

A REVIEW ON LUNG CANCER IN NON-SMOKERS: REVIEW OF DISEASE PROGRESSION AND PHARMACOLOGICAL TREATMENT PARADIGMS

Ashika S. S.^{1*}, Mrs. Anusha Jasmin R. J.², Dr. Kiran K. J.³, Mr. Shabin⁴, Ms. Amina S. S.⁵, Ms. Varsha Johnson⁶, Dr. Prasobh G. R.⁷

^{1,5,6}Student, Seventh Semester B. Pharm, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India, 695502.

²Associate Professor, department of Pharmacology Sreekrishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India, 695502.

³Professor and Head, Department of Pharmacology, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India, 695502

⁴Lecturer, Department of Pharmacology, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India, 695502.

⁷Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India, 695502.

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*Corresponding Author

Ashika S. S.

Student, Seventh Semester B.
Pharm, Sree Krishna College of
Pharmacy and Research Centre,
Parassala, Thiruvananthapuram,
Kerala, India, 695502.



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ABSTRACT

Lung cancer remains the leading cause of cancer-related mortality worldwide and in the USA, with smoking historically accounting for most cases. However, smoking prevalence has declined significantly, while the proportion of lung cancer in individuals who have never smoked (LCINS) is rising. In 2023, >20,000 lung cancer deaths in the USA were projected in never-smokers, making LCINS the 8th leading cause of cancer death in the USA and 5th globally. LCINS differs clinically and molecularly from smoking-related lung cancer. It occurs predominantly as adenocarcinoma and is more common in women and individuals of Asian ancestry. Genomically, LCINS is enriched for targetable alterations such as EGFR mutations and ALK rearrangements. Key risk factors for LCINS include second-hand smoke, air pollution, radon exposure, occupational carcinogens, chronic respiratory inflammation, hormonal factors, and germline or somatic gene

mutations including EGFR, KRAS, ALK, TP53, and others. The main histologic types are non-small cell lung cancer (NSCLC, ~85%) and small cell lung cancer (SCLC, ~15%). Diagnosis relies on imaging, sputum cytology, and biopsy with molecular testing. Treatment options include surgery, chemotherapy, radiation, immunotherapy, and targeted therapies directed at specific mutations. Prevention strategies for non-smokers focus on radon testing, avoiding second-hand smoke, reducing air pollution exposure, occupational safety, and healthy lifestyle practices.

KEYWORDS: Lung Cancer in non-smokers (LCINS), Non-small cell lung cancer (NSCLC), Small cell lung cancer (SCLC)

INTRODUCTION

Lung cancer or bronchogenic carcinoma refers to tumours originating in the lung parenchyma or within the bronchi. Lung cancer is the leading cause of cancer-related death worldwide (see GLOBOCAN) and in every ethnic group in the USA^[1] Smoking-related lung cancers account for the majority of lung cancer diagnoses and continue to claim ~100,000 lives in the USA each year^[1]; however, smoking rates have been decreasing for several decades.

Although varying widely across the USA, cigarette smoking prevalence among adults reached an all-time low at 11.5% in 2021,^[2] down by more than two-thirds (from ~42%) since the first Surgeon General's Report linking cigarette smoking to lung cancer and heart disease in 1964^[3] and is projected to fall further to 7.5% overall by 2065.^[4] As smoking prevalence has declined, some reports indicate that the proportion of lung cancers occurring in individuals who have never smoked (LCINS) has increased, particularly among women and in younger age groups.^[5] In 2023, >20,000 lung cancer-related deaths in the USA were projected to occur in people who have never smoked^[1], making LCINS the eighth leading cause of cancer-related mortality in the USA; data suggest that LCINS is currently the fifth most common cause of cancer-related deaths worldwide.^[6]

EPIDEMIOLOGY

Lung cancer is the leading cause of cancer death in the United States and around the world. Almost as many Americans die of lung cancer every year than die of prostate, breast, and colon cancer combined. Lung cancer has been the most common cancer worldwide since 1985, both in terms of incidence and mortality. Globally, lung cancer is the largest contributor to new cancer diagnoses (1,350,000 new cases and 12.4% of total new cancer

cases) and to death from cancer (1,180,000 deaths and 17.6% of total cancer deaths). The 5-year survival rate in the United States for lung cancer is 15.6%, and although there has been some improvement in survival during the past few decades, the survival advances that have been realized in other common malignancies have yet to be achieved in lung cancer.

Approximately half (49.9%) of the cases now occur in developing countries whereas in 1980, 69% of cases were in developed countries. The estimated number of lung cancer cases worldwide has increased by 51% since 1985.

CAUSES OF LUNG CANCER IN NON-SMOKERS

- Second-hand Smoke
- Air pollution
- Radon Exposure
- Hormonal Factors
- Occupational Hazards
- Respiratory Infections and Chronic Inflammation
- Gene mutations
- Tumor protein p53

MET (Mesenchymal –epithelial transition) EGFR (Epidermal growth factor receptor) ALK (Anaplastic lymphoma kinase)

HER2(Human epidermal growth factor receptor 2)

TYPES OF LUNGS CANCER

- **Non-small cell lung cancer**
- Non-small cell lung cancer is a type of epithelial lung cancer other than small cell lung cancer, NSCLC accounts for about 85% of all lung cancers. The most common types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma and adenocarcinoma
- **Lung adenocarcinoma**
- Adenocarcinoma of the lung is currently the most common type of lung cancer in never smokers. Historically, adenocarcinoma was more often seen peripherally in the lungs than squamous cell lung cancer

- **Squamous cell lung carcinoma**
- Squamous cell carcinoma of the lung is more common in men than in women, it is closely correlated with a history of tobacco smoking, more than most other types of lung cancer
- **Large cell lung carcinoma**
- Large cell lung carcinoma is differentiated from small cell lung cancer primarily by the larger size of anaplastic cells
- **Small cell lung carcinoma**
- Compared to non-small cell carcinoma, small cell carcinoma is more aggressive, with a shorter doubling time, higher growth fraction and earlier development, it is also known as oat cell carcinoma

STAGES OF LUNG CANCER

Non-Small Cell Lung Cancer (NSCLC) - 6 Stages

- Occult / Hidden Stage: Cancer cells found in sputum or bronchial washings but not seen on imaging or bronchoscopy. Tumour location unknown. No distant spread.

- Stage 0: Abnormal cells in the lining of airways. Not invasive yet.

Subtypes: Adenocarcinoma in situ and Squamous cell carcinoma in situ.

- Stage 1: Cancer confined to the lung only, no lymph node spread.

1A: Tumour ≤ 3 cm.

1B: Tumour 3-4 cm OR tumour ≤ 4 cm that has reached main bronchus, innermost lung lining, or caused collapse/pneumonitis.

- Stage 2: Larger tumour and/or limited local involvement. No or limited lymph node spread.

2A: Tumour 4-5 cm, no lymph nodes, OR tumour with main bronchus/pleura/lung collapse involvement.

2B: Tumour ≤ 5 cm with nearby lymph nodes OR tumour 5-7 cm OR tumour invading chest wall, lining, heart sac, or diaphragm nerve, without lymph nodes.

- Stage 3: Locally advanced. Spread to lymph nodes and/or larger local invasion.

3A: Lymph nodes on same side of chest involved OR larger tumours with local invasion

.3B: Lymph nodes on opposite side or above collarbone involved OR tumour invading key structures.

3C: Any size tumour with lymph nodes on same/opposite side AND additional tumours or invasion of chest wall/diaphragm/etc.

-Stage 4: Metastatic disease.

4A: Tumour in opposite lung, or spread to lining around heart/lungs, or fluid around them, or single distant organ like brain/liver/kidney.

4B: Cancer spread to multiple distant organs.

Small Cell Lung Cancer (SCLC) - 2 Stages

Limited stage: Cancer confined to one side of the chest. May include one lung and nearby lymph nodes. Can be treated with radiation to one area.

Extensive stage: Cancer has spread beyond one side of the chest. May involve the other lung, distant lymph nodes, fluid, or other organs like bone.

DIAGNOSIS AND TREATMENT OF LUNG CANCER

Diagnosis

Imaging tests: Tests include X-ray, MRI, CT and positron emission tomography

Sputum cytology: Sputum that is coughed up from the lungs can sometimes show lung cancer cells when looked at under a microscope

Biopsy: A biopsy is a procedure to remove a sample of tissue for testing in a lab. Lung cancer biopsy can be performed by several ways such as Bronchoscopy and Mediastinoscopy. In bronchoscopy a healthcare professional passes a lighted tube with a camera down the throat into the lungs to examine the area whereas in mediastinoscopy an incision is made at the base of neck and then surgical tools are inserted behind the breastbone to take samples from lymph nodes.

Treatment

Lung Cancer Surgery

Surgery is a common treatment option for lung cancer, particularly in cases where it hasn't spread widely. The types of surgical procedures include.

- **Lobectomy**

This surgery involves removing one lobe of the lung. It is often recommended when the lung cancer is at an early stage and confined to one part of a single lobe.

- **Pneumonectomy**

In this procedure, Lung cancer doctors remove an entire lung, usually when lung cancer is centrally located or has spread throughout the entire lung.

- Wedge Resection

This surgery involves removing a small portion of the lung, typically suitable for patients with very early-stage non-small-cell lung cancer or when the cancer is limited to a small area within the lung.

Chemotherapy for Lung Cancer Treatment

Chemotherapy uses anti-cancer medications designed to inhibit the growth and division of cancer cells, thereby destroying them. It works differently for the two primary types of lung cancer:

- Small Cell Lung Cancer (SCLC): Chemotherapy is often the first line of treatment for SCLC, frequently used in combination with radiotherapy or immunotherapy to extend life and control symptoms. Commonly prescribed chemotherapy drugs for SCLC include carboplatin, cisplatin, and topotecan.
- Non-Small Cell Lung Cancer (NSCLC): In NSCLC, chemotherapy may be administered alone or combined with other treatments for advanced cancer that can't be treated with surgery or for patients who cannot undergo surgery due to other health problems. Usual chemotherapy drugs for NSCLC include docetaxel, paclitaxel, and gemcitabine.

Radiation Therapy for Lung Cancer Treatment

Radiation therapy involves the use of high-energy rays to destroy cancer cells. There are two primary kinds of radiation therapies:

1. External beam radiation therapy: Radiation is delivered from a machine outside the patient's body, targeted towards the cancer cells. Various techniques under EBRT include:
 - Stereotactic body radiation therapy: Utilizes highly concentrated beams of high-dose radiation in fewer treatments, suitable for early-stage lung cancer or when surgery isn't an option.
 - Three-Dimensional Conformal Radiation Therapy (3D-CRT) and Intensity-Modulated Radiation Therapy (IMRT): These technologies accurately map the tumour's location and contour the radiation beams to minimize harm to surrounding healthy tissues.
 - Proton Therapy: Uses protons to target tumours with minimal damage to surrounding healthy tissues.
2. Brachytherapy: Involves placing radioactive sources directly into or near the tumour, aiming to destroy cancer cells and reduce tumour size while minimizing damage to

surrounding healthy tissue.

Common side effects of radiation therapy for lung cancer include general weakness, fatigue, dry skin, shortness of breath, swallowing difficulties, sore throat, and cough.

Immunotherapy for Lung Cancer Treatment

Immunotherapy revolutionizes cancer treatment by activating the body's immune system to combat cancer cells, particularly targeting proteins PD-1 and PD-L1 used by cancer cells to evade detection. FDA-approved immunotherapy drugs like atezolizumab, durvalumab, nivolumab, and pembrolizumab offer promising results for advanced non-small cell lung cancer patients by enabling the immune system to recognize and destroy cancer cells effectively.

RECENT ADVANCES IN LUNG CANCER

Immunotherapy

Checkpoint Inhibitors: A class of immunotherapy drugs called checkpoint inhibitors are often prescribed as an initial treatment for lung cancer, either alone or in combination with chemotherapy. Immunotherapy can be also provided before surgery to shrink tumours.

TIL Therapy: A new type of immunotherapy called TIL therapy is also showing promise. TIL (pronounced “till”) stands for tumour-infiltrating lymphocytes, a specialized type of white blood cell. The approach involves removing TIL cells from the tumour, growing them into large numbers outside the body, and then putting them back into patient.

Lung Cancer Vaccines: There are two clinical trials testing a therapeutic lung cancer vaccine after surgery to prevent recurrence of non-small cell lung cancer. The approach is similar to a vaccine being tested in pancreatic cancer using messenger RNA (mRNA). After surgery, tumour samples are used to design a personalized vaccine based on the specific mutations in the individual patient's cancer. The vaccine is given along with the checkpoint inhibitor pembrolizumab to prevent the lung cancer from returning.^[44]

Drugs

1. Tarlatamab

Bispecific T-cell engager (DLL3-targeting)

2. Repotrectinib

ROS1/ TRK tyrosine kinase inhibitor

3. Amivantamab

EGFR/MET bispecific antibody^[45]

4. Taletrectinib

ROS1 inhibitor

5. Telisotuzumab

Antibody-Drug Conjugate (ADC) targeting c-MET^[46]

Surgical trends

1. Video-Assisted Thoracoscopic Surgery:

A minimally invasive technique where small incisions and a thoracoscope (camera) are used instead of open thoracotomy.

2. Robotic-Assisted Thoracic Surgery

An advanced minimally invasive technique using robotic systems that provide 3D visualisation, enhanced precision and better instrument control.

CONCLUSION

Lung cancer in non-smokers highlights that this disease is not limited to tobacco exposure. It involves diverse risk factors, unique tumour types, and distinct molecular features. With advances in early diagnosis and targeted treatments, outcomes are improving, but greater awareness and preventive measures remain essential. Overall, a multidisciplinary and research-driven approach is key to effectively addressing this growing health concern.

Furthermore, the rising incidence of lung cancer among non-smokers emphasizes the need for broader public health strategies that go beyond tobacco control. Reducing environmental and occupational exposures, improving air quality, and promoting routine screening in high-risk groups can play a crucial role in early detection. At the same time, continued advancements in precision medicine and research into novel therapies offer hope for more effective and individualized care in the future.

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