, A., Ward, E.M., (2007). Global cancer facts & figures 2007.Atlanta, GA: American Cancer Society 2007.
27-Mosavi-Jarrahi,A., Gouya, M.M. and Ramazani, R., (2009). Cancer incidence and mortality in Iran. Ann Oncol, 20, 556-63.

28-Howlader, N., Noone, A.M., Krapcho, M., Neyman, N., Aminou, R., Waldron,W., Altekruse, S.F., Kosary, C.L., Ruhl, J., Tatalovich, Z., Cho, H., Mariotto, A., Eisner,M.P., Lewis, D.R., Chen, H.S., Feuer, E.J.and Cronin, K.A. (eds).(2012). SEER Cancer Statistics Review, 1975-2009. Bethesda, MD: National Cancer Institute.
29- Zheng, R., Zeng, H., Zhang, S., Chen, T., Chen, W.,(2016). National estimates of cancer prevalence in China, 2011Cancer letters.; 370(1):33–8.
30- Zeng, H., Zheng, R., Guo, Y., Zhang, S., Zou, X. and Wang, N., (2015)Cancer survival in China, 2003China, 2011Cancer-based study. International Journal of Cancer.; 136(8):1921–30.
31-Siegel, R.L., Miller,K.D. and Jemal, A.,(2015). Cancer statistics, 2015. CA: a cancer journal for clinicians.; 65(1):5–29.
32- De- Angelis, R., Sant, M., Coleman,M.P., Francisci S., Baili, P., and Pierannunzio, D., (2014). Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. The lancetoncology.; 15(1):23–34.
33-Siegel, R.L., Miller, K.D. and Jemal, A.,(2017). Cancer Statistics, 2017. CA Cancer J Clin;67:7-30.
34- Sun, S., Schiller, J.H. and Gazdar, A.F.,(2007). Lung cancer in never smokers–a different disease. Nat Rev Cancer;7:778 –790.
35- Shaper, A.G., Wanname thee, SG and Walker, M.,(2003). Pipe and cigar smoking and major cardiovascular events, cancer incidence and all-cause mortality in middle-aged British men. Int J Epidemiol;32(5):802–808.
36- Henley SJ, Thun MJ, Chao Aand Calle EE(2004). Association between exclusive pipe smoking and mortality from cancer and other diseases. J Natl Cancer Inst;96(11):853–861.
37-Khuder, S.A., (2001). Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. Lung Cancer 31:139-148.
38-Ezzati, M.& Lopez, A.D.,(2003). Estimates of global mortality attributable to smoking in 2000. Lancet.;362:847–852.
39- Atlanta, GA (2004):US Dept of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. US Department of Health and Human Services, Centers for Disease Control and Prevention.
40- Jha,P., Ramasundarahettige, C., Landsman,V., Rostron, B., Thun, M., Anderson. RN, Mcafee, T.and Peto, R., (2013).21-st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med.;368:341–35.
41- Yang, L., Parkin,D.M., Li,L.and Chen, Y.,(2003). Time trends in cancer mortality in China: 1987–1999. Int J Cancer;106:771–783.
42- Li, C. Wang, Lei,W., Sabrina, K., Jennifer, A. W., Li, Q. Wu., Hong, Z., Li Z. Z, Na, L. S., and Lei, Z., (2011)." Analysis on the clinical features of 22 basaloid squamous-cell carcinoma of the lung".Journal of Cardiothoracic Surgery,; 6(10).
43- Parkin, D.M., Bray, F., Ferlay, J., Pisani, P. and Parkin, D.M.,(2005). Global cancer statistics, 2002. CA Cancer J Clin.;55:74–108.

44- Saika, K. and Machii, R.,(2012). Cancer mortality attributable to tobaccoby region based on the WHO Global Report. Jpn J Clin Oncol.;42:771–772.
45- Saccone, S.F., Hinrichs, A.L. and Saccone, N.L., (2007). Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. Hum Mol Genet;16:36-49
46-Benowitz, N.L.(2008). Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. Clin Pharmacol Ther;83:531-41.
47-Costa, F.& Soares, R.,(2009). Nicotine: a pro-angiogenic factor. Life Sci;84:785-90.
48-Hecht, S. (2003). Tobacco carcinogens, their biomarkers and-tobacco-induced cancer. Nat Rev Cancer, 3, 733-44.
49- Sopori, M., (2002). Effects of cigarette smoke on the immune-system. Nature reviews. Immunology, 2, 372-7.
50-Torre, L.A., Siegel, R.L., Jemal, A.,(2016). Lung Cancer Statistics. Adv Exp Med Biol;893:1-19.
51-Torre, L.A., Siegel, R.L., Jemal, A.,(2016). Lung Cancer Statistics. Adv Exp Med Biol;893:1-19.
52-Shamseddine, A., Saleh, A., Charafeddine, M., Seoud, M., Mukherji, D. and Temraz, S., (2014).Cancer trends in Lebanon: a review of incidence rates for the period of 2003–2008 and projections until 2018. Popul Health Metrics;12:4.
53-Siegel,R.L., Miller, K.D., Jemal, A.,(2018). Cancer statistics, 2018. CA Cancer J Clin;68:7-30..
54- Patel, J.D., (2005). Lung cancer in women. J Clin Oncol;23:3212-8.
55- Planchard,D., Loriot, Y. and Goubar, A., (2009). Differential expression of biomarkers in men and women. Semin Oncol;36:553-65.
56- Matakidou, A., Eisen, T. and Houlston, R.S., (2005). Systematic review of the relationship between family history and lung cancer risk. Br J Cancer;93:825– 833.
57- Nitadori, J., Inoue, M., Iwasaki, M., (2006). Association between lung cancerincidence and family history of lung cancer: data from a large-scale population-based cohort study, the JPHC Study. Chest;130:968–975.
58- Schwartz,A.G. and Ruckdeschel, J.C.,(2005): ir pollutionfrom lung to heart. Swiss Med Wkly;135(47–48):697–702
59- Vineis, P. and Husgafvel-Pursiainen, K.,(2005). Air pollution and cancer: biomarker studies in human populations.Carcinogenesis 2005 Nov;26(11):1846–1855.
60- Boffetta, P.(2006). Human cancer from environmental pollutants: the epidemiological evidence. Mutat Res2006 Sep 28;608(2):157–162.
61- Govindan,R., and Subramanian, J. (2007). Lung cancer in never smokers: a review J Clin Oncol;25:561–570.
62- De- Matteis, S., Consonni, D., Bertazzi, P.A.,(2008). Exposure to occupational carcinogens and lung cancer risk. Evolution of epidemiological estimates of attributable fraction. Acta Biomed;79 Suppl 1:34-42.
63- Dela –Cruz, C.S., Tanoue, T.L.and Matthany, R.A,.(2009). Lung Cancer: Epidemiology and Carcinogenesis. In: Shields TW, editor. General Thoracic Surgery. 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins,:1281-98.
64- Alberg, A.J., Brock,M.V., Ford, J.G., Samet,J.M. and Spivack, S.D. (2013). Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest;143:e1S-29S.
65- Alberg, Rex, C. Yung, Paul Timothy Strickl and, Jonas Nelson (2002). Respiratory cancer and exposure to arsenic, chromium, nickel and polycyclic aromatic hydrocarbons. Clin Occup Environ Med;2:779-801.
66- Torok, S.1., Hegedus, B., Laszlo, V., Hoda,M.A., Ghanim, B., Berger, W., Klepetko, W., Dome, B. and Ostoros, G., (2011). Lung cancer in never smokers. Future Oncol;7:1195-211.
67- Lee, Y.J., Kim, J.H., Kim, S.K., Ha, S.J., Mok,T.S., Mitsudomi, T. and Cho, B.C., (2011). Lung cancer in never smokers: change of a mindset in the molecular era. Lung Cancer;72:9-15.
68- Wakelee, H.A., Chang, E.T., Gomez, S.L., Keegan, T.H., Feskanich, D., Clarke, C.A., Holmberg, L.and Yong, L.C., (2007). Lung cancer incidence in never smokers. J Clin Oncol;25:472– 478.
69- Brenner, D.R., McLaughlin, J.R., Hung, R.J,(2011). Previous lung diseases and lung cancer risk: a systematic review and meta-analysis. PLoS One;6:e17479.
70- Krewski,D.1., Lubin, J.H., Zielinski, J.M., Alavanja,M., Catalan, V.S., Field, R.W., Klotz, J.B., Létourneau,E.G. and Lynch, C.F. (2005). Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. Epidemiology;16:137-45
71- Turner,M.C., Krewski,D., Chen, Y., Pope, C.A., Gapstur,S.M. and Thun, M.J., (2012). Radon and COPD mortality in the American Cancer Society Cohort. Eur Respir J;39:1113-9
72- Ruano-Ravina, A., Figueiras, A. and Barros-Dios,J.M.,(2010). Diet and lung cancer: a new 45- De Stefani E, Fontham ET, Chen V, et al. Fatty foods and the risk of lung cancer: a case-control study from Uruguay. Int J Cancer.;71(5):760–766.
73-De Stefani E,Fontham ET, Chen V, et al. Fatty foods and the risk of lung cancer: a case-control study from Uruguay. Int J Cancer.;71(5):760–766.
74- Goodman, M,T., Kolonel, L.N. and Yoshizawa, CN, (2011). The effect of dietary cholesterol and fat on the risk of lung cancer in Hawaii. Am J Epidemiol.;128(6):1241–1255
75- Lissowska,J., Foretova, L., Dabek, J., Zaridze, D., Szeszenia-Dabrowska, N., Rudnai,P., Fabianova, E. and Cassidy, A., (2010). Family history and lung cancer risk: international multi centre case-control study in Eastern and Central Europe and meta-analyses. Cancer Causes control;21:1091-104.

76- Azzoli, C. G.S.,Baker, Jr. S., Temin, (2009). "American society of clinical oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer," Journalof Clinical Oncology, vol. 27, no. 36, pp. 6251–6266.
77- Travis, W. D., Brambilla,E. and Burke, A.P., (2010). Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart (PDF). World Health Organization.WHO press,;7(7): 412 pages
78- Travis,W.D., Noguchi, M., Yatabe, Y., Brambilla, E.,Nicholson, A.G., Aisner, S.C., Austin, J.H.M., Devesa,S.S., Hirsch, F.R., Ladanyi, M., Meyerson, M., Mino-Kenudson, M., Powell, C.A., Rami-Porta, E., Rekhtman, N., Riely, G., Russell, P., Samet, J., Scagliotti, G.,Thunnissen, E., To, K.F., Tsuta, K., van –Schil, P.,Warth, A., Wistuba, I.I. and Yankelevitz, D., (2015). Adenocarcinoma. In: WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart. Sep;10(9):1240-1242.
79- Barletta, J.A., Yeap, B.Y., Chirieac, L.R.(2010). Prognostic significance of grading in lung adenocarcinoma. Cancer;116:659–669. Pawlina, W.Histology a Text & Atlas. 7th edition, pp. 670–678.
80- Lane, D. and Levine, A.(2010). p53 Research: the past thirty years and the next thirty years. Cold Spring Harb Perspect Biol.; 2(12).
81- Szymanska, K.; Hainaut, P.,(2003). TP53 and mutations in human cancer.Acta Biochim. Pol., 50 (1), 231–8.
82- Dumont, P., Leu, J.I., Della, P.A., George, D.L. and Murphy, M.,(2003). The codon 72polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet;33:357 – 65.
83- Zhou, J. and Ben, S.,(2018). Comparison of therapeutic effects of EGFR-tyrosine kinase inhibitors on 19Del and L858R mutations in advanced lung adenocarcinoma and effect on cellular immune function. Thorac Cancer;9:228-33.