Lung Cancer Among Non-Smokers: A Distinct Entity

Introduction

Lung cancer is generally associated with smoking, but a significant proportion of cases occur in individuals who have never smoked. Non-smoker lung cancer represents a distinct clinical and biological entity with unique epidemiological, genetic, and molecular characteristics. This review explores the risk factors, molecular features, clinical presentation, treatment approaches, and preventive measures for lung cancer among non-smokers.

Epidemiology

Approximately 10-25 % of lung cancer cases occur in never-smokers worldwide. The incidence is notably higher in women and in certain geographic regions, particularly in Asia. Non-smokers with lung cancer tend to present with adenocarcinoma more frequently than other histological subtypes. Studies suggest that genetic predisposition, environmental exposures, and hormonal factors may contribute significantly to the development of lung cancer among smokers.

In developing countries like India, lung cancer among non-smokers is a growing concern. Studies indicate that up to 30 % of lung cancer cases in India occur in never-smokers, with a higher proportion among women. Indoor air pollution due to biomass fuel combustion is a significant risk factor in rural households where firewood is used for heating and cooking purposes. Furthermore, rapid urbanization and industrialization have led to an increase in air pollution-related lung cancer cases in major cities such as Delhi and Mumbai. Limited access to early screening and diagnosis further exacerbates the problem, leading to late-stage detection and poor prognosis in many cases.

Risk Factors

Several risk factors contribute to lung cancer in non-smokers, including:

1. **Secondhand Smoke Exposure or Passive Smoking:** Passive smoking increases the risk of lung cancer, particularly in individuals with prolonged exposure in households or workplaces. Passive smoke contains many of the carcinogens that are present in direct smoking.
2. **Air Pollution:** Exposure to fine particulate matter (PM 2.5) and nitrogen oxides from traffic and industrial emissions has been linked to an increased risk of lung cancer. Long-tern exposure to high pollution levels has been associated with genetic mutations linked to lung cancer development. In countries like India, exposure to air pollution in metropolitan areas is a major public health concern.
3. **Radon Exposure:** A naturally occurring radioactive gas that accumulates in poorly ventilated indoor spaces, radon is a well-documented carcinogen. It decays into radioactive particles that can damage lung tissue over time, increasing cancer risk due to inhalation of the radiation gas.
4. **Occupational Exposure:** Carcinogenic substance like asbestos, arsenic, and silica found in certain workplaces contribute to lung cancer risk. Individuals working in construction, mining, and chemical industries are particularly vulnerable. In India, exposure to industrial pollutants and poorly regulated occupational safety measures contribute to higher incidences of lung cancer.
5. **Genetic and Molecular Factors:** Genetic predisposition plays a crucial role in non-smoker lung cancer. Specific mutations such as EGER, ALK, ROS1, and BRAF alterations are more common in lung cancer among non-smokers. Family history of lung cancer has also been identified as a risk factor.

6. **Hormonal and Metabolic Influences:** Estrogen and other hormonal factors may play a role in lung cancer pathogenesis, particularly in women. Some studies suggest that estrogen receptor signaling influences tumor growth and progression in non-smoker lung cancer patients.
7. **Infections and Inflammation**: Chronic lung infections, including tuberculosis, human papillomavirus (HPV), and Epstein-Barr virus (EBV), have been implicated in lung cancer development. Chronic inflammation from infections can lead to DNA damage and malignant transformation of lung cells. In India, a high burden of tuberculosis (TB) has been linked to increased lung cancer risks due to chronic lung inflammation and fibrosis.

Molecular and Clinical Characteristics

Lung cancer in non-smokers differs from smoking-related lung cancer based on molecular and clinical characteristics.

The lung cancer is more common among women predominantly histologic type is adenocarcinoma.

- EGFR mutations and ALK, ROS1, and RET rearrangements are more common in non-smokers, influencing targeted therapy options. Other alterations such as MET amplification and HER2 mutations also occur frequently.
- As stated above Adenocarcinoma is the predominant subtype, while squamous cell carcinoma is less frequent. A small percentage of non-smokers also develop small cell lung cancer (SCLC).
- Symptoms such as chronic cough, dyspnea, hemoptysis, and chest pain are similar to those in smokers. However, diagnosis is often delayed due to

lower clinical suspicion in non-smokers, leading to late-stage presentation in many cases resulting in poor outcome.

Diagnosis and Treatment

Diagnosis

- Chest X-rays, CT scans, and PET scans are essential for detecting lung cancer. High resolution CT (HRCT) can provide detailed imaging for early-stage detection of the cancer.
- Tissue biopsy obtained via bronchoscopy, transthoracic needle aspiration, or surgical biopsy is required for histological confirmation.
- Genetic testing for mutations such as EGFR, ALK, ROS1, and MET amplification helps determine eligibility for targeted therapies.
- A non-invasive method that detects tumor-derived DNA in blood, enabling early diagnosis and monitoring of treatment response.
- Serum biomarkers such as CEA, CYFRA 21-1, and NSE can support diagnosis and prognosis assessment in certain cases.

Treatment

Targeted Therapy: Newly developed targeted treatments have shown promise in the treatment due to specific genetic mutation.

- **EGFR Inhibitors:** Osimertinib, erlotinib, and gefitinib target EGFR-mutant lung cancers.
- **ALK Inhibitors:** Alectinib, crizotinib and brigatinib are used for ALK-positive tumors.

- **ROS 1 and MET Inhibitors:** Entrectinib and capmatinib target ROS 1 and MET mutations.

Immunotherapy:

- PD-1/PD-L 1 inhibitors **(**e.g., pembrolizumab, nivolumab) have limited efficacy in non-smokers but are used in select cases.
- Combination therapy with chemotherapy may improve responses in non-smoker lung cancer patients.

Chemotherapy:

- Platinum-based regimens (cisplatin/carboplatin with pemetrexed) remain a standard option, particularly for patients without mutations as described above.

Surgical Approaches:

- **Lobectomy** and **Segmentectomy** are preferred for localized tumors**.**
- **Minimally invasive techniques** like VATS and robotic-assisted surgery improve outcomes with reduced recovery times.

Radiotherapy:

- **Stereotactic Body Radiotherapy (SBRT)** is used for early-stage lung cancer in patients who are not surgical candidates.
- **Whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS)** are options for patients with brain metastases.

Prevention and Future Directions

Efforts to reduce lung cancer risk in non-smokers include:

- Reducing environmental exposure to air pollution and radon exposure through policy regulations and indoor air quality improvement measures. In India, policies targeting industrial emissions and vehicular pollution are critical in reducing lung cancer risks.
- Implementing stricter regulations on occupational carcinogens and providing protective measures for at risk workers.
- Increasing awareness and early screening in high-risk individuals, particularly those with a family history of lung cancer.
- Advancing research on genetic and biomarker-driven therapies to develop personalized treatment approaches.
- Exploring the role of hormonal factors and developing targeted therapies addressing hormone-related pathways in lung cancer pathogenesis.

Conclusion

Lung cancer among non-smokers is a distinct disease entity with unique risk factors, genetic characteristics, and treatment responses. Improved awareness, early detection strategies, and personalized treatment approaches are essential for better patient outcomes. Further research is required to uncover additional genetic and environmental factors contributing to lung cancer in never-smokers and to develop more effective preventive and therapeutic strategies. In developing countries like India, addressing environmental and occupational exposures, improving access to healthcare, and enhancing screening programs will be crucial in mitigating the rising burden of lung cancer in non-smokers.

Note: This article is intended for public reading to raise awareness about the disease.