
Never Smokers with Lung Cancer: Analysis of Genetic Variants

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Abstract

It is well-known that tobacco smoke is a definite causative agent important for human health. Epidemiological research has proven that smoking is a cause of various serious and fatal diseases. However, never-smokers comprise a high proportion of non-small-cell lung cancer (NSCLC) patients. To determine whether lung cancer patients in never smokers have different genetic mutations from their counterparts in smokers, we comprehensively searched the Cochrane Library, Medline and EMBase from 1966 to Jun 2010 for the following terms: (“non-smoker” or “never-smoker”) and (“lung cancer”) and (“gene”) limited to English and clinical trials. Although a 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 metabolic gene CYP1AIIle462Val polymorphism. These genes 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 delineation of underlying biologic differences, identifying potential non-tobacco-related risk factors, and refining treatment strategies for different groups of lung cancer patients.

Keywords: Lung cancer - genetic variants - smokers - non-smokers - China

Introduction

Currently, there are 1.3 billion smokers in the world, and children are picking up smoking at the alarming rate of 80,000 to 100,000 a day. It is well-known that cigarette smoking is a risk factor for several diseases, including lung cancer. However, these results are come from epidemiology researches, retrospective studies and medical experiments, which might not reflect the real hazard of cigarette smoking.

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. In the United states, and estimated 10% of lung cancers occur in never smokers (Wakelee et al., 2007). Higher percentages of never smokers, up to 30%, have been observed in East Asian countries (Koo and Ho, 1990). Furthermore, although smoking is a major cause of lung cancer, the proportion of lung cancer cases among Japanese women who never smoked is high. These studies have demonstrated differences in epidemiologic characteristics and histologic subtypes between smokers and never-smokers, which led to the suggestion of existence of non-tobacco related risk factors in the pathogenesis of non-small-cell lung cancer (NSCLC) in a subgroup of patients. Additional evidence that suggested differences in tumor biology between the never-smokers and smokers lay in the mutational frequencies and spectra observed in the tumor tissue itself (Gealy et al., 2001; Hainaut and Hainaut.,. 2001). Lynch et al recently reported that a subgroup of patients with NSCLC, mainly adenocarcinoma, harbored a specific activating mutation in the epidermal growth factor receptor gene that correlated with clinical responsiveness to the tyrosine kinase inhibitor gefitinib(Lynch et al., 2004). This was subsequently confirmed by other groups which showed consistently that mutations in the tyrosine kinase domain of epidermal growth factor receptor was more commonly found among women, never-smokers, Asians, and adenocarcinomas (Janne et al., 2005; Pao and Miller, 2005; Shigematsu et al., 2005). All these data suggest that the pathogenesis of NSCLC in the never-smokers could possibly be different from the smokers. The question is whether lung cancer patients in never smokers have different genetic mutations.

Literature Sources

We comprehensively searched the Cochrane Library, Medline and EMBase from 1966 to Jun 2010 for the following terms: (“non-smoker” or “never-smoker”).

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and (“lung cancer”) and (“gene”) limited in English and clinical trials.

**EGFR gene mutation and lung cancer risk in non-smokers**

The association of smoking as a risk factor for lung cancer has been well established from epidemiologic evidence since the 1950 (Doll and Hill, 1950; Wynder and Graham, 1985). All of the earlier landmark studies were conducted in the Western countries where an estimate of 85% to 90% of lung cancer cases were attributed to smoking (Parkin et al., 1994). As a result, never-smokers with lung cancer were under-represented and not well studied.

With advances in molecular biological research, the majority of molecular analyses of lung cancer have focused on genetic profiling of pathways responsible for metabolism of primary tobacco carcinogens. Recent studies summarized here suggest that lung cancers arising in never smokers have a distinct natural history and profile of oncogenic mutations. Rudin et al. (2009) found that lung cancer in never smokers has peak incidence at a younger age than in smokers, is more likely to arise in women, and is more likely to be of adenocarcinoma histology.

Intensive molecular research by multiple groups seeking to explain these evident population differences ultimately led to three key publications in 2004, reporting that mutations affecting the ATP binding site of the tyrosine kinase domain of EGFR are strongly associated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (Lynch et al., 2004; Paez et al., 2004). Mutations in EGFR have become a primary focus of research in lung cancer. Compared with other patients with lung cancer, “never smokers” with lung cancer have a unique clinical course (Toh et al., 2006; Janjijian et al., 2008): they have a better prognosis, their tumors are more likely to harbor somatic mutations in the gene encoding the EGFR. In 2004, Pao et al. (2004) proved that EGFR gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. Recently, it is reported that single nucleotide polymorphism (SNP) in intron 1 of EGFR implicated in female never smokers with lung cancer (Jou et al., 2009). That was further proved in a preliminary report, made by Girard et al. in 2010. Furthermore, EGFR tyrosine kinase inhibitor emerged as a potential breakthrough for the treatment of metastatic adenocarcinoma of the lung in never smokers (Lee et al., 2005).

**P53 mutation and lung cancer risk in non-smokers**

Genetic alterations, in particular, mutations in genes controlling cell growth and proliferation, have potential in discovering crucial biological alterations associated with long-term exposure to carcinogens; consequently, they may aid in unraveling pathways leading to tumor formation. In this context, mutations of the tumor suppressor gene p53, which encodes a multifactorial transcription factor controlling cellular response to DNA damage (Levine, 1997), represent a potentially useful biomarker in the search for etiology, molecular mechanisms and, hopefully, prevention of environmental cancers (Harris, 1996; Sidransky and Hollstein, 1996). Mutations of p53 gene occur in about 50% of human lung tumors (Hollstein et al., 1991), and the mutations observed in lung cancer appear to have typical features (Greenblatt et al., 1994; Hussain and Harris, 1998). The international database on p53 mutations records mutation data for about 1000 cases of lung cancer (Hainaut and Pfeifer, 1998). Husgafvel-Pursiainen et al. (2000) conducted a multicenter case-control study to investigate the association between ETS exposure and lung cancer in never-smokers using p53 mutations as a biomarker of tobacco-related carcinogenesis. They found the mutation patterns observed also suggested a difference between smokers and never-smokers, and suggested that p53 mutation could serve as a sensitive marker of tobacco-related carcinogenesis. That was confirmed using quantitative analysis (Hagiwara et al., 2006).

**2.3 metabolic genes polymorphisms and lung cancer risk in non-smokers**

Genetic polymorphisms have been identified in metabolic genes, and the biological consequence of such changes in an altered enzyme activity which may influence the ratio between activation and deactivation, and thus the cancer risk. In 2005, Raimondi et al. (2005) evaluated the role of the metabolic gene polymorphisms in non-smoker lung cancer patients from the International Collaborative Study on Genetic Susceptibility of Environmental Carcinogens. Their results confirmed their previous finding that CYP1AIIle462Val polymorphism may play a role in lung carcinogenesis in Caucasian non-smokers (Huang et al., 2003).

**Conclusions**

The majority of lung cancers are caused by long term exposure to the several classes of carcinogens present in tobacco smoke. Although a 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 metabolic gene CYP1AIIle462Val polymorphisms. These genes will help doctors to separate never-smoker lung cancer from smokers, and present a promising therapy target to treat never-smoker lung cancer.

The etiology of lung cancer in never smokers is poorly understood, second-hand smoke and radon possibly accounting for as many as 50% of cases (Darby et al., 2005). Outdoor air pollution, cooking oil fumes, coal fumes, and asbestos may also contribute as risk factors. Giving the lack of direct exposure to known carcinogens, never smokers with lung cancer may represent a subgroup for which predisposing genetic factors might be prominent and distinct from those of smokers. Future efforts should focus on conducting studies to further delineate underlying biologic differences, identify potential non-tobacco-related risk factors, and further refine treatment strategies for these two groups of patients.
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References


