Lung Cancer Epidemiology, Risk Factors and The Role of ZNF24

Xizun Tang*

Westtown School, Commonwealth of Pennsylvania, The United States of America

Abstract. Lung cancer is still one of the top cancer types that require worldwide effort in screening and prevention, as well as development of treatment. In this paper, the epidemiology of lung cancer has been summarized and the risk factors contributing to lung cancer have been discussed. In addition, a novel target for lung cancer treatment - ZNF24, has been discussed in brief.

Keywords: lung cancer, epidemiology, risk factors, genetics, ZNF24.

1. Lung Cancer Epidemiology

1.1. The importance of lung cancer epidemiology studies

Nowadays, with the improvement of primary and secondary prevention for cardiovascular diseases, cancer has become one of the leading factors of premature death in many countries. As shown in Figure 1, cancer is ranked as the first and second contributing factors of premature death in over 70% of the countries as well as 3rd-4th leading cause in 24% of the countries investigated. In addition, researchers have found out that, in general, cancer mortality rates are related to various factors, including socioeconomic status[1]. For example, in countries with longer life expectancy, higher average education level and higher average income, cancer mortality rates are declining due to earlier detection, more efficient intervention methods and state-of-the-art medical treatments[2].

Lung cancer is the most common type of cancer in the world, leading in both incidence rates and mortality rates compared to other types of cancers. Lung cancer incidence and mortality rates vary mainly because of different exposure to tobacco smoking, reflected on the different trends shown by different sexes in respective countries. As shown in Figure 2, in men, countries like the UK, the USA, New Zealand and Canada where the first smoking epidemic took place were also the countries in which the trend of smoking decreased earlier. This is probably because, in countries like these, the smoking epidemic took place before the study timeframe. Thus, the incidence rate and mortality rate decreased in the studied timeframe. In countries with historically low lung cancer incidence rates like Costa Rica, Ecuador and India or intermediate lung cancer incidence rates like Japan and Turkey, the incidence rate and mortality rate has increased or stabilized over the past 40 years. As shown in Figure 3, in women, the tobacco smoking habit developed more recently so that in most countries the incidence rates and mortality rates reached a peak and started to drop recently.

1.2. Lung Cancer Classification

Lung cancer classification allows one to categorize cancers based on cellular identity and in turn can guide the therapeutic approach. According to the WHO, there are 80 different forms of lung cancer classified into 9 main categories[4]. These can also be classified in, adenomas, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, which traditionally have been classified as Non Small Cell Lung Cancer (NSCLC), and account for about 85% of lung cancer cases. The other main category of lung cancers is neuroendocrine tumors, which also comprise Small Cell Lung Cancer (SCLC). Adenocarcinoma is the most common type of lung cancer, it approximately accounts for 40% of lung cancers.

1.2.1. Different Stages of Lung Cancer or TNM Stages

Correct staging classification can facilitate clinical research and communication of research results. TNM staging is represented by three factors: the feature/extent of the primary tumor (T), involvement of lymph node(s) (N), and metastases (M) into distant organs/tissues, as shown in Table 1. In

summary, based on the histopathology and size of the primary tumor, lung cancer can be classified into 7 stages[5]. Additionally, N stages are evaluated based on the extent of involvement of various lymph nodes and, lastly, M staging is assigned to classify the cancer based on the presence of metastases.

Another staging system is the one that classifies lung cancer depending on the extent to which it has spread in the body. As such, the cancer can be localized, if there is no evidence it has spread outside lung tissues; regional, if it has spread to lymph nodes or nearby structures; and lastly, distant, if it has metastasized. Based on this classification, the Surveillance, Epidemiology, and End Results (SEER) database[6],which is overseen by the National Cancer Institute, reported 5-year survival rates that can be found in Table 2. The table illustrates the poorer prognosis seen in SCLC patients as compared to NSCLC patients.

2. Environmental Risk Factors Related to Lung Cancer

Studying etiology of cancer is important and essential in the research of cancer prevention because it brings the knowledge of the root cause of cancer, which helps people know about the cause of cancer. Elucidating risk factors that contribute to cancer development and progression is crucial to decrease cancer risk.

2.1. Smoking

Smoking plays a substantial role in cancer progression. Cigarette smoking causes at least 20 different forms of cancer. It is estimated that about 1.3 billion people use tobacco in the world and about 2.4 million tobacco-related cancer-death happen per year[3]. Tobacco smoking is responsible for 63% of overall global deaths from lung cancer, and 90% of lung cancer deaths in countries where smoking is prevalent. The use of electronic nicotine delivery systems (e-cigarettes) has been growing in popularity in the past decade, yet, there is still a dearth of knowledge regarding the harmful effects caused by nicotine vaping. While work published by Haussman and colleagues suggests that nicotine is not a carcinogen in humans and rodents[7], other studies disagree and propose that nicotine exposure may cause toxicity and inflammation as well as promote DNA damage and inhibit repair mechanisms and the production of DNA repair proteins[8], thus in turn promote cancer progression[9]. However, carcinogens in cigarette smoking are more than nicotine. As pointed out by Li et al., there are more than 69 carcinogens in smoking cigarettes, including acrylamide, benzene and more[10]. Similarly, cannabis smoking might also lead to lung cancer. As cannabis smoke contains polycyclic aromatic hydrocarbons and other carcinogens[11], its connection with lung cancer has been a focus of recent studies[12], [13]. Yet, more research is needed to corroborate these claims.

2.2. Air Pollution

Air pollution is a well-established factor that contributes to cancer progression and it can be classified as outdoor pollution, such as particles of aerodynamic diameter less than 2.5 μm or ambient ozone, and indoor pollution, such as particles produced due to incomplete combustion of solid fuels for cooking and heating[14]. All these are collectively classified as carcinogens and have been assigned IARC monographs based on risk.

2.3. Heavy Metals

Heavy metals can cause cancer[3]. They can damage our DNA directly, leading to changes that cause abnormal cellular growth. This can cause cell cycle dysfunction and promote cancer progression cycle dysfunction and promote cancer progression. Also, these metals contribute to the production of reactive oxygen species, known as ROS, which in turn promote inflammation and cell damage. These particles can damage proteins, lipids and DNA, thus causing mutations. The risk

depends on the kind of metal, the amount of exposure, exposure time, and the human body's resistance to the metal.

2.4. Ionizing Radiation

Ionizing radiation has the potential to cause double strand breaks and in turn cause mutations and genomic instability, thus further contributing to cancer progression. Normally, cells can repair DNA damage. But if the damage is too extensive, or if the repair process fails, mutations accumulate. When these mutations occur in protooncogenes or oncosuppressors, such as for instance genes coding for proteins controlling cell proliferation, differentiation, apoptosis and cell cycle regulation, they can contribute to cancer development. Risk level depends on the amount and type of radiation, as well as the duration of exposure to radiation,

3. Genetic Factors That Contribute to Lung Cancer

3.1. Somatic vs Germline Mutations

Somatic mutations and germline mutations can both contribute to cancer progression[15]. Current research suggests that somatic mutations give a major contribution to cancer. Yet, recent studies investigate germline participation in lung cancer[15]. Irrespective of the origin of such mutations, studies show that there are a handful of key pathways that are altered in cancerous cells. These include those involved in proliferation, cell cycle, motility and epigenetics regulation.

3.2. Key Genes and Pathways

EGFR & Proliferation (Adenocarcinoma & Squamous Cell Carcinoma): In both adenocarcinoma and squamous cell carcinoma, the activation of the EGFR pathway promotes cell proliferation, leading to tumor progression. EGFR is involved in cell signaling pathways that control cell division and survival. Gain-of-function-mutations on the EGFR gene can increase its expression level thus leading to faster growth and cancer development.

p53 & Cell Cycle (Adenocarcinoma): In adenocarcinoma, mutations in the p53 gene disrupt normal cell cycle regulation, facilitating uncontrolled cell division. p53 is a key oncosuppressor gene that is also called the guardian of the genome as it plays a major role in regulation of cell-division stimulation protein (cdk2). p53 is vital in maintaining proper cell division cycles in cells working as a sentinel to detect and repair genomic instability.

Motility & LKB1 (Adenocarcinoma): LKB1 gene mutations in adenocarcinoma can impair cellular motility, influencing tumor spreading and metastasis. LKB1 positively regulates AMPK and its downstream kinases, which in turn controls cell growth and metabolism.

Epigenetics & SMARCA4 (Adenocarcinoma): Alterations in the SMARCA4 gene impact epigenetic regulation in adenocarcinoma, affecting gene expression and contributing to tumor progression. SMARCA4 is vital in chromatin remodeling, which in turn regulates many of the key gene expression pathways involved in cancer development.

In addition to these genes and pathways, transcription factors are recently gaining more and more attention on their role played in cancer progression. Zinc fingers and SCAN-domain are a promising field of study. The ZSCAN factors have a zinc finger and a SCAN-domain (leucine rich region). Recent studies have identified 54 members of the ZSCAN family that share similar structure, most of them contain C2H2-domain and a SCAN-domain[16]. All these have different biological functions in cancer progression.

4. The Role of ZNF24 in Cancer

ZNF24, also called Zinc finger transcription factor 24, is a member of the zinc finger transcription factor family. ZNF24 was first discovered via molecular cloning from hematopoietic cells by Han et al. in 1999[17]. Studies carried out by Liu Xinyang et al. have shown that ZNF24 has tumor

suppression functions in gastric cancer[18]. In addition, Bo Pang et al. performed studies that showed that ZNF24 can suppress NSCLC growth by inhibiting the Wnt pathway[19]. This study was corroborated by the in vivo genome-wide CRISPER screening of lung cancer tumor suppressor genes conducted by Lu Liu et al[20].

5. Summary

In this paper, the current epidemiology studies about lung cancer were discussed and summarized. In addition, the environmental risk factors that can contribute to lung cancer were also discussed and summarized. Furthermore, some new studies about a novel genetic target - ZNF24, were also summarized and discussed.

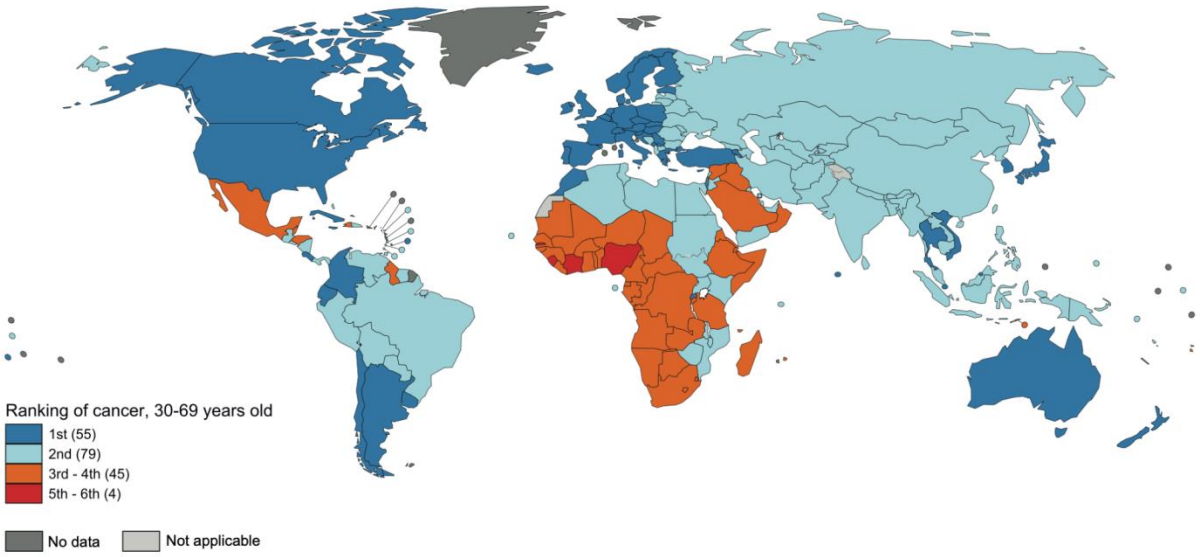

Figure 1. Map of cancer as the leading cause of premature death.

In the figure, the importance of cancer as a cause of premature death between the ages of 30-69 was marked by different colors on the map[3].

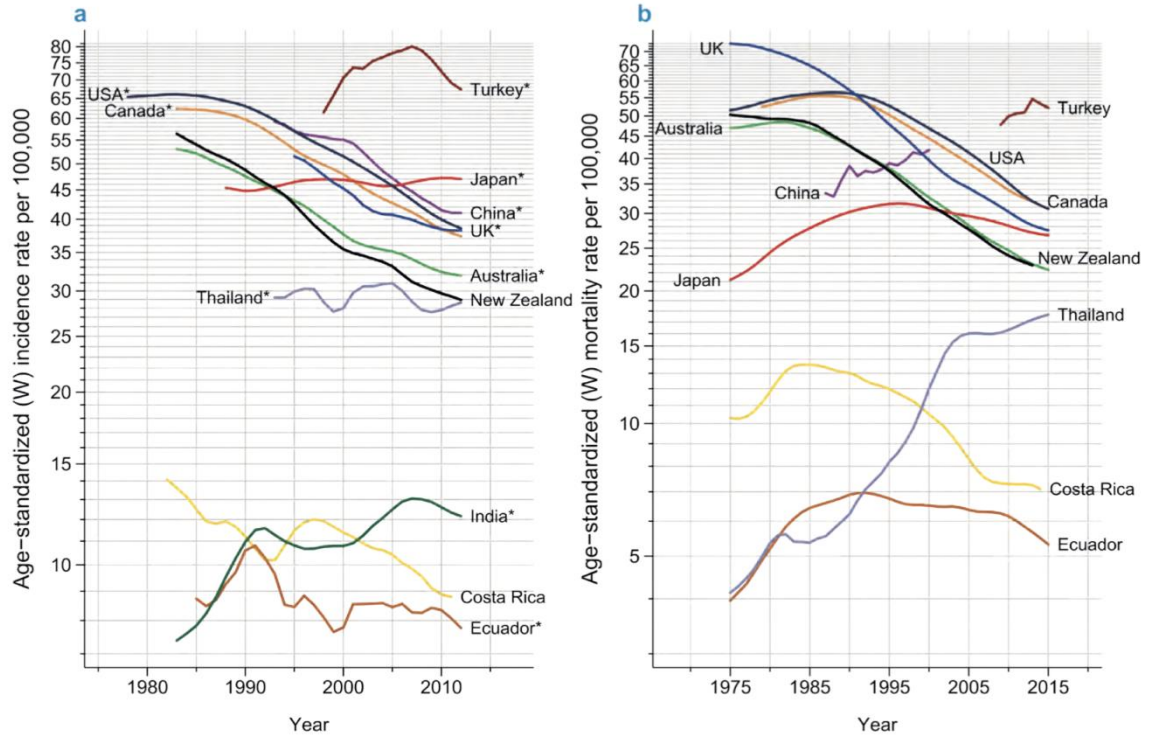

Figure 2. Trendlines of age-standardized lung cancer incidence rates and mortality rates of men from different countries[3].

Figure 2a describes the trends of lung cancer incidence rates for men in various countries. Figure 2b shows the mortality rates trends of lung cancer in men in various countries.

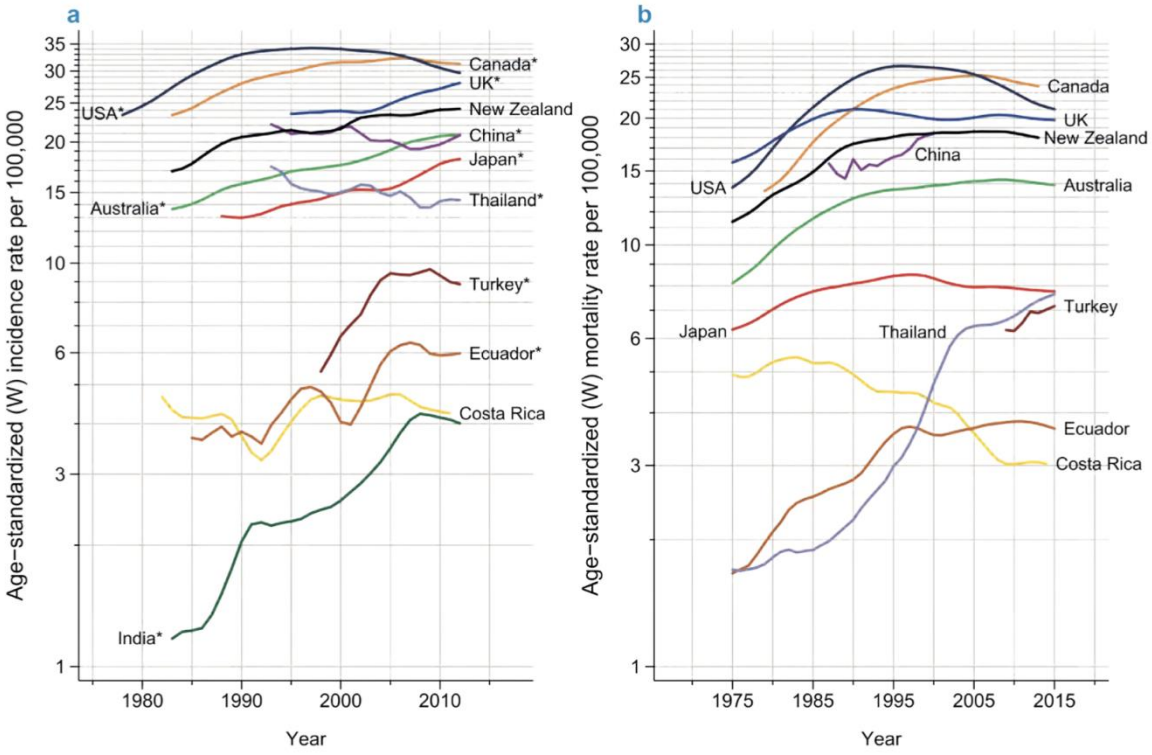

Figure 3. Trendlines of age-standardized lung cancer incidence rates and mortality rates of women from different countries[3].

Figure 3a shows the lung cancer incidence rates vs time in various countries. Figure 3b shows the lung cancer mortality rates vs time in various countries.

There is also a sex-related relationship between Human Development Index (HDI)[1] and lung cancer incidence and mortality rates. In Countries with high HDI, sex is a risk factor for cancer. For women, high HDI countries exhibit a higher incidence and mortality rates than low HDI countries. For men, high HDI countries exhibit a lower incidence and mortality rates than low HDI countries.

Table 1. TNM staging criteria explained in brief description[5].

Descriptor	Definition
Tx	Malignant cells found by washing or histopathological testings but not visible radiologically.
T0	Primary tumor not visible.
Tis	Carcinoma found in situ.
T1-T4	Tumors are separated into T1-T4 based on the size between < 3 cm to > 7 cm. From T1 to T4, the tumor also shows progressive invasion of nearby tissues.
Nx	Evaluation of regional lymph nodes not available.
N0	No sign of involvement of regional lymph nodes.
N1-N3	From N1 to N3, more involvements of lymph nodes are observed.
M0	Metastases not detected
M1	Metastases present
Mx	Evaluation of metastases not available.

Table 2. 5-year survival rate based on lung cancer stages.

5-year survival rate based on SEER lung cancer stage [%]		
SEER Stage	NSCLC	SCLC
Localized	65	30
Regional	37	18
Distant	9	3
All combined	28	7

References

[1] P. Kanavos, “The rising burden of cancer in the developing world,” Ann. Oncol., vol. 17, pp. viii15–viii23, Jul. 2006, doi: 10.1093/annonc/mdl983.

[2] V. Sopik, “International variation in breast cancer incidence and mortality in young women,” Breast Cancer Res. Treat., vol. 186, no. 2, pp. 497–507, Apr. 2021, doi: 10.1007/s10549-020-06003-8.

[1] HDI: a composite index taking into account the length and healthiness of life, education level, and income.

[3] C. Wild, E. Weiderpass, and B. Stewart, Eds., World Cancer Report: Cancer Research for Cancer Prevention., vol. 2020. Lyon, France: International Agency for Reseach on Cancer. [Online]. Available: http://publications.iarc.fr/586

[4] A. G. Nicholson et al., "The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015," J. Thorac. Oncol., vol. 17, no. 3, pp. 362–387, Mar. 2022, doi: 10.1016/j.jtho.2021.11.003.

[5] O. Lababede and M. A. Meziane, "The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams," The Oncologist, vol. 23, no. 7, pp. 844–848, Jul. 2018, doi: 10.1634/theoncologist.2017-0659.

[6] N. Howlader, "SEER Cancer Statistics Review, 1975-2010, National Cancer Institute", [Online]. Available: https://seer.cancer.gov/archive/csr/1975_2010/

[7] H.-J. Haussmann and M. W. Fariss, "Comprehensive review of epidemiological and animal studies on the potential carcinogenic effects of nicotine per se," Crit. Rev. Toxicol., vol. 46, no. 8, pp. 701–734, Sep. 2016, doi: 10.1080/10408444.2016.1182116.

[8] P. G. Shields et al., "A Review of Pulmonary Toxicity of Electronic Cigarettes in the Context of Smoking: A Focus on Inflammation," Cancer Epidemiol. Biomarkers Prev., vol. 26, no. 8, pp. 1175–1191, Aug. 2017, doi: 10.1158/1055-9965.EPI-17-0358.

[9] "Can electronic-cigarette vaping cause cancer?," J. Cancer Biol., vol. 2, no. 3, Oct. 2021, doi: 10.46439/cancerbiology.2.027.

[10] Y. Li and S. S. Hecht, "Carcinogenic components of tobacco and tobacco smoke: A 2022 update," Food Chem. Toxicol., vol. 165, p. 113179, Jul. 2022, doi: 10.1016/j.fct.2022.113179.

[11] D. Moir et al., "A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions," Chem. Res. Toxicol., vol. 21, no. 2, pp. 494–502, Feb. 2008, doi: 10.1021/tx700275p.

[12] R. C. Callaghan, P. Allebeck, and A. Sidorchuk, "Marijuana use and risk of lung cancer: a 40-year cohort study," Cancer Causes Control, vol. 24, no. 10, pp. 1811–1820, Oct. 2013, doi: 10.1007/s10552-013-0259-0.

[13] L. R. Zhang et al., "Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium," Int. J. Cancer, vol. 136, no. 4, pp. 894–903, Feb. 2015, doi: 10.1002/ijc.29036.

[14] J. D. Stanaway et al., "Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017," The Lancet, vol. 392, no. 10159, pp. 1923–1994, Nov. 2018, doi: 10.1016/S0140-6736(18)32225-6.

[15] R. J. Hung et al., "A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25," Nature, vol. 452, no. 7187, pp. 633–637, Apr. 2008, doi: 10.1038/nature06885.

[16] [16] M. Huang, Y. Chen, D. Han, Z. Lei, and X. Chu, "Role of the zinc finger and SCAN domain-containing transcription factors in cancer," Am. J. Cancer Res., vol. 9, no. 5, pp. 816–836, 2019.

[17] Z.-G. Han et al., "Molecular Cloning of Six Novel Krüppel-like Zinc Finger Genes from Hematopoietic Cells and Identification of a Novel Transregulatory Domain KRNB," J. Biol. Chem., vol. 274, no. 50, pp. 35741–35748, Dec. 1999, doi: 10.1074/jbc.274.50.35741.

[18] X. Liu et al., "MicroRNA-940 promotes tumor cell invasion and metastasis by downregulating ZNF24 in gastric cancer," Oncotarget, vol. 6, no. 28, pp. 25418–25428, Sep. 2015, doi: 10.18632/oncotarget.4456.

[19] B. Pang, Y. Wang, and X. Chang, "A Novel Tumor Suppressor Gene, ZNF24, Inhibits the Development of NSCLC by Inhibiting the WNT Signaling Pathway to Induce Cell Senescence," Front. Oncol., vol. 11, p. 664369, Jul. 2021, doi: 10.3389/fonc.2021.664369.

[20] L. Liu et al., "In vivo genome-wide CRISPR screening identifies ZNF24 as a negative NF-κB modulator in lung cancer," Cell Biosci., vol. 12, no. 1, p. 193, Dec. 2022, doi: 10.1186/s13578-022-00933-0.