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A Comprehensive Review of Lung Cancer: Epidemiology, Diagnosis, Treatment, and Risk Factors in Iraq

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Abstract

Lung cancer, which is characterized by uncontrolled cell division in the lungs, is the leading cause of cancer-related death worldwide, accounting for one-fifth of all cancer deaths. This review aims to provide a comprehensive analysis of lung cancer, focusing on its epidemiology, diagnosis, treatment, and risk factors, particularly non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). The objective is to explore recent advancements in diagnostic techniques, including low-dose computed tomography (LDCT), liquid biopsies, and biomarker-based approaches, which enhance early detection and monitoring. Additionally, the review examines treatment strategies, including surgical interventions, chemotherapy, radiation therapy, targeted therapies, and immunotherapy, with a focus on personalized treatment plans based on cancer type and stage. Emerging risk factors, such as genetic predispositions and environmental exposures, are also discussed to highlight their implications for prevention and early intervention. In conclusion, this review underscores the importance of integrating the latest research and clinical advancements to improve diagnostic accuracy, develop innovative treatments, and implement preventive measures. By doing so, it aims to contribute to reducing the global burden of lung cancer and improving patient outcomes.

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Introduction

Cancer is a metastatic disease characterized by the uncontrolled development and proliferation of abnormal cells (1). If the expansion is not stopped, it can cause death. It is caused by 90-95% related to environmental factors including tobacco, radiation, and pathogenic organisms, and 5-10% related to internal factors including immunological disorders, hormones, hereditary, and metabolic mutations. These causing characteristics might act simultaneously or sequentially to promote or initiate cancer development. Perhaps it takes years or more between exposure to environmental factors and identifiable malignancies (2).

Common environmental factors contributing to cancer deaths include tobacco use, which accounts for 25–30%, and diet and obesity, which together account for 30–35% of deaths. Infection is responsible for 15–20% of cancer-related deaths, whereas ionizing and nonionizing radiation contribute to up to 10% of cancer-related deaths (3). In addition, stress and a lack of physical activity are important factors in overall cancer mortality (4).

Lung cancer is one of the most prevalent and deadly malignancies worldwide and presents significant challenges in public health and oncology. This comprehensive review aims to explore the epidemiology of lung cancer and its clinical characteristics, with an emphasis on non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). Its incidence, risk factors, prevalence, and mortality trends across different populations are highlighted.

Lung cancer

The term "lung cancer" refers to the development of abnormal cells within the lungs. These cells proliferate far faster than normal cells do, eventually resulting in the growth of a lump. If irregular lung cells are eliminated as they circulate through the bloodstream or lymphatic system, they may start to proliferate in other areas of the body, such as the bones. This change can be identified as a secondary tumor or metastasis (5). It is the leading cause of cancer-related deaths worldwide, with smoking being the most significant risk factor. Lung cancer is the most often diagnosed type of cancer, accounting for 12% of all cases, and the incidence and fatality rates of this cancer are increasing internationally (6).

Globally, lung cancer is the leading cause of cancer-related death (2). According to the "World Health Organization (WHO)" report, 1.8 million new cases (12.9% of all new cancer cases) and 1.6 million deaths (19.4% of all cancer deaths) occurred in 2012 (7). It is a major public health risk and accounts for a substantial number of deaths globally. The "GLOBOCAN 2020" estimates of cancer incidence and mortality released by the "International Agency for Research on Cancer (IARC)" reported that lung cancer remains the leading cause of cancer-related deaths, with an expected 1.8 million deaths globally, representing 18% of all cancer deaths in 2020 (8). In the United States, Canada, and the European Union, lung cancer is the leading cause of cancer mortality among both men and women (9). In 2020, a comprehensive investigation of lung cancer in Canada revealed that it is the most frequently diagnosed cancer and the leading cause of cancer-related deaths. By 2050, the global cancer burden is expected to double, with lung cancer being the most common (10).

Lung cancer often leads to fatalities because it is frequently not detected until it has reached an advanced stage. Effective treatment of lung cancer depends on appropriate medications, early detection, and a detailed understanding of its pathogenesis. As a consequence, early detection of lung cancer is critical, especially in screening high-risk populations (e.g., smokers, fumes, workers with asbestos, oil fields, radon, and arsenic, among others), where new biomarkers must be identified. Moreover, the most suitable treatment for lung cancer patients depends on an accurate diagnosis (11).

Types of Lung Cancer

Lung cancer can be divided into two types, non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), as shown below and compared in Table 1(11).

Non-small cell lung cancer

Non-small cell lung cancer (NSCLC) represents between 85% and 90% of all lung cancers (12,13). This type of cancer is classified into three subtypes: squamous cell (epidermoid) carcinoma, adenocarcinoma, and large cell carcinoma. These subtypes have different cell sizes, shapes, and chemical compositions. However, they are categorized because their treatment techniques and prognoses are comparable (14,15).

NSCLC is histologically classified as squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma. The "American Joint Committee on Cancer (AJCC)" developed the "TNM Staging System" to classify cancer stages. The TNM system guides the determination of the stage of cancer via the extent of the primary tumor (T), the spread of the tumor to the lymph nodes (N), and the presence of metastasis (M) (16). Consequently, the final TNM classification is a composite of three factors: the presence (M1) or absence of (M0) metastasis, the extent of lymph node involvement (N0–N3), and the tumor characteristics (T) categorized from T1 to T4 (11).

Lass T2 is characterized by atelectasis or insufficient bronchial inflation on one side of the bronchi, with abscesses found in the bronchi and main bronchi located more than 2 cm from the carina. This usually occurs at T3, where atelectasis affects the entire lung. The tumor advances toward the main bronchus, less than 2 cm from the carina, and infiltrates the phrenic nerve, diaphragm, chest wall, and mediastinal pleura. Stage T4, also known as the invasion stage, is characterized by the spread of the tumor to the lung carina, vertebral bodies, and mediastinal organs (17). Depending on the stage, lymph node involvement can range from involvement (N0) to ipsilateral or contralateral involvement, as categorized by N0 to N3 (18). Metastasis

is classified as M1 when bilateral lesions, distant metastasis, or malignant pleural effusion are present. On the other hand, M0 macrophages lack metastasis (19).

• Squamous Cell Cancer (Epidermoid)

Squamous cell carcinomas account for approximately 25–30% of all lung cancers (20). These malignancies begin with early variations in squamous cells, flat cells lining the main airways of the lungs. They are often connected with a history of smoking and tend to be located in the center of the lungs, near the left or right bronchus. In addition, it tends to grow more slowly and may be detected earlier because it can cause symptoms such as coughing or breathing problems (21).

• Adenocarcinoma

Adenocarcinomas account for approximately 40% of all lung cancers (20). It originates in the cells that line the alveoli and produce mucus. These tumors begin in the early stages of cells and are often found in the outer parts of the lungs, where they typically release substances such as mucus. Smokers are more likely to have this type of lung cancer but are more likely to be nonsmokers and women (22). In fact, adenocarcinoma is commonly found in the outer layers of the lung. It grows more slowly than other types of lung cancer and is more likely to be detected before it spreads beyond the lung (21).

• Large Cell Carcinoma (Undifferentiated)

Large cell carcinoma represents approximately 10% to 15% of all lung cancers. It can develop in any part of the lung and is known for its rapid growth and spread, making it difficult to treat (23).

Small Cell Lung Cancer

Small cell lung cancer (SCLC) accounts for 10% to 15% of all lung cancers. The name refers broadly to cancer cells viewed under the microscope. Small cell carcinoma usually starts in the lungs in the center of the chest and spreads very quickly throughout the body. Small-cell lung cancer is extremely rare in people who have never smoked (24).

SCLC is a central tumor that develops as a perihilar mass from the airway submucosa. Histological studies indicate that this form of cancer develops from neuroendocrine cells in the basal bronchial epithelium (25). The cells are small, spindle shaped, or round, with minimal cytoplasm and granular chromatin. Typically, necrosis is observed (26). SCLC may also be subtyped either alone or in combination with NSCLC. This cancer is divided into limited or extensive phases and has the potential to metastasize to the liver, brain, and bone (27).

The limited SCLC stage affects only one radiation site, the ipsilateral mediastinum, as well as the supraclavicular or ipsilateral mediastinal lymph nodes. It is categorized as a supraclavicular lymph node if it is located on the same side of the malignant chest. In contrast, extensive SCLC is not confined to a single radiation site within the lung. It spreads to the second lung lobe, lymph nodes, and other areas of the body, including the bone marrow (11).

Table 1. Comparison of NSCLC and SCLC (11).

Feature	NSCLC	SCLC
Prevalence	85-90% of lung cancers	10-15% of lung cancers
Common Symptoms	Persistent cough, chest pain, weight loss	Rapid onset, shortness of breath, fatigue
Treatment Options	Surgery, chemotherapy, radiation, targeted therapy	Chemotherapy, radiation, immunotherapy
5-Year Survival Rate	Varies by stage (e.g., 60% for Stage I)	Poor prognosis, often diagnosed at advanced stages

Stages of Lung Cancer

As demonstrated above, there are two types of lung cancer: non-small cell lung cancer and small-cell lung cancer. The most significant threat to public health associated with lung cancer is its poor prognosis, which is a result of its advanced stage. The majority of patients (>75%) are diagnosed with either stage III or IV disease. Additionally, the stage of the disease plays a crucial role in determining the prognosis of patients with lung cancer. Patients with clinical stage IA disease have a 5-year survival rate of approximately 60%, whereas those with clinical stage II-IV disease have 5-year survival rates ranging from 40% to less than 5% (28), as shown in Figure 1, and each stage is defined as follows:

- On the basis of the TNM classification, the stages of non-small cell lung cancer are (29):

Stage 0 (Carcinoma in Situ): Cancer cells are found solely in the innermost lining of the lung and have not spread. This is an extremely early stage, often known as “precancer” or “in situ”.

Stage I: Malignancy is found only in the lungs and has not progressed to the lymph nodes.

• Stage IA: The tumor is 3 cm or smaller, confined to the lung, and has not spread to the lymph nodes.

• Stage IB: The tumor is larger than 3 cm but not larger than 4 cm, or it has grown slightly into the main bronchus or the lung’s inner lining (visceral pleura) but has not spread to the lymph nodes.

Stage II: The cancer is located in the lung and has spread to adjacent lymph nodes.
• **Stage IIA:** The tumor is between 4 cm and 5 cm in size, but there is no spread to nearby lymph nodes.
• **Stage IIB:** The tumor is 5 cm or smaller and has spread to nearby lymph nodes, or it is larger than 5 cm but not exceeding 7 cm and has not spread to the lymph nodes.
Stage III: Cancer is located in the lungs and lymph nodes in the center of the chest; it is also known as a locally progressive disorder.
• **Stage IIIA:** The cancer has spread only to the lymph nodes on the same side of the chest where it originated.
• **Stage IIIB:** The cancer has spread to lymph nodes on the opposite side of the chest or above the collarbone.
• **Stage IIIC:** The tumor is larger than 7 cm or has grown into nearby structures or lymph nodes and involves multiple areas, but there is still no distant spread.
Stage IV: This is the most advanced stage of lung cancer and is often known as an advanced stage. This happens when the cancer spreads to both lungs, the fluid surrounding the lungs, or other parts of the body, such as the liver or other organs.
• **Stage IVA:** Cancer spreads within the chest or to a single distant organ (e.g., the liver, brain, or bone).
• **Stage IVB:** Cancer spreads to multiple distant sites in one or more organs.
The stages of SCLC are as follows (30):
1. In the limited stage, the cancer is confined to just one lung, fluid around the lung (known as a pleural effusion), or surrounding lymph nodes.
2. Extensive stage: The cancer has spread across the lung, within the chest, or to other parts of the body.

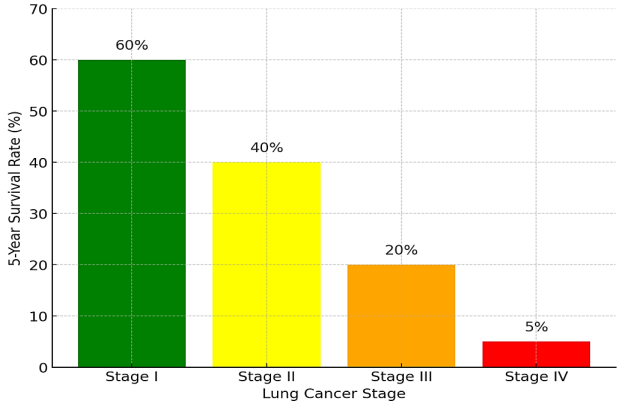

Figure 1. 5-year survival rates for patients with different lung cancer stages.

Signs and Symptoms of Lung Cancer
The most common signs of lung cancer include a chronic dry cough that never seems to go away or worsen with time and may also produce sputum or phlegm. Chest pain, particularly during deep breaths or laughing, and hoarseness are also frequent symptoms. Patients may experience weight loss, loss of appetite, and coughing up blood (hemoptysis) or rust-coloured sputum. Common symptoms include shortness of breath (dyspnoea), fatigue or weakness, and chronic infections such as bronchitis and pneumonia that do not clear or continue to resurface. Furthermore, a new phase of wheezing may be identified (31).
When lung cancer metastasizes to distant organs, it can lead to specific symptoms such as bone pain, which is often felt in the back or hips, and neurologic changes such as headaches, weakness or numbness in an arm or leg, dizziness, balance problems, or seizures, which are caused by cancer spreading to the brain or spinal cord. If the cancer spreads to the liver, it may also cause yellowing of the skin and eyes (jaundice). Furthermore, lumps near the surface of the body, such as those in the neck or above the collarbone, may develop if the cancer spreads to the skin or lymph nodes (32).
Diagnosis and screening of lung cancer
The diagnosis and screening of lung cancer have improved significantly due to technological advances. The limited use of computed tomography (CT) remains the primary screening method for lung cancer. The development of approaches such as liquid biopsies, particularly circulating tumor DNA analysis, provides noninvasive possibilities for early detection and monitoring (33).
Historically, the only techniques for early lung cancer detection were lung cytology and chest X-rays. Nonetheless, the results revealed that these two approaches failed in clinical trials and could not be shown to be viable as mass screening tools (34). Lung cancer screening via low-dose CT (LDCT) is recommended for high-risk populations, which are defined as individuals aged 50 to 80 years who have a smoking history of at least 20 pack-years. This includes individuals who are currently smoking or have quit within the past 15 years and who are disease free at the time of screening (35).
Additionally, recent advancements in genetics have been utilized to identify high-risk populations, making them more suitable for lung cancer screening and helping to enable earlier diagnosis (36). Furthermore, a NELSON "Netherlands Leuvens Screening Study" trial demonstrated that this particular screening method achieved a selectivity of 85% and a specificity of 99% compared with no screening (37). Additionally, the integration of radiomic and clinical data has shown promise in increasing the diagnostic accuracy for pulmonary nodules, suggesting that a multifaceted approach could improve early detection (38,39). However, while radiomics has strong potential, further research is needed to optimize its integration with

other diagnostic modalities (40). The sensitivity of tumor detection in the diagnosis of lung cancer via chest radiography is approximately 1 cm in diameter. It already has over 109 cells that have the ability to damage bronchial and vascular epithelia. Screening for lung cancer is now frequently performed via computed tomography (CT), either in conjunction with or without auxiliary testing, such as sputum cytology (41).

The cytological examination of sputum, particularly multiple samples, is another diagnostic procedure for lung cancer. This procedure is especially useful for identifying central tumors originating from the larger bronchi, such as squamous cell carcinomas and small-cell carcinomas. In general, sputum samples are not effective at detecting small adenocarcinomas (with a diameter of ≤ 2 cm) that arise from smaller airway branches, including the small bronchi, bronchioles, and alveoli (42). For the diagnosis and surveillance of lung cancer, sputum cytology has been demonstrated to be inadequately sensitive. Sputum cytology was not recommended for diagnosis because of its low positivity rate, as only 4.5% of lung cancer patients had positive results, according to a previous study (43). This is although central squamous cell carcinoma has a high prediction rate. In addition, sputum cytology, a noninvasive and cost-effective procedure, has lost its diagnostic utility in favor of more invasive techniques, such as bronchoscopy, which provides a greater degree of sensitivity (44). Recent developments in sputum analysis, including DNA methylation detection, have demonstrated significantly increased sensitivity (up to 100%) for the detection of early-stage lung cancer. This suggests that despite the limitations of traditional sputum cytology, innovative approaches may improve its diagnostic capabilities (45). Therefore, despite the potential of sputum cytology, its current application in the diagnosis of lung cancer is insufficient in the absence of further refinement and standardization (42).

Bronchoscopy, which encompasses the use of robotic bronchoscopy and fluorescence-guided biopsy, is essential for the diagnosis and screening of lung cancer. Compared with white light bronchoscopy (45.2% sensitivity), fluorescence-guided biopsy has been shown to have greater sensitivity (60.3%) and specificity (100%) in patients with bronchial mucosal lesions, indicating its potential as an adjunct diagnostic tool (46). Despite its widespread use, the efficacy of traditional bronchoscopy can vary. Although robotic bronchoscopy currently has a lower diagnostic yield than does transthoracic needle biopsy, it provides a safer alternative with lower complication rates (47). Furthermore, bronchoscopy with bronchoalveolar lavage (BAL) has demonstrated a restricted diagnostic yield (52.3% for lung cancer), particularly in the presence of lymphangitis and central lesions (48). Despite these constraints, advancements in bronchoscopic techniques are indispensable for enhancing diagnostic accuracy and confronting obstacles in lung cancer screening (49,50).

Cytokeratin fragments (CYFRA 21-1), carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and progastrin-releasing peptide (ProGRP) are among the specific biomarkers that have been investigated in the process of diagnosing lung cancer, such as blood circulating antigens (BCAs) (51,52). In lung cancer patients, these antigens are secreted into the bloodstream by cancer cells or adjacent tissues, providing potential markers for early detection, monitoring treatment response, and assessing prognosis (53,54). In addition, lung cancer has been linked to a variety of tumor markers in the serum. Ma et al. (2015) reported that the levels of CEA, CA-125, and Cyfra21-1 are elevated in lung cancer and can be used to diagnose this disease (55,56). In addition, prior research has demonstrated that CEA, Cyfra21-1, and CA-125 are linked to poor prognosis in non-small cell lung cancer patients. Furthermore, tumor markers may have the potential to accurately predict metastasis (57,58).

Current research suggests that biomarkers have the potential to reduce overdiagnosis rates associated with traditional imaging methods, such as low-dose computed tomography (LDCT), enhance risk stratification for high-risk individuals, and clarify indeterminate lung nodules (59,60). Numerous biomarkers, such as circulating microRNAs, proteins, and cfDNA, have demonstrated potential for early detection, with specific markers exhibiting high sensitivity and specificity in studies (54,61,62). Nevertheless, obstacles persist, including the implementation of these biomarkers within existing LCS frameworks and the necessity for rigorous clinical validation (54,60,63). Despite the fact that liquid biopsies provide a less invasive alternative for biomarker collection, additional research is needed to establish standardized protocols and evaluate the cost-effectiveness of these methods in a variety of healthcare settings (59,60). Any delay in diagnosis and treatment may negatively affect patient outcomes, as may other factors, such as active smoking and a longer waiting time for biopsy (64,65).

Treatment of Lung Cancer

Lung cancer treatment is determined by the specific cell type of the cancer and how far it has spread. Furthermore, accurate diagnosis is essential for the most appropriate treatment of individual patients with lung cancer (66). The treatment methods include the following:

Surgery

When surgery is possible, it is the primary treatment for lung carcinoid tumors. If the cancer has not spread, surgery is typically sufficient to cure it. Surgery is the primary treatment for eligible individuals with stage I to II lung cancer and early-stage NSCLC, and there is minimal disagreement on this point (67). Although lobectomy is the usual treatment in many cases, sublobular resections have been shown to have exceptional potential in select patients with stage I cancer. This is because they result in

similar overall survival rates and better retained pulmonary function (68). The timing of surgery varies for resectable stage IIIA patients since either neoadjuvant or adjuvant systemic therapy can increase the 5-year survival rate by 5% (69). The goal of surgery is to completely remove the lung tumor and any adjacent lymph nodes in the chest. The following methods of surgery can be performed for lung cancer according to the patient's stage (70):

1- Pneumonectomy: In this type of surgery, a full lung is removed, which is necessary when the cancer is located near the center of the chest.

2- Lobectomy: The lungs typically have five lobes: three in the right lung and two in the left lung. A lobectomy is a surgical procedure in which an entire portion of the patient's lungs is removed. For NSCLC, lobectomy has been shown to be the most effective surgical approach, even when the tumor is relatively small. (29).

3- Segmentectomy or wedge resection: This operation removes a small part of the lung lobe (70).

• Chemotherapy

Chemotherapy is the use of anticancer medications to treat cancer. The primary goal of chemotherapy is to kill cancer cells, which can occur anywhere in the body. It also destroys cells isolated from primary tumors and circulates through the blood and lymph systems to different parts of the body (71). Chemotherapy is commonly used to treat lung cancer and has been shown to prolong survival and improve outcomes at all stages of the disease. It is the primary treatment for SCLC, either alone or in combination with radiation (72). For NSCLC, chemotherapy is often used as part of a palliative treatment plan for locally advanced or metastatic disease to prolong survival and enhance quality of life. It may also be administered before surgery (neoadjuvant) or after surgery (adjuvant) to reduce the risk of relapse (73).

Systemic chemotherapy involves injection via the bloodstream to target cancer cells throughout the body. Chemotherapy is commonly administered either via an intravenous tube inserted into a vein with a needle or via a pill or capsule ingested (orally). Most treatments for lung cancer involve intravenous injection. Chemotherapy can produce significant side effects. These side effects vary depending on the individual and the dose, but they may include exhaustion, nausea, infection risk, vomiting, hair loss, lack of appetite, and diarrhea. These side effects normally subside once treatment is completed. Furthermore, chemotherapy may destroy normal cells in the body, such as skin cells, blood cells, and nerve cells (72).

NSCLC patients are most likely to receive cisplatin or carboplatin with at least one other chemotherapy drug, such as pemetrexed, gemcitabine, vinorelbine, docetaxel (Taxotere), or paclitaxel (Taxol). However, patients might receive the above drugs with immunotherapy or a targeted cancer drug depending on the cancer stage and any gene changes that are caused by the cancer (74). Patients with metastatic NSCLC might receive chemotherapy, such as paclitaxel, bevacizumab, carboplatin, atezolizumab, paclitaxel, carboplatin, pembrolizumab, paclitaxel, carboplatin, atezolizumab, or carboplatin or cisplatin with pembrolizumab and pemetrexed. Patients typically receive a combination of chemotherapy drugs, which may include cisplatin and etoposide or carboplatin and etoposide. In some cases, chemotherapy is combined with an immunotherapy drug, such as cisplatin and etoposide with durvalumab, or carboplatin and etoposide with atezolizumab or durvalumab (75).

• Radiation Therapy

Radiation therapy uses high-energy X-rays or other types of particles to destroy cancer cells. Radiation therapy cannot be utilized to treat metastatic cancer, as it only targets cancer cells within its direct path, potentially affecting nearby healthy cells as well. Patients who receive radiation therapy to the neck or middle chest may have a sore throat, trouble swallowing, weariness, and lack of appetite (72). Typically, two types of radiation are used to treat lung cancer: external beam radiation therapy (EBRT) and internal radiation therapy (also known as brachytherapy) (72):

1- EBRT: This type is the most common form of radiation treatment, where radiation is delivered by a machine located outside the body.

2- SBRT: This is sometimes referred to as brachytherapy radiation, and it involves the insertion of radioactive materials directly near or within the tumor.

• Targeted Therapy

Targeted therapies are treatments that target specific proteins, genes, or tissues that contribute to cancer growth. This treatment inhibits the growth and spread of cancer cells and reduces damage to healthy cells (76). Monoclonal antibodies (proteins that adhere to cell surface receptors and disrupt signals telling the cell what to do) and small-molecule medicines (such as kinase inhibitors) make up the vast majority of targeted therapies. Compared with standard chemotherapy agents, targeted pharmaceuticals function differently. They can be used in cases where chemotherapy prescription drugs are ineffective, and they often have different (and less severe) side effects. Currently, they are most typically used for advanced lung cancer patients, either in combination with chemotherapy or on their own (77).

Some common drugs used for targeted therapy include epidermal growth factor receptor (EGFR) inhibitors, such as erlotinib, gefitinib, and osimertinib, which block the activity of a protein (78); c-ros oncogene 1 (ROS1) inhibitors, such as crizotinib and lorlatinib, which are often the first treatment options for advanced NSCLC and block the activity of an abnormal protein called (ROS1) fusion protein (79); and anaplastic lymphoma kinase (ALK) inhibitors, such as crizotinib and brigatinib, which are used for NSCLC and function by binding to the ATP pocket of the

abnormal ALK protein, blocking its energy and deactivating it (80).

• Immunotherapy

Immunotherapy does not target tumor mutations. Instead, it focuses on the communication between the immune system and the tumor, assisting the immune system in fighting cancer. It is often described as advanced NSCLC or SCLC that does not respond to other treatments to treat patients with stage III or IV disease. Long-term survival is expected in more than 15% of NSCLC patients treated with immunotherapy (81). Immunotherapy is the primary treatment for the vast majority of cancer patients. Immunotherapy is occasionally used in conjunction with chemotherapy. The first type of immunotherapy includes inhibitors of programmed cell death protein 1 (PD-1), such as nivolumab and pembrolizumab, or its ligand, PD-L1, such as atezolizumab. The second type involves inhibitors of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), such as ipilimumab (82). These drugs eliminate specific mechanisms of checkpoint inhibition that limit detrimental immune responses to self-antigens during healthy immune responses; in cancer patients, removing such inhibition increases immunological responses to malignancy (83). However, only a small subset of patients experience a durable response to immunotherapy. Most patients either do not respond to therapy or relapse after an initial response. The immune response is influenced by genetic and environmental factors, as well as other immunomodulatory therapies, such as chemotherapy, radiation, and various targeted treatments (84).

• Combination therapies

Several studies have shown that combination therapy can be used to maximize the benefits of individual drugs and that combinations of drugs or time-dependent action can alter the effects on target cells and is frequently not resectable in advanced lung cancer or where it is used (85). Over the last few decades, combination therapy has been extensively researched in oncology and other complex disease areas through the use of a combination of chemotherapy, radiation, immunotherapy, or targeted therapy for a more comprehensive approach. Drug combinations have the potential to improve therapeutic efficacy, limit drug resistance development, and/or reduce side effects that would otherwise be associated with monotherapy (86). One example is the combination of two tyrosine kinase inhibitors (TKIs) targeting separate signaling pathways, which have been demonstrated to convert drug-resistant cells to drug-sensitive cells (87). Combining TKIs with other chemotherapeutic medicines that inhibit the cell cycle has been shown to improve anticancer efficacy in several cell lines that express certain cancer-related genes (88,89).

Table 2 compares the treatment options for NSCLC and SCLC, including surgery, chemotherapy, radiation, targeted therapy, and immunotherapy.

Table 2. Comparison of the treatment options for NSCLC and SCLC.

Treatment	NSCLC	SCLC	.Ref
Surgery	Lobectomy, pneumonectomy	Rarely used due to advanced stage	(90–92).
Chemotherapy	Cisplatin, carboplatin	Primary treatment	(93,94).
Radiation Therapy	External beam radiation (EBRT), stereotactic body radiation therapy (SBRT)	Often combined with chemotherapy	(95–97).
Targeted Therapy	EGFR inhibitors (e.g., Erlotinib), ALK inhibitors (e.g., Crizotinib)	Less common	(98–100).
Immunotherapy	PD-1 inhibitors (e.g., Pembrolizumab)	Used in advanced stages	(101,102).

Risk Factors

A risk factor is a situation that enhances a person's likelihood of developing a health disease or condition, such as lung cancer. A DNA mutation can cause lung cancer. Cells reproduce by dividing and replicating to produce identical cells, allowing the organism to continually replace itself. Inhaling cancer-causing substances (such as cigarette smoke, radon, and asbestos) harms the cells that line the lungs (103). The body may initially be capable of self-repair. The cells were further harmed by prolonged exposure. They begin to act erratically and develop uncontrollably as a result of repeated exposure. As more damage accumulates, so does the risk of cancer (104). There are various types of lung cancer risk factors, including the following:

• Lifestyle factors

Tobacco smoking is the leading cause of lung cancer, accounting for approximately 90% of men and 65% of women (105). Cigarette smoke contains approximately 73 recognized carcinogens, such as radioactive polonium-210,

1,3-butadiene, nicotine-derived nitrosamine ketone (NNK), aromatic amines, benzo[α]pyrene, ethylene oxide, and cadmium (106,107). According to reports, the risk of lung cancer from smoking cigarettes increases with the quantity of cigarettes smoked each day and the length of time smoked. Smokers are approximately 20 times more likely to develop lung cancer than nonsmokers are (108).

• Environmental factors

Various environmental factors or exposures can increase the risk of developing lung cancer, including the following:

1. Passive smoking: The term "second-hand smoking or passive smokers" refers to being exposed to tobacco smoke but not actively smoking (109). According to multiple studies, passive smoking is linked to lung cancer. Compared with nonsmokers, nonsmokers living with smokers have a 24% greater risk of developing lung cancer (110).

2. Radon gas: Radon is an odorless, colorless gas produced by the breakdown of radioactive radium, a decay product of uranium found in the Earth's crust. Radiation decay products ionize genetic material, causing mutations that can eventually progress to cancer. Radon gas is a leading cause of lung cancer worldwide. It is the second leading cause of lung cancer in the "United States" (111).

3. Air pollution: Long-term exposure to ambient air pollution, such as emissions high in various polycyclic aromatic compounds or hydrocarbons, can lead to lung cancer, most likely through chronic inflammation, oxidative stress, and autonomic nervous system dysfunction. An estimated 11% of lung malignancies in Europe are caused by urban air pollution (112).

4. Asbestos: Asbestos is a naturally occurring fire retardant and fire retardant that is often used in building materials, and the manufacturing of asbestos can cause a wide range of respiratory problems, including lung cancer. Tobacco smoking and asbestos exposure increase the risk of lung cancer. Compared with the general population, smokers of asbestos cigarettes are 45 times more likely to develop lung cancer (113).

5. Occupational exposure: Exposure to various industrial chemicals that cause cancer (i.e., carcinogens), such as diesel exhaust fumes; radiation; and certain metals, such as cadmium, arsenic, nickel, and chromium. Such exposure is related to specific trades or industries. Mining and quarrying, shipbuilding, metal industries, gas production, railway equipment manufacturing, and construction have all been related to an increased risk of lung cancer (114).

Figure 2 shows the distribution of risk factors for lung cancer in Iraq. The pie chart shows that smoking is the most common risk factor, accounting for 90% of cases, followed by radon exposure (5%), air pollution (3%), and occupational risk (2%). The graphic representation emphasizes smoking's significant involvement in the incidence of lung cancer, highlighting the necessity for focused public health measures (115–118).

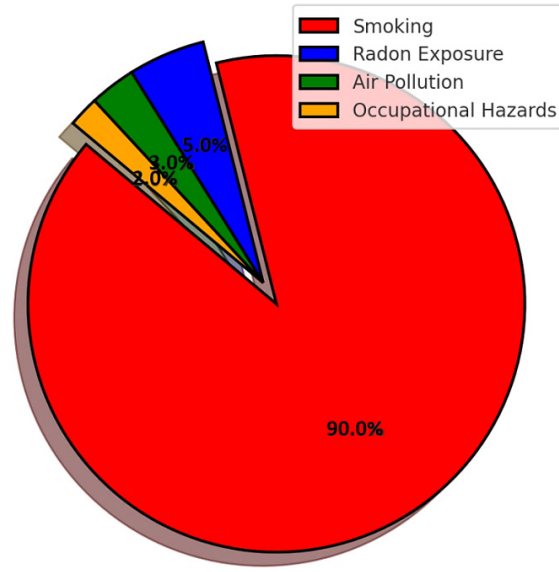

Figure 2. Pie chart representing lung cancer risk factors in Iraq (115–118).

• Biomedical factors

1. Family history: Studies have shown that individuals with more than one first-degree relative diagnosed with lung cancer have a greater likelihood of developing the disease. This increased risk may be due to genetic factors, but it could also be linked to shared behaviors, such as smoking (105).

Recent research has identified specific genetic polymorphisms that contribute to susceptibility to lung cancer. For example, polymorphisms in the P21 and MDM2 genes have been linked to a higher risk of non-small cell lung cancer (NSCLC), particularly in older male smokers. These genetic variants are associated with increased odds ratios, indicating a significant correlation with lung cancer risk (119). Additionally, variants in the epidermal growth factor receptor (EGFR) gene are strongly associated with NSCLC, suggesting that these genetic markers could aid in early detection and personalized treatment strategies (120). Genome-wide association studies (GWASs) have also revealed several single nucleotide polymorphisms (SNPs) in genes such as CHRNA3, CHRNA5, and TERT that are associated with an increased risk of lung cancer, particularly in smokers. These genes are involved in nicotine dependence and telomere maintenance, highlighting the complex interplay between genetic predisposition and environmental factors (121). A 2021 study by Zhang et al. identified novel genetic variants in the TP53 and KRAS genes that are associated with an increased risk of lung adenocarcinoma, particularly in nonsmokers. These findings suggest that genetic testing for these variants could help

identify high-risk individuals for early screening (122).

2. Previous lung diseases: Individuals with a history of respiratory conditions, such as silicosis, tuberculosis (TB), chronic obstructive pulmonary disease (COPD), or pneumonia, may have an increased risk of developing lung cancer. Furthermore, diseases such as lung fibrosis, emphysema, chronic bronchitis, and pulmonary tuberculosis have been linked to an increased risk of lung cancer (123). Recent studies have also explored the role of epigenetic modifications in the development of lung cancer. Sandoval, J., et al. reported that the methylation of DNA patterns in genes such as p16, RASSF1A, and APC is altered in lung cancer patients, suggesting that epigenetic changes may serve as potential biomarkers for early detection and prognosis (124). A 2022 study performed by Li et al. demonstrated that hypermethylation of the CDKN2A gene is strongly associated with early-stage NSCLC and could be used as a noninvasive biomarker for early diagnosis (125). Additionally, research has highlighted the role of microRNAs (miRNAs) in lung cancer pathogenesis. Certain miRNAs, such as miR-21 and miR-155, are overexpressed in lung cancer tissues and have been implicated in tumor progression and metastasis. These miRNAs could serve as noninvasive biomarkers for the early diagnosis and monitoring of lung cancer (126). A 2023 study performed by Wang et al. identified a panel of circulating miRNAs (miR-21, miR-155, and miR-210) that could distinguish between benign pulmonary nodules and early-stage lung cancer with high accuracy (127). Furthermore, advances in liquid biopsy technologies have enabled the detection of circulating tumor DNA (ctDNA) and RNA in blood samples, providing a noninvasive method for identifying genetic mutations and monitoring treatment response. A 2024 study by Chen et al. demonstrated that ctDNA analysis could detect EGFR mutations in NSCLC patients with high sensitivity and specificity, suggesting that ctDNA analysis is a promising tool for personalized therapy (128).

The lifestyle, environmental, and biomedical risk factors for lung cancer are summarized in Table 3.

Table 3. Risk factors for lung cancer.

Category	Risk Factors	Impact
Lifestyle	Smoking, poor diet, lack of exercise	Smoking accounts for 90% of cases
Environmental	Radon, asbestos, air pollution	Radon is the second leading cause
Biomedical	Family history, previous lung diseases	Genetic predisposition increases the risk

Addressing Lung Cancer in Iraq

Lung cancer in Iraq presents significant health challenges, with various studies highlighting its prevalence, genetic factors, and advancements in detection methods. Studies indicate a high incidence of non-small cell lung carcinoma (NSCLC) and identify specific genetic polymorphisms that increase susceptibility among the Iraqi population. Iraq has been at war for four decades, causing significant damage to the healthcare system. The incidence of various cancer risk factors, including smoking, obesity, poor diet, and diabetes, has recently changed in Iraq, and no effective preventive strategies have been implemented. Iraq has high incidence rates of breast, lung, and bladder cancers, as well as an increasing burden of numerous other types (129). According to a study by Hussain et al. (2000–2016), the rate of lung cancer significantly increased from 4.08% to 5.6%, with a higher incidence in males than in females (130). The percentage increased to 13% by 2018, as reported by Aamir et al. (131). A study by "Al Najaf" reported 120 lung cancer cases, predominantly non-small cell carcinoma, with squamous cell carcinoma being the most common type (80%) in 2024 (132). The study also revealed that the majority of cases were males, particularly those with a history of smoking, reflecting the strong association between tobacco use and lung cancer in Iraq. Iraqi researchers have made significant strides in understanding the genetic and molecular basis of lung cancer. A 2023 study identified specific genetic polymorphisms in the P21 and MDM2 genes that were linked to a higher risk of NSCLC, particularly in older male smokers, with odds ratios indicating significant associations (119). Another study conducted in 2022 by Lawi et al. explored the role of epidermal growth factor receptor (EGFR) gene mutations in NSCLC patients in Iraq. One study revealed that 15% of NSCLC patients in Iraq carry EGFR mutations, which are associated with an increased risk of lung cancer and could serve as potential targets for personalized treatment strategies (120). These findings underscore the importance of genetic research in improving early detection and treatment outcomes for lung cancer patients in Iraq.

Data for this study were gathered from the Iraqi National Cancer Registry (INCR), which is administered by the Iraqi Ministry of Health. The INCR gathers and consolidates cancer-related data, including lung cancer incidence, mortality, and treatment results, from a national database of major oncology centers, hospitals, and pathology laboratories. This organized registry has been crucial in following epidemiological changes in lung cancer over the last two decades, forming the basis for the complete information shown in Table 4 (130,131). Table 4 and Figure 3 present significant registry data and trends from 2000 to 2024 to show how the burden of lung cancer in Iraq has

changed over time. This table includes a variety of indicators, including incidence and death rates, sex distribution, affected age groups, geographical differences, leading risk factors, treatment outcomes, and the availability of screening programs (8,130–132).

Table 4. Comprehensive Lung Cancer Registry Data and Trends in Iraq (2000–2024) (130,131)

Metric	2000	2016	2018	2024
Incidence (per 100,000)	5.2	5.6	13.0	14.5
Mortality (per 100,000)	4.1	4.8	10.5	12.0
Gender Distribution				
Male -	70%	72%	75%	78%
Female -	30%	28%	25%	22%
Age Groups (Most Affected)				
years 59–50 -	35%	38%	40%	42%
years 69–60 -	45%	47%	50%	52%
years 70+ -	20%	15%	10%	6%
Most Common Type	NSCLC	NSCLC	NSCLC	NSCLC
Predominant Subtype	Squamous Cell Carcinoma	Squamous Cell Carcinoma	Squamous Cell Carcinoma	Squamous Cell Carcinoma
Regional Variations				
Baghdad -	40%	42%	45%	48%
Basra -	20%	22%	25%	27%
Mosul -	15%	16%	18%	20%
Najaf -	10%	12%	15%	17%
Leading Risk Factors				
Smoking -	90%	90%	90%	90%
Environmental Pollution -	5%	6%	8%	10%
Occupational Exposure -	3%	4%	5%	6%
Treatment Outcomes				
5-Year Survival Rate -	10%	12%	15%	18%
Advanced Stage at Diagnosis -	75%	78%	80%	82%
Surgery Utilization -	20%	22%	25%	28%
Chemotherapy Utilization -	60%	65%	70%	75%
Radiation Therapy Utilization -	30%	35%	40%	45%
Screening Programs				
Low-Dose CT (LDCT) Availability -	Limited	Limited	Limited	Limited
Early Detection Rate -	5%	6%	8%	10%

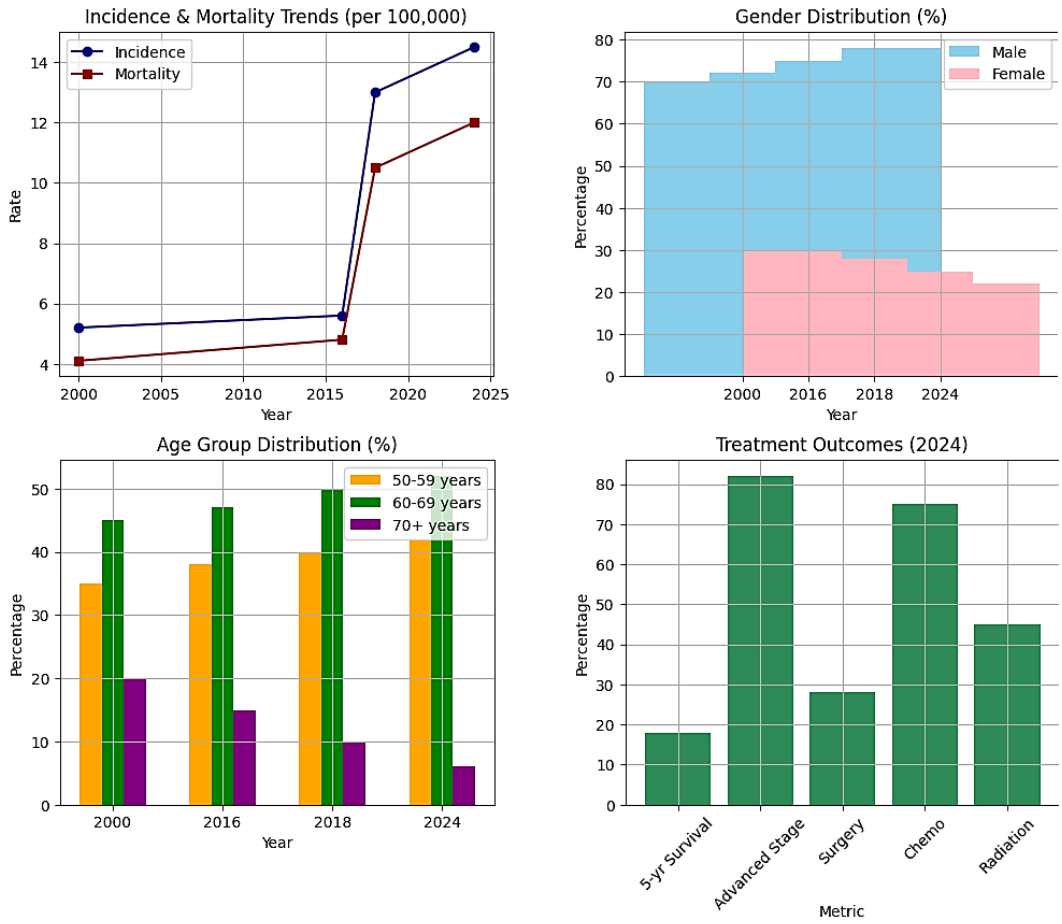

Figure 3. Lung Cancer Epidemiology and Treatment Trends in Iraq (2000–2024) (130,131).

Conclusion

Lung cancer begins in the lungs and is considered one of the most prevalent and deadly forms of cancer worldwide. It is one of the most common malignant tumors, accounting for more than 90% of all lung tumors. Lung cancer accounts for more than 1.4 million deaths worldwide each year. The majority of lung cancer research has focused on the well-established involvement of tobacco in carcinogenesis. Smokers are at least 20 times more likely to develop lung cancer than nonsmokers are.

Unfortunately, smoking habits are rapidly spreading, with young people beginning to smoke at an earlier age, particularly shisha. As a result, we firmly believe that smoking in cafés should be strongly curtailed and strictly controlled. Smoking must be restricted in Iraq by more stringent legislation; consequently, the minimum legal age for smoking should be at least twenty years. In fact, preventive measures play crucial roles in reducing the incidence of lung cancer. Therefore, reducing smoking rates and exposure to environmental carcinogens is essential in the fight against this disease.

In conclusion, although lung cancer remains a significant challenge, a deeper understanding of the disease and the development of innovative treatments can help reduce its global burden and improve patients' quality of life.

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