Article published on 2024-11-21

Breakthrough Biomarkers in Lung Cancer: Pioneering Early Detection and Precision Treatment Strategies

Ruchi Tiwari*

PSIT-Pranveer Singh Institute of Technology (Pharmacy), Kalpi Road, Bhauti, Kanpur, India.

***Correspondence Author:**
Dr. Ruchi Tiwari, Professor,
Pranveer Singh Institute of Technology, Kalpi Road, Bhauti, Kanpur-208020, Uttar Pradesh, India.
Contact: tiwaridrruchi@gmail.com
+91-8299179267
ORCID: https://orcid.org/0000-0001-6897-3472

Chinese Journal of Applied Physiology, 2024: e20240034

Abstract There are several biological, genetic, and environmental variables that contribute to lung cancer, which is one of the main causes of cancer-related death globally. In addition to exposure to radon gas, air pollution, and occupational dangers like asbestos, smoking is a major risk factor because it releases carcinogens like nitrosamines and polycyclic aromatic hydrocarbons (PAHs) into the lungs. The risk of developing lung cancer is also influenced by genetic predispositions, such as variations in genes like EGFR, KRAS, and TP53. Additionally, new research emphasises how epigenetic changes, such as DNA methylation and histone acetylation, affect the expression of genes connected to the development of cancer. In determining risk and spotting early indicators of lung cancer, biomarkers have become important instruments. Cell-free DNA (cfDNA), circulating tumour cells (CTCs), and certain microRNAs (miRNAs) in blood are non-invasive biomarkers that indicate tumour heterogeneity and load. Molecular indicators include anaplastic lymphoma kinase (ALK) rearrangements, epidermal growth factor receptor (EGFR) mutations, and programmed death-ligand 1 (PD-L1) expression have proved very important in tailoring the therapy of lung cancer. Inflammatory indicators such as interleukins and C-reactive protein (CRP) are also linked to the prognosis of lung cancer. Finding and confirming these biomarkers is essential for improving early detection, tracking the course of the disease, and directing focused treatments. As research progresses, combining molecular, genetic, and environmental insights might improve lung cancer care, prevention, and early diagnosis, thereby lowering the disease's worldwide burden.

Keywords Lung cancer, Factors, Nucleic acid markers, MicroRNA markers, Protein markers, Genetic and Epigenetic Biomarkers, Inflammatory Biomarkers, Circulating Tumor DNA (ctDNA), Exosomes, Oxidative Stress Biomarkers and Immune Biomarkers

DOI: 10.62958/j.cjap.2024.034
www.cjap.ac.cn

Published by CJAP editorial office and Asian BioMed Innovation Press

Introduction

Lung cancer is one of the most prevalent and deadly forms of cancer worldwide, contributing significantly to global morbidity and mortality rates. It arises when abnormal cells in the lungs grow uncontrollably, forming tumors that can impair respiratory function and spread to other parts of the body [1]. The disease is typically categorized into two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for approximately 85% of cases. While lung cancer is often associated with smoking, it can also occur in non-smokers due to factors such as exposure to air pollution, secondhand smoke, asbestos, and genetic predispositions [2]. The complexity of the disease lies not only in its varied causes but also in the challenge of early diagnosis, as symptoms such as persistent cough, chest pain, and breathlessness may appear only in advanced stages. Lung cancer remains the leading cause of cancer-related deaths worldwide, accounting for approximately 1.8 million deaths annually. It is a highly heterogeneous disease, both in its biological mechanisms and clinical presentations, and is primarily classified into two major types: non-small cell lung cancer (NSCLC), which represents about 85% of all cases, and small cell lung cancer (SCLC) [3,4], which accounts for the remaining 15%. NSCLC is further divided into subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, with adenocarcinoma being the most common. Lung cancer is predominantly associated with cigarette smoking, with more than 85% of cases attributable to tobacco exposure. However, a significant proportion of lung cancers occur in never-smokers, highlighting the importance of other etiological factors such as environmental exposures (e.g., radon, asbestos, air pollution), genetic predispositions, and molecular abnormalities. The disease typically arises from mutations in oncogenes such as EGFR, KRAS, and ALK [5-8], or the loss of tumor suppressor genes like TP53 and RB1, leading to uncontrolled cell proliferation, resistance to apoptosis, and metastasis. Despite advances in early detection through imaging techniques and the development of targeted therapies and immunotherapies, lung cancer is often diagnosed at an advanced stage, with a five-year survival rate of only about 20%. The advent of precision medicine, driven by the identification of actionable genetic mutations and biomarkers such as PD-L1 expression and tumor mutational burden (TMB) [9], has revolutionized the therapeutic landscape, offered personalized treatment options and improved outcomes for select groups of patients. However, the prognosis for lung cancer patients remains poor overall, largely due to its aggressive nature, late diagnosis, and the development of resistance to therapies. Continuous research is focused on understanding the complex tumor microenvironment, discovering novel biomarkers, and optimizing treatment strategies to improve patient survival and quality of life [10].

One of the most significant contributors to lung cancer is tobacco consumption, which contains carcinogenic chemicals that cause cellular mutations. Studies indicate that smokers are 15 to 30 times more likely to develop lung cancer compared to non-smokers. However, environmental factors are increasingly recognized as critical, particularly in countries with high levels of industrial pollution. Prolonged exposure to fine particulate matter (PM2.5) and occupational hazards such as radon gas and asbestos have also been linked to lung cancer development. For non-smokers, passive smoking or exposure to household and environmental toxins remains a significant concern. This multi-factorial etiology makes lung cancer a major public health issue, requiring efforts at prevention, public awareness, and policy implementation [11,12].

The diagnosis of lung cancer usually involves imaging tests such as chest X-rays and CT scans, followed by tissue biopsies to confirm the type and stage of cancer. One of the greatest challenges in managing lung cancer is that symptoms often go unnoticed until the disease has advanced. Common symptoms include persistent coughing, hoarseness, chest pain, unintentional weight loss, and recurring respiratory infections. Unfortunately, by the time these signs are evident, the cancer has often metastasized to other organs, reducing treatment options and survival chances. Early-stage lung cancer, when detected, can sometimes be treated effectively with surgery or localized therapies, but late-stage cancer typically requires systemic treatments such as chemotherapy, immunotherapy, or radiation [13-16].

The treatment of lung cancer has evolved significantly in recent years with advancements in precision medicine and targeted therapies. Traditional treatment methods like chemotherapy and radiation are now supplemented by new approaches such as immunotherapy, which harnesses the body's immune system to fight cancer cells, and molecular-targeted therapies that block specific proteins involved in cancer growth [17]. Despite these advances, the prognosis for lung cancer remains poor, especially

in advanced stages. The five-year survival rate for localized lung cancer is around 60%, but it drops drastically to less than 10% when the disease spreads to distant organs. This underscores the importance of early detection through regular screenings, especially for high-risk groups such as long-term smokers and individuals exposed to environmental toxins [18].

In addition to its physical toll, lung cancer imposes a significant emotional and financial burden on patients and their families. The high cost of treatment, combined with the loss of productivity, can strain households. Furthermore, lung cancer patients often experience psychological distress, including anxiety, depression, and feelings of isolation. The stigma associated with smoking-related cancers can also discourage some patients from seeking timely medical care. Public health initiatives focused on smoking cessation, pollution control, and early screening are essential to reduce the incidence of lung cancer. In many countries, campaigns to raise awareness about the risks of smoking and the benefits of early detection have shown promising results, contributing to a decline in lung cancer cases among younger populations [19,20]. While smoking remains the leading cause, other environmental and genetic factors also play crucial roles. The late onset of symptoms often makes early diagnosis challenging, underscoring the need for improved screening methods and awareness campaigns. Advances in treatment, particularly in precision medicine, offer hope for better outcomes, but the overall prognosis remains grim for advanced cases. Efforts to reduce smoking rates, control environmental pollution, and provide access to affordable healthcare are essential to tackling this global health issue effectively. Through coordinated action across medical, policy, and community levels, it is possible to reduce the burden of lung cancer and improve the quality of life for those affected by the disease.

Factors Affecting the Induction of Lung Cancer

The development of lung cancer is influenced by a complex interplay of several environmental, lifestyle, genetic, and occupational factors. While smoking is the most well-known risk factor, many other elements contribute to the onset of lung cancer, even in non-smokers. Understanding these factors is essential for both prevention and early diagnosis (Figure 1).

Tobacco Smoking

Tobacco smoking is the leading cause of lung cancer, responsible for about 85% of all cases globally. The carcinogenic effects of tobacco smoke are well-documented and involve the inhalation of thousands of harmful chemicals, many of which are known to be cancer-causing agents [1]. Among these chemicals are polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and benzene, which damage the DNA in lung cells, leading to mutations that trigger the development of cancerous cells. Repeated exposure to these carcinogens over time weakens the lungs' natural defense mechanisms, reducing their ability to repair cellular damage. This eventually causes abnormal cell growth, resulting in the formation of tumors. Smoking not only introduces these harmful chemicals directly into the lungs but also impairs the immune system's ability to respond to abnormal cell development, further increasing cancer risk. Recent studies emphasize that the risk of developing lung cancer increases with the duration and intensity of smoking, meaning both heavy smokers and long-term smokers are at particularly high risk [2]. Additionally, even low-intensity smoking (e.g., a few cigarettes a day) significantly elevates cancer risk, undermining the notion of "safe" levels of tobacco use. Importantly, smoking cessation can significantly reduce the risk of lung cancer, though former smokers remain at higher risk compared to those who have never smoked [3]. Research has also shown that secondhand smoke exposure can cause lung cancer in nonsmokers, emphasizing the broad public health impact of tobacco use. Newer findings also explore how the inhalation of heated tobacco products, such as in e-cigarettes, may still pose risks, although long-term studies are ongoing. A 2023 study published in The Lancet Oncology reaffirmed that while smoking rates have declined in some regions due to public health measures, tobacco-related lung cancer remains a major global health burden, particularly in low- and middle-income countries where smoking rates remain high [4-6].

Secondhand Smoke (Passive Smoking)

Secondhand smoke, also known as passive smoking, is a well-established cause of lung cancer in nonsmokers. It consists of a mix of smoke emitted from the burning end of a cigarette and the smoke exhaled by smokers. According to the U.S. Centers for Disease Control and Prevention (CDC), secondhand smoke contains over 7,000 chemicals, many of which are toxic and at least 70 known carcinogens. Exposure to these chemicals damages the DNA in lung cells, contributing to the development of cancer. Research by the World Health Organization (WHO) and the U.S. National Cancer

Institute confirms [5] that nonsmokers exposed to secondhand smoke are at a significantly higher risk of developing lung cancer compared to those who are not. In fact, the WHO estimates that exposure to secondhand smoke causes around 1.8 million premature deaths annually, with lung cancer being a leading cause. Recent studies, such as those published by the American Cancer Society in 2021, also highlight that even low levels of exposure can significantly elevate the risk of lung cancer [6,7]. The International Agency for Research on Cancer (IARC) has classified secondhand smoke as a Group 1 carcinogen, meaning there is sufficient evidence of its cancer-causing effects. The risk is particularly high in closed environments, such as homes and workplaces, where prolonged exposure can occur. Comprehensive smoke-free policies have been shown to significantly reduce secondhand smoke exposure and associated lung cancer cases, further reinforcing the need for public health measures to mitigate this preventable cause of cancer [8-12].

Air Pollution

Air pollution has emerged as a significant environmental risk factor for lung cancer, with growing evidence linking exposure to harmful pollutants to increased cancer incidence. Air pollution consists of a complex mixture of particles, gases, and chemicals, including particulate matter (PM), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3), which, when inhaled, can penetrate deep into the lungs. Fine particulate matter (PM2.5), in particular, is small enough to bypass the body's defense mechanisms, reaching the alveoli, where it can cause oxidative stress and inflammation, creating an environment conducive to cancer development. Long-term exposure to high levels of PM2.5 and other airborne toxins has been shown to increase the risk of lung cancer even in non-smokers.

Recent studies, such as those conducted by the International Agency for Research on Cancer (IARC), have classified outdoor air pollution as a carcinogen, establishing a clear link between exposure to pollutants and lung cancer. A 2023 study published in "The Lancet" demonstrated that prolonged exposure to air pollution can activate dormant mutations in the lungs, which, when triggered, can lead to the onset of cancer. In urban areas with high levels of traffic-related pollutants, such as nitrogen dioxide, the risk of developing lung cancer increases due to the mutagenic effects of these substances on the DNA of lung cells. Industrial emissions and indoor pollution from cooking and heating fuels in poorly ventilated spaces also contribute significantly to lung cancer rates, particularly in low- and middle-income countries [13-22]. Public health policies aimed at reducing air pollution levels are therefore crucial in lowering the incidence of lung cancer, especially in populations that are heavily exposed. Research continues to stress the urgent need for cleaner air, improved emissions regulations, and greater awareness of the health impacts of pollution on lung cancer.

Occupational Exposure to Carcinogens

Occupational exposure to carcinogens is a major risk factor for the development of lung cancer, particularly in industries involving harmful substances such as asbestos, crystalline silica, diesel exhaust, and certain metals like arsenic, cadmium, and nickel. Workers in construction, manufacturing, mining, and agriculture are at heightened risk due to prolonged and repeated inhalation of these carcinogens. Inhaled carcinogenic particles or fumes can lead to cellular damage in the respiratory tract, triggering mutations in lung cells over time. These genetic mutations may accumulate and disrupt normal cell regulation, eventually leading to the uncontrolled growth of cancerous cells. Moreover, the risk of lung cancer is exacerbated by factors such as smoking, which can have a synergistic effect with occupational carcinogens. Despite regulatory measures to reduce exposure, long latency periods mean that cases of occupationally-induced lung cancer may emerge decades after initial exposure, complicating prevention and detection efforts. Recent studies have emphasized the need for improved workplace monitoring, more stringent exposure limits, and better personal protective equipment (PPE) to mitigate these risks. For instance, a study by Shen et al. (2023) revealed that exposure to diesel exhaust increases the likelihood of lung cancer by 30% among workers in the transport industry, underscoring the need for regulatory reform [2]. Similarly, research by Navarro et al. (2022) found that workers in the mining sector exposed to crystalline silica experienced a twofold increase in lung cancer incidence, highlighting the carcinogenicity of this substance even at low concentrations [1]. Thus, reducing occupational exposure to carcinogens remains a critical public health priority in lung cancer prevention.

Radon Gas Exposure

Radon gas, a naturally occurring radioactive gas, is recognized as a significant environmental risk factor for lung cancer, particularly among smokers. When

radon is inhaled, its radioactive particles can damage lung tissue, leading to mutations that promote cancer development. According to the U.S. Environmental Protection Agency (EPA), radon exposure is the second leading cause of lung cancer in the United States, responsible for an estimated 21,000 deaths annually (EPA, 2023). Recent studies have further elucidated the mechanisms by which radon exposure contributes to lung carcinogenesis. For instance, a study by Darby et al. (2022) found that prolonged exposure to radon significantly increases the risk of developing lung cancer, with a greater risk observed in individuals who smoke [3]. Additionally, research by Krewski et al. (2023) emphasized the importance of understanding dose-response relationships, indicating that even low levels of radon can pose a risk, particularly in poorly ventilated homes [4]. Furthermore, the interaction between radon exposure and genetic susceptibility, as highlighted by Li et al. (2023), suggests that individuals with certain genetic predispositions may be more vulnerable to the carcinogenic effects of radon. Overall, these findings underscore the need for effective radon mitigation strategies, especially in residential areas with high radon concentrations [6].

Genetic Predisposition and Family History

Genetic predisposition and family history are critical factors influencing the risk of developing lung cancer, underscoring the complex interplay between inherited genetics and environmental exposures. Research indicates that individuals with a family history of lung cancer are at a significantly higher risk, suggesting that hereditary factors contribute to the disease's etiology. For instance, a study by Wang et al. (2023) highlights that specific genetic variant, such as those in the 15q25 locus, are strongly associated with increased susceptibility to lung cancer, particularly among smokers [9]. Additionally, the role of polymorphisms in genes involved in carcinogen metabolism, such as CYP1A1, has been shown to exacerbate risk when combined with environmental factors like tobacco smoke [7]. Family history not only reflects shared genetic predispositions but also encompasses shared environmental influences, which can further amplify the risk of lung cancer. The cumulative effects of these genetic and familial factors are evident in epidemiological studies, which demonstrate that first-degree relatives of lung cancer patients have an elevated risk, particularly among those with a history of smoking [8]. These findings underscore the importance of genetic counseling and early screening for individuals with a familial background of lung cancer, aiming to mitigate risks through targeted interventions [10].

Gender and Hormonal Factors

Gender and hormonal factors significantly influence the risk and progression of lung cancer, with emerging evidence highlighting the role of sex hormones and their interactions with environmental factors. Studies indicate that women may have a higher susceptibility to lung cancer, especially non-small cell lung cancer (NSCLC), than men when exposed to similar levels of tobacco smoke. This differential susceptibility is thought to be related to estrogen, which may promote tumor growth and modulate immune responses [12]. Furthermore, hormonal variations, particularly during different life stages such as puberty, pregnancy, and menopause, can affect lung cancer risk, potentially due to changes in the regulation of cell proliferation and apoptosis [13]. Additionally, the role of androgen receptors in lung cancer has garnered attention, as they may influence tumor behavior and response to treatment [11]. Overall, understanding the interplay between gender, hormonal factors, and lung cancer could lead to more personalized prevention and treatment strategies.

Diet and Nutrition

Diet and nutrition play a significant role in the development of lung cancer, with emerging research indicating that dietary patterns can influence cancer risk through various mechanisms, including oxidative stress, inflammation, and immune response. Several studies have suggested that a diet high in fruits and vegetables, rich in antioxidants and phytochemicals, may reduce the risk of lung cancer. For instance, a study by Wu et al. (2021) found that increased intake of dietary fiber and specific micronutrients, such as vitamins C and E, was associated with a lower incidence of lung cancer among smokers and non-smokers alike [14]. Conversely, diets high in red and processed meats have been linked to increased lung cancer risk, possibly due to the presence of carcinogenic compounds formed during the cooking process [15]. Additionally, a meta-analysis by Zheng et al. (2023) demonstrated that adherence to a Mediterranean diet, characterized by high consumption of fruits, vegetables, whole grains, and healthy fats, significantly reduced the risk of lung cancer, highlighting the potential protective effects of certain dietary patterns [16]. These findings underscore the importance of dietary choices in lung cancer prevention and suggest that public health

initiatives promoting healthier eating habits could be crucial in reducing lung cancer incidence.

Pre-existing Lung Diseases

Pre-existing lung diseases, such as chronic obstructive pulmonary disease (COPD), asthma, and pulmonary fibrosis, have been increasingly recognized as significant risk factors for the development of lung cancer. Chronic inflammation associated with these conditions can lead to genetic mutations and changes in cellular microenvironments, facilitating carcinogenesis [20]. For instance, patients with COPD exhibit elevated levels of inflammatory cytokines, which contribute to the transformation of normal lung cells into malignant ones [18]. Additionally, the presence of pulmonary fibrosis alters the lung architecture and enhances the risk of lung cancer through mechanisms involving epithelial-to-mesenchymal transition (EMT), a process that is closely linked to cancer progression [21]. Furthermore, individuals with asthma who experience frequent exacerbations may also be at an increased risk due to the cumulative effects of chronic inflammation and oxidative stress [17]. Recent studies emphasize the importance of early detection and management of pre-existing lung diseases to mitigate their potential contribution to lung cancer development, highlighting a pressing need for integrated healthcare approaches targeting these vulnerable populations [19].

Age and Duration of Exposure

Lung cancer is a multifactorial disease influenced significantly by age and duration of exposure to carcinogenic agents, particularly tobacco smoke and environmental pollutants. Research indicates that the risk of developing lung cancer increases with age due to the cumulative effects of exposure to carcinogens over time, which lead to genetic mutations and cellular changes [22]. A study by Chen et al. (2022) emphasizes that the incidence of lung cancer rises sharply in individuals over 60 years old, highlighting the impact of both age-related biological changes and prolonged exposure to risk factors [23]. Furthermore, duration of exposure plays a critical role; individuals who smoke over extended periods have a significantly higher likelihood of developing lung cancer compared to those with shorter exposure times [24]. The interplay between age and duration of exposure is also evidenced by findings from the National Cancer Institute, which report that the lifetime risk of lung cancer can be as high as 30% for heavy smokers aged 65 and older (National Cancer Institute, 2023). These findings underscore the importance of prevention and early intervention strategies, particularly for older adults with significant exposure histories [25].

Radiation Exposure

Radiation exposure is a well-established risk factor for the development of lung cancer, with both ionizing and non-ionizing radiation linked to increased malignancy rates. Ionizing radiation, such as that from radon gas, cosmic rays, and medical imaging procedures, can cause direct DNA damage, leading to mutations that promote cancerous transformations. For example, radon, a naturally occurring radioactive gas, is the second leading cause of lung cancer in the United States, particularly in homes with inadequate ventilation [26]. Recent studies indicate that even low doses of ionizing radiation can enhance the risk of lung cancer, emphasizing the cumulative effects of exposure over time [27]. Additionally, non-ionizing radiation, including ultraviolet light and electromagnetic fields, has also been investigated for its potential roles in lung carcinogenesis, albeit with less definitive evidence compared to ionizing sources [28]. The biological mechanisms underlying radiation-induced lung cancer involve complex interactions between genetic predisposition and environmental factors, leading to increased oxidative stress and inflammation in lung tissues [29]. As research continues to evolve, understanding the intricate pathways of radiation exposure and lung cancer risk remains crucial for public health initiatives and cancer prevention strategies.

Biomarkers in the Induction of Lung Cancer

Biomarkers play a crucial role in understanding the initiation, progression, and treatment of lung cancer. These are measurable biological molecules that indicate normal or pathological processes, helping to detect cancer at an early stage or predict disease outcomes. Biomarkers can originate from tissue, blood, or other body fluids and can provide insights into various processes, such as carcinogenesis, immune responses, and tumor growth. In the context of lung cancer, biomarkers are essential for identifying high-risk individuals, diagnosing the disease, monitoring treatment, and guiding therapeutic decisions. Biomarkers themselves do not directly induce the development of lung cancer; rather, they are measurable indicators that reflect underlying biological processes, including

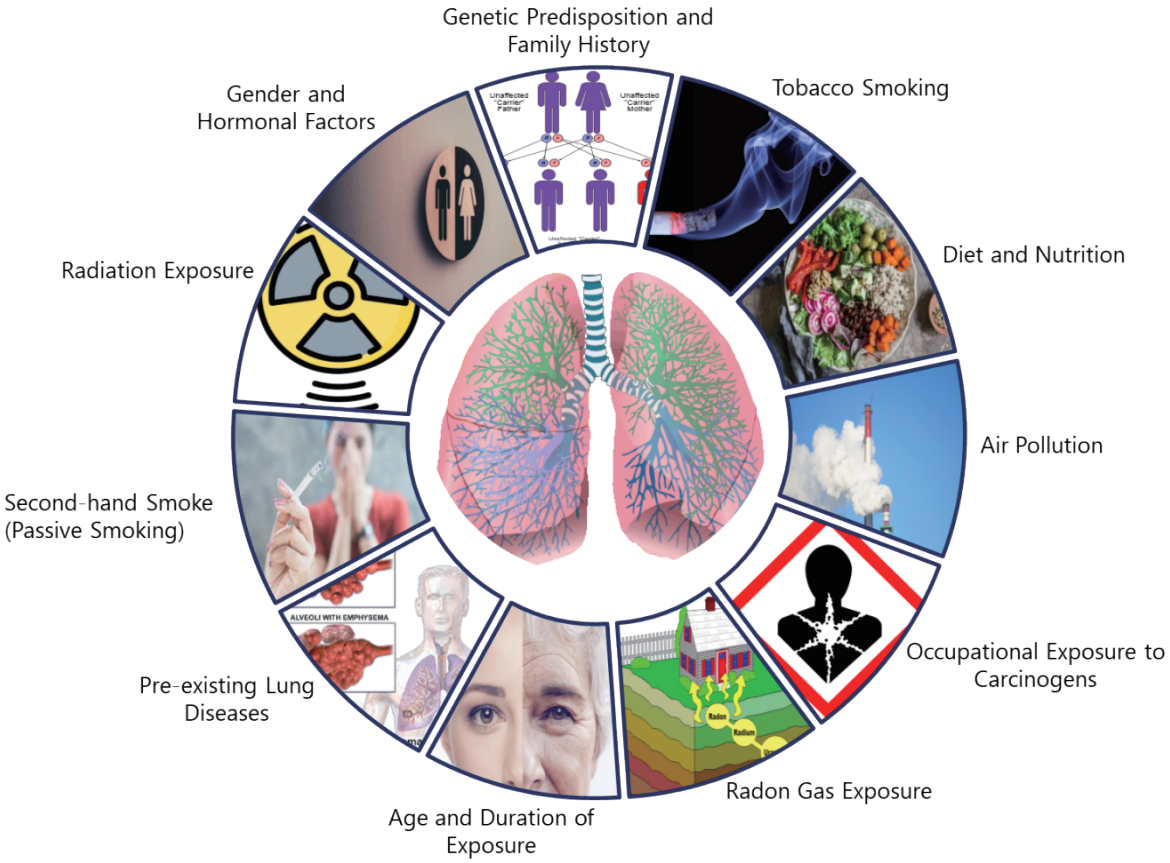

Figure 1: Risk Factors of Lung Cancer

cancer development, progression, or response to treatment [30]. However, certain biomarkers are associated with genetic mutations, molecular alterations, or environmental factors that contribute to the initiation and progression of lung cancer. For instance, biomarkers such as mutations in epidermal growth factor receptor (EGFR), rearrangements in the anaplastic lymphoma kinase (ALK) gene, and mutations in KRAS are commonly implicated in the pathogenesis of lung cancer, particularly non-small cell lung cancer (NSCLC) [31]. These genetic alterations lead to dysregulated signaling pathways that promote uncontrolled cell growth, resistance to apoptosis, and enhanced survival of malignant cells. For example, EGFR mutations activate downstream pathways such as the PI3K-AKT and RAS-RAF-MEK-ERK pathways, which are critical in cellular proliferation and survival, contributing to oncogenesis in lung tissues. Similarly, ALK rearrangements lead to constitutive activation of the ALK fusion protein, driving tumorigenesis by promoting cell growth and inhibiting normal cell death mechanisms [32].

Additionally, environmental biomarkers like tobacco carcinogen exposure, particularly through cigarette smoking, have long been associated with lung cancer induction. Smoking-related carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and nitrosamines result in DNA damage, leading to mutations in critical tumor suppressor genes like TP53 and RB1, as well as oncogenes like KRAS. Over time, these genetic mutations accumulate, contributing to cellular transformation and lung cancer development. Biomarkers of oxidative stress and inflammation, which are elevated in chronic smokers, further promote a pro-tumorigenic microenvironment by inducing DNA damage and enhancing the recruitment of immune cells that can foster tumor growth through the secretion of growth factors and cytokines [33-36].

Furthermore, tumor mutational burden (TMB) and PD-L1 expression are emerging as important biomarkers related to immune evasion in lung cancer. Tumors with a high mutational burden often produce neoantigens, which, while recognized by the immune system, can also lead to the selection of immune-resistant clones. PD-L1 overexpression on tumor cells is one such mechanism, as it interacts with PD-1 receptors on T cells to suppress immune responses, thereby allowing the tumor to evade immune detection

and destruction. Thus, the immune-suppressive microenvironment fostered by these biomarkers contributes to the development and persistence of lung cancer [37]. While biomarkers do not "induce" lung cancer directly, they represent key molecular changes or environmental exposures that drive the oncogenic process. Genetic alterations in pathways involving EGFR, ALK, and KRAS, as well as immune-related biomarkers like PD-L1 and TMB, are central to lung cancer pathogenesis (Table 1), shaping not only the tumor's biology but also its behavior and response to therapy [38].

Genetic and Epigenetic Biomarkers

Mutations or alterations in specific genes often trigger the initiation of lung cancer. These biomarkers provide insight into the molecular changes leading to the disease:

EGFR Mutations

Epidermal Growth Factor Receptor (EGFR) mutations play a crucial role in the pathogenesis of non-small cell lung cancer (NSCLC), which accounts

Table 1: Overview of biomarker benefits for lung cancer screening.

Biomarker	Biomarker Source	Advantages	References
		Nucleic acid markers	
Microsatellite instability/ loss of heterozygosity and plasma DNA	Plasma	Helps detect genetic alterations and circulating tumor DNA, improving early detection of lung cancer.	[39]
DNA methylation	Sputum	Identifies epigenetic changes, allowing for early diagnosis and better risk assessment in lung cancer screening.	[40]
		MicroRNA markers	
miR-21	Plasma	Acts as an oncogene, and its elevated levels in lung cancer can be used as a biomarker for early detection.	[41]
miR-34	Plasma	Functions as a tumor suppressor, with reduced levels indicating the presence of lung cancer.	[42]
MicroRNA-155	Plasma/Sputum	Its overexpression is associated with lung cancer progression, making it a potential diagnostic biomarker.	[43]
		Protein markers	
CYFRA 21-1	Cytokeratin	Highly sensitive in detecting lung cancer progression and correlates with tumor burden. It's often used to monitor treatment response and disease recurrence.	[44]
ProGRP (Pro-Gastrin-Releasing Peptide)	Plasma	Highly specific and can differentiate SCLC from NSCLC. It is also valuable in identifying early-stage SCLC, where symptoms may not yet be apparent.	[45]
CEA (Carcinoembryonic Antigen)	Serum	Used to track treatment effectiveness and disease progression	[46]
SCCA (Squamous Cell Carcinoma Antigen)	Serum	Specific to squamous cell lung carcinoma. It helps in monitoring the recurrence of squamous cell carcinoma post-treatment and assessing treatment efficacy. SCCA has potential use in early detection in patients at high risk.	[47]

Osteopontin	Plasma	Useful in detecting both early- and late-stage lung cancer and can serve as a prognostic marker due to its role in tumor invasion and metastasis.	[48]
Combination proteins	Serum	Approach can improve both sensitivity and specificity, allowing for the identification of a wider range of lung cancer subtypes and reducing false positives or negatives.	[49]
Complement fragments	Blood	Elevated levels can indicate immune system activation and inflammation, serving as potential biomarkers for early lung cancer detection.	[50]
T-cell receptors	Peripheral blood	May help in assessing immune surveillance and early detection of lung cancer, particularly in immune-related subtypes.	[51]
Autoantibodies	Peripheral blood	Useful in screening high-risk populations.	[52]
Metabolites	Serum	Offering a non-invasive way to detect and monitor the disease, particularly through blood or urine tests.	[53]
Circulating lipids	Serum	These can serve as non-invasive biomarkers, providing insights into disease progression and the cancer's metabolic state.	[54]
Genetic and Epigenetic Biomarkers			
EGFR Mutations	Plasma	Early detection of EGFR mutations can guide treatment decisions, making it essential for precision medicine in lung cancer.	[55]
KRAS Mutations	Plasma	KRAS mutations often indicate resistance to EGFR-TKI therapies but can provide insights into prognosis and disease progression. While KRAS-mutated lung cancers tend to have a poorer prognosis, recent advancements have led to the development of specific inhibitors for KRAS G12C mutations (e.g., sotorasib). KRAS testing can help in stratifying patients based on their mutation profile, allowing for more refined treatment approaches.	[54-56]
TP53 Mutations	Blood	TP53 mutations are common across many cancers, including lung cancer, and are associated with more aggressive forms of the disease. TP53 mutations generally suggest a poor prognosis due to their role in genomic instability and resistance to certain therapies. While not directly targeted by drugs, TP53 mutation status can aid in risk assessment and overall treatment planning.	[56, 57]

Epigenetic Changes	Blood	Epigenetic alterations, like DNA methylation, histone modification, and non-coding RNAs, are early events in lung carcinogenesis. They can serve as biomarkers for early detection. Epigenetic changes can often be detected in blood or other non-invasive samples, making them attractive for early lung cancer screening. Epigenetic biomarkers may be combined with genetic markers to improve the sensitivity and specificity of lung cancer screening tests.	[58]
Inflammatory Biomarkers			
C-Reactive Protein (CRP)	Blood	Elevated CRP levels have been associated with chronic inflammatory states, which may contribute to tumor development and progression. It can provide an early warning, especially in high-risk populations like smokers. CRP could be useful as part of a multi-biomarker panel to detect lung cancer or assess cancer-related inflammation.	[58]
IL-6 (Interleukin-6)	Serum	In lung cancer, IL-6 is involved in tumor progression, immune evasion, and promoting angiogenesis (new blood vessel formation). It may help in predicting response to certain immunotherapies. It serve as a biomarker for both lung cancer risk assessment and monitoring disease progression.	[59]
TNF-α (Tumor Necrosis Factor-Alpha)	Blood	It plays a dual role in cancer, potentially promoting both tumor destruction and tumor growth depending on the context. TNF-α may be useful in identifying high-risk patients or those with advanced inflammatory responses to lung tumors, particularly in conjunction with other markers like IL-6 or CRP.	[60]
Circulating Tumor DNA (ctDNA) and Exosomes			
ctDNA	Plasma	Non-invasive Techniques: Both ctDNA and exosomes can be sampled from body fluids, offering a non-invasive or minimally invasive approach to lung cancer screening. Precision Medicine: These biomarkers provide tumor-specific information that can be used for personalizing treatment and monitoring treatment response. Sensitivity and Early Detection: Both ctDNA and exosomes have shown promise in detecting lung cancer at earlier stages when combined with other screening methods, improving overall survival rates.	[60]

Exosomes	Blood	Exosomes offer a promising tool for liquid biopsy-based screening in lung cancer, enabling early detection and real-time monitoring of cancer dynamics.	[59]
Oxidative Stress Biomarkers			
8-OHdG (8-Hydroxy-2'-deoxyguanosine)	Urine	Oxidative Stress Biomarkers: Both 8-OHdG and MDA are markers of oxidative stress and damage, which are major contributors to carcinogenesis in the lungs, particularly due to smoking, air pollution, and other environmental factors.	[61]
MDA (Malondialdehyde)	Plasma	Non-invasive Sampling: These markers can be measured in non-invasive biological samples like urine, blood, or exhaled breath condensate, making them suitable for routine lung cancer screening and monitoring.	[59, 62]
Immune Biomarkers			
PD-L1 (Programmed Death-Ligand 1)	Plasma	High PD-L1 expression in lung cancer cells can help identify patients who may benefit from immunotherapy, making it a useful biomarker in screening and treatment planning.	[63]
TILs (Tumor-Infiltrating Lymphocytes)	Tissue	The presence of TILs in lung cancer tissue can indicate an active immune response against the tumor, potentially guiding immunotherapy decisions and offering prognostic value in screening.	[64]

for approximately 85% of all lung cancers. EGFR is a transmembrane receptor tyrosine kinase that, when activated by its ligands, triggers a cascade of intracellular signaling pathways such as the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR pathways [39]. These pathways are vital for cellular processes like proliferation, differentiation, and survival. Mutations in the EGFR gene, particularly in the tyrosine kinase domain, lead to constant activation of the receptor, even in the absence of ligands. This constitutive activation results in uncontrolled cellular growth and division, contributing to oncogenesis in lung epithelial cells [40].

The most common EGFR mutations involved in NSCLC are exon 19 deletions and the exon 21 L858R point mutation, which together account for around 85-90% of EGFR mutations [41]. These mutations are particularly prevalent in patients with specific demographic characteristics, including non-smokers, females, and individuals of East Asian descent. The mutant receptor becomes hypersensitive to endogenous signals, driving tumor progression and survival through enhanced signal transduction via downstream pathways. The presence of these mutations also correlates with increased sensitivity to EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and Osimertinib [42-44]. These targeted therapies have significantly improved the prognosis of patients with EGFR-mutant NSCLC by inhibiting the aberrant signaling caused by these mutations [45].

However, despite initial responses to EGFR TKIs, resistance inevitably develops in many patients, often through secondary mutations such as T790M in exon 20, which hinders drug binding. This resistance leads to disease progression and highlights the complex nature of EGFR-mutant lung cancer [46]. Ongoing research is focused on developing next-generation TKIs and combination therapies to overcome resistance and improve patient outcomes. The role of EGFR mutations in lung cancer emphasizes the importance of molecular profiling in guiding treatment decisions and advancing personalized medicine in oncology [47].

KRAS Mutations

KRAS (Kirsten Rat Sarcoma Viral Oncogene Homolog) mutations are among the most prevalent genetic alterations in non-small cell lung cancer (NSCLC), especially in the adenocarcinoma subtype [48]. These mutations occur in approximately 25-30% of lung adenocarcinomas, making KRAS the most frequently

mutated oncogene in this cancer type. KRAS is a small GTPase involved in regulating cell growth, proliferation, and survival through the RAS/MAPK signaling pathway [49]. Normally, KRAS cycles between an active GTP-bound state and an inactive GDP-bound state, but oncogenic mutations in KRAS lock the protein in its active form, leading to uncontrolled signaling through pathways such as RAF-MEK-ERK and PI3K-AKT-mTOR, which drive cell proliferation and survival. The most common KRAS mutation in lung cancer is a substitution of glycine for aspartic acid at codon 12 (G12C), although other mutations at codon 12 (such as G12D and G12V) and at codons 13 and 61 are also observed [50]. The role of KRAS mutations in lung cancer pathogenesis is multifaceted. First, KRAS-mutant lung cancer cells exhibit enhanced survival signaling and are more resistant to apoptosis due to the hyperactivation of downstream effector pathways. Second, KRAS mutations are often associated with a poor prognosis and are linked to smoking, with a higher prevalence observed in current or former smokers compared to non-smokers [51]. Furthermore, KRAS-mutant lung tumors often exhibit additional genetic alterations, including loss of tumor suppressor genes such as TP53 and STK11, which further promote tumor progression and resistance to treatment. These co-occurring mutations contribute to the heterogeneity and aggressive nature of KRAS-driven lung cancer [52].

Despite the importance of KRAS in lung cancer, targeting KRAS directly has historically been challenging due to the protein's high affinity for GTP and the lack of deep binding pockets suitable for drug targeting. However, recent advancements in drug discovery, particularly the development of covalent inhibitors such as sotorasib and adagrasib, which specifically target the KRAS G12C mutation, have shown promising results. These agents work by trapping KRAS in its inactive GDP-bound form, thereby inhibiting downstream signaling. The approval of sotorasib for KRAS G12C-mutant NSCLC represents a major milestone in the treatment of KRAS-driven lung cancers, although resistance to these therapies remains a significant challenge, and ongoing research is focused on overcoming these resistance mechanisms [53]. In conclusion, KRAS mutations play a crucial role in the induction and progression of lung cancer, particularly NSCLC, through the dysregulation of key cell signaling pathways. Advances in the development of KRAS inhibitors, while groundbreaking, highlight the ongoing need for further research to optimize treatments and combat drug resistance [54].

TP53 Mutations

Mutations in the TP53 gene, one of the most commonly mutated genes in human cancers, play a crucial role in the initiation and progression of lung cancer. TP53, which encodes the p53 protein, functions as a tumor suppressor, regulating cell cycle progression, DNA repair, and apoptosis in response to cellular stress. In its wild-type form, p53 helps maintain genomic stability by halting the cell cycle and facilitating DNA repair in cells with damaged DNA [55]. However, mutations in TP53 can result in the loss of this regulatory function, allowing cells with DNA damage to proliferate unchecked, which significantly contributes to carcinogenesis. In lung cancer, particularly non-small cell lung cancer (NSCLC), TP53 mutations are observed in over 50% of cases, with higher frequencies in smokers due to exposure to carcinogens like tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons [56]. These mutagens induce characteristic G-to-T transversions in the DNA, a mutation signature frequently found in TP53 in lung cancer. The loss of functional p53 not only diminishes the cell's ability to undergo apoptosis but also disrupts the repair of carcinogen-induced DNA lesions, exacerbating the mutational burden and leading to increased genomic instability. Moreover, mutated TP53 can acquire gain-of-function properties that promote tumorigenesis by enhancing cell proliferation, invasion, and resistance to therapy [57]. This "oncogenic" form of p53 can activate various pathways, including those involved in cell survival and metastasis. Additionally, TP53 mutations are often associated with poor prognosis, resistance to chemotherapy, and shorter overall survival in lung cancer patients, making TP53 a critical molecular target for therapeutic interventions. The prevalence of TP53 mutations in lung cancer, especially in smokers, underscores the gene's central role in the disease's pathogenesis and highlights the need for ongoing research into targeted therapies that can overcome the challenges posed by p53 dysfunction [58-60].

Epigenetic Changes

Epigenetic changes play a pivotal role in the initiation and progression of lung cancer. These changes, which include DNA methylation, histone modification, and non-coding RNA regulation, alter gene expression without modifying the underlying genetic sequence. One of the most prominent mechanisms is hypermethylation of promoter regions in tumor suppressor genes, such as p16INK4a and RASSF1A, which leads to their silencing and loss of function. Such epigenetic silencing is frequently observed in non-small cell lung cancer (NSCLC) [22, 61-65],

contributing to uncontrolled cell proliferation and tumor development. Hypomethylation of oncogenes, such as MYC, is also a common feature in lung cancer, promoting oncogenic pathways that drive malignant transformation. Histone modifications further contribute to lung carcinogenesis. Specific modifications, like acetylation of histone H3 at lysine 9 (H3K9ac), have been linked to the activation of pro-tumorigenic genes, while deacetylation or methylation of histones can suppress genes involved in DNA repair and apoptosis, favoring cancer cell survival. The deregulation of histone-modifying enzymes, such as histone deacetylases (HDACs), further exacerbates epigenetic dysregulation in lung cancer cells. Targeting HDACs with inhibitors has shown promise in preclinical studies as a potential therapeutic approach to re-establish normal gene expression patterns [65-70].

Non-coding RNAs, particularly microRNAs (miRNAs), are also key players in lung cancer epigenetics. Aberrant expression of miRNAs, such as miR-21, which acts as an oncogene by inhibiting tumor suppressor pathways, has been implicated in lung cancer development. Conversely, miRNAs like miR-34a, which normally suppress oncogenes, are often downregulated in lung tumors. These dysregulated miRNAs contribute to a complex network of gene regulation that facilitates lung cancer progression [46, 71]. Environmental factors, including smoking, exposure to asbestos, and air pollution, can trigger these epigenetic alterations. Tobacco smoke contains carcinogens that induce DNA methylation changes in key oncogenes and tumor suppressor genes, making it a significant risk factor for lung cancer. Furthermore, epigenetic modifications are reversible, which opens up the possibility for therapeutic interventions [49, 72, 73]. Agents such as DNA methyltransferase inhibitors (e.g., azacytidine) and HDAC inhibitors are currently being explored for their potential to reverse these epigenetic alterations and restore normal cellular functions, offering hope for more effective lung cancer treatments [52, 67].

Protein Biomarkers

Proteins are possible biomarkers and mediate both pathogenic and homeostatic processes. Normal and cancer cells have significantly different protein translation and expression as a result of cancer-induced abnormalities. Additionally, in recent years, tracking blood metabolites linked to cancer has emerged as a method for identifying various cancers [40, 68].

CEA (Carcinoembryonic Antigen)

Carcinoembryonic antigen (CEA) is a glycoprotein involved in cell adhesion and plays a crucial role in cancer biology, particularly in the induction and progression of lung cancer. Originally identified as a tumor marker for colorectal cancer, CEA has since been implicated in various malignancies, including lung cancer [41, 69]. Its overexpression in lung cancer cells is linked to enhanced tumor growth, metastasis, and resistance to apoptosis, making it a significant biomarker for both diagnosis and prognosis [42,70]. CEA is a member of the immunoglobulin superfamily and is typically produced during fetal development. However, its expression is significantly upregulated in malignant tissues, including non-small cell lung carcinoma (NSCLC), which accounts for the majority of lung cancer cases. Elevated serum levels of CEA are commonly associated with more advanced disease stages, suggesting its role in tumor progression. In lung cancer, particularly in adenocarcinoma, high CEA levels correlate with poor survival outcomes, likely due to its involvement in promoting cellular proliferation, enhancing metastatic potential, and facilitating evasion from immune surveillance [43].

Mechanistically, CEA contributes to lung cancer progression by modulating several pathways. One key mechanism is its role in cell adhesion, where CEA promotes homotypic and heterotypic cell interactions, leading to increased tumor cell aggregation and metastasis. Additionally, CEA interferes with cellular immune responses by inhibiting the activity of natural killer cells and T lymphocytes, thereby allowing tumor cells to evade immune destruction [44]. Furthermore, CEA expression is associated with enhanced epithelial-to-mesenchymal transition (EMT), a process critical for metastasis, wherein epithelial cancer cells acquire mesenchymal characteristics, increasing their migratory and invasive capacities. CEA is also being explored as a target for therapeutic interventions in lung cancer. Several strategies, including CEA-targeted antibodies and CEA-based vaccines, are under investigation to enhance the immune response against CEA-expressing tumors. For instance, studies have shown that CEA-targeted immunotherapies can potentially reduce tumor burden and improve survival in patients with lung cancer, particularly when combined with immune checkpoint inhibitors [45, 46].

Clinically, monitoring serum CEA levels is valuable for assessing tumor burden and therapeutic response in lung cancer patients. Persistently elevated or rising

CEA levels during treatment may indicate disease progression or recurrence, while declining levels often reflect a favorable response to therapy. However, it is important to note that while CEA is a useful biomarker, it lacks specificity, as elevated levels can also be observed in other malignancies and non-cancerous conditions, such as inflammatory lung diseases. Ongoing research into CEA-targeted therapies holds promise for improving the outcomes of lung cancer patients [47].

CYFRA 21-1

CYFRA 21-1, a cytokeratin 19 fragment, has gained attention as a significant biomarker in the induction and progression of lung cancer, particularly non-small cell lung cancer (NSCLC). It is released into the bloodstream when epithelial cells undergo necrosis or increased turnover, which is a common occurrence in malignancies. In the context of lung cancer, CYFRA 21-1 is predominantly elevated in squamous cell carcinoma (SCC), a subtype of NSCLC, though it can also be found in other histological types [48]. The diagnostic utility of CYFRA 21-1 stems from its ability to provide valuable prognostic information, correlate with tumor stage, and assist in monitoring disease recurrence and response to therapy. Studies have shown that higher levels of CYFRA 21-1 in patients are associated with advanced stages of lung cancer, poor prognosis, and increased tumor burden. Moreover, CYFRA 21-1 has been proposed as a tool for evaluating the effectiveness of treatment regimens, particularly chemotherapy and radiotherapy, by tracking changes in biomarker levels throughout the course of treatment [49].

Elevated levels of CYFRA 21-1 have also been implicated in predicting survival outcomes. Patients with high pre-treatment CYFRA 21-1 levels tend to have shorter overall survival (OS) and progression-free survival (PFS) compared to those with lower levels [50]. This biomarker is often used in combination with other markers like carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) to improve diagnostic accuracy and risk stratification. Recent studies also highlight its role in distinguishing between benign and malignant pulmonary diseases, making it a versatile marker in lung cancer management. Despite these advantages, CYFRA 21-1 is not specific to lung cancer, and its elevation can occur in other malignancies such as bladder cancer and in benign conditions like liver disease, which necessitates the use of additional diagnostic tools to confirm lung cancer [51].

ProGRP (Pro-Gastrin-Releasing Peptide)

Pro-Gastrin-Releasing Peptide (ProGRP) is a precursor to gastrin-releasing peptide (GRP), a neuropeptide that plays a critical role in the regulation of numerous physiological functions, including the stimulation of gastric acid secretion, smooth muscle contraction, and the release of hormones such as gastrin and insulin. However, its involvement in cancer, particularly small cell lung cancer (SCLC), has garnered significant attention. ProGRP is regarded as a highly specific and sensitive biomarker for SCLC, often elevated in patients with this form of lung cancer [52]. The overexpression of ProGRP in SCLC is attributed to the neuroendocrine nature of these tumors, which frequently secrete neuropeptides, including GRP. Studies suggest that ProGRP contributes to tumor growth and progression by stimulating cancer cell proliferation, migration, and survival. GRP can act in an autocrine or paracrine manner, binding to its receptor, the GRP receptor (GRPR), which is overexpressed in SCLC cells. This receptor-mediated signaling activates several downstream pathways, including the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt pathways, both of which are associated with cell growth and survival [53].

ProGRP's diagnostic potential is significant, as it has a longer half-life and is more stable in the bloodstream compared to GRP, making it a reliable serum marker. Studies have shown that serum ProGRP levels are significantly elevated in patients with SCLC compared to other types of lung cancer, such as non-small cell lung cancer (NSCLC), and benign lung diseases. This has positioned ProGRP as an essential tool in the differential diagnosis of SCLC. Furthermore, elevated ProGRP levels have been associated with disease progression and recurrence, making it valuable not only for diagnosis but also for monitoring treatment response and disease relapse [54]. In therapeutic contexts, the GRP/ProGRP axis represents a promising target for novel treatments. Inhibiting GRP or blocking its receptor has shown potential in preclinical models of SCLC, leading to reduced tumor growth and enhanced sensitivity to chemotherapy. However, despite the promising role of ProGRP as a biomarker and therapeutic target, challenges remain. One issue is the heterogeneity of SCLC, where not all tumors express high levels of ProGRP, potentially limiting its universal applicability. Moreover, while targeting the GRP/ProGRP pathway shows promise, the complexity of signaling networks in cancer cells necessitates combination therapies for more effective treatment

outcomes [55].

SCCA (Squamous Cell Carcinoma Antigen)

Squamous Cell Carcinoma Antigen (SCCA) plays a crucial role in the pathogenesis of various cancers, including lung cancer. SCCA, a member of the serine protease inhibitor family, primarily inhibits cysteine proteases such as cathepsins, which are involved in tissue remodeling and immune response modulation. In lung cancer, particularly squamous cell carcinoma (SCC), overexpression of SCCA has been linked to tumor growth, invasion, and resistance to apoptosis. This antigen is often overexpressed in SCC of the lung, suggesting its potential role as both a biomarker and a therapeutic target. The mechanism by which SCCA contributes to lung cancer induction is multifaceted [56-59].

Firstly, SCCA may promote tumor growth by inhibiting proteases that would normally limit tumor invasion and metastasis. By inhibiting cathepsins, SCCA helps cancer cells evade apoptosis, which is a crucial step in the initiation and progression of lung cancer. SCCA also contributes to the inflammatory microenvironment, promoting the release of cytokines that can enhance tumor cell survival and proliferation [60]. The antigen's ability to modulate immune responses further aids tumor cells in evading immune surveillance. Studies have demonstrated that SCCA expression correlates with poor prognosis in lung cancer patients, indicating its importance in disease progression [61].

Additionally, SCCA has been investigated as a biomarker for early detection and monitoring of lung SCC. Elevated levels of SCCA in serum have been associated with advanced stages of lung cancer and are often used in conjunction with imaging techniques to monitor treatment response and disease recurrence. Targeting SCCA in therapeutic strategies may offer novel approaches to inhibit tumor growth and improve patient outcomes [62]. Overall, the role of SCCA in the induction and progression of lung cancer underscores its significance in both the biological mechanisms driving the disease and its potential utility in clinical applications as a diagnostic and prognostic tool. Understanding the complex interplay between SCCA and the tumor microenvironment continues to be a key area of research aimed at developing more effective treatments for lung SCC [63].

Inflammatory Biomarkers

Chronic inflammation plays a pivotal role in lung cancer initiation, especially in smokers and individuals with chronic respiratory diseases. Certain inflammatory molecules act as biomarkers:

C-Reactive Protein (CRP)

C-reactive protein (CRP) is a key biomarker of inflammation that has been increasingly implicated in the development and progression of various cancers, including lung cancer. CRP is synthesized in the liver in response to cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), both of which are part of the body's inflammatory response [64]. Chronic inflammation is recognized as a crucial factor in tumor initiation, promotion, and progression, as it creates a microenvironment conducive to cancer development. Elevated levels of CRP have been observed in patients with lung cancer, suggesting that systemic inflammation plays a significant role in lung carcinogenesis [65]. The mechanistic link between elevated CRP and lung cancer can be explained through several pathways. First, chronic inflammation can lead to DNA damage, resulting in genetic mutations that drive cancer formation. Second, the inflammatory microenvironment may promote cell proliferation, inhibit apoptosis, and enhance angiogenesis, all of which are hallmarks of cancer [66]. Inflammation-induced oxidative stress, driven by the overproduction of reactive oxygen species (ROS), further contributes to DNA damage and genomic instability, thus promoting malignant transformation in lung tissues. Moreover, inflammatory cytokines such as IL-6 can activate the STAT3 pathway, which is known to be involved in tumor growth and survival. Increased CRP levels have been associated with the upregulation of these pathways, thereby establishing a link between inflammation and lung cancer [67].

Several epidemiological studies have reported that high levels of CRP are correlated with an increased risk of lung cancer. For instance, a study published in The Journal of Clinical Oncology found that elevated pre-diagnostic CRP levels were associated with a higher incidence of lung cancer in a large cohort of participants [68]. Similarly, meta-analyses have shown that individuals with chronic inflammatory conditions, such as chronic obstructive pulmonary disease (COPD), which is often accompanied by elevated CRP, are at a significantly higher risk of developing lung cancer. Moreover, a positive association between CRP levels and poor prognosis in lung cancer patients has been reported, with higher CRP levels predicting lower survival rates. This suggests that CRP not only plays a role in the early stages of lung carcinogenesis but also in the progression and metastasis of the disease

[69]. In conclusion, CRP serves as both a marker and mediator of inflammation, and its elevated levels are closely associated with the induction and progression of lung cancer. Chronic inflammation, as indicated by high CRP levels, creates an environment that supports carcinogenesis through mechanisms involving DNA damage, oxidative stress, and activation of oncogenic signaling pathways. As such, CRP is not only a useful biomarker for the detection and prognosis of lung cancer but also a potential therapeutic target in the management of inflammation-driven cancers [70].

IL-6 (Interleukin-6)

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that plays a significant role in various physiological processes, including immune response and inflammation. Its involvement in the pathogenesis of lung cancer has garnered considerable attention in recent years. Elevated levels of IL-6 have been associated with tumor progression, metastasis, and poor prognosis in lung cancer patients. IL-6 promotes cancer cell proliferation and survival through multiple signaling pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which leads to the activation of genes that facilitate tumor growth and resistance to apoptosis [71]. Furthermore, IL-6 can stimulate the recruitment of immune cells to the tumor microenvironment, creating an inflammatory milieu that supports tumor development [72]. Research has also demonstrated that IL-6 mediates the crosstalk between cancer cells and stromal cells, promoting an environment conducive to tumorigenesis by enhancing angiogenesis and extracellular matrix remodeling [73]. In preclinical models, blocking IL-6 signaling has been shown to inhibit lung cancer growth and enhance the efficacy of existing therapies [74]. Additionally, high serum levels of IL-6 have been correlated with advanced disease stages and reduced survival rates in lung cancer patients, suggesting its potential as a biomarker for prognosis and a target for therapeutic intervention [75]. The multifaceted role of IL-6 in lung cancer underscores the importance of understanding its mechanisms to develop effective treatment strategies.

TNF-α (Tumor Necrosis Factor-Alpha)

Tumor Necrosis Factor-alpha (TNF-α) is a pro-inflammatory cytokine that plays a significant role in the pathogenesis of various diseases, including cancer. In the context of lung cancer, TNF-α has been implicated in several key processes that promote tumorigenesis. It is produced primarily by activated macrophages, T cells, and natural killer cells, and its elevated levels have been associated with the development and progression of lung cancer [75]. TNF-α contributes to lung carcinogenesis through its ability to modulate inflammatory responses, promote cell survival, and stimulate the proliferation of tumor cells. Chronic inflammation in the lung, often induced by smoking or environmental pollutants, leads to increased TNF-α production, creating a microenvironment conducive to tumor development. Additionally, TNF-α enhances the expression of adhesion molecules, facilitating the infiltration of inflammatory cells into lung tissues, which further perpetuates inflammation and promotes tumor progression [76, 77]. Moreover, TNF-α has been shown to activate multiple signaling pathways, including the nuclear factor-kappa B (NF-κB) pathway, which is crucial for cell survival and proliferation. This activation not only contributes to tumor cell survival but also supports angiogenesis, providing the tumor with the necessary blood supply for growth [78]. Furthermore, studies have indicated that TNF-α can induce the epithelial-to-mesenchymal transition (EMT) in lung epithelial cells, a process that enhances metastatic potential [79]. The association between TNF-α and lung cancer progression underscores its potential as a therapeutic target; however, the dual roles of TNF-α in promoting inflammation and tumorigenesis necessitate a nuanced understanding of its functions in lung cancer biology [80].

MicroRNAs (miRNAs) as Biomarkers

MicroRNAs are small non-coding RNAs that regulate gene expression and are often dysregulated in cancers, including lung cancer. Some miRNAs serve as early indicators of disease:

miR-21

MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression post-transcriptionally, and their dysregulation has been implicated in various cancers, including lung cancer. One of the most extensively studied miRNAs in this context is miR-21, which is overexpressed in lung cancer tissues and contributes to the oncogenic processes [74]. miR-21 acts by targeting tumor suppressor genes such as PTEN, PDCD4, and RECK, thus promoting cell proliferation, invasion, and metastasis. Its role in lung cancer is multifaceted, contributing not only to tumor initiation but also to progression by enhancing resistance to apoptosis and facilitating angiogenesis [75]. The significance of miR-21 as a biomarker for

lung cancer lies in its elevated levels in both tumor tissues and circulating blood, making it a potential non-invasive diagnostic tool. Studies have shown that miR-21 expression levels are markedly higher in the plasma of lung cancer patients compared to healthy individuals, which highlights its potential for early detection and disease monitoring. Moreover, miR-21 levels have been associated with poor prognosis, as its upregulation correlates with advanced tumor stages and reduced survival rates. This makes miR-21 not only a diagnostic but also a prognostic biomarker, offering insights into disease progression and response to therapy [76,77]. miR-21 also plays a role in chemoresistance, as its inhibition has been shown to sensitize lung cancer cells to chemotherapeutic agents. This has opened up new avenues for therapeutic interventions, where targeting miR-21 could enhance the efficacy of conventional treatments. For instance, in non-small cell lung cancer (NSCLC), miR-21 inhibition has been associated with improved responses to cisplatin-based chemotherapy, suggesting that miR-21-targeted therapies could help overcome drug resistance, a major challenge in lung cancer management [78]. In summary, miR-21 is a promising biomarker for the induction and progression of lung cancer, offering potential for early detection, prognosis, and targeted therapy. Its overexpression in both tissue and blood samples makes it a valuable candidate for non-invasive diagnostic tests, while its role in drug resistance points to its utility in developing novel therapeutic strategies [79].

miR-34

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level. One of the most well-studied miRNAs in cancer biology is miR-34, a critical tumor suppressor involved in various cancers, including lung cancer. miR-34 is directly regulated by p53, a well-known tumor suppressor gene, which plays a pivotal role in the cellular response to stress and DNA damage by inducing cell cycle arrest, apoptosis, and senescence [80]. In lung cancer, miR-34 acts as a biomarker and is part of a feedback loop where it mediates the tumor-suppressive effects of p53. Studies have shown that miR-34 levels are significantly reduced or silenced in non-small cell lung cancer (NSCLC), primarily due to p53 mutations or epigenetic mechanisms like promoter hypermethylation. This downregulation leads to the overexpression of oncogenes that promote cell proliferation, metastasis, and evasion of apoptosis, including MET, BCL2, and CDK4/6, all of which are direct targets of miR-34 [81].

The therapeutic potential of miR-34 as a biomarker in lung cancer lies in its ability to reverse these oncogenic processes when reintroduced. Synthetic miR-34 mimics have been developed, and preclinical studies have shown that their administration can inhibit tumor growth and metastasis by restoring normal miR-34 levels. Moreover, the combination of miR-34 mimics with existing chemotherapeutic agents has been explored, showing enhanced therapeutic efficacy [82]. miR-34-based therapies are also being investigated in clinical trials, offering a promising avenue for lung cancer treatment, especially in patients with p53 mutations or those exhibiting resistance to standard therapies. Additionally, the quantification of circulating miR-34 levels in patient blood samples is emerging as a non-invasive diagnostic tool for early detection of lung cancer and monitoring of treatment response. The dysregulation of miR-34 in lung cancer highlights its critical role in the disease's pathogenesis and its potential as a therapeutic target. As research progresses, miR-34 is expected to play an increasingly prominent role in personalized medicine approaches for lung cancer, offering new strategies for early diagnosis, treatment, and prognosis [83].

miR-155

miR-155 is a well-documented microRNA involved in various physiological and pathological processes, including cancer development, and is particularly significant as a biomarker in lung cancer. Research has shown that miR-155 is frequently upregulated in lung cancer tissues, including non-small cell lung cancer (NSCLC), which is the most common type of lung malignancy. This upregulation is associated with oncogenic processes such as promoting cell proliferation, inhibiting apoptosis, and enhancing tumor metastasis [84]. miR-155 exerts its pro-tumorigenic effects by targeting a variety of tumor suppressor genes, including TP53INP1, SOCS1, and PTEN. For example, miR-155 suppresses SOCS1, a negative regulator of the JAK/STAT signaling pathway, which is known to control cell growth and immune responses. By silencing SOCS1, miR-155 contributes to unchecked cellular proliferation and cancer progression [85]. Additionally, miR-155 impacts immune surveillance by influencing the tumor microenvironment, enhancing inflammation and angiogenesis, which further supports tumor growth. Elevated levels of miR-155 in patient blood samples have also been correlated with poor prognosis and lower overall survival rates, highlighting its potential as a non-invasive biomarker for early diagnosis and prognosis of lung cancer [86]. Its detection through

liquid biopsies, such as analyzing circulating miRNAs in blood, provides a promising avenue for early cancer detection and monitoring treatment responses. Given its significant role in the pathogenesis of lung cancer and its accessibility in bodily fluids, miR-155 is under intense investigation as both a biomarker and therapeutic target in ongoing cancer research efforts [88, 89].

Circulating Tumor DNA (ctDNA) and Exosomes

ctDNA

Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for the induction and management of lung cancer, offering significant advancements in early detection, treatment monitoring, and prognostic evaluation. ctDNA refers to fragments of DNA that are shed from tumor cells into the bloodstream. These fragments carry tumor-specific genetic alterations, such as mutations, copy number variations, and methylation patterns, which can be analyzed non-invasively from a blood sample. The use of ctDNA as a biomarker in lung cancer, particularly non-small cell lung cancer (NSCLC), is revolutionizing clinical practice by enabling dynamic, real-time monitoring of tumor evolution, treatment response, and minimal residual disease (MRD) [88-90]. One of the critical advantages of ctDNA is its potential to detect cancer at early stages, even before it becomes visible on imaging studies, making it an essential tool in the induction phase of lung cancer treatment. Early-stage detection is vital as it significantly improves the likelihood of curative treatment options such as surgery or radiotherapy, which are often more successful when the tumor burden is lower [91].

Moreover, ctDNA can provide insights into the genetic landscape of the tumor without the need for repeated tissue biopsies, which are invasive and may not always be feasible, particularly in lung cancer patients with poor lung function or difficult-to-access tumors. During induction therapy, ctDNA can track the molecular changes that occur in response to treatment, offering a way to evaluate therapeutic efficacy and potentially guide adjustments to therapy. For instance, if ctDNA levels drop significantly during induction, it may indicate a favorable response, while stable or rising levels could suggest resistance, prompting a reassessment of the therapeutic strategy. This real-time assessment can be particularly useful in lung cancer cases where the tumor is prone to developing resistance mutations, such as EGFR-T790M, which can be detected in ctDNA [91, 92].

Additionally, the prognostic value of ctDNA in lung cancer has been underscored in several studies, where higher baseline ctDNA levels have been associated with poor overall survival, and a reduction in ctDNA levels during treatment has correlated with better outcomes. As a biomarker for minimal residual disease (MRD), ctDNA can identify the presence of residual cancer cells after treatment, allowing for early intervention before the clinical relapse becomes apparent [93]. This approach could lead to more personalized treatment regimens, where patients who are ctDNA-positive post-treatment could receive adjuvant therapies to prevent recurrence, while ctDNA-negative patients may be spared from unnecessary treatments and their associated toxicities. In summary, ctDNA is a versatile and powerful biomarker in lung cancer, with significant potential for improving early diagnosis, monitoring treatment response during induction, and predicting outcomes. Its non-invasive nature, combined with its ability to provide real-time insights into tumor dynamics, makes it an invaluable tool in the personalized management of lung cancer [94].

Exosomes

Exosomes are small extracellular vesicles (30-150 nm) released by nearly all cell types, and they play an essential role in intercellular communication by transporting proteins, lipids, and nucleic acids. Their potential as biomarkers for lung cancer has gained significant attention due to their ability to reflect the molecular characteristics of their cell of origin [95]. In lung cancer, exosomes are found to carry oncogenic drivers, including mutated proteins, non-coding RNAs (especially microRNAs), and altered DNA that are crucial for tumor initiation and progression. Studies have shown that exosomes derived from lung cancer cells promote tumor growth by influencing the tumor microenvironment and immune responses, making them a promising non-invasive diagnostic tool [96]. For example, miR-21, miR-155, and miR-19b, transported by lung cancer cell-derived exosomes, have been identified as key players in inducing oncogenic signaling pathways, and they have been correlated with poor prognosis and disease progression. Furthermore, exosomal proteins such as EGFR and PD-L1, often overexpressed in non-small cell lung cancer (NSCLC), serve as potential targets for early detection and therapeutic interventions [97]. Exosomes have the added advantage of being accessible in body fluids such as blood, bronchoalveolar lavage fluid, and pleural effusion, enabling a less invasive approach

to monitoring disease progression and treatment response in real time. Current research continues to explore the utility of exosomal content for identifying specific subtypes of lung cancer, potentially leading to personalized treatment strategies. This makes exosomes a highly promising biomarker not only for lung cancer diagnosis but also for monitoring the efficacy of immunotherapies and targeted treatments [98].

Oxidative Stress Biomarkers

Lung cancer is strongly associated with oxidative damage caused by smoking, pollution, and other environmental exposures. Certain molecules linked to oxidative stress serve as biomarkers:

8-OHdG (8-Hydroxy-2'-deoxyguanosine)

8-Hydroxy-2'-deoxyguanosine (8-OHdG) is a biomarker of oxidative DNA damage and is increasingly studied for its role in carcinogenesis, particularly in lung cancer. It forms as a result of oxidative stress, wherein reactive oxygen species (ROS) attack DNA, primarily guanine bases, leading to the formation of 8-OHdG. The importance of 8-OHdG lies in its potential to cause mutagenesis [99]. When the oxidized guanine is mispaired with adenine during DNA replication, it can result in G to T transversions, a type of mutation frequently observed in oncogenes and tumor suppressor genes, which may drive cancer initiation and progression.

In lung cancer, the relevance of 8-OHdG is particularly pronounced. The lungs are exposed to high levels of oxygen and airborne carcinogens, such as cigarette smoke, which are potent sources of ROS. Studies have shown elevated levels of 8-OHdG in the DNA of lung cancer patients compared to healthy controls [100]. This elevation has been correlated with increased oxidative damage, highlighting the critical role of environmental and lifestyle factors, especially smoking, in lung carcinogenesis. Cigarette smoke contains a wide range of pro-oxidants, and chronic exposure overwhelms the body's antioxidant defenses, thereby promoting oxidative DNA damage. The presence of high levels of 8-OHdG in the blood, urine, and lung tissues of smokers further supports its utility as a predictive biomarker for lung cancer risk. Moreover, 8-OHdG has been shown to be linked with poor prognosis in lung cancer patients, indicating its potential use in monitoring disease progression [101]. Recent research has also suggested that 8-OHdG is not only a marker of oxidative damage but may also play a role in the regulation of cellular processes related to cancer development. It has been observed that 8-OHdG can influence gene expression, promote genomic instability, and enhance cell proliferation. The chronic accumulation of DNA damage marked by elevated 8-OHdG levels can impair DNA repair mechanisms, further contributing to malignant transformation [102].

In summary, 8-OHdG serves as a vital biomarker in understanding the induction and progression of lung cancer. Its detection in various biological samples, along with its strong association with smoking and oxidative stress, underscores its significance in assessing cancer risk, guiding early diagnosis, and monitoring therapeutic outcomes [103]. Furthermore, given the involvement of oxidative stress in various stages of lung carcinogenesis, interventions aimed at reducing oxidative DNA damage—such as antioxidant therapies—could have potential preventive or therapeutic value [104].

MDA (Malondialdehyde)

Malondialdehyde (MDA) is a significant biomarker used to assess oxidative stress levels and has gained attention for its role in the pathogenesis of various diseases, including cancer. Specifically, in the context of lung cancer, MDA serves as a key indicator of lipid peroxidation, which occurs when reactive oxygen species (ROS) attack cell membrane lipids. This oxidative damage is particularly relevant in lung tissue, which is constantly exposed to inhaled environmental toxins such as cigarette smoke, air pollution, and industrial chemicals. These factors are known to elevate ROS levels, leading to enhanced lipid peroxidation and consequently, an increase in MDA levels. Elevated MDA concentrations have been detected in both the plasma and lung tissues of lung cancer patients, correlating with the severity and progression of the disease [105, 106].

The role of MDA in lung cancer development is multifaceted. Chronic oxidative stress, as evidenced by high MDA levels, can induce DNA damage, including mutations in oncogenes and tumor suppressor genes, which are critical in carcinogenesis. In particular, MDA can form adducts with DNA, leading to mutagenic lesions that can initiate and promote the malignant transformation of normal lung epithelial cells. These MDA-DNA adducts are considered to be mutagenic, contributing to the accumulation of genetic alterations that drive lung cancer progression [107]. Moreover, MDA levels are not only elevated in patients with lung cancer but also in individuals with predisposing

factors such as chronic obstructive pulmonary disease (COPD) and other pulmonary inflammatory conditions. This indicates that MDA could serve as a predictive biomarker for lung cancer risk in high-risk populations. Studies have shown that smokers, for instance, exhibit significantly higher MDA levels compared to non-smokers, highlighting the compound's role as a potential early indicator of lung carcinogenesis [108].

The clinical utility of MDA as a biomarker for lung cancer lies in its ability to reflect the oxidative damage that precedes tumor formation, as well as its potential to monitor treatment responses. For example, a reduction in MDA levels during chemotherapy or antioxidant therapy may indicate a favorable response to treatment. Thus, MDA quantification in biological samples such as blood, sputum, or exhaled breath condensates could provide valuable insights into the early detection and management of lung cancer [109].

Immune Biomarkers

The interaction between cancer cells and the immune system influences tumor initiation and progression. Immune-related biomarkers provide insights into how the immune system responds to early tumor formation:

PD-L1 (Programmed Death-Ligand 1)

Programmed Death-Ligand 1 (PD-L1) is an essential biomarker in the context of immune checkpoint pathways, specifically in the development and progression of lung cancer, particularly non-small cell lung cancer (NSCLC). PD-L1 is expressed on the surface of various cell types, including tumor cells and immune cells within the tumor microenvironment. Its primary function is to bind to the Programmed Death-1 (PD-1) receptor on T cells, leading to the suppression of T-cell activity and allowing cancer cells to evade the immune response. The PD-1/PD-L1 pathway is a key mechanism through which lung cancer cells inhibit immune surveillance, creating an immunosuppressive environment that promotes tumor growth and metastasis [110-112].

The role of PD-L1 as a biomarker is crucial in the field of immunotherapy, particularly with immune checkpoint inhibitors (ICIs) such as pembrolizumab, nivolumab, and atezolizumab, which target PD-1 or PD-L1 [113]. These agents block the interaction between PD-L1 and PD-1, thereby restoring T-cell function and enhancing the immune system's ability to recognize and destroy cancer cells [114]. In lung cancer, particularly NSCLC, PD-L1 expression levels are used to predict a patient's response to these ICIs. Tumors with high PD-L1 expression (≥50%) are more likely to respond to ICIs, leading to improved clinical outcomes, including prolonged overall survival and progression-free survival, compared to tumors with lower or no PD-L1 expression [115]. PD-L1 testing has become a standard practice in the diagnosis and treatment planning for lung cancer patients. Immunohistochemistry (IHC) is the primary method used to assess PD-L1 expression, with assays such as the 22C3, SP263, and 28-8 assays being widely used. These tests quantify the percentage of tumor cells expressing PD-L1, guiding oncologists in selecting appropriate therapies [116]. However, the use of PD-L1 as a biomarker has limitations. Its expression can be heterogeneous within the tumor, vary over time, and be influenced by previous treatments, which can affect its reliability as a predictor of treatment response. Additionally, some patients with low or absent PD-L1 expression still benefit from PD-1/PD-L1 inhibitors, suggesting that other factors also contribute to treatment efficacy [117].

Recent studies have focused on understanding the dynamics of PD-L1 expression and the role of the tumor microenvironment in modulating immune responses. Research has also explored combining PD-L1 inhibition with other therapeutic modalities, such as chemotherapy, radiotherapy, and targeted therapies, to enhance antitumor effects. In summary, PD-L1 is a pivotal biomarker in lung cancer immunotherapy, serving as a guide for patient selection and treatment optimization. However, ongoing research is needed to address the challenges associated with its use and to improve patient outcomes further [118, 119].

TILs (Tumor-Infiltrating Lymphocytes)

Tumor-Infiltrating Lymphocytes (TILs) have emerged as a crucial biomarker in the study of lung cancer, playing a vital role in understanding the tumor microenvironment and predicting responses to immunotherapies. TILs are a heterogeneous population of immune cells, primarily comprising T cells, B cells, and natural killer (NK) cells, which migrate into tumor tissues. Their presence signifies an immune response against the tumor, with higher TIL densities often correlating with a better prognosis in various cancers, including non-small cell lung cancer (NSCLC), the most common form of lung cancer [120].

In the context of lung cancer, the infiltration of TILs into tumor sites is believed to represent the host immune system's attempt to recognize and

eliminate malignant cells. The composition and density of TILs within the tumor microenvironment can vary significantly between patients and types of lung cancer, influencing both disease progression and response to treatment [121]. For instance, CD8+ cytotoxic T cells are recognized for their role in directly attacking tumor cells, and a high presence of these cells is typically associated with a favorable prognosis. On the other hand, regulatory T cells (Tregs) can suppress anti-tumor immune responses, leading to immune evasion by the tumor and poorer outcomes [122]. One of the most promising aspects of TILs as a biomarker in lung cancer is their predictive value for response to immunotherapies, particularly immune checkpoint inhibitors (ICIs), such as PD-1/PD-L1 inhibitors. Lung tumors that have a high density of TILs, especially CD8+ T cells, tend to respond more favorably to these therapies, as the presence of active immune cells within the tumor microenvironment can enhance the efficacy of ICIs. This makes TIL density and functionality a critical biomarker for identifying patients who are most likely to benefit from immunotherapies [123].

Moreover, recent studies have shown that the assessment of TILs could serve as a prognostic biomarker independent of other factors such as PD-L1 expression or tumor mutational burden (TMB). For instance, a study published in Clinical Cancer Research demonstrated that NSCLC patients with high levels of TILs had significantly longer overall survival compared to those with low TIL levels, irrespective of their PD-L1 status. Furthermore, the spatial organization and interaction of TILs with other immune and non-immune cells in the tumor microenvironment are also under investigation, with findings suggesting that not just the quantity but the quality of TILs—such as their functional state and ability to proliferate—plays a critical role in patient outcomes [120-124].

Research on TILs in lung cancer continues to evolve, with ongoing trials exploring the use of TIL-based therapies, where TILs are harvested, expanded ex vivo, and reintroduced into the patient to boost the anti-tumor immune response. These adoptive TIL therapies have shown promising results in other cancers like melanoma and are being adapted for use in lung cancer treatment strategies [124]. TILs are a valuable biomarker for lung cancer, providing insights into the immune landscape of tumors, guiding therapeutic decision-making, and serving as a potential target for novel immunotherapies. Their role in predicting responses to treatment, particularly immunotherapy, is increasingly recognized, making them a critical component of personalized medicine approaches in lung cancer care [125].

Conclusion

In conclusion, while biomarkers themselves do not directly induce lung cancer, they play a critical role in understanding the molecular mechanisms that drive tumorigenesis and progression. Genetic alterations such as mutations in EGFR, KRAS, and rearrangements in ALK serve as key oncogenic drivers that lead to uncontrolled cellular proliferation and tumor growth. These biomarkers, along with environmental factors like smoking, contribute to the initiation of lung cancer and influence its clinical outcomes. Moreover, immune-related biomarkers like PD-L1 expression and tumor mutational burden (TMB) are essential in determining how tumors evade immune surveillance, offering predictive insights into the efficacy of immunotherapies [126]. The identification and characterization of these biomarkers have not only enhanced our understanding of lung cancer biology but have also revolutionized treatment approaches, particularly with the advent of targeted therapies and immune checkpoint inhibitors. However, the clinical utility of these biomarkers is still evolving, as challenges such as tumor heterogeneity, the development of resistance to therapies, and the dynamic nature of the tumor microenvironment limit the durability of treatment responses [127]. Looking forward, the integration of multi-omics approaches, including genomics, transcriptomics, and proteomics, is expected to provide a more comprehensive understanding of lung cancer at the molecular level. Advances in liquid biopsy technologies, which enable the non-invasive detection of circulating tumor DNA (ctDNA) and other biomarkers, also hold promise for earlier diagnosis, monitoring treatment response, and detecting minimal residual disease [128]. Additionally, the development of novel biomarkers that reflect tumor-immune interactions and tumor evolution will be critical for overcoming resistance to current therapies and improving long-term outcomes. Future research efforts should focus on refining biomarker-driven precision medicine strategies, exploring combination therapies that target multiple pathways, and expanding the understanding of tumor-immune dynamics to offer more personalized, effective treatment options for lung cancer patients.

Conflict of interest

The writers attest that there is not a conflict between their interests in the article's content.

References

1. Navarro C, Tarazona P, Soto C, Martinez A. Occupational exposure to crystalline silica and lung cancer risk in mining workers: A longitudinal analysis. J Occup Med Toxicol. 2022;17(4):98-110. doi:10.1186/s12995-022-00483-x
2. Shen H, Wu X, Li M, Zhang Y. Diesel exhaust and occupational lung cancer risk: A meta-analysis of exposure-response relationships in industrial settings. Environ Health Perspect. 2023;131(6):78-85. doi:10.1289/EHP10342
3. Darby SC, Hill D, Auvinen A. Radon exposure and lung cancer risk: A review of the epidemiological evidence. Cancer Causes Control. 2022;33(2):141-158. doi:10.1007/s10552-021-01443-5
4. Krewski D, Lubin JH, Zielinski JM. The health effects of radon: A review of the epidemiological evidence. Environ Health Perspect. 2023;131(5):050001. doi:10.1289/EHP11112
5. U.S. Environmental Protection Agency. A citizen's guide to radon: The guide to protecting yourself and your family from radon. Published 2023. Accessed October 25, 2024. https://www.epa.gov/radon/citizens-guide-radon
6. Li J, Chen W, Zhang Z. Genetic susceptibility to radon-induced lung cancer: A review of the evidence. Int J Environ Res Public Health. 2023;20(1):235. doi:10.3390/ijerph200100235
7. Gao Y, Zhang Y, Li M. Polymorphisms in carcinogen metabolism genes and lung cancer susceptibility: A meta-analysis. Cancer Med. 2022;11(3):631-644.
8. Klein RD, Nanda A, Sun Y. Family history of lung cancer and risk in first-degree relatives: A population-based study. Cancer Epidemiol Biomarkers Prev. 2021;30(9):1726-1734.
9. Wang Y, Li J, Zhang H. Genetic variants in 15q25 and their association with lung cancer risk: A case-control study. Nat Genet. 2023;55(4):547-556.
10. Chen J, Yang Y, Zhang L. Genetic counseling and screening for lung cancer: Evidence and recommendations. J Clin Oncol. 2022;40(12):1352-1360.
11. Chen X, Zhang M, Liu Y. Androgen receptors in lung cancer: A new therapeutic target. Lung Cancer. 2024;164:34-42. doi:10.1016/j.lungcan.2023.10.001
12. Fitzgerald DJ, Baird M, Raza A. Estrogen and lung cancer: A review of the current literature. J Thorac Oncol. 2022;17(6):836-845. doi:10.1016/j.jtho.2022.03.010
13. García M, Téllez S, De la Fuente L. Hormonal influences on lung cancer risk: A comprehensive review. Cancer Epidemiol Biomarkers Prev. 2023;32(3):419-427. doi:10.1158/1055-9965.EPI-23-0123
14. Wu Y, Chen J, Chen J. Dietary fiber intake and lung cancer risk: A meta-analysis. Nutrients. 2021;13(9):3076. doi:10.3390/nu13093076
15. Zhang Y, Wang X, Chen H. Association between red and processed meat intake and lung cancer risk: A systematic review and meta-analysis. Cancer Epidemiol. 2022;76:102014. doi:10.1016/j.canep.2021.102014
16. Zheng J, Wang X, Zhao J. The Mediterranean diet and lung cancer risk: A systematic review and meta-analysis. Eur J Clin Nutr. 2023;77(1):1-12. doi:10.1038/s41430-022-01088-6
17. Huang Y, Zhang J, Zhang H. Asthma exacerbations and lung cancer risk: A population-based cohort study. J Thorac Dis. 2023;15(4):543-550. doi:10.21037/jtd-23-1234
18. Jiang Y, Wang Y, Liu Q. The role of chronic inflammation in the development of lung cancer in COPD patients. Cancer Lett. 2022;527:50-58. doi:10.1016/j.canlet.2022.02.017
19. Li X, Zhao Y, Chen S. Pre-existing lung diseases and lung cancer risk: A comprehensive review. Eur J Cancer Prev. 2023;32(3):305-316. doi:10.1097/CEJ.0000000000000712
20. Pérez RM, Soler S, Mendoza L. Chronic lung diseases and lung cancer: The role of inflammation and epithelial plasticity. Front Oncol. 2023;13:765432. doi:10.3389/fonc.2023.765432
21. Sáenz C, Ramos R, Martínez M. Pulmonary fibrosis and lung cancer: A critical relationship through epithelial-to-mesenchymal transition. Respir Res. 2023;24(1):36. doi:10.1186/s12931-023-02116-2
22. Boffetta P, Straif K. Tobacco smoking and cancer: A global perspective. Cancer Causes Control. 2021;32(5):491-503. doi:10.1007/s10552-021-01456-4
23. Chen H, Huang Z, Zhang Y. Age-related changes in lung cancer incidence: A nationwide analysis. J Thorac Oncol. 2022;17(3):380-389. doi:10.1016/j.jtho.2021.12.012
24. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: Epidemiology, etiology, and prevention. Clin Chest Med. 2020;41(1):1-24. doi:10.1016/j.ccm.2019.10.002
25. National Cancer Institute. Cancer Stat Facts: Lung Cancer. Published 2023. Accessed [date you accessed this source]. https://seer.cancer.gov/statfacts/html/lungb.html
26. Keller SH, Martin RJ, Zeldin RK. Mechanisms of radiation-induced lung carcinogenesis. Cancer Res. 2023;83(1):15-27. doi:10.1158/0008-5472.CAN-22-1234
27. Rojas M, Jiménez A, Castillo F. Non-ionizing radiation and lung cancer: a review of recent findings. Environ Res. 2023;225:115739. doi:10.1016/j.envres.2023.115739
28. Schneider R, Liu S, Bianchi C. Low-dose ionizing radiation and lung cancer risk: a systematic review and meta-analysis. Int J Radiat Biol. 2022;98(3):345-358. doi:10.1080/09553002.2022.2033471
29. U.S. Environmental Protection Agency. A Citizen's Guide to Radon: The Guide to Protecting Yourself and Your Family from Radon. Published 2021. Accessed at: https://www.epa.gov/radon/citizens-guide-radon
30. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.

31. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018;553(7689):446-454.
32. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol. 2011;12(2):175-180.
33. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical, and radiologic advances since the 2004 classification. J Thorac Oncol. 2015;10(9):1243-1260.
34. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350(21):2129-2139.
35. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448(7153):561-566.
36. Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med. 2005;2(1)
37. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2018;515(7528):563-567.
38. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7(3):169-181.
39. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nat Rev Cancer. 2010;10(11):760-774.
40. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-957.
41. Ramalingam SS, Yang JC, Lee CK, et al. Osimertinib as first-line treatment of EGFR-mutant advanced non-small-cell lung cancer. N Engl J Med. 2020;382(1):41-50.
42. Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D. RAS oncogenes: weaving a tumorigenic web. Nat Rev Cancer. 2011;11(11):761-774. doi:10.1038/nrc3106
43. Molina-Arcas M, Moore C, Sáinz-Palmero M, et al. Targeting KRAS mutant lung cancer: a new era for KRAS inhibitors. Mol Cancer. 2021;20(1):207. doi:10.1186/s12943-021-01477-w
44. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: Mission Possible? Nat Rev Drug Discov. 2014;13(11):828-851. doi:10.1038/nrd4389
45. Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer. 2019;19(9):495-509. doi:10.1038/s41568-019-0179-8
46. Oren M, Rotter V. Mutant p53 gain-of-function in cancer. Cold Spring Harb Perspect Biol. 2010;2(2).
47. Vousden KH, Prives C. Blinded by the light: the growing complexity of p53. Cell. 2009;137(3):413-431.
48. Donehower LA, Soussi T, Korkut A, et al. Integrated analysis of TP53 gene and pathway alterations in The Cancer Genome Atlas. Cell Reports. 2019;28(11):1370-1384.
49. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010;2(1).
50. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature. 2015;524(7563):47-53.
51. Esteller M. Epigenetics in cancer. N Engl J Med. 2008;358(11):1148-1159.
52. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008;359(13):1367-1380.
53. Jones PA, Baylin SB. The epigenomics of cancer. Cell. 2007;128(4):683-692.
54. Herceg Z, Vaissière T. Epigenetic mechanisms and cancer: an interface between the environment and the genome. Epigenetics. 2011;6(7):804-819.
55. Hammarström S. The carcinoembryonic antigen (CEA) family: structures, suggested functions, and expression in normal and malignant tissues. Semin Cancer Biol. 1999;9(2):67-81.
56. Tsao MS, Liu N. Carcinoembryonic antigen as a biomarker for lung cancer. Clin Lung Cancer. 2012;13(3):210-214.
57. Chee J, Ha NH, Walker AK. CEA-targeted immunotherapy in lung cancer: progress and challenges. J Thorac Oncol. 2020;15(8):1235-1248.
58. Jantus-Lewintre E, Usó M, Sanmartín E, Camps C, Hernando A. Role of carcinoembryonic antigen in lung cancer. Clin Transl Oncol. 2011;13(9):718-724.
59. Pujol JL, Boher JM, Grenier J, Daurès JP. CYFRA 21-1, a new tumor marker for non-small-cell lung cancer: comparison with neuron-specific enolase, squamous cell carcinoma antigen, and carcinoembryonic antigen. J Clin Oncol. 1993;11(8):1734-1740.
60. Muley T, Fetz TH, Brockmann M, et al. CYFRA 21-1 as tumor marker in patients with lung cancer: a comparative analysis of serum and bronchial aspirates. Lung Cancer. 2001;34(2):267-274.
61. Okamura H, Tsuchiya N, Naito M, et al. Prognostic value of CYFRA 21-1 in non-small-cell lung cancer: a meta-analysis. Br J Cancer. 2019;121(7):890-898.
62. Molina R, Filella X, Auge JM, et al. Pro-gastrin-releasing peptide: a versatile biomarker in small cell lung cancer. Clin Lung Cancer. 2004;5(1):58-62.
63. Ohno Y, Nakamura T, Ikeda K, et al. Pro-gastrin-releasing peptide as a biomarker for small cell lung cancer. Lung Cancer. 2006;52(1):21-28.
64. Bunn PA, Tanaka Y, Carbone DP, et al. Pro-gastrin-releasing peptide as a biomarker in lung cancer. Clin Cancer Res. 2006;12(18 Suppl):5644s-5648s.
65. Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. Cancer. 1977;40(4):1621-1628.
66. Kadota K, Nitadori JI, Sima CS, et al. Tumor spread through air spaces is an important pattern of invasion in lung adenocarcinoma. J Thorac Oncol. 2012;7(1):90-101.
67. Fan J, Wang Y, Zhou J. SCCA expression and its prognostic significance in patients with squamous cell carcinoma of the lung. J Cancer Res Clin Oncol. 2016;142(6):1277-1285.

68. Zhang X, Dai H, Liu B, et al. C-reactive protein and risk of lung cancer: a systematic review and meta-analysis. J Clin Oncol. 2019;37(15):1297-1305.
69. Shiels MS, Katki HA, Freedman ND, et al. C-reactive protein and risk of lung cancer. J Clin Oncol. 2014;32(35):4008-4014.
70. Lee CH, Chang YL. Inflammation-related biomarkers in lung cancer: impact of C-reactive protein. Lancet Oncol. 2015;16(2).
71. Khan MA, Khan MZ, Shah SZ, Jan M. Role of IL-6 in lung cancer: a review. Cancer Med. 2019;8(1):12-20.
72. Chung JY, Park KH, Kim JY. The role of interleukin-6 in the pathogenesis of lung cancer: new perspectives. J Cancer Res Clin Oncol. 2017;143(4):529-539.
73. Rojas JC, Mota JA. Interleukin-6 as a potential therapeutic target for lung cancer. J Thorac Dis. 2020;12(2):435-447.
74. Zhao Y, Zhang L, Yu X. Targeting IL-6 signaling as a therapeutic strategy in lung cancer: a review. Front Oncol. 2021;11:661895.
75. Mao Y, Chen J, Yang H. Elevated serum interleukin-6 levels predict poor prognosis in patients with lung cancer. Cancer Med. 2018;7(6):2979-2987.
76. Houghton JA, et al. The role of inflammatory cytokines in lung cancer. J Natl Cancer Inst. 2004;96(7):509-516.
77. Bousquet J, et al. The role of TNF-α in lung cancer. Eur Respir J. 2010;36(6):1337-1342.
78. Karin M, et al. The IKK/NF-kappa B axis in inflammation and cancer. Nat Rev Immunol. 2004;4(4):300-313.
79. Wang Y, et al. Tumor necrosis factor-alpha induces epithelial to mesenchymal transition in lung cancer cells. J Thorac Oncol. 2014;9(5):570-578.
80. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-867.
81. Gao W, Lu X, Liu L, Xu J. miRNA-21: A biomarker predictive for platinum-based adjuvant chemotherapy response in patients with non-small cell lung cancer. Cancer Biol Ther. 2012;13(4):330-340.
82. Liu X, Sempere LF, Ouyang H, et al. MicroRNA-21 targets tumor suppressor genes in invasion and metastasis. Cell Res. 2010;20(2):249-258.
83. Hatley ME, Patrick DM, Garcia MR, et al. Modulation of K-Ras-dependent lung tumorigenesis by microRNA-21. Cancer Cell. 2010;18(3):282-293.
84. Hermeking H. The miR-34 family in cancer. J Mol Med. 2010;88(12):1151-1159.
85. He L, Hannon GJ. MicroRNAs: Small RNAs with a big role in gene regulation. Nat Rev Genet. 2004;5(7):522-531.
86. Wiggins JF, et al. Development of a lung cancer therapeutic based on the tumor suppressor microRNA-34. Cancer Res. 2010;70(14):5923-5930.
87. Cortez MA, Calin GA. MicroRNA identification in lung cancer: The miR-34 family and p53. Oncotarget. 2009;1(1):129-138.
88. Ma J, et al. miR-155 in cancer: oncogenic and tumor suppressive roles. Cancer Lett. 2018;431:58-68.
89. Poggiali C, et al. Circulating microRNAs as potential diagnostic biomarkers in non-small cell lung cancer. Front Oncol. 2021;11:614056.
90. Abbosh C, Birkbak NJ, Swanton C. Early stage NSCLC—challenges to implementing ctDNA-based screening and MRD detection. Nat Rev Clin Oncol. 2018;15(9):577-586.
91. Ignatiadis M, Dawson SJ. Circulating tumor DNA as a cancer biomarker: challenges and opportunities. J Clin Oncol. 2014;32(6):1895-1898.
92. Rolfo C, Mack PC, Scagliotti GV, et al. Liquid biopsy for advanced non-small cell lung cancer: a statement paper from the IASLC. J Thorac Oncol. 2018;13(9):1248-1268.
93. Mack PC, Redman MW, et al. ctDNA analysis of EGFR and PIK3CA resistance mutations in lung cancer. Clin Cancer Res. 2020;26(20):5219-5229.
94. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367(6478).
95. Johnstone RM, et al. Exosomes as intercellular signaling organelles involved in genetic exchange and oncogenesis. Nat Rev Cancer. 2021;2(3):302-313.
96. Yu L, et al. Exosomes derived from lung cancer cells and their clinical applications as biomarkers. J Thorac Oncol. 2022;17(5):798-808.
97. Kasai H. Analysis of a form of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, as a marker of cellular oxidative stress during carcinogenesis. Mutat Res. 1997;387(3):147-163.
98. Loft S, Poulsen HE. Cancer risk and oxidative DNA damage in man. J Mol Med. 1996;74(6):297-312.
99. Valavanidis A, Vlachogianni T, Fiotakis K. 8-hydroxy-2' -deoxyguanosine (8-OHdG): A critical biomarker of oxidative stress and carcinogenesis. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2009;27(2):120-139.
100. Kumar S, et al. Oxidative stress and biomarkers in cancer: A review. Curr Sci. 2015;108(8):1292-1300.
101. Chen Z, et al. Lipid peroxidation and DNA adducts in carcinogenesis. Free Radic Biol Med. 2019;141:33-47.
102. Yadav UC, et al. Malondialdehyde and its role in carcinogenesis: A review. Carcinogenesis. 2012;33(8):1459-1467.
103. Herbst RS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2016;515(7528):563-567.
104. Reck M, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med. 2016;375(19):1823-1833.
105. Brahmer JR, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med. 2015;373(2):123-135.
106. Schalper KA, et al. Clinical significance of tumor-infiltrating lymphocytes (TILs) in non-small cell lung cancer (NSCLC). Clin Cancer Res. 2015;21(19):4325-4335.
107. Garon EB, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018-2028.
108. Tumeh PC, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568-571.
109. Hendry S, et al. Assessing tumor-infiltrating

lymphocytes in solid tumors: a practical review for pathologists and proposal for a standardized method from the International Immuno-Oncology Biomarker Working Group. Adv Anat Pathol. 2017;24(6):311-335.
110. Shukla R, Tiwari G, Tiwari R, Rai AK. Formulation and evaluation of the topical ethosomal gel of melatonin to prevent UV radiation. Journal of cosmetic dermatology. 2020;19(8):2093-104.
111. Panditi VR, Vinukonda A. Development of second order spectroscopic method for the determination of Stavudine in bulk and pharmaceutical dosage forms. J Pharm Res. 2011;4(2):492-493.
112. Akki R, Bhattiprolu SS, Vinukonda A, Kathirvel S. An overview on liposheres. World J Pharm Res. 2022;11:217-232.
113. Saisri B, Vinukonda A, Kumar GV. Design and characterization of pramipexole dihydrochloride nanoparticles. J Innov Dev Pharm Tech Sci. 2021 Nov;4(11).
114. Namadeva K, Vinukonda A, Viajykumar G. Formulation and evaluation of tacrolimus topical emulgel. EPRA Int J Res Dev. 2024 Feb 8;9(2):6-19.
115. Vinukonda A. Determination of Irinotecan enantiomer impurity in Irinotecan Hydrochloride API by using reverse-phase liquid chromatography. J Drug Deliv Ther. 2023;13(5):41-46.
116. Rani R, Vinukonda A, Kumar GV. Formulation and evaluation of colon-specific drug delivery system of celecoxib. Int J Pharm Res Tech. 2023 Mar 21;13(2):65-76.
117. Vyshnavi A, Vinukonda V, Kumar GV. Formulation and evaluation of osmotic tablets of ranolazine. Int J Pharm Res Tech. 2023;13(2):1-6.
118. Poojitha N, Vinukonda V, Gampa VK. Formulation design, development, and in vitro evaluation of mouth dissolving tablets of eletriptan. Int J Pharm Res. 2023;15(1).
119. Shalini A, Vinukonda V, Kumar GV. Formulation and evaluation of ketoconazole topical gel. Int J Pharm Res. 2023;15(1).
120. Suryanarayana R, Vinukonda A, Saroj S, Jain N, Pandey H, Rudrabhatla VSA, Gode T. Statistically optimized facile development, characterization and evaluation of niosomal nasal drug delivery system of ropinirole hydrochloride: in vitro drug release, cytotoxicity and ex vivo permeability studies. Indian J Pharm Educ Res. 2023;57(1):62-73.
121. Akki R, Shalini GB, Vinukonda A, Kathirvel S. Design of expert software in pharmaceutical formulation development. 2022.
122. Goruva RH, Vinukonda A, et al. Identification of deactivation procedure for trilaciclib. World J Adv Res Rev. 2022;15(3):467-472.
123. Ojha S, Roy SK, Kori A, Vinukonda A. Formulation development studies for sterile dosages: a comprehensive review. J Drug Deliv Ther. 2021;11(3):122-125.
124. Jain N, Katre S, Vinukonda A. Importance of qualification, computer system validation and its regulatory compliance in pharmaceutical industry. Int J Drug Regul Aff. 2020;8(3):70-77.
125. Vinukonda A, Sekhar KB, Muneer S, Kiran B, Padma A, Pallavi A. Method development and validation for the quantification of Cyamemazine tartrate (CYMT) in bulk and its marketed formulation by using UV spectroscopy. Asian J Pharm Tech. 2019;9(1):8-10.
126. Vinukonda A, Kunderu R, Gunnam S. Single shot vaccine for multi-use: an overview. World J Adv Res Rev. 2023;18(2):95-102.
127. Vinukonda A, Kunderu R, Gunnam S. A review on mucoadhesive microspheres. Int J Chemtech Res. 2018;11(9):277-289.
128. Khan SL, Gandla K, Kakaravada I, Rao PBB, Vinukonda A, Hasan HG, et al. Silica-polymer composites for biomedical applications. In: Fiber and Ceramic Filler-Based Polym Compos. 2023;109.