



Lung cancer incidence in never smokers: Genetic and gender basis



Vidyullatha Peddireddy

Department of Biotechnology and Bioinformatics, University of Hyderabad, Hyderabad -500046, India

ARTICLE INFO

Article history:

Received 28 January 2016

Received in revised form 6 June 2016

Accepted 6 June 2016

Available online 8 June 2016

Keywords:

Never smoker

Lung cancer

Gene polymorphisms

Mutations

Gender

ABSTRACT

Lung cancer is a leading clinical condition for the high rates of mortality throughout the world. For a long time, it was considered that the risk of lung cancer is associated with smoking. With the advent of new technologies that allowed better diagnostic approaches, knowledge on the genetic basis of lung cancer in never smokers is expanding. In an epidemiological and biological stand point, lung cancer in never smokers is now recognized as a distinct disease entity. In this review, we provide a comprehensive view of the factors that contribute to lung cancer in never smokers. Epidemiological and non-genetic factors such as pollution, occupational exposure, socioeconomic status, infections and medical history determine the risk of lung cancer in never smokers. With regard to genetic factors, chromosomal aberrations, gene polymorphisms, mutations and epigenetic changes in a variety of genes involved in drug metabolism, inflammation, DNA repair and cell proliferation exert a significant effect on the risk of lung cancer in never smokers. Interestingly, it is now believed that the risk of lung cancer is higher in women and the role of female hormones in lung cancer is gaining momentum. The fact that lung cancer is a disease of the smokers is slowly waning and a rethink on the risk factors that cause this disease is very much important. Recent advances using epigenetic screening suggests that lung cancer in never smokers is a distinct disease entity. Epidemiological and clinical studies that screen for lung cancer should opt for a biological rather than a clinical selection. Diagnostic and treatment strategies should be carefully planned for lung cancer patients without a history of smoking because of the differences in the genetics, epigenetics, pathobiology and treatment outcomes in these set of patients.

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Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor; HRT, hormone replacement therapy; ETS, environmental tobacco smoke; PAH, polycyclic aromatic hydrocarbon; HPV, human papilloma virus; IP, interstitial pneumonia; COPD, chronic obstructive pulmonary disease.

E-mail address: vidyullatha.p@gmail.com.

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1. Introduction

Among the various types of cancer, lung cancer is the most prevalent and contributed to 1.6 million deaths last year (Brambilla and Travis, 2014). Lung cancer is considered as “disease of the smokers” since it is strongly associated with smoking (Siegel et al., 2013). Further, the importance of smoking in lung cancer is evident since there was a decline in its incidence and mortality due to decline in smoking (Siegel et al., 2016). However, recent data shows that lung cancer in never smokers ranks seventh position in terms of cancer-related mortality (Siegel et al., 2013). Recent statistics indicate that about 1.59 million deaths were projected due to lung cancer in never smokers (Siegel et al., 2014). Among the two types of lung cancers, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), the incidence of the latter is very low in never smokers (Kurahara et al., 2012). Historically, there has been an increase in the proportion of never smokers among lung cancer patients. In a Swedish population, the incidence of lung cancer in non-smokers was 1.5 and 5.4 per 100,000 during the time frames of 1976–1980 and 1991–1995 respectively (Boffetta et al., 2001). However, such a trend was not observed in the population of USA for the same time frame (Thun et al., 2006, 2008). A gender dependent incidence of lung cancer in never smokers was observed. In a recent study it was demonstrated that cooking oil smoke exposure (domestic exposure) was higher in women (41% for women and 18% for men) (Couraud et al., 2015). Further, exposure to passive smoking was also higher in women than men (64% versus 38%). However, the differences in the base line risk in non-smoking women are not properly compared to men who have never smoked (exposed to work related lung carcinogens. Recent trends obtained based on one of the largest prospective European trials that included 384 French participants who were never smokers, indicated that the reasons for the cause of lung cancer included domestic exposure (cooking and passive smoking) and it was more in women (Couraud et al., 2015). A review of six cohort studies on the status of lung cancer trends in never smokers after 2004 suggested that not enough time has passed between the earlier studies and collection of recent data to make a concrete conclusions (Wakelee et al., 2007). In the Indian context high numbers of lung cancer patients were never smokers in accordance with the global trends (Noronha et al., 2012). It is also believed that due to anti-smoking awareness programs, there is a decline in the number of smokers and this could indirectly contribute to the statistics of lung cancers patients who are never smokers (Han et al., 2010). Despite these complexities, it is agreed that lung cancer incidence in never smoker is true (Couraud et al., 2012, 2015).

Lung cancer of smokers and non-smokers are considered to be different disease entities since they have distinguishably clinical presentation, genetic and biochemical background, pathomorphological diagnosis, natural history, prognosis and survival rate. The tumor biology in smokers and never smokers is quite different because of the spectrum and frequency of mutations. For example, mutation in the tyrosine kinase domain of EGFR was thought to be more common in smokers. However, it was also frequently observed in never smokers, women and adenocarcinomas (Black and Khurshid, 2015). Further, whole genome sequencing revealed large differences in the genomic profile of lung cancer patients with and without smoking history (Govindan et al., 2012). Whole genome sequencing of lung cancer samples obtained from Asians indicated a distinct lung cancer genetic signature between smoker and never smokers (Krishnan et al., 2014), thus

eliminating the possibility that second hand smoke or other carcinogens that cause oxidative stress are unlikely to be major risk factors in this ethnic group. Though the pathobiology of lung cancer differs in smokers and never smokers, the treatment strategy had been the same. Adding to this, misdiagnosis of lung cancer in never smokers as tuberculosis resulted in these individuals receiving anti-tuberculosis treatment (Singh et al., 2009). A latest study indicates that proper tracking of occupational exposure and somatic molecular alterations should be given importance in never smokers with lung cancer (Couraud et al., 2015). Regardless of smoking status, it is suggested that routine EGFR testing is required during diagnosis for lung cancer (Krishnan et al., 2014). Physicians should exert more caution in the treatment strategy to be adopted for lung cancer patients who were never smokers. Because of the growing evidence on the role of factors not related to smoking in lung cancer, emphasis on this area of research has gained momentum. Among these factors, screening for epigenetic modifications specific for non-smoking lung cancer patients is the latest development (Langevin et al., 2015). In this review, we present the factors (epidemiological, genetic, epigenetic, environmental, hormonal, and viral) that contribute to lung cancer in never smokers.

2. Clinical and pathological presentation

Never-smokers with lung cancer present with more advanced disease and among them NSCLC is more frequent (Kurahara et al., 2012). The most frequent histological type among them is adenocarcinoma with a 3.5 times more frequency compared to squamous cell carcinomas (Radzikowska et al., 2002). The age at which the patients are diagnosed with lung cancer in non-smokers has been a controversy. Lung cancer was frequent in nonsmokers whose average was 59 years (Kawaguchi et al., 2010). On the contrary, age-dependent increase in the proportion of lung cancer patients who were never smokers was observed (Quoix et al., 2010). Besides the age, representation of females is very high in non-smokers diagnosed with lung cancer (Radzikowska et al., 2002; Sun et al., 2007; Yano et al., 2008; Govindan, 2010; Scagliotti et al., 2009).

3. Epidemiological factors

Incidence of lung cancer in never smokers is associated with geographical locations. In Southeast Asia, the proportion of lung cancer patients who were non-smokers is reported to be 50%, whereas the same was only 6% in Western countries (Scagliotti et al., 2009; Subramanian and Govindan, 2007). Within the epidemiology, there seems to be an effect of gender on the incidence. In a French study, 1.4% men and 28.9% women who had no history of smoking were diagnosed with lung cancer (Foegle et al., 2007); and was projected as the third leading cause of death in French women. However, in the European context, lung cancer among never smokers is rated as the 17th cause of cancer mortality in general and 9th for women (Observatory EC). Diagnosis of lung cancer in smokers is more frequent in Asia than in United States, and more frequent in United States than in Europe. In the Indian context, increase in the number of lung cancer cases among non-smokers is evident (Noronha et al., 2012). Since the ethnic, genetic and environmental factors vary among the geographical regions, the exact reasons for the variations in the incidence of lung cancer in never smokers across geographical locations remains obscure.

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