COMMENTARY

Never Smokers with Lung Cancer: Analysis of Genetic Variants

Haijun Xiao[1], Jie Ding[2], Shan Gao[1*], Shujuan Yang[3], Yuchuan Huang[4,5]

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 CYP1AIIe462Val 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 cancerpatients.

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

Asian Pacific J Cancer Prev, **12**, 2807-2809

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 adenocacinomas (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")

*[1]Shanghai Jiao Tong University Affiliated Sixth People's Hospital Fengxian Branch, Shanghai, [2]Department of Neurology, Tianjin Medicine Union Center, Tianjin, [3]Department of Hygiene of Children and Adolescents, West China School of Public Health, Sichuan University, [4]Technology Research and Development Center, China Tobacco Chuanyu Industrial Corporation, [5]Key Laboratory of Transplant Engineering and Immunology, Ministry of Health, West China Hospital, Chengdu, China *For correspondence: rekinyyang@gmail.com, gaoshanwater@163.com*

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., 1944). 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 adenocacinoma 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 response to 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 nudeotide 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 multifctorial 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 suggest 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.

Acknowledgements

This work was financially supported by China National Tobacco Corporation (110200701007), Chongqing Research Program(06-1-173) and Post-Doctor Research Program of China Tobacco Chuanyu Industrial Corporation (Measurement of the hazard biomarkers from tobacco smoking).

References

Darby S, Hill D, Auvinen A, et al (2005). Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ*, **330**, 223.

Doll R, Hill AB (1950). Smoking and carcinoma of the lung: Preliminary report. *BMJ*, **2**, 739-48.

Gealy R, Zhang L, Siegfried JM, Luketich JD, Keohavong P (2001).Comparison of mutations in the p53 and K-ras genes in lung carcinomas from smoking and nonsmoking women. *Cancer Epidemiology Biomarkers Prev,* **8**, 297-302,1999; Erratum in: *Cancer Epidemiology Biomarkers Prev*, **10**, 1309.

Girard N, Lou E, Azzoli CG, et al (2010). Analysis of genetic variants in never-smokers with lung cancer facilitated by an internet-based blood collection protocol: a preliminary report. *Clinical Cancer Research*, **16**, 755-63.

Greenblatt MS, Bennett W P, Hollstein M, Harris CC(1994). Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis. *Cancer Research*, **4**, 4855-78.

Hagiwara N, Mechanic LE, Trivers GE, et al (2006). Quantitative detection of p53 mutations in plasma DNA from tobacco smokers. *Cancer Research*, **66**, 8309-17.

Hainaut P, Hernandez T, Robinson A, et al (1998). IARC database of p53 gene mutations in human tumors and cell lines: updated compilation, revised formats and new visualization tools. *Nucleic Acids Reseach*, **26**, 205-13.

Hainaut P, Pfeifer GP (2001). Patterns of p53 G3T transversions in lung cancers reflect the primary mutagenic signature of DNA-damage by tobacco smoke. *Carcinogenesis*, **22**, 367-74.

Harris CC (1996). p53 tumor suppressor gene: at the crossroads of molecular carcinogenesis, molecular epidemiology, and cancer risk assessment. Environ Health Perspect, 104, 435-9.

Hollstein M, Sidransky D, Vogelstein B, Harris CC (1991). p53 mutations in human cancers. *Science*, **253**, 49-53.

Huang RJ, Boffetta P, Brockmoller J, et al (2003). CYP1A1 and GSTM1 genetic polymorphisms and lung cancer risk in Caucasian non-smokers: a pooled analysis. *Carcinogenesis,* **24**, 875-82.

Husgafvel-Pursiainen K, Boffetta P, Kannio A, et al (2000). p53 mutations and exposure to environmental tobacco smoke in a multicenter study on lung cancer. *Cancer Res*, **60**, 2906-11.

Hussain SP, Harris CC (1998). Molecular epidemiology of human cancer: contribution of mutation spectra studies of tumor suppressor genes. *Cancer Research*, **58**, 4023-37.

Janjijian Y, Kris MG, Miller VA, Riely G (2008). Pack years of cigarette smoking as a predictor of survival in 2,010 patients with stage IIIb/IV nonsmall cell lung cancer (NSCLC). *J Clin Oncol*, **26**, 8005.

Janne PA, Engelman JA, Johnson BE (2005). Epidermal growth factor receptor mutations in non-small cell lung cancer: Implications for treatment and tumor biology. *J Clin Oncol*, **23**, 3227-34.

Jou YS, Lo YL, Hsiao CF, et al (2009). Association of an EGFR intron 1 SNP with never-smoking female lung adenocarcinoma patients. *Lung Cancer*, **64**, 251-6.

Koo LC, Ho JH (1990). Worldwide epidemiological patterns of lung cancer in nonsmokers. *Internal J Epidemiology*, **19**, S14-23.

Kurahashi N, Inoue M, Liu Y, et al (2008). Passive smoking and lung cancer in Japanese non-smoking weomen: a prospective study. *Int J Cancer*, **122**, 653-7.

Lee DH, Han Ji-Youn, Lee HG, et al (2005). Gefitinib as a first-line therapy of advanced or metastatic adenocarcinoma of the lung in never-smoker. *Clin Cancer Res* **11**, 3032-7.

Levine AJ (1997). p53, the cellular gatekeeper for growth and division. *Cell*, **88**, 323-31.

Lynch TJ, Bell DW, Sordella R, et al (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. *New Eng J Med*, **350**, 2129-39.

Paez JG, Janne PA, Lee JC, et al (2004). EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*, **304**, 1497-500.

Pao W, Miller VA (2005). Epidermal growth factor receptor mutations, small molecule kinase inhibitors, and non-small cell lung cancer: Current knowledge and future directions. *J Oncology*, **23**, 2556-68.

Pao W, Miller V, Zakowski M, et al (2004). EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA*, **101**, 13306-11.

Parkin DM, Pisani P, Lopez AD, Masuyer E (1944). At least one in seven cases of cancer is caused by smoking: Global estimates for 1985. *Int J Cancer*, **59**, 494-504.

Raimondi S, Boffetta P, Anttila S, et al (2005). Metabolic gene polymorphisms and lung cancer risk in non-smokers an update of the GSEC study. *Mutat Res*, **592**, 45-47.

Rudin CM, Avila-Tang E, Harris CC, et al (2009). Lung cancer in never smokers: molecular profile and therapeutic implications. *Clin Cancer Res*, **15**, 5646-61.

Shigematsu H, Lin L, Takahashi T, et al (2005). Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J of the National Cancer Institute*, **97**, 339-46.

Sidransky D, Hollstein M (1996). Clinical implications of the p53 gene. *Annual Review Medicine*, **47**, 285-301.

Toh CK, Gao F, Lim WT, et al (2006). Never smokers with lung cancer: epidemiologic evidence of a distinct disease entity. *J of Clinical Oncology*, **24**, 2245-51.

Wakelee HA, Chang ET, Gomez SL, et al (2007). Lung cancer incidence in never smokers. *J Clin Oncol*, **25**, 472-8.

Wynder EL, Graham EA(1985). Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma: A study of six hundred and eighty-four proved cases. *J Am Medical Assoc*, **253**, 2986-94.