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Genetic variations in the IGF-IGFR-IGFBP axis confer susceptibility to lung and esophageal cancer

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ABSTRACT. Recent evidence suggests that genetic variations in the insulin-like growth factor (IGF)-IGF receptor (IGFR)-IGF binding proteins (IGFBP) axis may impact an individual's susceptibility to lung and esophageal cancer, but individually published results are inconclusive. Our meta-analysis aimed at providing a more precise estimation of these associations. An extensive literature search was conducted for appropriate articles published before May 15th, 2013. This meta-analysis was performed using the STATA 12.0 software. The crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each study and then pooled using a random effect model. Twelve case-control studies were included with a total of 2686 lung cancer patients, 771 esophageal cancer patients, and 5918 healthy controls. Our meta-analysis indicated that genetic variations in the IGF-IGFR-IGFBP axis may be associated with increased risk of lung and esophageal cancer, especially among Asian populations. Further subgroup analysis by gene type indicated that common polymorphisms in the IGF1/2, IGF-1R, and IGFBP-3/5 genes may be the main determinants for lung cancer risk, while IGF-1, IGF-1R, and IGFBP-1 genetic polymorphisms may increase the risk of esophageal

cancer. The current meta-analysis suggests that genetic variations in the IGF-IGFR-IGFBP axis confer susceptibility to lung and esophageal cancer, especially among Asian populations. Common polymorphisms in the IGF-IGFR-IGFBP axis may serve as useful biomarkers for predicting the risk of lung and esophageal cancer.

Key words: Lung cancer; Esophageal cancer; Polymorphism; Insulin-like growth factor; Meta-analysis

INTRODUCTION

Cancer remains an important public health problem in both developed and developing countries (Braithwaite et al., 2012). In 2008, an estimated 7.6 million people died of cancer worldwide, accounting for 13% of the global mortality (Jemal et al., 2011). It is generally recognized that cancer is a multifactorial disease caused by complex interactions between environmental and genetic factors (Ponder, 2001). However, the exact cellular and molecular mechanisms leading to the development of cancer remain unclear. Recently, a large number of candidate genes responsible for the genesis of various cancers have been identified (Vogelstein and Kinzler, 2004). Determination of single nucleotide polymorphisms (SNPs) in candidate genes may prove reliable in predicting the genetic risk of cancer, and might thus contribute to the primary prevention of this condition (Tabor et al., 2002).

The insulin-like growth factor (IGF) signaling pathway plays an important role in regulating cellular proliferation and apoptosis (Pollak et al., 2004). The biological activities of the IGFs are modulated by IGF-binding proteins (IGFBPs) and mediated by IGF receptors (IGFRs) (Yi et al., 2005). Emerging interest in the IGF-IGFR-IGFBP axis and its effect on carcinogenesis has recently increased because high IGF-1 serum concentrations were associated with an increased risk of lung, gastric, esophageal, breast, prostate, and colorectal cancers (Furstenberger and Senn, 2002). Therefore, it was hypothesized that genetic variations in the IGF-IGFR-IGFBP axis might be associated with cancer risk. A recent meta-analysis of 17 case-control studies by Chen et al. (2008) assessed the association between the IGF-1 (CA)19 repeat polymorphism and the risk of prostate, breast, and colorectal cancers. Their results indicated that the IGF-1 (CA)19 polymorphism may not be a major determinant of susceptibility to cancer. Because this previous meta-analysis did not provide convincing and reliable evidence in associating the IGF-IGFR-IGFBP axis to the risk of cancer risk, we performed a meta-analysis of published data to provide a more comprehensive and reliable conclusion on the associations between genetic variations in the IGF-IGFR-IGFBP axis and susceptibility to lung and esophageal cancer.

MATERIAL AND METHODS

Search strategy and selection criteria

An extensive literature search for relevant studies was conducted in the PubMed, Embase, Web of Science, Cochrane Library, and CBM databases from inception through May 15th, 2013. We used the following keywords and MeSH terms: “lung cancer”, “esophageal cancer”, “IGF”, “IGFR”, “IGFBP”, and “polymorphism”. There was no language restriction. Manual searches of

reference lists from potentially relevant articles were also performed to identify other potential studies. To be included in the analysis, these studies had to meet the following criteria: (1) case-control studies focusing on the associations between genetic variations in the IGF-IGFR-IGFBP axis and susceptibility to lung or esophageal cancer; (2) all patients diagnosed with lung or esophageal cancer were confirmed by histopathological examinations; (3) published data about genotype frequencies of polymorphisms was sufficient; (4) the genotype distribution in healthy controls conformed to Hardy-Weinberg equilibrium (HWE). Studies were excluded if they did not meet all of these inclusion criteria. Any disagreements were resolved by discussions and subsequent consensus.

Data extraction

Two authors independently extracted data from eligible studies by using a standardized form. The following information was collected prospectively: surname of first author, year of publication, source of publication, country of origin, ethnicity, language of publication, study type, total number of subjects, source of cases and controls, pathological type, gene type, DNA sample, SNP detection method, genotype frequencies, and evidence of HWE in controls. In cases of conflicting evaluations, disagreements of inconsistent data from the eligible studies were resolved through discussions and careful reexaminations of the full text by the authors.

Quality assessment

The quality of studies included was assessed independently by two authors (W.H.Z. and Y.F.Z.) based on the STROBE quality score systems (da Costa et al., 2011). Forty assessment items related to quality appraisal were used in this meta-analysis with scores ranging from 0 to 40. The included studies were classified into three levels based on their scores: low quality (0-19), moderate quality (20-29), and high quality (30-40), respectively. Disagreements of STROBE scores of the included studies were resolved through a comprehensive reassessment by the authors.

Statistical analysis

The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated under five genetic models: allele model (mutant [M] allele versus wild [W] allele), dominant model (WM + MM versus WW), recessive model (MM versus WW + WM), homozygous model (MM versus WW), and heterozygous model (MM versus WM). The significance of the pooled estimate was determined using the *Z* test. Genotype distributions in the control subjects were tested for HWE by the chi-squared test. We estimated the degree of heterogeneity among studies using Cochran's *Q*-statistic, which was considered significant at $P < 0.05$ (Jackson et al., 2012). The I^2 test was also used to quantify the heterogeneity (ranging from 0 to 100%) (Peters et al., 2006). When a significant *Q*-test with $P < 0.05$ or $I^2 > 50\%$ indicated heterogeneity among studies, the random effects model (DerSimonian Laird method) was applied to the meta-analysis; otherwise, the fixed effects model (Mantel-Haenszel method) was used. In order to explore sources of heterogeneity, subgroup analyses were performed based on ethnicity, gene type, source of control, and SNP detection method. To evaluate the influence of individual studies on the overall risk estimate, we conducted a sensitivity analysis by omitting each study in turn. Funnel plots and Egger's linear regression test were used to assess the potential publication bias of included studies (Zintzaras and Ioannidis, 2005). All tests were two-sided, and a

P value of <0.05 was considered to be statistically significant. All analyses were conducted using the STATA software, version 12.0 (Stata Corp; College Station, TX, USA).

RESULTS

Baseline characteristics of studies included

A total of 161 articles relevant to the searched keywords were initially identified. Of these articles, 82 were excluded after reviewing titles and key words. After reviewing the abstracts and full texts, another 65 papers were excluded. Finally, 12 case-control studies met our inclusion criteria (Moon et al., 2006; Rudd et al., 2006; Han et al., 2008; Kotsinas et al., 2008; Hoyo et al., 2009; Jia et al., 2008, 2009; MacDonald et al., 2009; McElholm et al., 2010; Dong et al., 2011; Li et al., 2012; Lin et al., 2012). The publication years of the studies involved ranged from 2006 to 2012. A flow chart of the selection procedures is shown in Figure 1. A total of 9375 subjects were involved in this meta-analysis, including 2686 lung cancer patients, 771 esophageal cancer patients, and 5918 healthy controls. Overall, there were six lung cancer studies and six esophageal cancer studies. Six studies used hospital-based controls, while the other six studies used population-based controls (community populations). Seven studies were conducted in Asian populations and five studies were conducted in Caucasian populations. The DNA samples used for examination of genetic polymorphisms were extracted from blood in all included studies. Genotype methods included polymerase chain reaction-restriction fragment length polymorphism (PCR-RELP), direct DNA sequencing, TaqMan assay, and the high resolution melting method. Seven genes in the IGF-IGFR-IGFBP axis were addressed, including the IGF-1, IGF-2, IGF-1R, IGF-2R, IGFBP1, IGFBP3, and IGFBP5 genes. HWE tests were conducted on the genotype distribution of the controls in all twelve studies, and no study deviated from HWE (all P > 0.05). All quality scores of the included studies were higher than 20 (moderate-high quality). The characteristics and methodological quality of the included studies are summarized in Table 1.

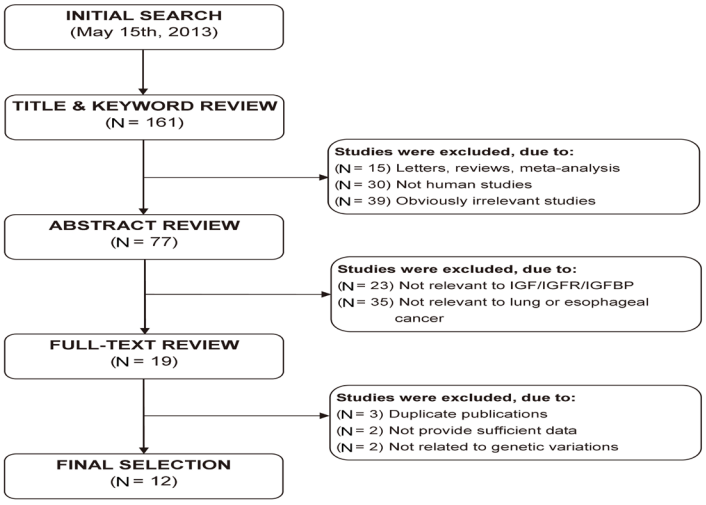

Figure 1. Flow chart of literature search and study selection.

Table 1. Main characteristics and methodological quality of all eligible studies.

First author	Year	Country	Ethnicity	Number		Gender (M/F)		Age (years)		Source		Genotype method	Gene	STROBE score
				Case	Control	Case	Control	Case	Control	Case	Control			
Lung cancer														
Moon et al.	2006	Korea	Asian	209	209	166/43	166/43	59.9 ± 10.2	60.1 ± 9.8	HB	HB	PCR-RFLP	IGFBP3	28
Rudd et al.	2006	UK	Caucasian	1529	2707	-	-	-	-	HB	PB	Direct sequencing	IGFBP5	24
Han et al.	2008	Korea	Asian	415	415	306/109	305/110	61.0 ± 9.7	60.8 ± 10.6	HB	HB	PCR-RFLP	IGFBP3	30
Kotsinas et al.	2008	Greece	Caucasian	103	117	100/3	106/11	66.8 (mean)	65.7 (mean)	HB	HB	Direct sequencing	IGF-2R	29
Li et al.	2012	China	Asian	260	258	173/87	171/87	61.1 ± 6.0	58.2 ± 5.8	PB	PB	PCR-RFLP	IGF-1R IGF-2R	26
Lin et al.	2012	Taiwan	Asian	170	340	204/136	102/68	66.2 ± 10.6	64.6 ± 10.6	HB	HB	PCR-RFLP	IGF-1 IGF-2 IGFBP3	32
Esophageal cancer														
Jia et al.	2008	China	Asian	78	470	57/21	388/82	64.0 ± 5.0	62.0 ± 4.0	HB	PB	TaqMan	IGF-1	25
Hoyo et al.	2009	USA	Caucasian	73	197	64/9	169/28	-	-	HB	HB	Direct sequencing	IGF-2	28
MacDonald et al.	2009	Canada	Caucasian	56	95	-	-	-	-	HB	PB	PCR-RFLP	IGF-1R	26
Jia et al.	2009	China	Asian	77	466	57/19	382/81	64.0 ± 5.0	62.0 ± 4.0	HB	PB	TaqMan	IGFBP1	24
McElholm et al.	2010	UK	Caucasian	227	260	192/35	220/40	63.0 (mean)	64.2 (mean)	HB	PB	TaqMan	IGF-1 IGFBP3 IGF-1R	30
Dong et al.	2011	China	Asian	260	384	187/73	260/124	63.1 ± 8.7	63.4 ± 7.2	HB	HB	HRM	IGF-1	25

IGF = insulin-like growth factor; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; HRM = high resolution melting; M = male; F = female; HB = hospital-based; PB = population-based.

Genetic variations in the IGF-IGFR-IGFBP axis and lung cancer risk

The association between genetic variations in the IGF-IGFR-IGFBP axis and lung cancer risk was evaluated in six studies. The heterogeneity was not significant (all P > 0.05), and therefore the fixed effects model was used. The meta-analysis results showed that genetic variations in the IGF-IGFR-IGFBP axis could increase the risk of lung cancer (allele model: OR = 1.37, 95%CI = 1.23-1.52, P < 0.001; dominant model: OR = 2.01, 95%CI = 1.24-3.27, P = 0.005; recessive model: OR = 1.24, 95%CI = 1.11-1.38, P < 0.001; homozygous model: OR = 2.14, 95%CI = 1.57-2.92, P < 0.001) (Figure 2 and Table 2). However, no significant associations were observed under the heterozygous models (OR = 1.05, 95%CI = 0.87-1.28, P = 0.609). Subgroup analysis by gene type indicated that the IGF1/2, IGF-1R, and IGFBP3/5 genes may be the main determinants of lung cancer risk, but the IGF-2R gene did not show any association with increased risk of lung cancer. Further subgroup analyses indicated that there were significant associations between genetic variations in the IGF-IGFR-IGFBP axis and lung cancer risk in Asian populations, population-based, hospital-based, and PCR-RFLP studies (as shown in Table 2). However, no statistically significant association was found in Caucasian populations and in non-PCR-RFLP studies (all P > 0.05).

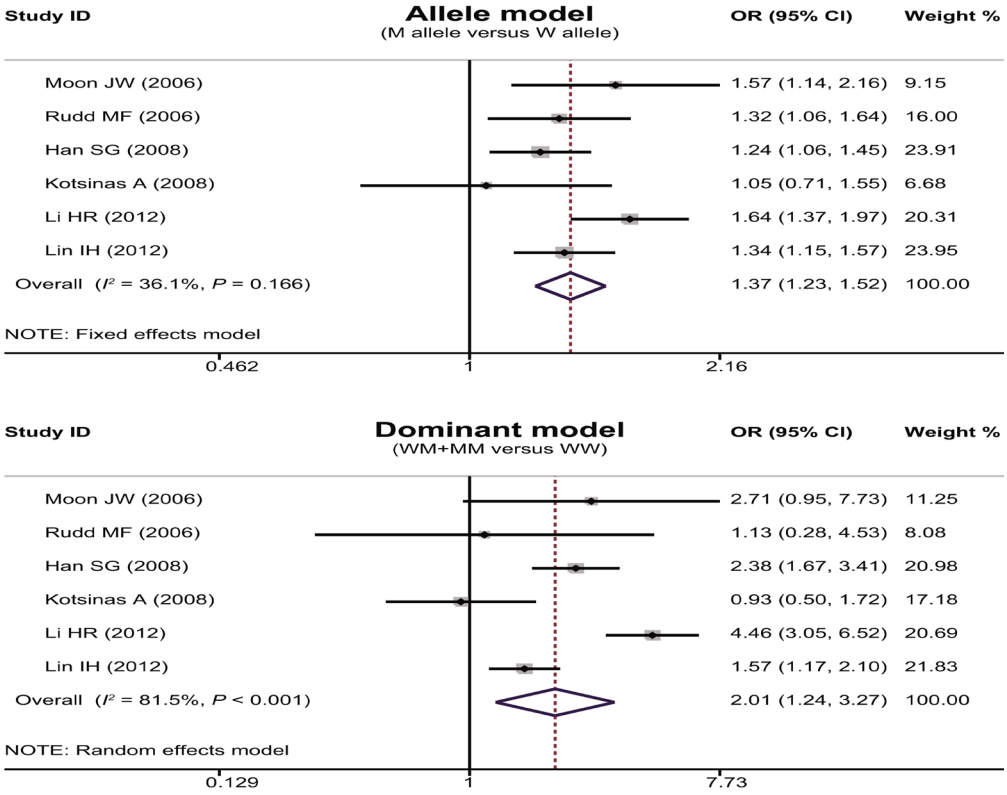

Figure 2. Forest plots for the associations between genetic polymorphisms in the IGF-IGFR-IGFBP axis and lung cancer risk. The squares and horizontal lines correspond to the study specific OR and 95%CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95%CI.

Table 2. Meta-analysis of the associations between genetic variations in the IGF-IGFR-IGFBP axis and lung cancer risk.

Subgroups	M allele *vs* W allele (allele model)			WM + MM *vs* WW (dominant model)			MM *vs* WW + WM (recessive model)			MM *vs* WW (homozygous model)			MM *vs* WM (heterozygous model)		
	OR	[95%CI]	P	OR	[95%CI]	P	OR	[95%CI]	P	OR	[95%CI]	P	OR	[95%CI]	P
Lung cancer															
Overall	1.37	[1.23-1.52]	<0.001	2.01	[1.24-3.27]	0.005	1.24	[1.11-1.38]	<0.001	2.14	[1.57-2.92]	<0.001	1.05	[0.87-1.28]	0.609
Gene															
IGFBP3	1.27	[1.12-1.44]	<0.001	2.12	[1.57-2.86]	<0.001	1.17	[0.97-1.42]	0.103	2.10	[1.54-2.86]	<0.001	1.04	[0.80-1.34]	0.780
IGFBP5	1.32	[1.06-1.65]	<0.001	1.13	[0.28-4.53]	0.862	1.34	[1.07-1.69]	0.012	1.16	[0.29-4.64]	0.835	1.35	[1.07-1.70]	0.012
IGF-2R	1.46	[0.79-2.69]	0.225	2.94	[0.30-28.81]	0.354	1.30	[0.97-1.75]	0.076	2.96	[0.36-24.61]	0.315	0.95	[0.59-1.54]	0.845
IGF-1R	1.47	[1.15-1.88]	0.002	3.38	[2.15-5.32]	<0.001	0.96	[0.67-1.37]	0.804	2.54	[1.54-4.19]	<0.001	0.59	[0.40-0.88]	0.009
IGF-1	1.42	[1.08-1.86]	0.012	1.45	[0.87-2.44]	0.157	1.58	[1.09-2.30]	0.016	1.78	[1.03-3.10]	0.040	1.51	[1.01-2.26]	0.044
IGF-2	1.47	[1.13-1.91]	0.004	1.85	[1.19-2.85]	0.006	1.41	[0.95-2.09]	0.089	1.99	[1.21-3.27]	0.007	1.14	[0.74-1.75]	0.558
Ethnicity															
Asian	1.41	[1.26-1.58]	<0.001	2.43	[1.70-3.48]	<0.001	1.23	[1.07-1.41]	0.004	2.39	[1.75-3.25]	<0.001	1.00	[0.801.24]	0.962
Caucasian	1.25	[1.03-1.51]	0.024	0.96	[0.55-1.69]	0.892	1.31	[1.06-1.62]	0.011	1.04	[0.58-1.88]	0.886	1.34	[1.08-1.67]	0.008
Source of controls															
Hospital-based	1.32	[1.19-1.47]	<0.001	1.90	[1.52-2.38]	<0.001	1.26	[1.07-1.48]	0.007	2.01	[1.59-2.55]	<0.001	1.11	[0.90-1.37]	0.329
Population-based	1.44	[1.15-1.80]	0.001	2.51	[0.92-6.86]	0.072	1.24	[1.06-1.46]	0.008	2.35	[0.94-5.87]	0.067	0.95	[0.61-1.46]	0.801
Genotype methods															
PCR-RFLP	1.41	[1.26-1.58]	<0.001	2.43	[1.70-3.48]	<0.001	1.23	[1.07-1.41]	0.004	2.39	[1.75-3.25]	<0.001	1.00	[0.80-1.24]	0.962
Non-PCR-RFLP	1.25	[1.03-1.51]	0.024	0.96	[0.55-1.69]	0.892	1.31	[1.06-1.62]	0.011	1.04	[0.58-1.88]	0.886	1.34	[1.08-1.67]	0.008

OR = odds ratios; 95%CI = 95% confidence interval; W = wild allele; M = mutant allele; WW = wild homozygote; WM = heterozygote; MM = mutant homozygote.

Genetic variations in the IGF-IGFR-IGFBP axis and esophageal cancer risk

Six studies evaluated the association between genetic variations in the IGF-IGFR-IGFBP axis and esophageal cancer risk. Since no significant heterogeneity was observed (all P > 0.05), the fixed effects model was used. Meta-analysis of these studies showed significant associations between genetic variations in the IGF-IGFR-IGFBP axis and increased risk of esophageal cancer (allele model: OR = 1.26, 95%CI = 1.08-1.47, P = 0.003; dominant model: OR = 1.40, 95%CI = 1.06-1.86, P = 0.020) (Figure 3), but no significant associations were observed under the other genetic models (all P > 0.05). In the subgroup analysis based on gene type, the results showed that the IGF-1, IGF-1R, and IGFBP1 gene polymorphisms could be associated with increased risk of esophageal cancer, but there was no evidence for any association of the IGF-2, IGF-2R, and IGFBP3 genes. We also performed further subgroup analyses based on ethnicity, source of controls, and SNP detection method. These results suggested significant associations between genetic variations in the IGF-IGFR-IGFBP axis and esophageal cancer risk in Asian populations, hospital-based, and TaqMan subgroups (as shown in Table 3).

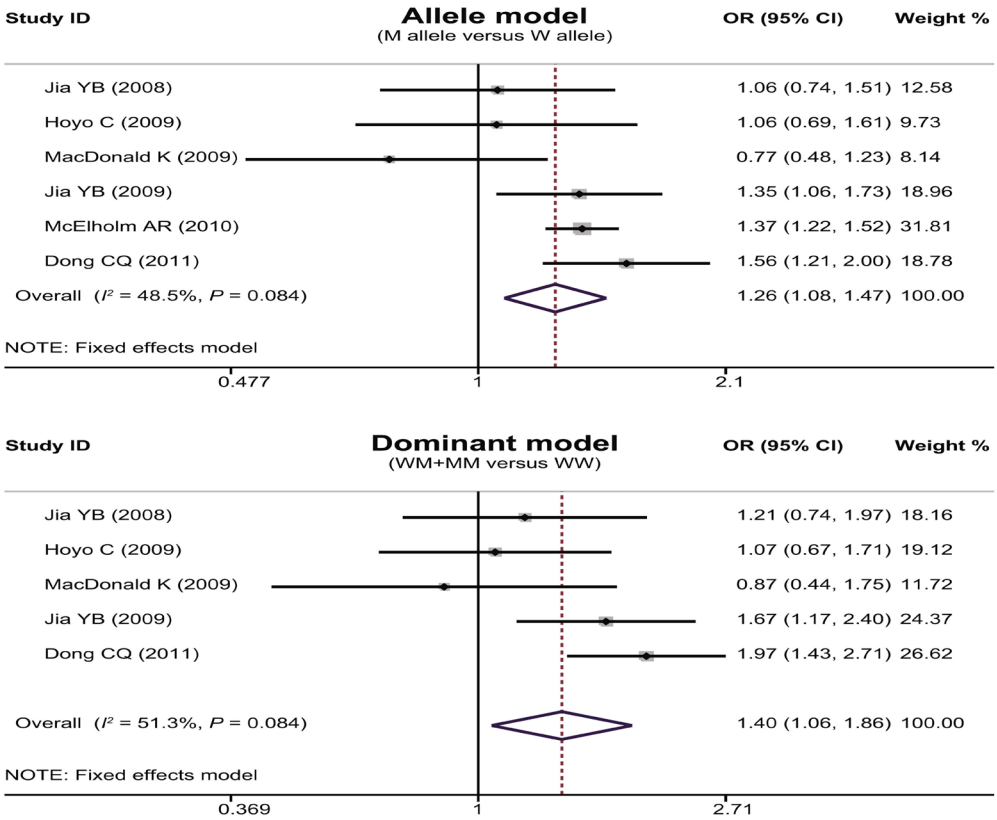

Figure 3. Forest plots for the associations between genetic polymorphisms in the IGF-IGFR-IGFBP axis and esophageal cancer risk. The squares and horizontal lines correspond to the study specific OR and 95%CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95%CI.

Table 3. Meta-analysis of the associations between genetic variations in the IGF-IGFR-IGFBP axis and esophageal cancer risk.

Subgroups	M allele *vs* W allele (allele model)			WM + MM *vs* WW (dominant model)			MM *vs* WW + WM (recessive model)			MM *vs* WW (homozygous model)			MM *vs* WM (heterozygous model)		
	OR	[95%CI]	P	OR	[95%CI]	P	OR	[95%CI]	P	OR	[95%CI]	P	OR	[95%CI]	P
Esophageal cancer															
Overall	1.26	[1.08-1.47]	0.003	1.40	[1.06-1.86]	0.020	0.98	[0.71-1.35]	0.902	1.23	[0.88-1.73]	0.232	0.79	[0.57-1.10]	0.164
Gene															
IGF-1	1.30	[1.05-1.61]	0.018	1.60	[1.00-2.57]	0.052	0.99	[0.61-1.61]	0.973	1.27	[0.77-2.10]	0.354	0.75	[0.45-1.24]	0.255
IGF-2	1.06	[0.69-1.62]	0.790	1.08	[0.67-1.72]	0.758	1.08	[0.27-4.32]	0.916	1.08	[0.27-4.36]	0.911	1.04	[0.21-5.10]	0.966
IGF-1R	1.36	[1.09-1.70]	0.007	0.87	[0.44-1.75]	0.699	0.52	[0.22-1.26]	0.149	0.54	[0.20-1.44]	0.217	0.51	[0.20-1.30]	0.158
IGFBP1	1.35	[1.06-1.74]	0.017	1.68	[1.17-2.41]	0.005	1.18	[0.71-1.97]	0.525	1.59	[0.90-2.78]	0.108	0.93	[0.55-1.59]	0.800
IGFBP3	1.26	[0.93-1.72]	0.134	-	-	-	-	-	-	-	-	-	-	-	-
Ethnicity															
Asian	1.36	[1.16-1.60]	<0.001	1.69	[1.37-2.10]	<0.001	1.08	[0.76-1.53]	0.681	1.40	[0.96-2.04]	0.078	0.83	[0.58-1.20]	0.316
Caucasian	1.31	[1.14-1.51]	<0.001	1.01	[0.68-1.49]	0.970	0.64	[0.31-1.36]	0.246	0.68	[0.31-1.52]	0.345	0.63	[0.29-1.39]	0.252
Source of controls															
Population-based	1.32	[1.17-1.49]	<0.001	1.38	[1.05-1.81]	0.022	0.93	[0.64-1.36]	0.703	1.13	[0.71-1.80]	0.614	0.79	[0.53-1.18]	0.246
Hospital-based	1.35	[1.02-1.79]	0.039	1.41	[0.86-2.30]	0.174	1.11	[0.62-1.97]	0.725	1.44	[0.80-2.59]	0.230	0.79	[0.43-1.44]	0.441
Genotype methods															
TaqMan	1.36	[1.23-1.50]	<0.001	1.49	[1.12-2.00]	0.007	1.06	[0.70-1.62]	0.789	1.34	[0.85-2.13]	0.209	0.87	[0.56-1.35]	0.537
Direct sequencing	1.06	[0.69-1.62]	0.790	1.08	[0.67-1.72]	0.758	1.08	[0.27-4.32]	0.916	1.08	[0.27-4.36]	0.911	1.04	[0.21-5.10]	0.966
PCR-RFLP	0.77	[0.47-1.23]	0.271	0.87	[0.44-1.75]	0.699	0.52	[0.22-1.26]	0.149	0.54	[0.20-1.44]	0.217	0.51	[0.20-1.30]	0.158
HRM	1.56	[1.21-2.00]	0.001	1.97	[1.43-2.71]	<0.001	1.12	[0.59-2.10]	0.734	1.53	[0.80-2.93]	0.203	0.74	[0.39-1.44]	0.379

OR = odds ratios; 95%CI = 95% confidence interval; W = wild allele; M = mutant allele; WW = wild homozygote; WM = heterozygote; MM = mutant homozygote.

Sensitivity analysis and publication bias

The results of the sensitivity analysis suggested that no individual studies significantly affected the pooled estimates under any of the genetic models (Figure 4). The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 5). The Egger test also showed that there was no strong statistical evidence of publication bias (all $P > 0.05$).

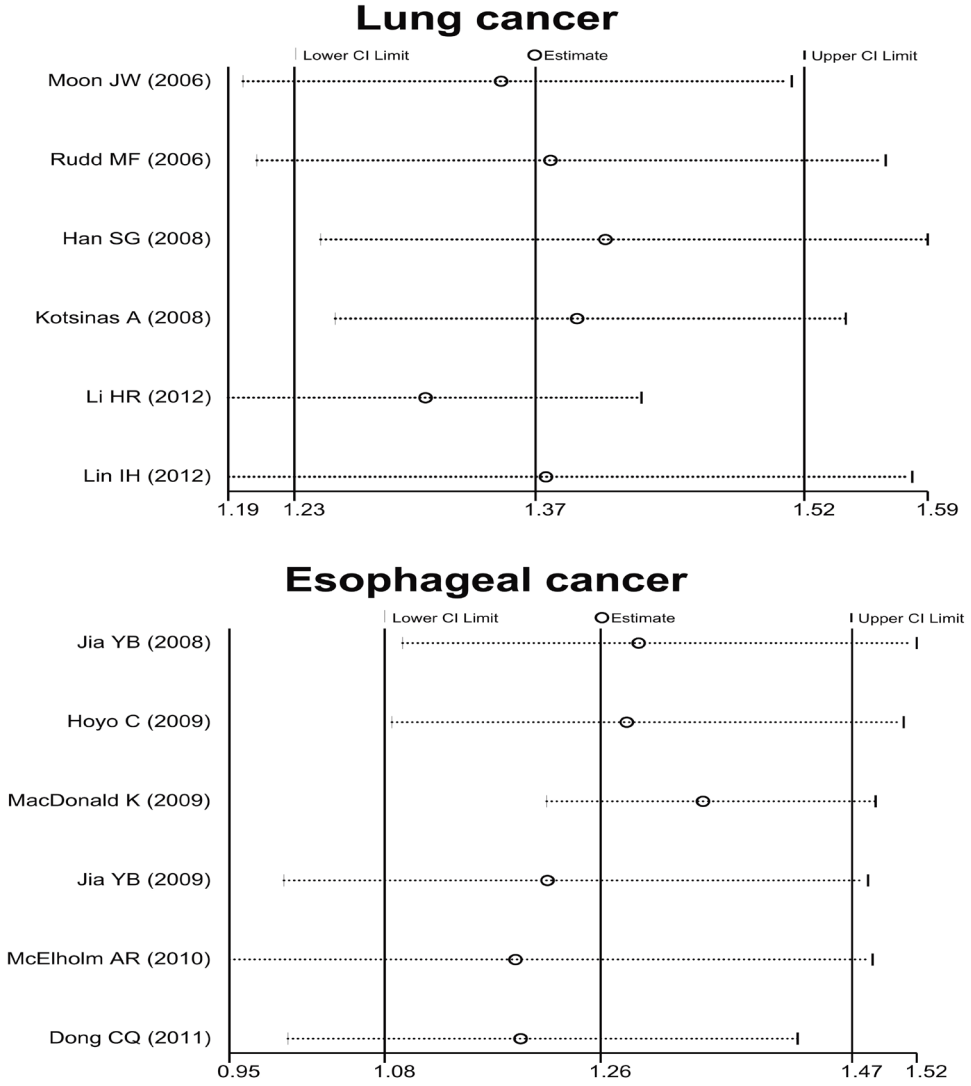

Figure 4. Sensitivity analysis for the associations between genetic polymorphisms in the IGF-IGFR-IGFBP axis and lung and esophageal cancer risk under allele model. Results were computed by omitting each study in turn. Meta-analysis random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95%CI.

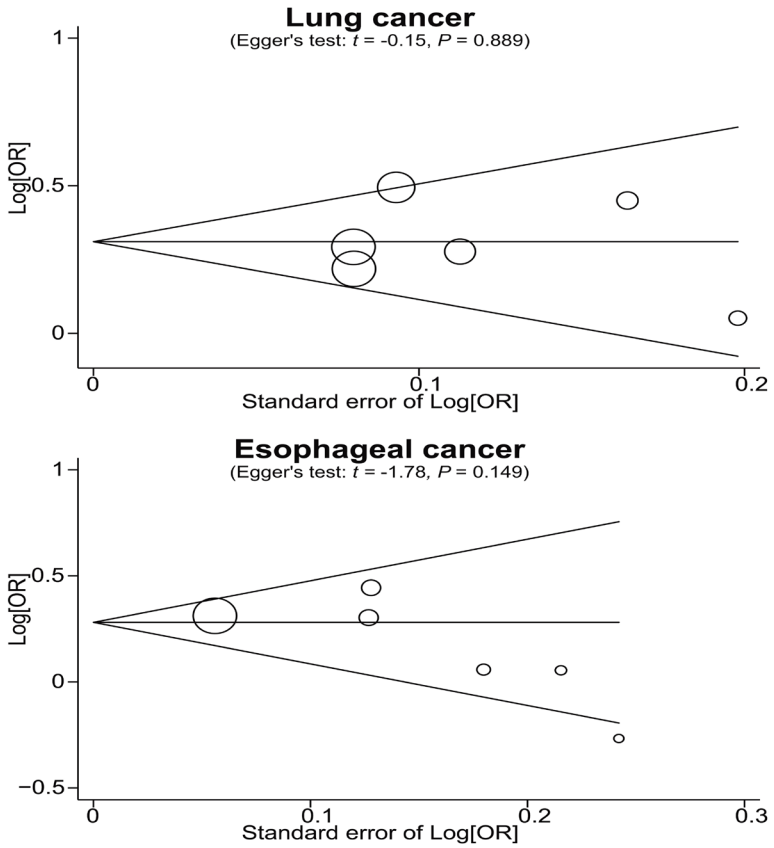

Figure 5. Funnel plots for the associations between genetic polymorphisms in the IGF-IGFR-IGFBP axis and lung and esophageal cancer risk under allele model. Each point represents a separate study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line means magnitude of the effect. Note: Funnel plot with pseudo 95% confidence limits was used.

DISCUSSION

IGFs are well known as key regulators of normal carbohydrate and lipid metabolism and growth (Jones and Clemmons, 1995; Kaaks, 2004). The bioactivity of IGFs is modulated by IGFBPs, which have high affinity for both IGF-1 and IGF-2. In general, IGFBPs limit IGFs' access to IGF-1R/2R, thereby attenuating the bioactivity of these growth factors (Pollak, 2008). Several genetic polymorphisms in IGF1/2, IGF-1R/2R, and IGFBP-1-6 (also called the IGF-IGFR-IGFBP axis) have been identified for predicting the development, progression, and clinical outcomes of lung and esophageal cancers (Rudd et al., 2006; Lettre et al., 2007). Many previous genetic studies have suggested that genetic polymorphisms in the IGF-IGFR-IGFBP axis may play an important role in lung and esophageal carcinogenesis (Moon et al., 2006; Rudd et al., 2006; Han et al., 2008; Kotsinas et al., 2008; Hoyo et al., 2009; MacDonald et al., 2009; McElholm et al., 2010; Dong et al., 2011; Li et al., 2012; Lin et al., 2012), while other studies found no convincing evidence of these polymorphisms in increas-

ing the risks of lung and esophageal cancer (Jia et al., 2008, 2009). This controversy could be explained by several factors, including differences in study designs, sample sizes, ethnicities, statistical methods, etc. Therefore, this meta-analysis aimed to provide a more comprehensive and reliable conclusion of these associations.

This is the first meta-analysis focused on the associations between genetic polymorphisms in the IGF-IGFR-IGFBP axis and the risk of lung and esophageal cancer. In the present meta-analysis, 12 independent case-control studies were included with a total of 2686 lung cancer patients, 771 esophageal cancer patients, and 5918 healthy controls. When all eligible studies were pooled into the meta-analysis, the results showed that common polymorphisms in the IGF-IGFR-IGFBP axis were associated with increased risks of lung and esophageal cancer, especially among Asian populations, while similar associations were not observed among Caucasian populations. Although ethnic differences in susceptibility to lung and esophageal cancer are well known, the molecular basis is not fully understood. One possible reason for these ethnic differences could be that large differences in common SNPs in the IGF-IGFR-IGFBP axis that influence the risk of lung and esophageal cancer are mostly due to genetic drift and natural selection (Serre et al., 2008). Further subgroup analysis by gene type indicated that common polymorphisms in the IGF1/2, IGF-1R, and IGFBP-3/5 genes may be the main determinants for lung cancer risk, whereas polymorphisms in the IGF-1, IGF-1R, and IGFBP-1 genes may increase the risk of esophageal cancer. Although no significant association was found for IGF-2R genetic polymorphisms, this result might have lacked sufficient reliability due to small sample size. These findings are consistent with the previous hypothesis that genetic variations in the IGF-IGFR-IGFBP axis may confer susceptibility to lung and esophageal cancer, suggesting that they may be useful as biomarkers for predicting an individual's genetic susceptibility to lung and esophageal cancer.

Our meta-analysis has several limitations that should be acknowledged. The first limitation is that the sample size of this meta-analysis was relatively small and may not have sufficient statistical power in estimating the relationships between the IGF-IGFR-IGFBP axis and lung and esophageal cancer risk. Therefore, more studies with larger sample sizes are still needed. On the other hand, a meta-analysis is a type of a retrospective study and may encounter recall or selection bias, thereby possibly influencing the reliability of our results (Stroup et al., 2000). Most important of all, lack of access to the original study data limited further evaluations of the potential value of these polymorphisms in the IGF-IGFR-IGFBP axis.

In conclusion, our meta-analysis indicates that genetic variations in the IGF-IGFR-IGFBP axis confer susceptibility to lung and esophageal cancer, especially among Asian populations. Common polymorphisms in the IGF-IGFR-IGFBP axis may serve as useful biomarkers for predicting the risk of lung and esophageal cancer. Considering the limitations mentioned above, detailed studies are needed to confirm our findings.

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