The correlation of FHIT gene mutation and smoking in patients with non-small cell lung cancer: a Meta-analysis

Song Fei-xiang[1], Xiao Yue-xing[2], Guo Su-fang[3], Zhang Hai-bo[4], Wang Ying-qiang[3], Zhang Xia[1], Cui Yu-mei[5]

[1]Department of Oncology, General Hospital of Beijing Military Area Command of Chinese PLA, China
[2]Department of Endocrinology. Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China
[3]Department of Oncology. The Sixth Hospital of Handan, China
[4]Institute of Biomedical Engineering Chinese Academy of Medical Sciences & Peking Union Medical College, China
[5]Department of Emergency, The Sixth Hospital of Beijing, Beijing, China
Tel.:+86-1057212550; Fax: +86-1057212550; Email: yum_cui@163.com

Abstract: Objective: The aim of this study was to determine the association between FHIT gene mutation in non-small cell lung cancer (NSCLC) and smoking status by meta-analysis. **Methods:** Publications addressing the association between FHIT gene mutation in non-small cell lung cancer and smoking status were selected from the MEDLINE, EMBASE, CBM, CNKI, VIP and Wanfang databases. Data was extracted from the studies by 2 independent reviewers. The meta-analysis was performed by RevMan 5.0.25 and STATA 10.0 softwares. From these data, odds ratio (OR) with 95% confidence interval (CI) were calculated. **Results:** Thirteen studies were retrieved reporting a total of 1649 NSCLC patients. Meta-analysis results showed a significant association between FHIT gene mutation and smoker with non-small cell lung cancer (OR=3.04, 95%CI=1.68-5.51, *P*=0.0002), especially in smoker with squamous cell carcinoma (OR=8.07, 95%CI=2.00-32.56, *P*=0.003). However, there was no significant association between FHIT gene mutation and smoker with adenocarcinoma (OR=1.41, 95%CI=0.60-3.28, *P*=0.43). **Conclusion:** Our meta-analysis suggests that there was a significant association between FHIT gene mutation in NSCLC and smoking status, especially in smoker with lung squamous cell carcinoma.

[Song Fei-xiang, Xiao Yue-xing, Guo Su-fang, Zhang Hai-bo, Wang Ying-qiang, Zhang Xia, Cui Yu-mei. **The correlation of FHIT gene mutation and smoking in patients with non-small cell lung cancer: a Meta-analysis.** *Life Sci J* .2014;11(11):39-42] (ISSN:1097-8135). http://www.lifesciencesite.com. 5

Key Words: Non-small cell lung cancer; Smoking status; FHIT gene; Gene mutation; Meta-analysis

1.Introduction

The FR3B site of FHIT gene may be the targets for tobacco carcinogens, which would cause the FHIT expression deletion, and weaken the tumor suppressor function (Kastury et al.,1996). A large number of epidemiological data showed that the tobacco contained many mutagenic chemicals, so smoking or passive smoking was the major factor for lung cancer occurrence (Sozzi et al.,1996). Since the FHIT gene contained the brittle fracture fragment FR3AB which was fractured easily by the external carcinogens, such as tobacco; therefore, the FHIT gene might be the targets for tobacco carcinogens and the early molecular phenomenon of lung cancer. The above results were also confirmed by immunohistochemistry (Wang et al.,2009;Yang et al., 2006; Huebner et al.,1998), which showed the negative expression rate of FHIT of bronchial epithelial in current smokers was significant higher than that in the past smokers (Wang et al.,2009). At present, more and more studies focus on the role of FHIT gene in the occurrence and development of cancer, but there was controversy about the correlation with smoking(Li et al.,2006). The mechanism of smoking-induced lung cancer is still not clear, the time of basic and clinical research is limited, which can't reflect the specific impact of gene mutations. Therefore, in this study, we used the systematic review and Meta-analysis to evaluate the correlation between FHIT gene mutation of non-small cell lung cancer (NSCLC) patients and smoking, to provide a scientific basis for the early diagnosis and treatment of NSCLC.

2.Materials and methods

2.1 Search strategy

We searched literature (including the references) from MEDLINE, EMBASE, CBM, CNKI, VIP and Wanfang database, the retrieve time was from database building to May, 2011. The relevant journals, conference proceedings and dissertation were searched by manual retrieval. The Chinese and English literatures about the correlation between FHIT gene mutation of NSCLC patients and smoking in clinic were collected. The search terms include non-small cell lung cancer, smoking status, FHIT gene and gene mutation in Chinese or English.

2.2 Inclusion and exclusion criteria

Inclusion criteria: 1) the clinical research on correlation of FHIT gene mutation of NSCLC patients and smoking; 2) all patients were pathologically

confirmed as NSCLC; 3) the sample size of included studies was more than 30 cases; 4) all included studies needed to provide complete data for further calculation together. Exclusion criteria: 1) abstracts, reviews and lectures; 2) incorrect or incomplete data; 3) no clear diagnostic criteria of included patients; 4) republished literature.

2.3 Data extraction

The data of included literatures were extracted by two independent reviewers: authors, published year, area, sample size, gender, age, diagnostic criteria, smoking status, FHIT gene mutation, etc. If there was a dispute, discuss with the third reviewer.

2.4 Quality evaluation

The quality of included studies was evaluated according to STROBE rating scale(Shi et al.,2009) by two reviewers, the rating scale includes 39 items, the minimum is 0 point and the maximum is 50 points, the higher the score the better the quality of the literature. If there was a dispute, discuss with the third reviewer.

2.5 Data analysis

The Meta-analysis was analyzed with Review Manager 5.0.25 and STATA 10.0 software. The association between FHIT gene mutation and smoking status was evaluated with odds ratio (OR) and 95% confidence interval (CI). The heterogeneity between studies was analyzed with Cochran's Q test and I^2 test (Huebner et al.,1998). The effect value range of I2 test was from 0% to 100%, the higher the effect percentage, the smaller the heterogeneity between groups. When there was heterogeneity (P<0.10 or I^2>50%), using a random effect model, and vice versa using a fixed effect model. According to the pathological types, the included patients were divided into squamous cell carcinoma and adenocarcinoma, the subgroup analysis were performed to explore the heterogeneity sources. The studies were deleted one by one to conduct sensitivity analysis, then to evaluate the influence of weight on overall results. The publication bias was determined by Begg's funnel plot and Egger's linear regression analysis, P<0.10 was considered publication bias existence(Otom et al.,1996). The data were input by two independent researchers and the results were calculated by computer to ensure the results reliable.

3.Results

3.1 The basic characteristics of included studies

The 127 literatures were retrieved at the first time, after reading the title and abstract, 40 literatures were screened; then after reading the full text and application of exclusion criteria, 13 literatures were included in this study, including 1649 cases of NSCLC patients. The publication time of included 13 literatures was from 1996 to 2009, and all patients were pathologically confirmed as NSCLC.

3.2 Meta-analysis results

The Meta-analysis results showed that all the included 13 studies had heterogeneity (P<0.00001, I^2=78%), combined analysis with random effect model showed that the FHIT gene mutation rate of NSCLC patients was closely related with smoking status (OR=3.04, 95%CI=1.68-5.51, P=0.0002), shown in Figure 1. According to the pathological types, the included patients were divided into squamous cell carcinoma and adenocarcinoma subgroups, the results showed that FHIT gene mutation rate of patients with squamous cell carcinoma was closely associated with smoking status (OR=8.07, 95%CI=2.00-32.56, P=0.003). However, there was no significant correlation between FHIT gene mutation of patients with adenocarcinoma and smoking status (OR=1.41, 95%CI=0.60-3.28, P=0.43). In addition, the studies were deleted one by one to conduct sensitivity analysis; the results showed that there was no significant influence of weight on overall results and subgroup analysis.

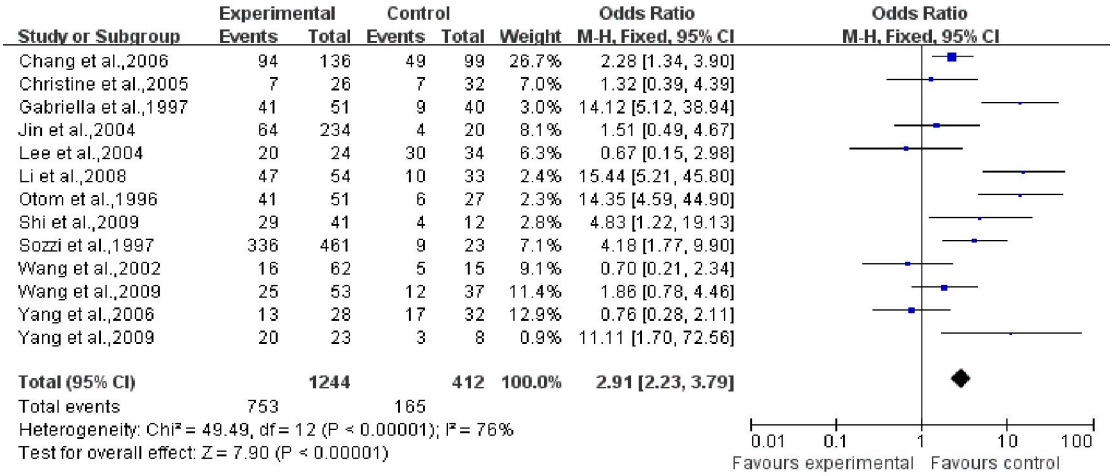

Fig 1. The relation between FHIT gene and smoking in non-small cell lung cancer.

4.Discussion

Studies have shown that the occurrence of lung cancer in 80%-90% male patients was associated with smoking, and women with lung cancer were 19.3%-40%. Tobacco contains carbon monoxide, nitric oxide, acrolein, nicotine, tar and other carcinogens. With the development of molecular pathology, it has been found that some carcinogens of tobacco could induce DNA mutations and chromosomal damage, as well as some related signal transduction pathways (Mountzios et al.,2000). Zanesi *et al* found that FHIT might be the suppressor gene in human through the FHIT gene knockout mouse. The deletion rate of FHIT gene was high in NSCLC patients, which was also higher in smokers, the FHIT gene mutation was usually exon 5 missing [23-26]. The expression of FHIT protein in NSCLC tissues was significantly lower than that in normal lung tissues, and the expression in smokers was lower than that in non-smokers (P<0.001), suggesting that FHIT gene might be the molecular target for tobacco carcinogens(Jin et al.,2004;Christine et al., 2005). Smoking was closely related to gene abnormalities of lung cancer, but it was different in different pathological types(Pylkkanen et al., 2002; 2 Sozzi et al., 1998;Zochbauer-Muller et al., 2000).

This study systematic evaluated the clinical research of the correlation between FHIT gene mutation of NSCLC patients and smoking status. Eventually, a total of 13 case-control studies were included in this systematic review, including 1649 cases of NSCLC patients. The Meta-analysis results showed that all the included studies had heterogeneity, combined analysis with random effect model showed that the FHIT gene mutation rate of NSCLC patients was closely related with smoking status (P<0.05). The subgroup-analysis results showed that FHIT gene mutation rate of patients with squamous cell carcinoma was closely associated with smoking status (P<0.05), but not the adenocarcinoma patients (P>0.05). The sensitivity-analysis results showed that there was no significant influence of weight on overall results and subgroup analysis. Begg's funnel plot and Egger's linear regression analysis showed that there was no significant publication bias in this systematic review. Although this study had rigorous research design and statistical analysis, there were still many limitations. Firstly, some valuable indicators couldn't be collected to calculate the relationship between smoking status and FHIT gene mutation rate; secondly, since the original data was incomplete or the sample size was too small, some studies didn't meet the inclusion criteria; thirdly, although the subgroup analysis and sensitivity analysis were performed, the potential heterogeneity couldn't be intervened; lastly, the included studies were mainly from Asia, the clinical value was limited.

Through the comprehensive evaluation of included studies, we believed that the FHIT gene mutation of NSCLC patients was closely associated with smoking, especially for patients with squamous cell carcinoma. However, since the quality of methodology was uneven in this systematic review, and there was difference in number of cases, evaluation methods, data description between groups, our results still needs large sample clinical studies to confirm.

Correspond to:
Cui Yu-mei
Department of Emergency, The Sixth Hospital of Beijing, BeiJing 100708, China. Tel.:+86-1057212550;
Fax: +86-1057212550;
Email: yum_cui@163.com

References

1.Kastury K,Baffa R,Druck T.Potential gastrointestinal tumor suppressor locus at 3p14.2 FRA3B site identified by homologous deletions in tumor cell lines.Cancer Res 1996;56:978-983.
2.Sozzi G,Veronese ML,Negrini M.The FHIT gene at 3p14.2 is abnormal in lung cancer.Cell 1996;85:17-26.
3. Wang XL, Chen C, Fei SD. Expression and Significance of Fragile Histidine Triad(FHIT) and Survivin in Non-small Cell Lung Cancer. Journal of Oncology 2009;15:1-3.
4.Li G, Qian XL, Zhang YP, Li XQ, Yuan ZQ. FHIT gene and squamous cell lung carcinoma. Shandong Medical Journal 2006; 4:41-42.
5. Wang HJ, Sun XW, Ma YY, Dai XD. The Relationship between FHIT Gene Expression and Cigarette Smoking in Non-small Cell Lung Cancer. BULLETIN OF CHINESE CANCER 2002;11:32-34.
6.Sozzi G, Sard L, Gregorio LD, et al. Association between cigarette smoking and FHIT gene alterations in lung cancer. Cancer Res, 1997,57(11):2121—2123
7.Chang XJ, Yang S, Zhang HQ, Wang H, Jiang Y. Expression of FHIT gene in precancerous lesions and primary lung cancer tissues. CHINESE JOURNAL OF LUNG CANCER 2006;9:21-23.
8. Yang ZH, Liu HM, Sun J, He J, Wang LZ, Xu Y. Expression of fragile histidine triad protein in lung cancer tissues and its correlation with multidrug resistance protein 1. ACADEMIC JOURNAL OF SECOND MILITARY MEDICAL UNIVERSITY 2006;27:1-3.
9.Shi SZ, Zhao JJ, Zhao WH, Xu XH. The expression and clinical significance of FHIT protein and mdm2 protein in non-small cell lung cancer. CHINESE CLINICAL ONCOLOGY 2009;14:54-55.
10.Huebner K, Druck T, Siprashvili Z, Croce CM,

Kovatich A, McCue PA. The role of deletions at the FRA3B/FHIT locus in carcinogenesis. Recent Results Cancer Res 1998;154:200-215.
11.Otom M, Znoue H, CotticelliMG. et a,l The FHIT gene spaning the chromosome 3P14. 2 fragile site and rena, l carcinoma-associated t(3; 8) breakpoint is abnormall in digestive tract cancers[J].Cell, 1996;84: 587-597
12. Yang SY, Cao YP, Wang MH, Kang MQ, Zhu CH. Expression and clinical significance of FHIT gene and TPX2 gene in lung cancer. LABORATORY MEDICINE AND CLINIC 2009;6:3-5.
13.Stein CK, GloverTW, Palmer JL, et a.l Direct correlation between FRA3B expression and cigarette smoking[J]. Genes Chromosomes Cancer 2002; 34: 333-340.
14. Y-C Lee,C-T Wu,J-Y Shih,Y-S Jou，Y-L Chang，Frequent allelic deletion at the FHIT locus associated with p53 overexpression in squamous cell carcinoma subtype of Taiwanese non-small-cell lung cancers. British Journal of Cancer 2004;90:2378–2383.
15. Li XB, Sun XF, Yin QW, Wang SZ. The study on the Association between expression of p21ras protein and FHIT protein and smoking in no-small-cell lung cancer tissue.J Toxicol August 2008;22:14-15.
16.Gabriella Sozzi,Laura Sard,Laura De Gregorio, Antonio Marchetti,Katia Musso,Fiamma Buttitta, Association between Cigarette Smoking and FHIT Gene Alterations in Lung Cancer. CANCER RESEARCH 1997;57:2121-2123.
17.Yutaka Shimada,Fumiaki Sato,Go Watanabe,Seiji Yamasaki, Masayuki Kato, Masato Maeda, Masayuki Imamura, Loss of Fragile Histidine Triad Gene Expression Is Associated with Progression of Esophageal Squamous Cell Carcinoma, but Not with the Patient's Prognosis and Smoking History.Cancer 2000;89:5–11.
18.Jin Seuk Kim,Hojoong Kim,Young Mog Shim, Joungho Han,Joobae Park,Duk-Hwan Kim, Aberrant methylation of the FHIT gene in chronic smokers with early stage squamous cell carcinoma of the lung. Carcinogenesis 2004;25:2165--2171.
19.Christine H.Holschneider,Rae Lynn Baldwin,Kiran Tumber, Chisa Aoyama,Beth Y.The Fragile Histidine Triad Gene:A Molecular Link Between Cigarette Smoking and Cervical Cancer. Clin Cancer Res 2005;11:5756-5763.
20.Pylkkanen L, Wolff H, Stjernvall T. Reduced Fhit protein expression and loss of heterozygosity at FHIT gene in tumours from smoking and asbestos-exposed lung cancer patients[J]. Int J Oncol, 2002;20: 285-290.
21.Sozzi G, Pastorino U, Moiraghi L. Loss of FHIT function in lung cancer and preinvasive bronchial lesions. Cancer Res 1998;58:5032-5037.
22.Zochbauer-Muller S, Wistuba II, Minna JD, Gazdar AF. Fragile histidine triad (FHIT) gene abnormalities in lung cancer. Clin Lung Cancer 2000;2:141-145.
23.Zochbauer-Muller S, Fong KM, Maitra A. 5VCpG island methylation of the FHITgene is correlated with loss of gene expression in lung and breast cancer. Cancer Res 2001;61:3581-3585.
24.Virmani AK, Muller C, Rathi A, Zochbauer-Muller S, Allelic deletion analysis of the FHIT gene predicts poor survival in non- small cell lung cancer. Cancer Res 1998.Jun 15:58:2533-2536
25.Mathis M, GazdarAF. Aberrant methylation during cer- vical carcinogenesis. Clin Cancer Res 2001;7:584-589.
26.Jemal A, Siegel R,Ward E,et al. Treatment of prostate cancer: therapeutic potential of targeted immunotherapy with APC8015Cancer statistics. CA Cancer J Clin,2007;57:43-66.
27.Mountzios G,Fouret P,Soria JC.Mechanisms of Disease: signal trans-duction in lung carcinogenesis-a comparison of smokers and never-smokers. Nat Clin Pract Oncol, 2008,5(10):610-618.[J]. Cancer Res, 2000; 60:3155-3159.
28.Sllebos RJ. Relationship between K-ras oncogene activation and smoking in adenocarcinoma of the human lung[J]. J Natl cancerInst, 1991;83: 1024-1027.

6/25/2014