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## Risk factors of Lung Cancer in nonsmoker



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Generally, the cause of lung cancer is attributed to tobacco smoking. But many of the new lung cancer cases have been reported in nonsmokers. Apart from smoking; air pollution, environmental exposure, mutations, and single-nucleotide polymorphisms are known to be associated with lung cancer. Improper diet, alcohol consumption, marijuana smoking, estrogen, infections with human papillomavirus (HPV), HIV, and Epstein-Barr virus are suggested to be linked with lung cancer but clear evidences to ascertain their relation is not available. This article provides a comprehensive review of various risk factors and the underlying molecular mechanisms responsible for increasing the incidence of lung cancer. The pathologic, histologic, and genetic differences exist with lung cancer among smokers and nonsmokers. A better understanding of the risk factors, differences in pathology and molecular features of lung cancer in smokers and nonsmokers and the mode of action of various carcinogens will facilitate the prevention and management of lung cancer.

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### Introduction

One of the leading causes of death around the world is lung cancer.<sup>1</sup> More number of Americans die of lung cancer every year than the deaths due to prostate, breast, colon cancer, and leukemia combined together (Fig 1).<sup>2</sup> It is the most common cancer worldwide, both in terms of incidence and

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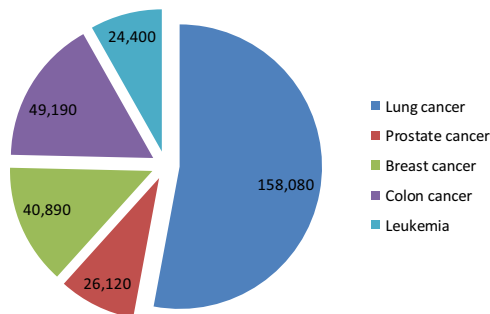
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mortality.<sup>3</sup> In 2012, 14.1 million new cases of lung cancer were diagnosed and 8.2 million people died of lung cancer globally.<sup>4</sup> Although, previously lung cancer incidence and mortality rates were found to be highest in the United States and other developed countries, but now a days there have been a large relative increase in the numbers of lung cancer cases in developing countries, which accounts for approximately half (49.9%) of the cases as compared to 1980 where 69% of cases were in developed countries.<sup>5</sup> Since 1985, the estimated numbers of lung cancer cases has been increased worldwide by 51% with 44% increase seen in men and 76% increase in women.<sup>3</sup> Women empowerment and marketing strategy of cigarette to women and girls have increased the number of female smokers in last 50 years. In countries where women are more empowered, the number of female smokers is higher than males.<sup>6</sup> This increase in female smokers is commensurate with the increasing rate of lung cancer in females. Also, women are at increased risk of lung cancer than men due to hormonal influences, reduced DNA damage reparability and elevated amount of DNA adduct.<sup>7</sup> In 2016 trends in the United States shows that cancer of the lung and bronchus is second most commonly diagnosed cancer in both the genders, trailing behind prostate cancer in men and breast cancer in women.<sup>2,8</sup>

Lung cancer is a malignant lung tumor characterized by uncontrolled cell growth in tissues of the lung. This growth can further spread to the nearby tissues or other body parts if left untreated. Most cancers which start in the lung, known as primary lung cancers, are carcinomas that are derived from epithelial cells. Small cell lung carcinoma (SCLC) and non-SCLC (NSCLC) are the main primary types. SCLC accounts for only 15% of all lung cancer cases but is a highly malignant tumor derived from cells exhibiting neuroendocrine characteristics. NSCLC, accounts for the remaining 85% of cases and is further divided into 3 major pathologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Exposure of central bronchi to low molecular weight polycyclic aromatic hydrocarbons, generated by tobacco smoking, was suggested to cause SCLC and exposure of peripheral lung tissue to nitrosamines found in tobacco smoke was associated with adenocarcinoma of lungs.<sup>9</sup> Along with histologic classification, lung cancer has also been classified on the basis of molecular subtypes. Primary molecular subtypes of lung cancer include mutations in the epidermal growth factor receptor (EGFR) gene or pathway, mutations in the K-ras gene and EML4-ALK oncogene.<sup>10</sup> Secondary subtypes include c-MET overexpression or mutation, PI3KCA amplification, PTEN deletions or methylation, overexpression of VEGFR, ROS1 translocation, epigenetic alterations, and IGF alterations.<sup>10</sup> Lung cancer in nonsmokers differs from lung cancer in smokers both at molecular and epigenetic level.<sup>11</sup> Histologically also, cancer in never smokers vary than that of cancer in tobacco smokers. Never smokers and women were mostly affected with adenocarcinoma of the lung whereas in male smokers squamous cell carcinoma was dominant.<sup>11,12</sup> Among never smokers women and East Asians are at increased risk of lung cancer.<sup>11</sup> Never smokers had increased rate of mutations of EGFR, HER2, EML4-ALK, RET, and ROS1 genes whereas mutations in K-ras gene was common in lung cancer in tobacco smokers and rare in lung cancer in never smokers.<sup>11,13</sup> A report by Govindan et al had demonstrated that tumor samples from tobacco smokers had more number of point mutations than tumor samples from nonsmokers. They also reported that the



**Fig. 1.** Incidence of lung cancer as compared to other cancer types. (Adapted with permission from American Cancer Society<sup>2</sup>)

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