Int J Clin Exp Med 2015;8(9):17006-17014
www.ijcem.com /ISSN:1940-5901/IJCEM0013283

Original Article

IGFBP3 polymorphisms and risk of esophageal cancer in a Chinese population

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Received July 22, 2015; Accepted September 3, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: Esophageal cancer is the sixth leading cause of cancer-related deaths worldwide. It is very aggressive with a poor prognosis. Besides environmental risk factors, genetic factors might contribute to the esophageal cancer carcinogenesis. To evaluate the association between the risk of esophageal squamous cell carcinoma (ESCC) and genetic variants in *IGFBP3*, we conducted a hospital-based case-control study to assess the genetic effects of these SNPs. A total of 380 esophageal squamous cell carcinoma (ESCC) cases and 380 controls were recruited for this study. The genotypes were determined using a matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). The *IGFBP3* single nucleotide polymorphisms (SNPs) rs2270628 C>T, rs10282088 C>A, and rs3110697 G>A were associated with a significantly decreased risk of ESCC. However, our results were obtained with a limited sample size. To confirm the current findings, larger studies with other ethnic populations are required.

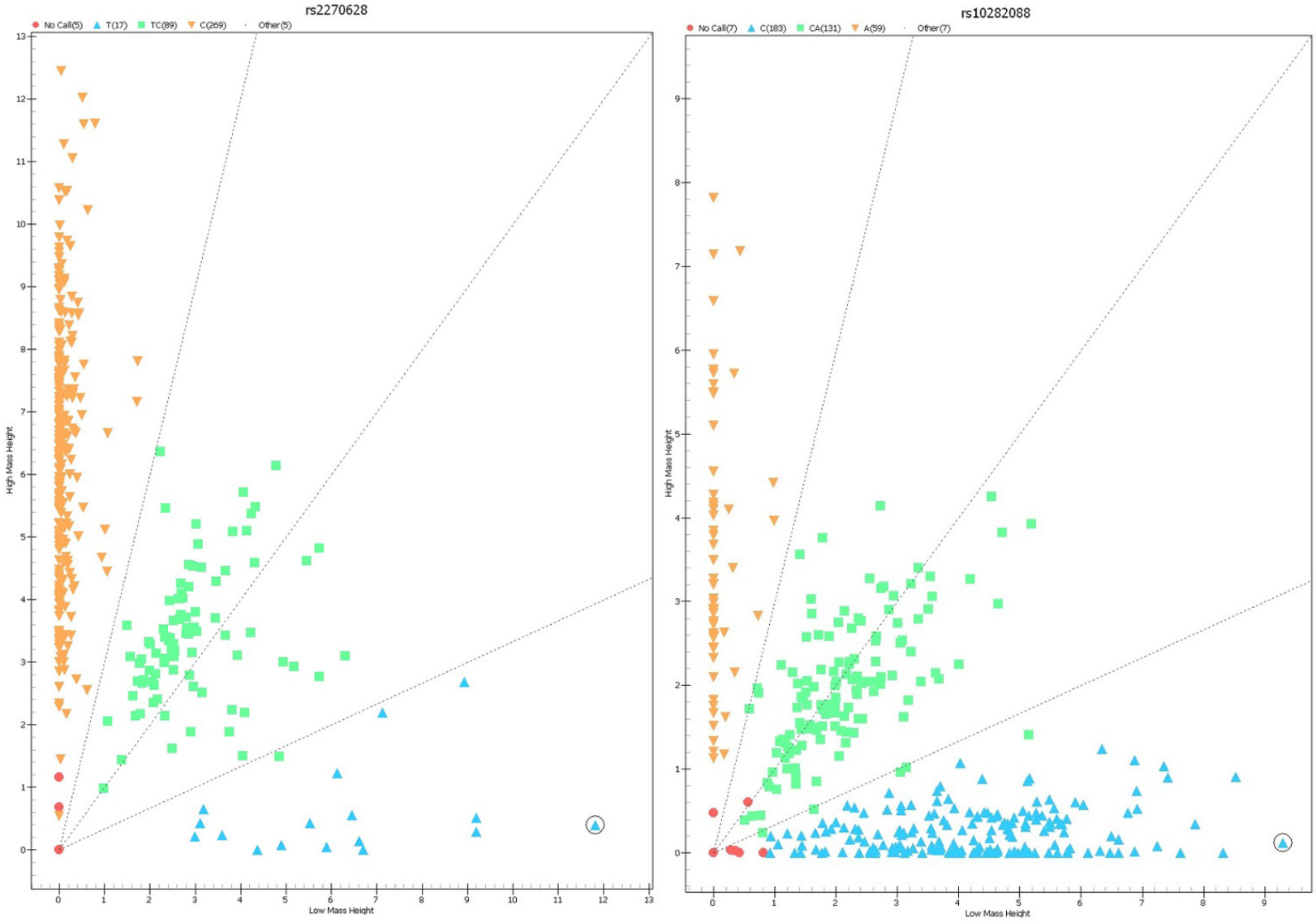
Keywords: Esophageal squamous cell carcinoma, *IGFBP3*, SNPs, molecular epidemiology

Introduction

Esophageal cancer as an aggressive carcinoma is the sixth most common diagnosed cancer in China in 2011 [1]. Esophageal cancer includes two major histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the most frequent subtype of esophageal cancer and accounts for more than 90% of cases [2]. The major risk factors for ESCC are not well understood now. The environmental exposure factors, such as tobacco and alcohol, have been linked to ESCC carcinogenesis, but only a subset of individuals exposed to the environmental risk factors would develop ESCC, it suggested that substantial genes play an important role in ESCC carcinogenesis, and genetic polymorphisms might explain individual differences in ESCC susceptibility partly [3].

The insulin-like growth factor (IGF) family includes interacting ligands, receptors, and IGF-binding proteins (IGFBPs). Insulin-like growth factor-1 (IGF-1) plays a pivotal role in mitogenesis and antiapoptosis as a potent mitogen [4]. IGF binding protein-3 (IGFBP-3) is the major binding protein of IGF-1 and regulates the biological activity of IGF-1, and it can antiproliferative and proapoptotic by inhibiting growth [5]. Both of IGF-1 and IGFBP-3 are produced by the liver primarily [5]. Epidemiological studies indicated that high levels of IGF-I and low levels of IGFBP-3 are associated with an increased risk of several common cancers, including prostatic cancer, colorectal cancer, lung cancer and breast cancer [6-10]. It seems that IGFBP-3 has two potentially opposing roles in the effect of malignancies; however, the association between genetic variants of *IGFBP-3* and common cancers risk was also inconclusive.

Due to the biological and pathological significance of *IGFBP-3*, functional genetic variations in the *IGFBP-3* may contribute to the development of ESCC. To investigate the association


rs2270628
No Call(5)
T(17)
TC(89)
C(269)
Other(5)
High Mass Height
Low Mass Height
rs10282088
No Call(7)
C(183)
CA(131)
A(59)
Other(7)
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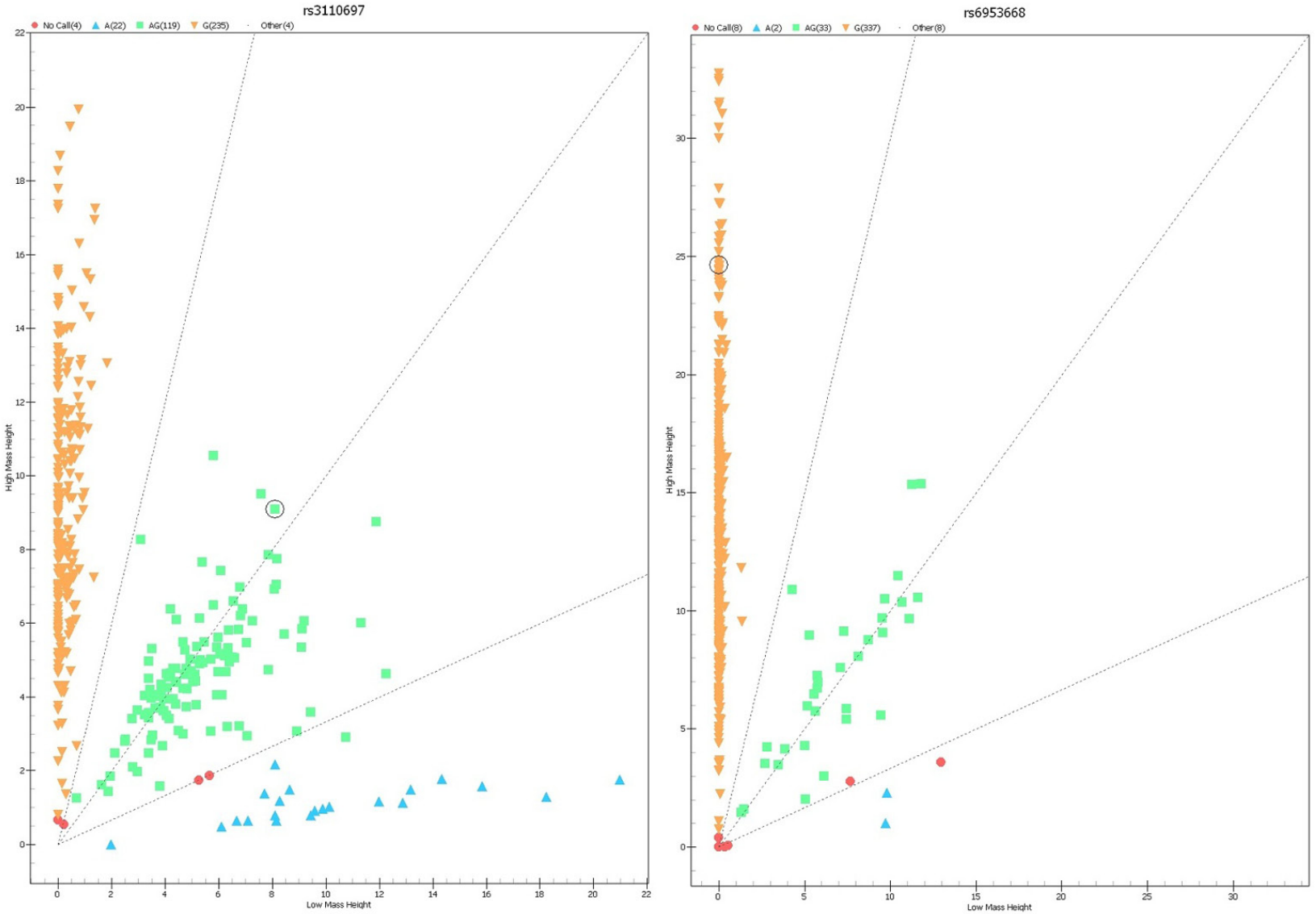

Figure 1. Genotyping of *IGFBP3* rs2270628 C>T, rs10282088 C>A, rs3110697 G>A and rs6953668 G>A.

between the *IGFBP-3* genotypes and ESCC susceptibility, we selected four single nucleotide polymorphisms (SNPs) of *IGFBP-3* with 380 ESCC cases and 380 controls in a Chinese population.

Materials and methods

Study population

Between October 2008 and November 2009, a total of 380 eligible ESCC cases and 380 control subjects were consecutively recruited from the Affiliated People's Hospital of Jiangsu University and Affiliated Hospital of Jiangsu University (Jiangsu, China). All esophageal cancer cases were confirmed as ESCC through pathological diagnosis. Patients who previously had cancer or any metastasized cancer, radiotherapy or chemotherapy were excluded. The control subjects were non-cancer patients and matched to the cases with regard to sex and age (±5 years); most of them were traumatic patients.

We obtain the information of patients on demographic data and related risk factors, such as age, gender, smoking and alcohol consumption by using a pre-tested questionnaire through trained interviewers. Individuals who smoked once per day for more than one year were defined as smokers. Subjects who consumed three or more alcoholic drinks per week for over six months were considered to be alcohol drinkers. After the interview, a 2 ml venous blood sample was collected from each subject.

Genotyping

Each blood sample was collected by vacutainer and then transferred to test tube with ethylenediaminetetraacetic acid (EDTA). Genomic DNA was extracted from whole blood using the QIAamp DNA Blood Mini kit (Qiagen, Berlin, Germany). Genotyping was conducted by matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). Sample DNA (10 ng) was amplified by PCR according to the manufacturer's recommendations. The rs2270628, rs10282088, rs3110-697 and rs6953668 SNPs genotyping work were performed using the MassArray system (Sequenom, San Eiego, CA, USA) by MALDI-TOF-MS according to the manufacturer's instructions. Completed genotyping reactions were spotted onto a 384-well spectroCHIP (Sequenom) using a MassARRAY Nanodispenser (Sequenom). The genotype calling was performed in real time with MassARRAY RT software version 3.1 (Sequenom, San Diego, California) and analyzed using the MassARRAY Typer software version 4.0 (Sequenom, San Diego, California) (**Figure 1**). For quality control, approximately 4% of samples underwent repeated genotyping randomly, and the results were concordant.

Statistical analysis

Differences between ESCC cases and control subjects in the distributions of the selected variables, demographic characteristics, risk factors and genotypes of the *IGFBP-3* rs227-0628 C>T, rs10282088 C>A, rs3110697 G>A and rs6953668 G>A variants were evaluated using Student's test and the X^2 test. The associations between the four SNPs and the riks of ESCC were estimated by calculating odds ratios(ORs) and their 95% confidence intervals (95% CIs) through logistic regression analyses for crude ORs and adjusted ORs when adjusting for age, gender, tobacco and drinking status. The Hardy-Weinberg equilibrium (HWE) for genotype distribution in controls was tested using a goodness-of-fit χ^2 test. All statistical analyses were conducted using SAS 9.1.3 software (SAS Institute, Cary, NC, USA).

Results

Population characteristics

In **Table 1**, there are total 380 ESCC cases and 380 controls. The mean age was 62.84 years (SD, 8.5 years) in ESCC subjects, and 63.44 years (SD, 7.19 years) in controls. There were no significant differences in age, sex and alcohol using between the cases and controls (P = 0.056, P = 0.346 and P = 0.183), but ESCC patients were more to be smokers than controls (P = 0.014).

Associations between IGFBP3 rs2270628 C>T, rs10282088 C>A, rs3110697 G>A and rs6953668 G>A polymorphisms and risk of ESCC

The genotype distributions of *IGFBP3* rs227-0628 C>T, rs10282088 C>A, rs3110697 G>A and rs6953668 G>A in the cases and controls

Table 1. Distribution of selected demographic variables and risk factors in ESCC cases and controls

Variable	Cases (n = 380)		Controls (n = 380)		P[a]
	n	%	n	%	
Age (years)					0.056
< 60	142	37.4	117	30.8	
≥ 60	238	62.6	263	69.2	
Age, years, mean ± SD	62.84 (±8.50)		63.44 (±7.19)		0.296[b]
Sex					0.346
Men	269	70.8	257	67.6	
Women	111	29.2	123	32.4	
Tobacco use					0.014
Never	220	57.9	253	66.6	
Ever	160	42.1	127	33.4	
Alcohol use					0.183
Never	253	66.6	270	71.1	
Ever	127	33.4	110	28.9	
Lymph node metastasis					
LN meta (+)	85	23.9			
LN meta (-)	270	76.1			
TNM stages					
I	51	15.6			
II	202	62.0			
III	60	18.4			
IV	13	4.0			

[a]Two-sided χ^2 test; [b]Student t test.

are summarized in **Table 2**. When the rs2270628 CC homozygote genotype was used as the reference group, the association between CT genotype and ESCC risk was reduced (adjusted OR = 0.70, 95% CI = 0.50-0.97, P = 0.033). Compared with the rs10282088 CC homozygote genotype, the CA genotype reduced the risk of ESCC (adjusted OR = 0.54, 95% CI = 0.39-0.74, P = 0.0002). In the dominant model, the rs10282088 CA/AA variants were associated with decreased risk of ESCC (adjusted OR = 0.63, 95% CI = 0.47-0.85, P = 0.0025). The GA genotype reduced the risk of ESCC (adjusted OR = 0.63, 95% CI = 0.46-0.86, P = 0.003), when compared with the rs3110697 GG genotype, and in the dominant model, rs3110697 GA/AA variants were decreased the risk of ESCC (adjusted OR = 0.65, 95% CI = 0.48-0.87, P = 0.004). When the G allele was used as the reference group, the A allele was associated with a significantly decreased risk of ESCC.

There was no significantly difference in the genotype and allele distributions between the ESCC patients and control subjects for the rs6953668 G>A variant (P = 0.355).

Discussion

There were few researches on the relationship between *IGFBP3* polymorphisms and the risk of ESCC. We therefore investigated the association between *IGFBP3* rs2270628 C>T, rs10282088 C>A, rs3110697 G>A and rs6953668 G>A SNPs and and the risk of ESCC in Chinese population through a hospital-based case-control study. Multivariable logistic analysis revealed that *IGFBP3* rs2270628 C>T, rs10282088 C>A and rs3110697 G>A associated with the decreased risk of ESCC. However, no significant association was observed between *IGFBP3* rs6953668 G>A polymorphism and the risk of ESCC.

IGFBP3 locates on chromosome 7p13. IGFBP3 is known to bind more than 90% of IGF-1 in circulating blood and regulate the bioavailability of insulin and IGFs by modulating their interactions with signaling receptors [11, 12]. IGFBP3 prevents tumor cell mitosis by inhibiting the combination of IGF-1 and it's receptors [13], it also has independent antiproliferative and proapoptotic effects [14]. Epidemiological studies suggested that high circulating levels of IGFBP3 might reduce the risk of some cancers, such as prostate caner, colorectal cancer, breast cancer and lung cancer [15]. Zhao *et al.* reported that low *IGFBP3* expression might reduce overall survival in ESCC cases [16].

A previous study suggested that *IGFBP3* rs2270628 C>T was associated with both higher ovarian cancer risk and increased IGF1 plasma levels [17]. The other studies showed *IGFBP3* rs2270628 C>T was not correlated with renal cancer [18], breast cancer [19] and prostate cancer [20]. Also included in our investigation are the SNPs *IGFBP3* rs3110697 G>A and *IGFBP3* rs10282088 C>A. Several prior study suggested that there was null association between *IGFBP3* rs3110697 G>A polymor-

Table 2. Logistic regression analyses of associations between *IGFBP3* polymorphisms and risk of ESCC

Genotype	Cases (n = 380)		Controls (n = 380)		Crude OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*
	n	(%)	n	(%)				
IGFBP3 rs2270628 C>T								
CC	268	72.04	252	66.49	1.00		1.00	
CT	88	23.66	116	30.61	**0.71 (0.52-0.99)**	**0.042**	**0.70 (0.50-0.97)**	**0.033**
TT	16	4.30	11	2.90	1.37 (0.62-3.00)	0.435	1.39 (0.63-3.06)	0.416
TT vs. CT vs. CC						0.074		
CT/TT	104	27.96	127	33.51	0.77 (0.56-1.05)	0.100	0.76 (0.56-1.04)	0.084
CC/CT	356	95.70	368	97.10	1.00		1.00	
TT	16	4.30	11	2.90	1.50 (0.69-3.29)	0.306	1.53 (0.70-3.36)	0.286
C allele	624	83.87	620	81.79	1.00		—	
T allele	120	16.13	138	18.21	0.86 (0.66-1.13)	0.287	—	—
IGFBP3 rs10282088 C>A								
CC	181	48.92	136	37.57	1.00		1.00	
CA	130	35.14	183	50.55	**0.53 (0.39-0.73)**	**< 0.0001**	**0.54 (0.39-0.74)**	**0.0002**
AA	59	15.95	43	11.88	1.03 (0.66-1.62)	0.895	1.02 (0.65-1.60)	0.940
AA vs. CA vs. CC						**< 0.001**		
CA/AA	189	51.08	226	62.43	**0.63 (0.47-0.84)**	**0.0020**	**0.63 (0.47-0.85)**	**0.0025**
CC/CA	311	84.05	319	88.12	1.00		1.00	
AA	59	15.95	43	11.88	1.41 (0.92-2.15)	0.113	1.38 (0.90-2.12)	0.137
C allele	492	66.49	455	62.85	1.00		—	
A allele	248	33.51	269	37.15	0.85 (0.69-1.06)	0.145	—	—
IGFBP3 rs3110697 G>A								
GG	234	62.73	195	52.00	1.00		1.00	
GA	117	31.37	156	41.60	**0.63 (0.46-0.85)**	**0.003**	**0.63 (0.46-0.86)**	**0.003**
AA	22	5.90	24	6.40	0.76 (0.42-1.40)	0.386	0.77 (0.42-1.42)	0.396
AA vs. GA vs. GG						**0.010**		
GA/AA	139	37.27	180	48.00	**0.64 (0.48-0.86)**	**0.003**	**0.65 (0.48-0.87)**	**0.004**
GG/GA	351	94.10	351	93.60	1.00		1.00	
AA	22	5.90	24	6.40	0.92 (0.51-1.67)	0.775	0.91 (0.50-1.67)	0.767
G allele	585	78.42	546	72.80	1.00		—	
A allele	161	21.58	204	27.20	**0.74 (0.58-0.93)**	**0.012**	—	—
IGFBP3 rs6953668 G>A								
GG	335	90.54	345	90.79	1.00		1.00	
GA	33	8.92	35	9.21	0.97 (0.59-1.60)	0.908	1.01 (0.61-1.67)	0.976
AA	2	0.54	0	0.00	—	0.980	—	0.979
AA vs. GA vs. GG						0.355		
GA/AA	35	9.46	35	9.21	1.03 (0.63-1.68)	0.907	1.07 (0.65-1.76)	0.778
GG/GA	368	99.46	380	100.00	1.00		1.00	
AA	2	0.54	0	0.00	—	0.980	—	0.979
G allele	703	95.00	725	95.39	1.00		—	
A allele	37	5.00	35	4.61	1.09 (0.68-1.75)	0.721	—	—

[a]Adjusted for age, sex, smoking and drinking status; Bold values are statistically significant ($P < 0.05$).

phism and the risk of prostate cancer [20-23], breast cancer [21], endometrial cancer [24], ovarian cancer [17] and colorectal cancer [10]. Nevertheless, Birmann et al. [25] reported that

IGFBP3 rs3110697 G>A polymorphism was associated with the risk of myeloma. In the current sutdy, our findings showed that the *IGFBP3* rs2270628 CT genotype, *IGFBP3* rs3110697 GA genotype and A allele associated with the decreased risk of ESCC cases, which was consistent with previous study [25]. Maybe, *IGFBP3* gene plays the different roles in different malignances, even the same SNP. This study is the first to evaluate possible correlations of the functional SNP rs10282088 C>A in the *IGFBP3* gene with ESCC in a high-risk Chinese population. Our findings suggested that *IGFBP3* rs10282088 C>A polymorphism was also associated with the decreased risk of ESCC. For in present study, only 380 ESCC cases and 380 controls were recruited in analysis, which might set a limit to the statistical power to obtain a real influence. In the future, larger sample size studies with an appropriately methodological quality should be conducted, to confirm or refute the association of *IGFBP3* functional polymorphisms and ESCC risk.

Several limitations of this study need to be pointed out. First, the sample size of this study was moderate. Second, because it was a hospital-based case-control study, the samples might not reflect the true genoytpe distribution of the Chinese population, so the inherent selection bias was unavoidable. Third, this experiment was lack of functional considerations. Finally, the *IGFBP3* SNPs should be associated with different risk in different ethnic groups and under different environmental exposures, because ESCC risk is likely to be influenced by gene-gene and gene-environment interactions.

In conclusion, our study results demonstrate that IGFBP3 rs2270628 C>T, rs10282088 C>A and rs3110697 G>A polymorphisms may reduce the risk of ESCC. However, further studies are needed to confirm the results of this preliminary study.

Acknowledgements

This study was supported in part by Jiangsu University Clinical Medicine Science and Technology Development Fund (JLY20140012).

Disclosure of conflict of interest

None.

Abbreviations

CI, confidence interval; OR, odds ratio; HWE, Hardy-Weinberg equilibrium; ESCC, esophageal squamous cell carcinoma; IGF, insulin-like growth factor; EAC, esophageal adenocarcinoma; IGFBPs, insulin-like growth factor-binding proteins.

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