

## Lung cancer in never smokers: Clinical epidemiology and molecular findings

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### ABSTRACT

Although lung cancer is predominantly caused by tobacco consumption, lung cancer among never smokers is an important health problem that is rapidly gaining recognition. The most common cause is long-term exposure to smoke, even though approximately 40% of lung cancers worldwide occur in lifelong never smokers and these cases are often attributed to a combination of genetic factors, and exposure to; radon gas, asbestos, and air pollution including second-hand smoke. We comprehensively searched to determine whether lung cancer patients in never smokers have different genetic mutations from their counterparts in smokers, although significant fraction of lung cancers in never smokers may also be attributable to tobacco, many such cancers arise in the absence of detectable tobacco exposure, and may follow a very different molecular pathway of malignant formation, including EGFR gene mutation, P53 mutation and other factors.

**Keywords:** Non-Smoker or Never-Smoker. Lung Cancer. Molecular Profile.

### 1. INTRODUCTION

Lung cancer is currently the 2<sup>nd</sup> most common cancer in both men and women (excluding skin cancer) and is the top cause of all cancer deaths. About 1.35 million new cases diagnosed worldwide each year. [1] There is a direct association of tobacco smoking and other pollutant and toxic exposures to lung cancer making it the leading preventable cause of death. Lung cancer was a rare disease before the advent of cigarette smoking and was not even identified as a distinct disease until 1761. [4] Since the early 1900's, lung cancer rates have grown until now where it is a national epidemic Lung cancer is the leading cause of cancer-related death worldwide. Cigarette smoking causes lung cancer in the most patients. However, the disease also arises in patients who are lifelong never smokers, i.e., individuals who smoked less than 100 cigarettes in their lifetime. Although tobacco smoking is responsible for about 90% of lung cancer cases, the epidemiology of lung cancers remains partially unresolved since the vast majority of tobacco users do not develop such tumors. [7] [10]

#### 1.1. Objective

The purpose of the study is to determine the epidemiological and molecular findings and

the possible risk factors for lung cancers in never smokers. [17] [15]

### 2. METHODOLOGY

We comprehensively searched the MEDLINE database using Pub Med for the following terms: ("non-smoker" or "never-smoker") and ("lung cancer") ("molecular profile") limited to English language

### 3. RESULTS

The large numbers of current and former smokers dying of lung cancer have obscured the important problem of lung cancer in never smokers. Currently, lung cancer in never smokers constitutes a significant portion of all lung cancers worldwide. [18] [9] Epidemiological, clinical, and molecular differences highlight how lung cancer is distinct in never smokers and in smokers. [20]

#### 3.1. Findings

##### 3.1.2. Molecular profiles

This is well exemplified by findings from several studies showing that mutations involving *TP53* and *KRAS* genes are more frequent in tobacco smokers with lung cancer, whereas LCINS is characterised by *EGFR TK* mutations, *ALK*, *RET* and *ROS* fusions. The differences between LCINS and lung cancer in tobacco smokers are not restricted to a few genes. [14] Recent next-

generation sequencing studies have found that the genome of LCINS is significantly different from the tumor genome of a tobacco smoker with lung cancer. Overall, the number of mutations is significantly lower in LCINS, and the point mutations are primarily G → A transitions. Lung cancer in never smokers is considered to be a distinct disease from those in smokers in the view of the pathogenesis, molecular alterations, drug responsiveness and prognosis. [3]

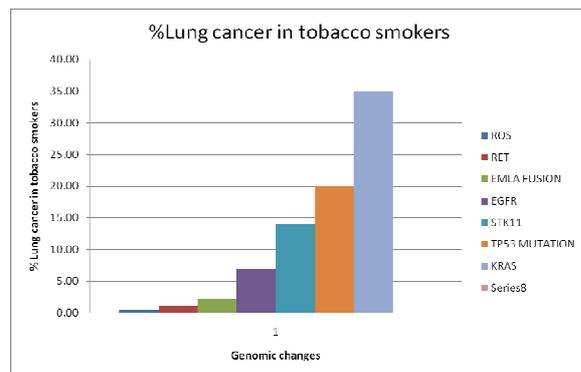


Figure -1: % of Lung cancer in smokers.

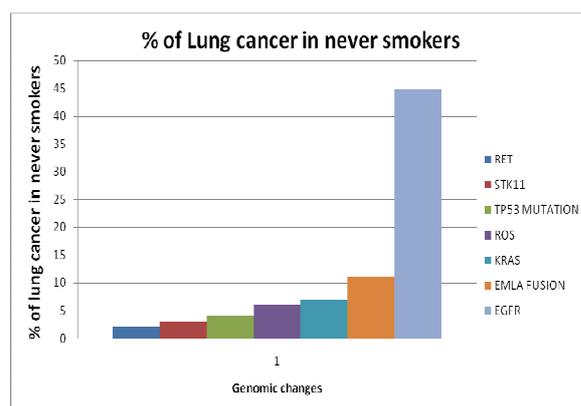


Figure - 2: % of Lung cancer in never smokers.

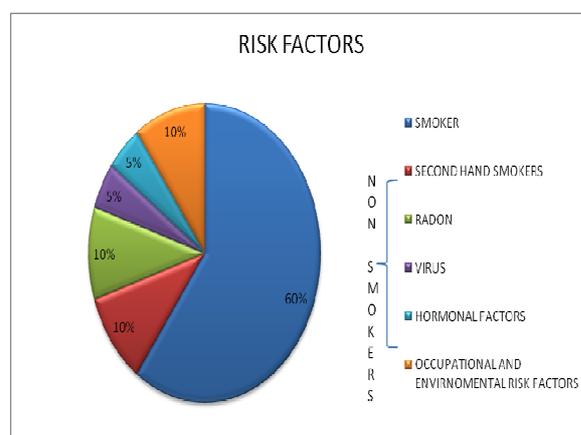


Figure -3: Risk factors

### 3.1.3. Clinical epidemiology

Lung cancer in never smokers has been difficult to verify due to the lack of smoking data

contained in most registries. [1] [8] [16] The literature that has looked at the overall incidence overtime of lung cancer in never smokers is limited .A European cohort study estimated the incidence of lung cancer [22] Data among 14399 male never smokers for the period 1971-1995. In this study rates have increased from 1.5/100000 to 5.4/100000 in 1971 to 1995. In the united states a retrospective study included 11969 patients ( 8762 smokers & 942 never smokers ) with non small lung cancer from 1995 to 2003 and found an increase in the rate of bronchioloalveolar carcinoma and NSCLC in never smokers between the period 1995-2003. [1] [24]

In contrast, two American cancer society cancer prevention study cohort, which measured age, sex, and race specific rates of death from lung cancer among more than 940000 never smokers between 1959-1979 and between 1982 - 2000, failed to find a significant increase in lung cancer incidence. [1]

## 4. DISCUSSION

Lung cancer is a leading cause of cancer-related mortality across the world. Although the majority of lung cancer is attributed to tobacco smoke, approximately 40% of lung cancers worldwide occur in lifelong never smokers. Over the past decades, the bulk of research on this disease suggested that several genetic, environmental, hormonal, and viral factors might increase the risk of lung cancer among never smokers. [25][21] However, there has been no dominant risk factor whose significance has been validated across racial and ethnic groups.

## 5. SIGNIFICANCE OF THE WORK

Up to 90% of lung cancer deaths can be attributed to smoking. But lung cancer in people who never smoked is still the seventh leading cause of cancer deaths worldwide. Lung cancer in never smokers has specific epidemiological and clinical characteristics, that is lung cancers that occur in never smokers differ from those that occur in smokers in their molecular profile and response to targeted therapy. The knowledge in molecular profile will help doctors to separate never-smoker lung cancer from smokers, and may present promising targets for therapy of never-smoker lung cancers. Future efforts should focus on further drawing of underlying biologic differences, identifying potential non-tobacco-related risk factors, and refining treatment strategies for different groups of lung cancer patients.

## 6. CONCLUSION

Lung cancer in never smokers is considered to be a distinct disease from those in

smokers in the view of the pathogenesis, molecular alterations, drug responsiveness and prognosis. Lung cancer in never smokers constitutes 40% while that in smokers constitutes 60%.<sup>[15] [19]</sup> The question of whether or not the incidence of lung cancer among never smokers is increasing overtime remains controversial. Lung cancer in never smokers is an important public health issue, and further exploration of its incidence patterns, etiology, and biology is needed.

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