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Lung Cancer Medical Documentation Paper

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Contents

1. Overview of Lung Cancer

1.1 Definition and Classification

Lung cancer is a malignant tumor characterized by the uncontrolled growth of abnormal cells in one or both lungs. These abnormal cells do not carry out the functions of normal lung cells and do not develop into healthy lung tissue. Instead, they divide rapidly and form tumors that can interfere with the lung's primary function of providing oxygen to the body via the bloodstream. Without treatment, these tumors can spread within the lungs and to other parts of the body, further impairing lung function and overall health.

Lung cancer is broadly classified into two main categories based on the appearance of the cancer cells under a microscope:

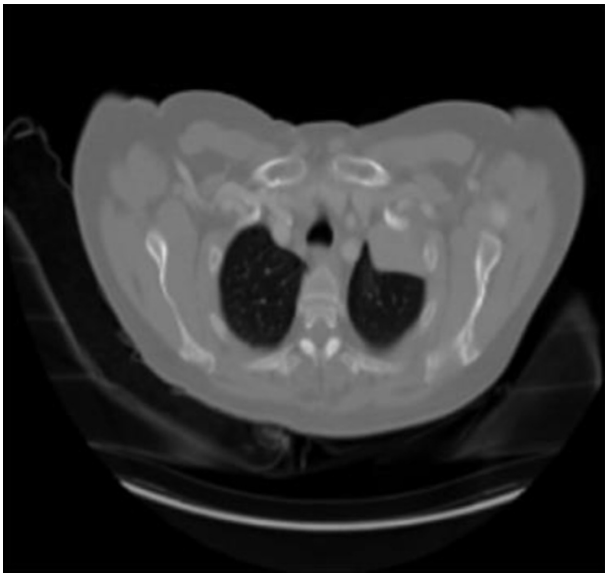
- **Non-Small Cell Lung Cancer (NSCLC)**: This is the most common type, accounting for approximately 85% of all lung cancer cases.
- **Small Cell Lung Cancer (SCLC)**: Less common and more aggressive, accounting for about 15% of cases.

These classifications are crucial as they guide the therapeutic strategy and have different prognosis and biological behaviors.

1.2 Histological Types: NSCLC vs. SCLC

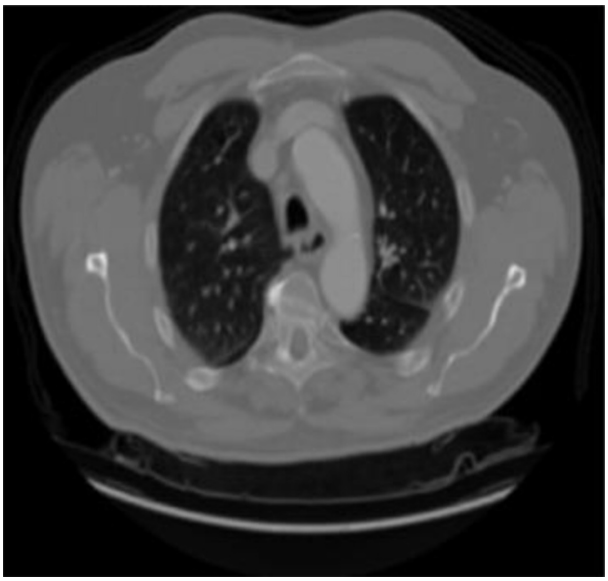
NSCLC comprises several histological subtypes, each with distinct pathological and clinical characteristics:

- **Adenocarcinoma**: The most prevalent subtype of NSCLC, particularly among non-smokers and younger individuals. It originates from glandular epithelial cells and is frequently located in the lung periphery. Adenocarcinomas exhibit significant histological heterogeneity and may present mixed patterns, such as acinar, papillary, solid, or bronchioloalveolar features. The WHO/IASLC classification recognizes several variants, including mucinous, fetal, and signet ring types. [8]



CT scan of patient diagnosed with lung Adenocarcinoma. [14]

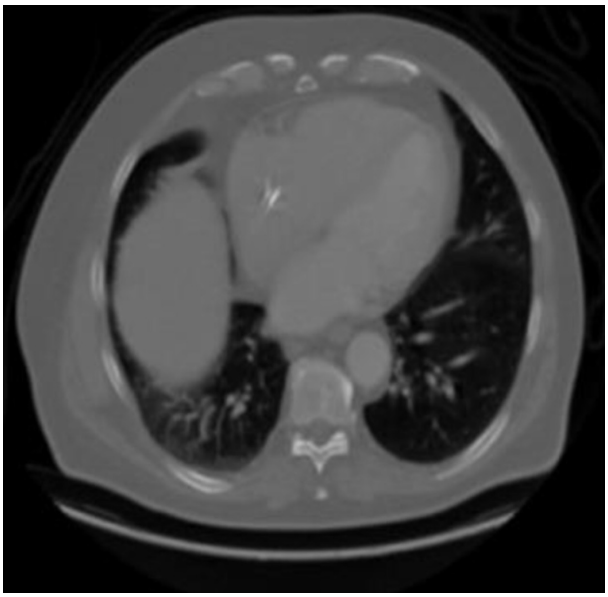
- **Squamous Cell Carcinoma**: Commonly found in the central airways, this subtype arises from squamous epithelial cells and is strongly associated with tobacco smoking. It is characterized histologically by keratinization and intercellular bridges. The incidence of squamous cell carcinoma has declined in recent years due to reduced smoking rates. [8]



CT scan of patient diagnosed with lung Squamous Cell Carcinoma. [14]

- **Large Cell Carcinoma**: A heterogeneous group of poorly differentiated tumors lacking glandular or squamous characteristics. It is often aggressive and located in peripheral lung tissue. The WHO/IASLC classification includes variants such as large cell neuroendocrine carcinoma (LCNEC), basaloid carcinoma, and large cell

carcinoma with rhabdoid phenotype. [8]



CT scan of patient diagnosed with lung Large Cell Carcinoma. [14]

- **Others**: This category encompasses a diverse group of rare or poorly differentiated NSCLC histologies.

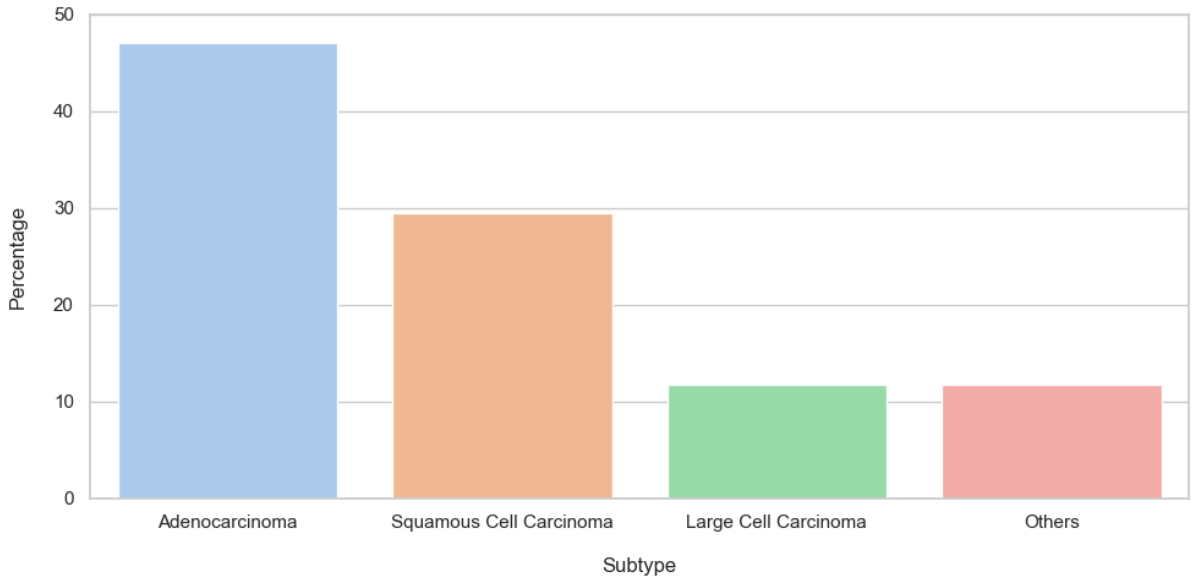
  Adenosquamous carcinoma exhibits both glandular (adenocarcinoma) and squamous components, and is typically more aggressive than either component alone.

  Sarcomatoid carcinomas are poorly differentiated tumors that show sarcoma-like features and include pleomorphic carcinoma, spindle cell carcinoma, and giant cell carcinoma. These are rare and generally associated with a poor prognosis.

  Salivary gland-type tumors, such as mucoepidermoid carcinoma and adenoid cystic carcinoma, are histologically similar to tumors of the salivary glands and are extremely rare in the lungs.

  Carcinoid tumors are neuroendocrine in origin and tend to be less aggressive, although atypical variants can exhibit more malignant behavior.

  Finally, some tumors remain *unclassified* due to ambiguous histological features or inadequate sampling, and are grouped as NSCLC not otherwise specified (NOS). [16]



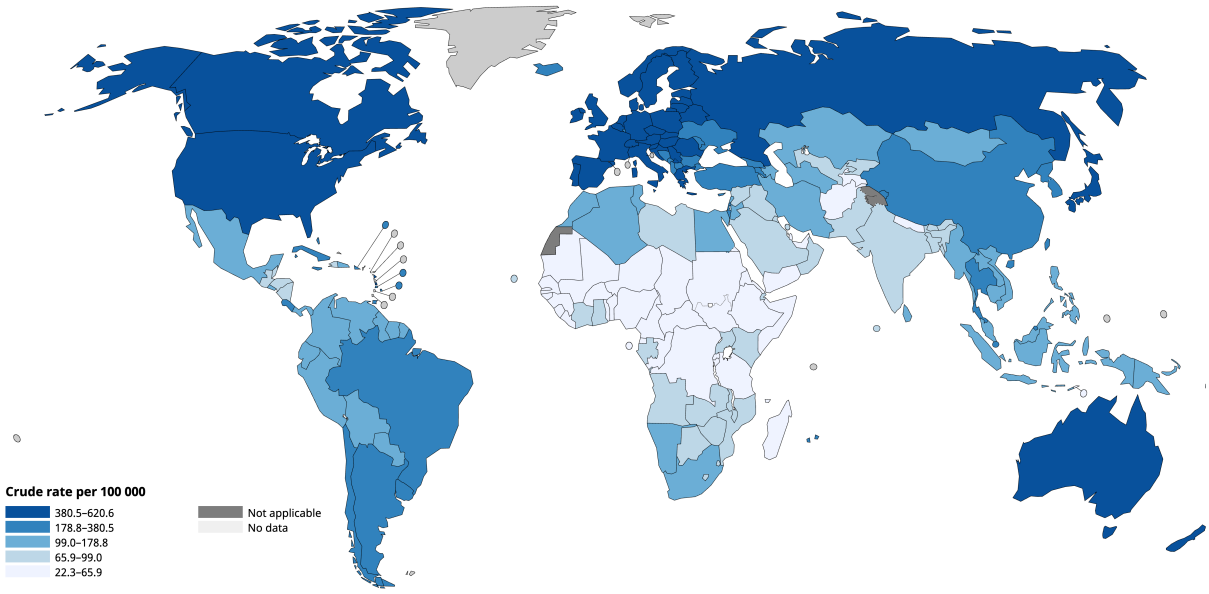
Distribution of NSCLC histological subtypes. Data source: [8].

SCLC, in contrast, tends to grow rapidly and spread early to distant body sites. It is strongly associated with cigarette smoking and is often diagnosed at an advanced stage.

1.3 Epidemiology and Global Burden

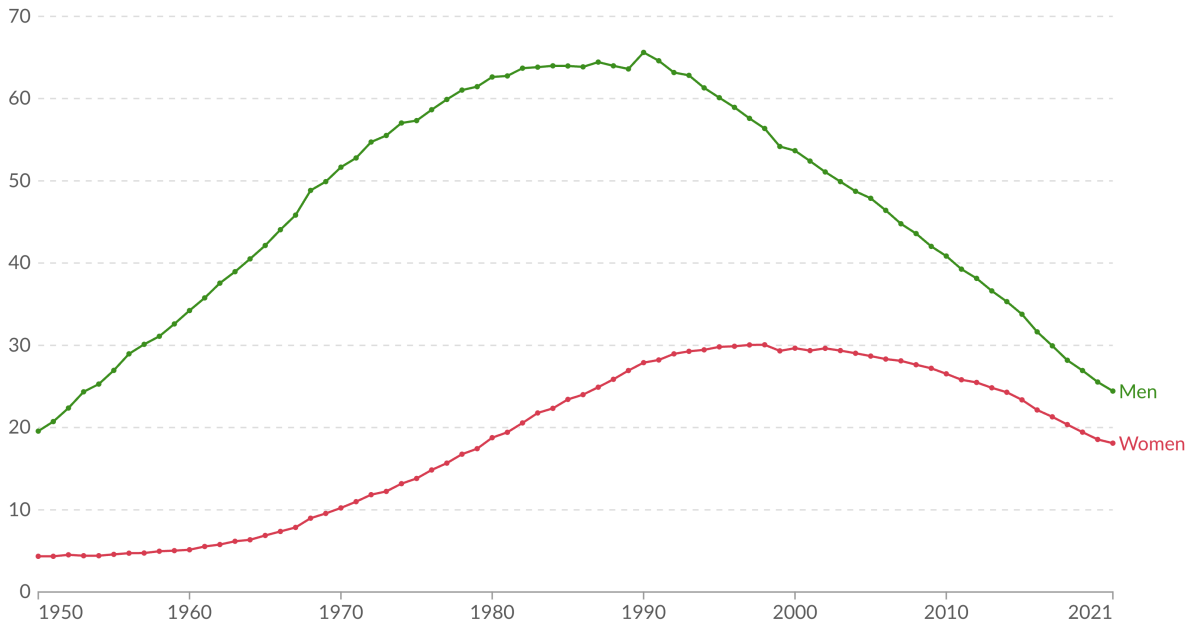
Lung cancer remains one of the leading causes of cancer-related deaths worldwide. According to the World Health Organization (WHO), lung cancer causes approximately 1.8 million deaths annually, making it the most lethal form of cancer. [18]

- **Incidence**: Varies globally, significantly depending by region, often reflecting differences in tobacco use, environmental exposure, and socioeconomic status. High-income countries generally show declining trends in incidence due to successful tobacco control efforts, while many low and middle-income countries are seeing rising rates due to increased smoking prevalence and industrial pollution.



Lung cancer estimated incidence crude rate (per 100.000 people). [18]

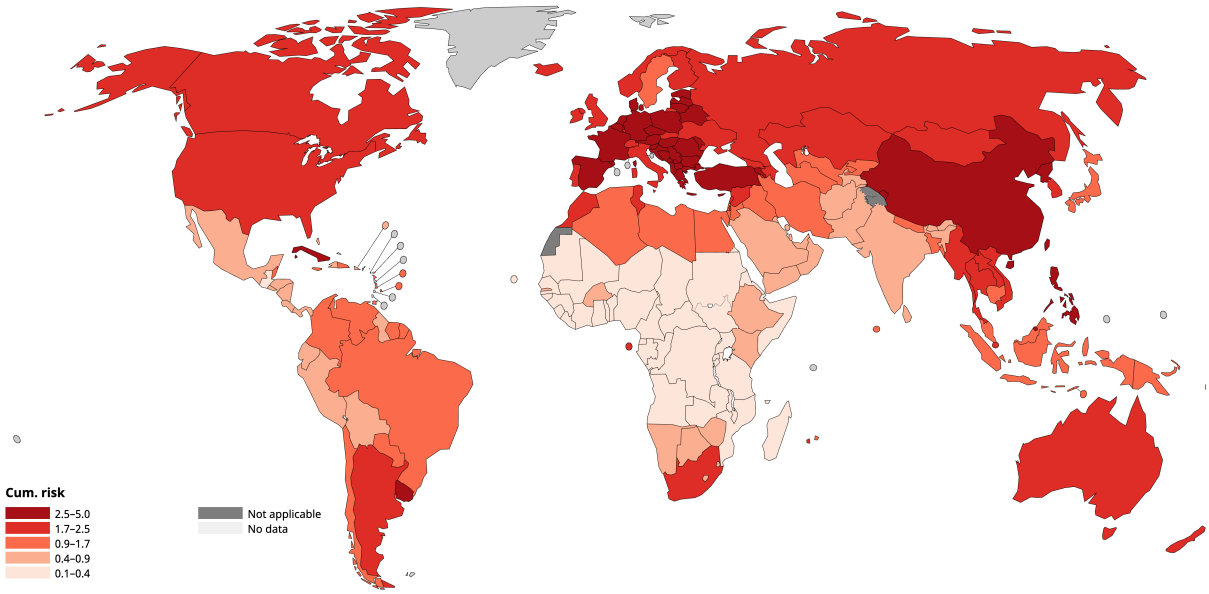
- **Gender Distribution**: Historically more prevalent in men, but the gap is narrowing due to increased smoking rates among women over time. Biological differences, including hormonal and genetic factors, may also contribute to distinct patterns of disease development and progression between sexes.



Lung cancer death rates (per 100.000 people). [11, 18]

- **Survival Rates**: The 5-year survival rate remains low (around 20%) [8], especially for cases diagnosed at a late stage. Mortality closely mirrors incidence rates, with lung cancer accounting for nearly one in five cancer deaths. Non-small cell lung

cancer (NSCLC), the most common type, generally has better outcomes than small cell lung cancer (SCLC), especially when diagnosed early.



Lung cancer estimated mortality cumulative risk (per 100.000 people). [18]

The global burden of lung cancer is not only reflected in mortality rates but also in the economic and social costs of treatment and loss of productivity. Prevention and early detection remain critical in reducing this burden.

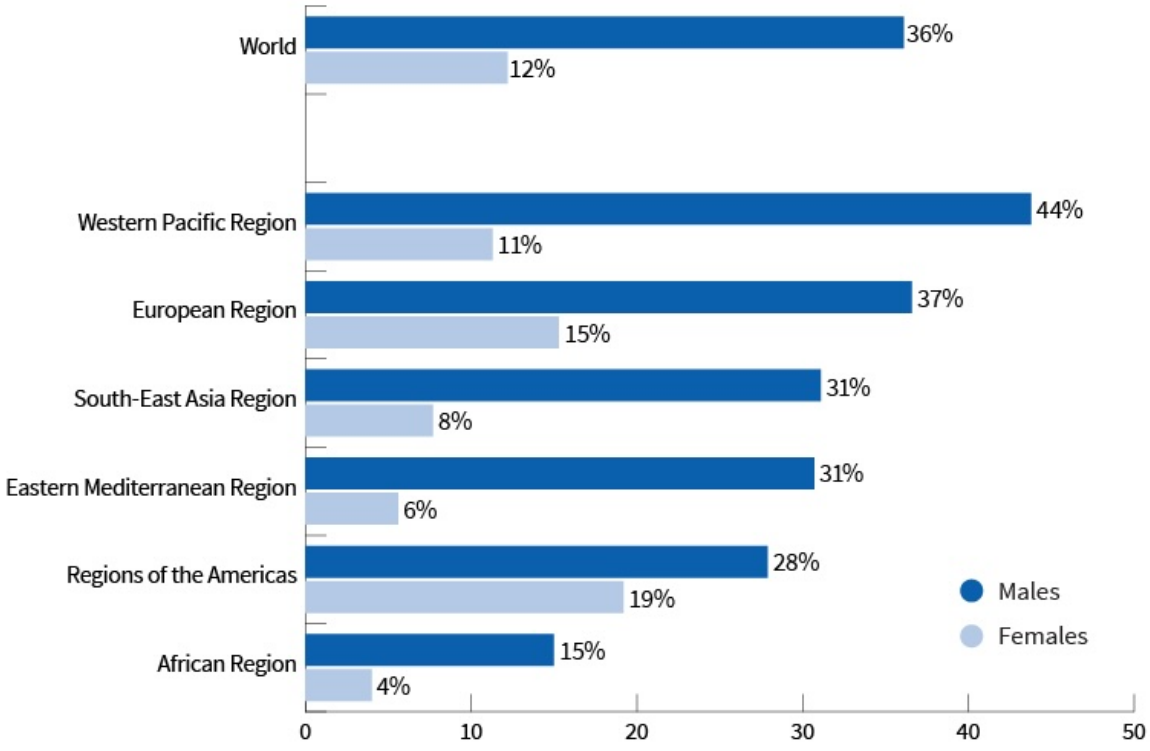
2. Etiological Risk Factors

Lung cancer is the leading cause of global cancer incidence and mortality. Tobacco smoking is the greatest preventable cause of death worldwide, accounting for up to 90% of lung cancer cases, and continued consumption is projected to increase global cancer incidence, particularly in developing nations such as China, Russia, and India. Second-hand smoke among children and spouses has likewise been implicated. Radon from natural underground uranium decay is the second leading cause of lung cancer in the developed world. Occupational hazards such as asbestos and environmental exposures such as air pollution, arsenic, and HIV and Tb infection have all been implicated in lung carcinogenesis, while cannabis smoking, electronic cigarettes, heated tobacco products, and COVID-19 have been hypothesized to increase risk.[1]

2.1 Tobacco Use and Exposure

While, at the beginning of the twentieth century, lung cancer was a rare disease, it was diagnosed progressively more often over the next 50 years, and various suggestions were made during this period that cigarette smoking might be the cause, deriving mainly from the simple fact that the incidence and cigarette consumption were increasing concomitantly.[6]

Tobacco smoke is a complex chemical mixture, containing several thousand compounds, including at least 60 known carcinogens. It is reported that there are an estimated 1.1 billion smokers globally, 1.8 million deaths from lung cancer each year, and about 80–90% of those deaths are attributable to tobacco smoke exposure.[13]

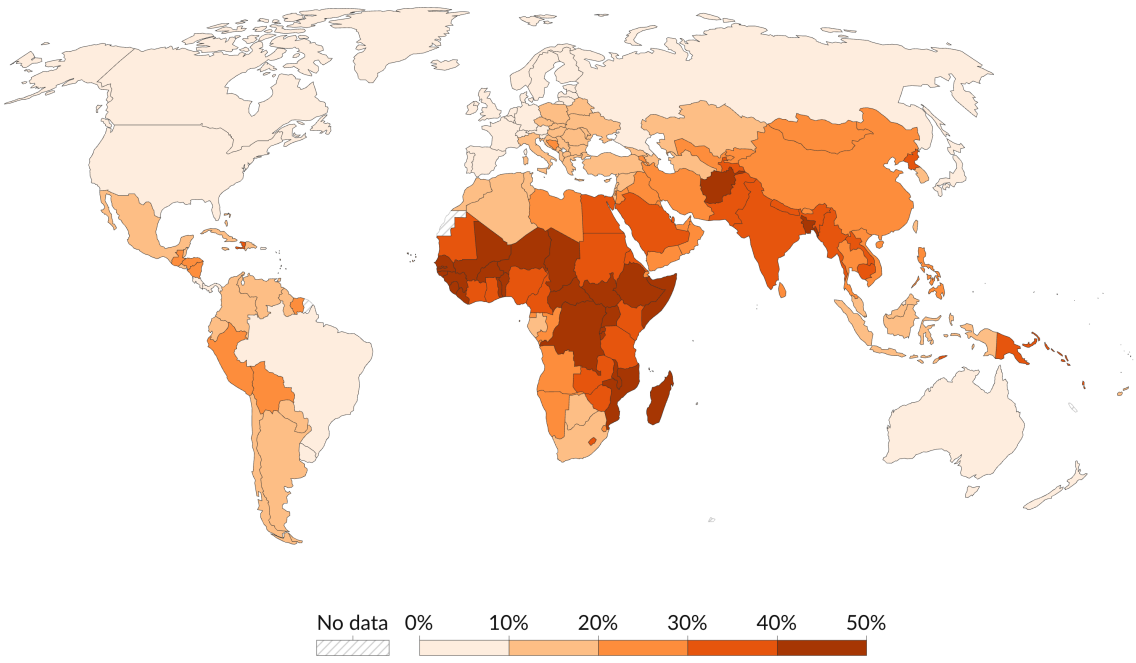


Deaths from Cancer Caused from Using Tobacco, Worldwide in 2019.[7]

There are several ways in which smoking promotes cancer. The primary method is harming our cells' DNA. Our cells' growth and behavior are governed by their DNA. Benzo[a]pyrene and nitrosamines, two carcinogenic substances found in tobacco smoke, are the main source of DNA damage because they are metabolically converted into reactive intermediates in the body. By directly binding to DNA, these intermediates create chemical lesions known as DNA adducts, which alter the structure of DNA and obstruct proper transcription and replication. High amounts of reactive oxygen species (ROS) produced by tobacco smoking also cause oxidative stress, which harms DNA bases. Tobacco smoke not only directly damages DNA but also disrupts essential DNA repair processes such as base excision repair and nucleotide excision repair, which permits mutations to accumulate. Tobacco smoke also causes epigenetic modifications, like aberrant DNA methylation, which inhibit tumor suppressor genes and accelerate the development of cancer. All of these processes work together to explain the molecular link between cigarette smoke and lung cancer.

2.2 Environmental and Air Pollutants

Environmental and air pollutants significantly influence lung cancer risk through both direct carcinogenic effects and chronic inflammatory mechanisms. The relationship varies by pollutant type, exposure duration, and geographic context, with outdoor and indoor sources contributing differently across income levels.



The estimated share of lung cancer deaths attributed to the risk factor air pollution, 2021.[10]

- **Outdoor Air Pollution**: Particulate matter is a major driver, with studies showing a 10 μg/m^3 increase in PM2.5 correlates with an 8% rise in lung cancer mortality[12] and long-term exposure increases lung adenocarcinoma risk, particularly in urbanized areas. Nitrogen dioxide (NO2) and ozone (O3) also contribute, with NO2 linked to a 3% higher incidence per 1% concentration increase. Geographically, middle-income countries see a 0.28% lung cancer risk increase per 1% rise in outdoor pollution, while high-income countries face a 0.51% increase.[3]
- **Indoor Air Pollution**: Sources like cooking fumes, coal burning, and radon disproportionately affect high-income countries: a 1% increase in indoor pollution raises lung cancer risk by 0.37% in these regions.[4]

Lung cancer incidence might be significantly decreased by mitigating air pollution through stronger emission restrictions and the use of clean energy, especially in areas with quickly industrializing economies.

2.3 Genetic and Familial Predisposition

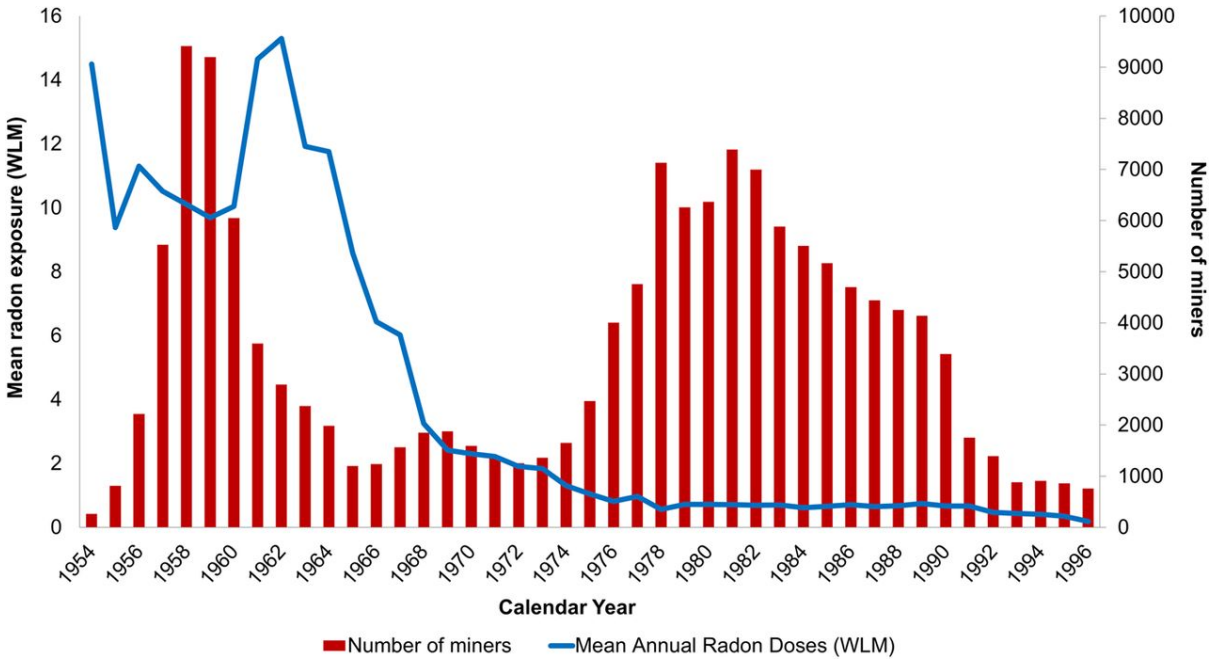
Genetic and familial predisposition play a significant but complex role in lung cancer risk, interacting with environmental factors like smoking.

- **Inherited Genetic Mutations**: Inherited mutations in BRCA1, BRCA2, and RAD51D increase small cell lung cancer risk. Carriers show better responses to platinum-based chemotherapy and PARP inhibitors due to impaired DNA repair mechanisms.
- **Familial Aggregation**: Having a parent or sibling with lung cancer confers a 1.5x higher risk after adjusting for smoking. Affected siblings correlate with a 1.8x increased risk, stronger than parental history (1.3–1.4x). Familial risk doubles (1.97x) for probands diagnosed before age 50.[2]

While only 8–15% of lung cancers[5] are linked to inherited factors, familial risk assessment remains critical for personalized prevention and treatment strategies.

2.4 Occupational and Industrial Hazards

Occupational and industrial hazards significantly increase lung cancer risk through exposure to various carcinogens commonly found in workplaces, often with a synergistic effect when combined with smoking.



Cancer incidence and mortality from exposure to radon progeny among Ontario uranium miners.[9]

- **Key Occupational Carcinogens**:
  - **Asbestos**: Strongly linked to lung cancer and mesothelioma; Risk escalates sharply with cumulative exposure, even at low doses (no safe threshold). It causes direct DNA damage via iron-generated reactive oxygen species (ROS) and chronic inflammation. [15]
  - **Silica dust (respirable crystalline silica)**: Predominantly associated with squamous cell and small cell carcinomas. Monotonic risk increase observed, with effects detectable at cumulative exposures as low as 0.22 mg/m^3-years. Accounts for 3% of lung cancer cases in industrialized nations, rising to 6%[17] if all exposure levels are considered.
- **High-Risk Occupations**: Workers who are exposed, such as miners, shipyard workers, insulators, textile plant workers, foundry workers, stonecutters, and ceramics manufacturers, are at a significantly increased risk.

Safety protocols to protect workers from key occupational carcinogens focus on minimizing exposure through a hierarchy of controls, combining elimination, engineering, administrative measures, and personal protective equipment (PPE). These protocols align with international occupational health guidelines and aim to keep exposure 'As Low As Reasonably Achievable' (ALARA), effectively reducing the incidence of occupational cancers.

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