RESEARCH COMMUNICATION

Lack of Associations of Polymorphisms of IL-7R, IL-13 and IL-15 with NSCLCs in Non-smoking Chinese

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Abstract

Studies have shown that immune cells play a key role in lung cancer development. Five SNPs (rs1494555, rs7737000, rs20541, rs1057972 and rs2857261) are associated with lung cancer risk among Caucasians and/or African-Americans, but the polymorphisms may be implicated in different susceptibilities for lung cancer across different populations because of underlying genetic heterogeneity. We therefore conducted a study to examine this relationship in non-smoking Chinese. As a result , no significant associations were observed between SNPs and NSCLCs, whetehr of squamous cell or adenocarcinoma type. Results indicated polymorphisms of IL-7R, IL-13 and IL-15 are not major contributors to NSCLC susceptibility, although we can not rule out synergistic effects with cigarette smoke in NSCLC development in smoking Chinese.

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Introduction

Cancer is a major public health problem in the United States and many other parts of the world, the overall estimate of approximately 1.53 million new cases in United Statesin 2010 (Jemal et al., 2010). Lung cancer is the first cause of cancer deaths in men, and it, in women, surpassed breast cancer as the leading cause of cancer death in 1987 (Jemal et al., 2010). Non-small lung cancers (NSCLCs) account for approximately 80% of lung cancers and the most effective treatment for them is surgery when the tumor is confined to primary site with minimal regional lymph node involvement (Yamamoto et al., 2009). However, the treatment record showed only 14% of Bangladeshi and 8% of white men received surgery within 6 months after diagnosis (Ferlay et al., 2008). The reason is a majority of patients present with advanced lung cancer, there are no cancer-specific symptoms to look for at an early stage. So, the 5-year survival rate of lung cancer has not changed over the last 30 years (Jemal A et al., 2002). Cigarette smoking is the most significant risk factor for lung cancer. This association was initially demonstrated by Doll et al in the 1950s in the UK. Since then, case-control studies (Wynder and Graham, 1950) and prospective cohort studies (Hammond and Horn, 1954) have affirmed this association. Although a lifetime smoker has a risk 20-30 times greater than of a nonsmoker (Parkin et al., 2001), the fact that only a portion of smokers (usually <20%) developed lung cancer during their lifetime. In addition, Eastern Asia is one of the areas where the age-standardised lung cancer incidence is highest (Ferlay et al., 2008). Those suggest environmental and genetic factors may increase susceptibility to lung cancer.

A very recent study shown single-nucleotide polymorphisms (SNPs) of rs1494555 and rs7737000 in Interleukin-7 receptor (IL-7R) were associated with an increased risk of lung cancer among Caucasians, and rs7737000 SNPs were associated with risk in African-Americans. SNPs of Interleukin-13 (IL-13) rs20541 were associated with risk of NSCLC among African-Americans, but not among Caucasians. The polymorphisms of rs2857261 and rs1057972 in interleukin-15 (IL-15) were associated with an increased risk of lung cancer among African-Americans, but no association was detected among Caucasians (Van et al., 2009). but the same gene polymorphism variant may be implicated different susceptibility for lung cancer across different populations because of underlying genetic heterogeneity. So, We conducted a matched case-control study to examine whether or not this relationship is reside in Chinese population. Furthermore, we selected non-smoker as eligible subjects for the purpose of avoiding the probable interferences from cigarette smoking .

Materials and Methods

Patients and controls

Totally, 200 NSCLC patients and 200 controls were included. The patients who consisted of 145 adenocarcinomas and 55 squamous cell carcinomas had clear histopathological confirmation. The averaged age was 57.6 years (range 36-77 years) in cases and 56.7 years

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Table 2. Oligonucleotide Sequence Used for Genotyping

Gender	SNPs	Primers	Sequences
IL-7R	rs1494555	1st	5'-ACGTTGGATGTTTCCAGTTAAACCTGAGGC-3'
		2nd	5'-ACGTTGGATGCACCACAAAGTCATTGGCTC-3'
		Extension	5'-CCGCTCCTTCCCGATAGA -3'
IL-7R	rs7737000	1st	5'-ACGTTGGATGCATCACACTTGCAAAAGAAG-3'
		2nd	5'-ACGTTGGATGTTTCATCCTTTTCCTGGCGG -3'
		Extension	5'-GTTGCCTGGCGGTAAGCTACATC -3'
IL-13	rs20541	1st	5'-ACGTTGGATGCCAGTTTGTAAAGGACCTGC-3'
		2nd	5'-ACGTTGGATGTGATGCTTTCGAAGTTTCAG -3'
		Extension	5'-GTGAGGCTTTCGAAGTTTCAGTTGAAC-3'
IL-15	rs1057972	1st	5'-ACGTTGGATGTACCAATGCTGCAGGTCAAC-3'
		2nd	5'-ACGTTGGATGGTCAATGAGAGCCAGTAGTC-3'
		Extension	5'-AGGGAGTCAGTGGTTCCACAC-3'
IL-15	rs2857261	1st	5'-ACGTTGGATGGACGACCTTTAAGGGAAATTC-3'
		2nd	5'-ACGTTGGATGCCGTGGCTTTGAGTAATGAG-3'
		Extension	5'-GGCGTAATGAGAATTTCGGTAAGAA-3'

Table 2. HWE Pearson's P in Cases and Controls

Genes	rs	HWE Pearson's P
IL-7R	rs1494555	NA
IL-7R	rs7737000	0.27235
IL-13	rs20541	0.87297
IL-15	rs1057972	0.053
IL-15	rs2857261	0.05179

(range 33-80 years) in controls. All participators were non-smokers. The controls were matched with the cases by age and sex. The study protocol was approved by the Ethical Review Committee at Zhejiang Cancer Hospital. Informed consent was provided by all cases and controls.

DNA preparation and genotyping

All subjects were genotyped for rs1494555, rs7737000, rs20541, rs1057972 and rs2857261. DNA was isolated from whole blood using the AxyPrep Blood Genomic DNA Miniprep kit (Axygen Biosciences, Union City, CA, USA).Genotyping was performed by using the SEQUENOM MassARRAY MALDI-TOF mass spectrometry platform (Sequenom, San Diego, CA, USA). Primers for PCR and single base extension were designed using the Assay Designers software version 3.0 (Sequenom) and was processed following standard protocols for iPLEX chemistry. Primers were synthesized by Sangon Biotech (Shanghai, China) (Table 1).

Statistical analysis

Hardy-Weinberg equilibrium (HWE) testing was carried out for all five SNPs. Single marker differences were accessed using Pearson's chi-squared tests, as well as the genotypes in cases and controls. Data of odds ratio (OR) and 95% confidence intervals (CIs) were calculated. Haploview software version 4.1 was used to analyze the association between haplotypes and the disease.

Results

All 400 subjects were genotyped (200 with NSCLC, 200 healthy controls). Data for IL-15 rs2857261 status were available in 199 cases and 199 controls. There was no evidence of deviation from Hardy- Weinberg equilibrium in each gene (Table 2). There was no significant difference for the five markers (rs1494555, rs7737000, rs20541, rs1057972 and rs2857261) in allele or genotype frequencies between NSCLC patients and controls, adenocarcinomas or squamous cell carcinomas and controls (Tables 3 and 4).

Discussion

We undertook the present study to investigate the association between NSCLC and polymorphisms of IL-7R, IL-13 and IL-15 in non-smoking Chinese population. Our findings show that none of IL-7R rs1494555 and rs7737000, IL-13 rs20541and IL- 15 rs2857261 and rs1057972 variant contributed to the susceptibility of NSCLC in non-smoking Chinese population. The results were disconcordant with that of Van et al's study (2009) .

The tumorigenesis is a complex process involving not only growth of the primary tumor and tumor stem cells, but also communication with surrounding tissues and cells (Vetvicka and Vetvickova, 2011). Immune cells and tumor cells play a key role in lung cancer immunity by secretion of cytokines and developing type 2 cell-mediated immune response (Terabe et al., 2004; Wei et al., 2004). IL-7 is produced mainly by thymus (Namen et al., 1988; Wiles et al., 1992), skin (Heufler et al., 1993), bone marrow, intestinal epithelium (Watanabe et al., 1995), stromal cells (Fry et al., 2005), and play a importantly role in the development and maturation of lymphocytes in the thymus and their maintenance in the periphery (Schluns et al., 2000). The IL-7R, IL-7 ligand receptor, could decrease differentiated Helper T lymphocyte-17 (TH17) cells susceptible to apoptosis (Llano et al., 2001) and its expression level and function change could affect the number and function of T cells (Juffroy et al., 2010; Liu et al., 2010). In vitro study, IL-7R expression has been shown in neoplastic lung cell lines (Cosenza et al., 2002). In vivo, IL-7 and IL-7R were able to induce cyclin D1 gene (nuclear accumulation of cyclin D1 induceing uncontrolled proliferation in normal cells, which could facilitate the development of invasive cancer (Gautschi et al., 2007)) expression via AP1 (a sequence-specific transcription factor has association with proliferation (Ming et al., 2009)) dependent pathway to promote cell growth in lung cancer. Moreover, NSCLC patients with

Table 3. Allele Distribution in Never-smoking Chinese with NSCLC and Controls

Gene allele	Controls	NSCLC[b] N=200			ADC[b] N=145			SCC[b] N=55		
	N=200 n(%)	n (%)	p value	OR(95% CI)	n (%)	p value	OR(95% CI)	n (%)	p value	OR(95% CI)
IL-7R rs1494555										
A	0(0)	1(0.3)						1(0.9)		
T	188(47.0)	190(47.5)			142(49.0)			48(43.6)		
C	212(53.0)	209(52.2)	0.5969	-	148(51.0)	0.6099	1.082 (0.799-1.464)	61(55.5)	0.1392	-
IL-7R rs7737000										
T	70(17.5)	78(19.5)			64(22.1)			14(12.7)		
C	330(82.5)	322(80.5)	0.4664	1.142 (0.799-1.632)	226(77.9)	0.1343	1.335 (0.914-1.950)	96(87.3)	0.232	0.688 (0.371-1.274)
IL-13 rs20541										
T	121(30.2)	131(32.8)			97(33.4)			34(30.9)		
C	279(69.8)	269(67.2)	0.4466	1.123 (0.833-1.514)	193(66.6)	0.3724	1.159 (0.838-1.602)	76(69.1)	0.8941	1.032 (0.653-1.629)
IL-15 rs1057972										
A	187(46.8)	189(47.2)			133(45.9)			56(50.9)		
T	213(53.2)	211(52.7)	0.8873	1.02 (0.773-1.347)	157(54.1)	0.8174	0.965 (0.713-1.307)	54(49.1)	0.4392	1.181 (0.774-1.802)
IL-15 rs2857261										
A	186(46.7)	189(47.5)			134(46.2)			55(50.9)		
G	212(53.3)	209(52.5)	0.8313	1.031 (0.780-1.362)	156(53.8)	0.8912	0.979 (0.723-1.326)	53(49.1)	0.4391	1.183 (0.773-1.810)

NSCLC, Non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; [b]compared with controls

Table 4. Genotypes in Lung Cancer Cases and Controls and Their Association with Risk of Lung Cancer

Gene allele	Controls	NSCLC[b] N=200			ADC[b] N=145			SCC[b] N=55		
	N=200 n(%)	n (%)	Chi^2	p value	n (%)	Chi^2	p value	n (%)	Chi^2	p value
IL-7R rs1494555										
AC	0(0)	1(0.5)						1(1.8)		
CC	62(31.0)	57(28.5)			41(28.3)			16(29.1)		
TT	50(25.0)	48(24.0)			38(26.2)			10(18.2)		
CT	88(44.0)	94(47.0)	1.4487	0.6942	66(45.5)	0.3003	0.8606	28(50.9)	4.9927	0.1723
IL-7R rs7737000										
CC	139(69.5)	130(65.0)			88(60.7)			42(76.4)		
TT	9(4.5)	8(4.0)			7(4.8)			1(1.8)		
CT	52(26.0)	62(31.0)	1.2371	0.5387	50.34.5)	3.0569	0.2169	12(21.8)	1.378	0.5021
IL-13 rs20541										
CC	100(50.0)	87(43.5)			60(41.4)			27(49.1)		
TT	21(10.5)	18(9.0)			12(8.3)			6(10.9)		
CT	79(39.5)	95(47.5)	2.6058	0.2717	73(50.3)	4.0256	0.1336	22(40.0)	0.0167	0.9917
IL-15 rs1057972										
AA	52(26.0)	46(23.0)			34(23.4)			12(21.8)		
TT	65(32.5)	57(28.5)			46(31.7)			11(20.0)		
AT	83(41.5)	97(48.5)	1.9808	0.3714	65(44.8)	0.4523	0.7976	32(58.2)	5.2239	0.0734
IL-15 rs2857261										
AG	84(42.2)	95(47.7)			64(44.1)			31(57.4)		
AA	51(25.6)	47(23.6)			35(24.1)			12(22.2)		
GG	64(32.2)	57(28.6)	1.2442	0.5368	46(31.7)	0.1519	0.9269	11(20.4)	4.3475	0.1138

NSCLC, Non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; [b]compared with controls

high expression of IL-7 and IL-7R were more likely to have poor prognosis (Ming et al., 2009). However, in our study, we were not found association between polymorphisms of IL-7R and NSCLC risk, and those suggested that the SNPs of two locus (rs1494555 and rs7737000) in IL-7R were not direct effect in NSCLC progression. But it is unknown whether or not IL-7R has synergistic effect with other carcinogenic agents, such as cigarette smoke exposure, in NSCLC development in Chinese population, and more studies need to be conducted to confirm this relationship.

Interleukin (IL)-13, a T-helper type 2 cytokine can block tumor rejection or promote tumor recurrence (Wynn, 2003) by mediate humoral immune responses (Ellyard et al., 2007), was identified by molecular cloning in activated human T lymphocytes (Murray et al., 2000), and its gene position was mapped on chromosome 5q 23–31 (Kaye et al., 2004). IL-13 is important in the generation of cell- mediated immunity (McFarlane et al., 2011) by mediates a variety of different effects on various cell types including B cells, monocytes, natural killer cells, endothelial cells, and fibroblasts (Joshi et al., 2006) and inducts B cell secreteing IgE (Murray et al., 2000). Moreover, IL-13 can inhibit tumor immunosurveillance by deviation of immune response from type 1 helper T cells to type 2 helper T cells (Wynn, 2003). In vitro, IL- 13

has the capacity to drive the clinical features of airways disease and contributes in pathogenesis of respiratory syncytial virus (Zhou et al., 2006; Brightling et al., 2010). The associations between different SNPs of IL-13 and lung diseases or atopy and allergy in the broader sense have been reported (Graves et al., 2000; Chiaramonte et al., 2001; Lee et al., 2007). But in Iranian population, the SNPs in IL-13 are not confer susceptibility to lung cancer (Sameni et al., 2009). Likewise, our study revealed the polymorphisms of IL-13 rs20541 were not associated with NSCLC risk in non-smoking Chinese population. In contrast, In African-Americans, the SNPs in IL-13 rs20541 were associated with risk of lung cancer development. These demonstrate again that ethnice effect was the main role in genetic polymorphism.

Interleukin-15 (IL-15) is a cytokine with ionterleukin-2-like activity. IL-15 might enhanced the antitumor responese by induces T-cell proliferation (Bamford et al., 1994; Bruton et al., 1994; Grabstein et al., 1994), enhances natural killer (NK) cell cytotoxicity, upregulates production of NK cell-derived cytokines, including interferon-γ, granulocyte/macrophage-colony-stimulating factor and tumor necrosis factor-α (Carson et al., 1994; Takeuchi et al., 2001; Kobayashi et al., 2005) and stimulates proliferation and differentiation of B cells activated with anti-immunoglobulin M (Armitage et al., 1995). In addition, IL- 15 stimulates locomotion and chemotaxis of normal T cells (Wilkinson et al., 1995). IL-15 has potential for the immunotherapy of lung cancer (Gamero et al., 1995; Takeuchi et al., 1996). Adjuvant IL-15 therapy has been shown to result in tumor regression in a murine lung tumor model (Chapoval et al., 1998). But in our study, it was not associtation between SNPs of rs2857261 and rs1057972 in IL-15 and NSCLC (adenocarcinoma or squamous cell carcinoma) risk. The reasons maybe were that IL-15 has a potentially interaction with cigarette smoke, just like shown among the Caucasian women: IL-15 rs2857261 was associated with a decreased risk of NSCLC among never smokers and an increased risk among smokers (Van et al., 2009).

To sum up, our results were remarkably different findings from African-Americans (Van et al., 2009), but concordant with Caucasian (Van et al., 2009) and Iranian (Sameni et al., 2009). The results maybe were connected with following two points: Firstly, in African-Americans, inverstigators were not analyzed association between polymorphisms and Lung cancer risk according to smoking state, which make it become difficulty to conclude the interaction between cigarette exposure and IL-7R, IL-13 and IL-15 expression in the prediction of lung cancer risk. Furthermore, Iran and China were located in Asia, environmental factors may play an important role in genetic polymorphism. Secondly, we believe this primarily be attributed to the significantly distinct genetic background of Asian populations from western populations, which was implicated in several published studies (Cox et al., 2001; Hoffmann et al., 2002; Hassan et al., 2003; Ness et al., 2004; Rady et al., 2004).

To conclude, the study showed no relationship between polymorphisms of the five SNPs (IL-7R rs1494555 and rs7737000, IL-13 rs20541, IL-15 rs2857261 and rs1057972) and NSCLC in Chinese populations. Based on our results, we deduced that the mechanism of the association between IL-7R, IL-13, IL-15 and NSCLC in Chinese patients can be explained more by the interaction effect of cigarette smoke exposure. Next, we will undertake a study to investigate the interaction effect between cigarette smoke exposure and polymorphisms of interleukin in Chinese Population and hope to find further evidence to demonstrate our deduction.

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