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Review Article

The association between the rs11549465 polymorphism in the hif-1α gene and cancer risk: a meta-analysis

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Abstract: Purpose: The associations between hypoxia-inducible factor-1 alpha (HIF-1alpha) and clinicopathological characteristics of cancers have been evaluated in various studies, with the conflicting results. The common rs11549465 (1772C/T) genetic polymorphism has been reported to be functional and may contribute to genetic susceptibility to cancers. However, the association between rs11549465 (1772C/T) and cancer risk remains inconclusive. Methods: To better understand the role of rs11549465 (1772C/T) polymorphism in global cancer, we conducted this comprehensive meta-analysis encompassing 7807 cases and 8633 controls. Results: Overall, the rs11549465 (1772C/T) genetic polymorphism was associated with higher cancer risk, especially exists in Asians. In the stratified analysis, significant associations were found between the HIF-1 rs11549465 polymorphism and gynecologic cancer among Caucasian population. We observed that the TT genotype might modulate gynecologic cancer (OR=9.92 [2.15-45.66]) risk comparing with the CC genotype. Moreover, a significantly increased lung and breast cancer risk was found among Asian population comparing with Caucasian population. When stratified by study design, significantly elevated susceptibility to cancer was found among hospital -based studies. Conclusions: Our meta-analysis suggested that the HIF-1 rs11549465 (1772C/T) genetic polymorphism is significantly associated with higher risk among Asian population and lower risk among Caucasian population in breast and lung cancer, and this SNP was significantly associated with the gynecologic cancer among Caucasian population. The effect of the rs11549465 polymorphism on cancer especially exists in Asians.

Keywords: Hif-1, rs11549465, cancer, genetic polymorphism, meta-analysis

Introduction

Cancer is one of the leading causes of death in the world. It has become a worldwide public health problem [1]. The exact mechanism of carcinogenesis is not yet fully elucidated [2]. Recently, it has become clear that genetic variation contributes to the development and progression of cancer [2, 3]. However, due to various reasons, including considerable heterogeneity of the disease, the identification of susceptibility genes is difficult and most associations have not been replicated.

One of the most important features of tumors is hypoxia. Intratumoral hypoxia occurs when cells are located further from a functional blood vessel than is required for adequate diffusion of oxygen, as a result of rapid tumor cell proliferation and abnormal blood vessels [4]. Hypoxia conditions in tumor tissues induce a molecular response, which drives the activation of transcription factors. Among these, hypoxia-inducible factor-1 (HIF-1) plays an essential role in adaptive responses to reduced oxygen levels [5, 6].

HIF-1 is a dimeric protein complex, consisting of α and β subunits. The activity of HIF-1 is predominantly regulated through the stability of the subunit [7]. Koshiji et al. demonstrated that hif-1α (PASD8) inhibits the DNA mismatch repair system (MSH2 and MSH6), which is responsible for genetic instability [8]. Other researchers have also reported that hypoxia down regulates the expression of DNA double-stranded break repair genes [9-12]. These data support the concept that defective DNA repair

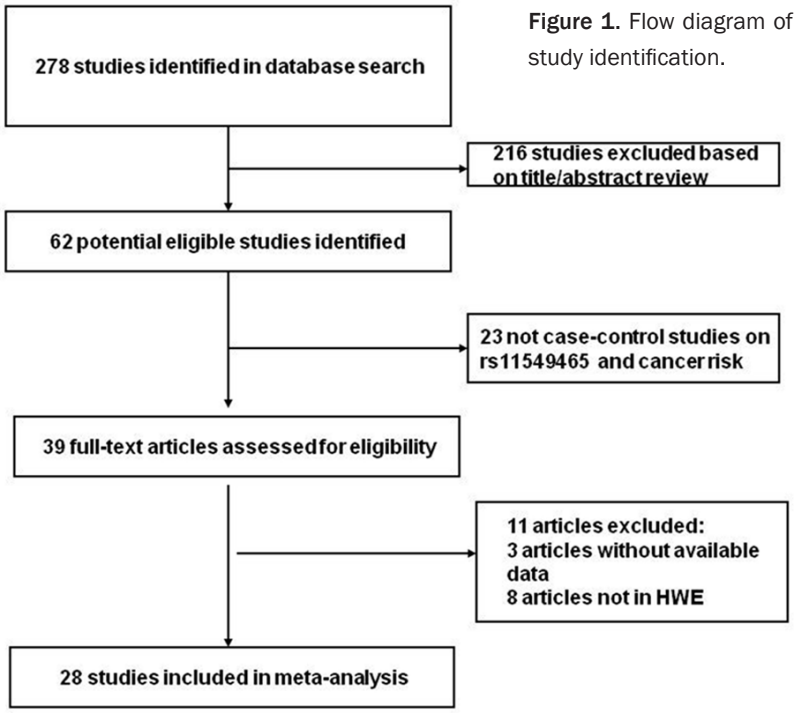

Figure 1. Flow diagram of study identification.

pathways cause genomic instability within the tumor microenvironment. PASD8 (Hif-1α) is overexpressed in >90% of colon, lung and prostate cancers, whereas no expression was detected in corresponding normal tissues [13], indicating a role of hif-1α in cancer. It is over expressed in several human cancers, such as head-neck, colon, breast, stomach, pancreas, prostate, kidney, esophagus, endometrial, and non-small-cell lung cancer [14-20]. The target genes of hif-1α are particularly relevant to cancer, encoding angiogenic factors, proliferation/survival factors, glucose transporters and glycolytic enzymes [21]. As such, variability in this protein is likely to influence individual risk to this pathology.

A number of investigators have studied the possible association between the hif-1 polymorphisms and cancer risk, but the results have been conflicting [20, 22-39]. Thus, the association between the HIF-1 polymorphisms and cancers requires further investigation. In an attempt to clarify this inconsistency, we have combined all the published studies of hospital and population up to July 2014 in a meta-analysis to give a comprehensive picture of the role of HIF-1α gene using multiple research methods and models.

In this study, a comprehensive meta-analysis was performed on previous reports to investigate the association of hif-1α rs11549465 (1772C/T) polymorphisms with all cancers, different kinds of cancers, different kinds of detection method, and different kinds of populations.

Methods

Search strategy and data extraction

In this meta-analysis, a comprehensive literature research of the US National Library of Medicine's PubMed database, ISI Web of Knowledge, Medline, Embase and Google Scholar Search (update to July 2014) was conducted using the search terms including "hif-1α" or "hypoxia-inducible factor-1" or "rs11549465" or "1772-C/T" or "P582S", "polymorphisms" or "variation" or "mutation" or "SNP", "tumour" or "tumor" or "cancer" or "neoplasm" or "phyma" or "oncoma" or "knub" or "carcinoma" or "malignancy", and the combined phrases in order to obtain all genetic studies on the relationship of rs11549465 polymorphism and cancers. We also used a hand search of references of original studies or reviewed articles on this topic to identify additional studies. Eligible studies were selected according to the following explicit inclusion criteria: (1) a case control study on the association between rs11549465 polymorphism and cancer risk, (2) detailed number of different genotypes for estimating an odds ratio (OR) with 95% confidence interval (CI), (3) when several publications reported on the same population data, the largest or most complete study was chosen, (4) cases with carcinomas were diagnosed by histopathology, (5) animal studies, case reports, review articles, abstracts, editorials, reports with incomplete data, and studies based on pedigree data were excluded (**Figure 1**). For each eligible study, the following information was recorded: the first author's name, the year of publication, ethnicity, genotyping methods, sources of control, racial descent of the study population, genotype and allele distributions and main results of each study.

Table 1. Main characteristics of included studies in the meta-analysis

Studies (cancer type)	Country	Ethnicity	Genotype assay	Source of control	Case/control	P
Tanimoto 2003 HNSCC	Japan	Asian	PCR-Sequencing	Population	55/110	0.545
Foley 2009 prostate cancer	Dublin	Caucasian	PCR-Sequencing	Population	95/188	0.623
Li 2007 prostate cancer	USA	Caucasian	PCR-RFLP	Population	1041/1234	0.159
Orr-Urtreger 2007 prostate cancer	Israel	Caucasian	PCR-RFLP	Population	402/300	0.137
Lee 2008 breast cancer	Korean	Asian	SNP-ITTM	Population	1332/1369	0.250
Apaydin 2008 breast cancer	Turkey	Caucasian	PCR-RFLP	Population	102/102	0.415
Kim 2008 breast cancer	Korea	Asian	PCR-Sequencing	Hospital	90/102	0.641
Konac 2007 gynecologic cancer	Turkey	Caucasian	PCR-RFLP	Hospital	102/107	0.229
Li 2012 prostate cancer	China	Asian	Taqman	Population	662/716	0.267
Fransen 2006 colorectal cancer	Sweden	Caucasian	PCR-RFLP	Hospital	198/258	0.916
Kuwai 2004 colorectal cancer	Japan	Asian	PCR-Sequencing	Population	100/100	0.561
Ling 2005 ESCC	China	Asian	PCR-RFLP	Population	95/104	0.569
Naidu 2009 breast cancer	Malaysia	Asian	PCR-RFLP	Hospital	410/275	0.922
Zagouri 2012 breast cancer	Greece	Caucasian	PCR-RFLP	Hospital	113/124	0.413
Kuo 2012 lung cancer	China	Asian	PCR-RFLP	Hospital	285/300	0.132
Wang 2011 pancreatic cancer	China	Asian	PCR-Sequencing	Hospital	263/271	0.352
Kang 2011 colorectal cancer	Korea	Asian	PCR-RFLP	Hospital	50/50	0.335
Xu 2011 Glioma	China	Asian	PCR-RFLP	Hospital	150/150	0.354
Hsiao 2010 hepatocellular carcinoma	China	Asian	PCR-RFLP	Hospital	102/347	0.722
Chen 2009 OSCC	China	Asian	PCR-RFLP	Population	174/347	0.722
Konac 2009 lung cancer	Turkey	Caucasian	PCR-RFLP	Hospital	141/156	0.335
Li 2009 gastric cancer	Tibetan	Asian	PCR-LDR	Hospital	87/106	0.501
Nadaoka 2008 bladder cancer	Japan	Asian	PCR-RFLP	Hospital	219/461	0.305
Kim 2011 cervical cancer	Korea	Asian	SNaPShot	Hospital	199/214	0.325
Qin 2012 renal cell carcinoma	China	Asian	Taqman	Hospital	620/623	0.219
Morris 2009 renal cell carcinoma	Poland	Caucasian	Taqman	Population	332/313	0.083
Putra 2011 lung cancer	Japan	Asian	PCR-Sequencing	Hospital	83/110	0.545
Shieh 2010 OSCC	China	Asian	PCR-Sequencing	Hospital	305/96	0.711

P Value of Hardy-Weinberg equilibrium in controls.

Statistics

The strength of relationship between rs11549465 polymorphism and cancer was assessed by using crude OR with 95% CI. We examined the association between the rs11549465 polymorphism and cancer risk using the following genetic models: homozygote comparison (TT vs. CC), heterozygote comparison (TC vs. CC), dominant genetic model (TT/TC vs. CC), recessive genetic model (TT vs. TC/CC) and additive model (T vs. C). Firstly, we checked the Hardy-Weinberg equilibrium (HWE) in controls for each study. Then we performed Q-test for evaluating the heterogeneity [40]. Fixed effects model was used to pool the data when the *P*-value of Q-test ≥0.05; otherwise, random effects model was selected [41]. I^2 was also used to assess the heterogeneity in this meta-analysis. If I^2 >50%, the heterogeneity exists [42]. We also performed sensitivity analysis and subgroup analysis to explore the reason of heterogeneity. Both funnel plot and Egger's test were used to assess the publication bias (P<0.05 was representative of statistical significance) [43]. All statistical analysis were performed using STATA 12.0 software (Stata Corp., College Station, Texas, USA) and Review Manager 5.2 (The Cochrane Collaboration, http://ims.cochrane.org/revman).

Results

Eligible studies

Overall, 28 relevant studies involving 7807 cases and 8633 controls were selected in this

Table 2. Distribution of rs11549465 polymorphism and the main results of eligible studies

Stuies (cancer type)	Case	Control	OR (95% CI)				
	(TT/TC/CC)	(TT/TC/CC)	TT vs. CC	TC vs. CC	TT/TC vs. CC	TT vs. TC/CC	T vs. C
Tanimoto 2003 HNSCC	55 (0/10/45)	110 (0/12/98)	-	1.81 (0.73-4.51)	1.81 (0.73-4.51)	-	1.73 (0.72-4.15)
Foley 2009 prostate cancer	95 (0/30/65)	188 (0/13/175)	-	6.21 (3.05-12.64)	6.21 (3.05-12.64)	-	5.24 (2.66-10.30)
Li 2007 prostate cancer	1041 (14/209/818)	1234 (18/221/995)	0.95 (0.47-1.91)	1.15 (0.93-1.42)	1.13 (0.92-1.39)	0.92 (0.46-1.86)	1.11 (0.92-1.33)
Orr-Urtreger 2007 prostate cancer	402 (16/99/287)	300 (3/80/217)	4.03 (1.16-14.01)	0.94 (0.66-1.32)	1.05 (0.75-1.46)	4.10 (1.18-14.21)	1.16 (0.87-1.56)
Lee 2008 breast cancer	1332 (6/119/1207)	1369 (1/123/1245)	6.19 (0.74-51.48)	1.00 (0.77-1.30)	1.04 (0.80-1.35)	6.19 (0.74-51.49)	1.08 (0.84-1.39)
Apaydin 2008 breast cancer	102 (2/21/79)	102 (5/29/68)	0.34 (0.06-1.83)	0.62 (0.33-1.19)	0.58 (0.31-1.08)	0.39 (0.07-2.05)	0.59 (0.34-1.02)
Kim 2008 breast cancer	90 (1/8/81)	102 (0/9/93)	3.44 (0.14-85.66)	1.02 (0.38-2.77)	1.15 (0.43-3.03)	3.44 (0.14-85.40)	1.27 (0.51-3.21)
Konac 2007 gynecologic cancer	102 (14/40/48)	107 (2/37/68)	9.92 (2.15-45.66)	1.53 (0.86-2.74)	1.96 (1.13-3.41)	8.35 (1.85-37.75)	2.11 (1.35-3.30)
Li 2012 prostate cancer	662 (2/48/612)	716 (0/57/659)	5.38 (0.26-112.36)	0.91 (0.61-1.35)	0.94 (0.64-1.40)	5.42 (0.26-113.18)	0.99 (0.67-1.45)
Fransen 2006 colorectal cancer	198 (3/28/167)	258 (2/43/213)	1.91 (0.32-11.58)	0.83 (0.50-1.39)	0.88 (0.53-1.45)	1.97 (0.33-11.90)	0.94 (0.59-1.49)
Kuwai 2004 colorectal cancer	100 (0/0/100)	100 (0/11/89)	-	0.04 (0.00-0.67)	0.04 (0.00-0.67)	-	0.04 (0.00-0.70)
Ling 2005 ESCC	95 (0/11/84)	104 (0/11/93)	-	1.11 (0.46-2.69)	1.11 (0.46-2.69)	-	1.10 (0.47-2.60)
Naidu 2009 breast cancer	410 (16/100/294)	275 (3/50/222)	4.03 (1.16-13.99)	1.51 (1.03-2.21)	1.65 (1.14-2.39)	3.68 (1.06-12.76)	1.69 (1.21-2.36)
Zagouri 2012 breast cancer	113 (0/15/98)	124 (0/17/107)	-	0.96 (0.46-2.03)	0.96 (0.46-2.03)	-	0.97 (0.47-1.98)
Kuo 2012 non–small-cell lung cancer	285 (38/94/153)	300 (11/73/216)	4.88 (2.42-9.84)	1.82 (1.26-2.63)	2.22 (1.57-3.13)	4.04 (2.02-8.08)	2.26 (1.70-3.00)
Wang 2011 pancreatic cancer	263 (0/54/209)	271 (0/29/242)	-	2.16 (1.32-3.51)	2.16 (1.32-3.51)	-	2.02 (1.27-3.23)
Kang 2011 colorectal cancer	50 (0/4/46)	50 (0/12/38)	-	0.28 (0.08-0.92)	0.28 (0.08-0.92)	-	0.31 (0.10-0.98)
Xu 2011 Glioma	150 (2/27/121)	150 (1/14/135)	2.23 (0.20-24.92)	2.15 (1.08-4.29)	2.16 (1.10-4.21)	2.01 (0.18-22.45)	2.05 (1.09-3.83)
Hsiao 2010 Hepatocellular carcinoma	102 (0/8/94)	347 (0/13/334)	-	2.19 (0.88-5.43)	2.19 (0.88-5.43)	-	2.14 (0.87-5.23)
Chen 2009 OSCC	174 (1/10/163)	347 (0/13/334)	6.14 (0.25-151.49)	1.58 (0.68-3.67)	1.73 (0.76-3.95)	6.01 (0.24-148.26)	1.87 (0.84-4.14)
Konac 2009 Lung cancer	141 (0/31/110)	156 (2/43/111)	0.20 (0.01-4.25)	0.73 (0.43-1.24)	0.70 (0.41-1.18)	0.22 (0.01-4.59)	0.70 (0.43-1.13)
Li 2009 Gastric cancer	87 (0/4/83)	106 (0/13/93)	-	0.34 (0.11-1.10)	0.34 (0.11-1.10)	-	0.36 (0.12-1.13)
Nadaoka 2008 TCC	219 (0/22/197)	461 (0/42/419)	-	1.11 (0.65-1.92)	1.11 (0.65-1.92)	-	1.11 (0.65-1.88)
Kim 2011 Cervical cancer	199 (0/22/177)	214 (0/27/187)	-	0.86 (0.47-1.57)	0.86 (0.47-1.57)	-	0.87 (0.49-1.55)
Qin 2012 renal cell carcinoma	620 (2/46/572)	623 (2/43/578)	1.01 (0.14-7.20)	1.08 (0.70-1.66)	1.08 (0.71-1.65)	1.00 (0.14-7.16)	1.07 (0.71-1.61)
Morris 2009 renal cell carcinoma	332 (3/39/290)	313 (5/46/262)	0.54 (0.13-2.29)	0.77 (0.48-1.21)	0.74 (0.48-1.16)	0.56 (0.13-2.37)	0.74 (0.49-1.11)
Putra 2011 lung cancer	83 (0/9/74)	110 (0/12/98)	-	0.99 (0.40-2.48)	0.99 (0.40-2.48)	-	0.99 (0.41-2.42)
Shieh 2010 OSCC	305 (0/23/282)	96 (0/7/89)	-	1.04 (0.43-2.50)	1.04 (0.43-2.50)	-	1.04 (0.44-2.45)

The numbers in parentheses represent 95% confidence interval [CI].

Table 3. Results of meta-analysis for rs11549465 polymorphism and cancer risk

Study Groups	NO.of studies	Case (TT/TC/CC)	Control (TT/TC/CC)	TT vs. CC		TC vs. CC		TT/TC vs. CC		TT vs. TC/CC		T vs. C	
				OR (95% CI)	P^a; P^b; I^2 (%)	OR (95% CI)	P^a; P^b; I^2 (%)	OR (95% CI)	P^a; P^b; I^2 (%)	OR (95% CI)	P^a; P^b; I^2 (%)	OR (95% CI)	P^a; P^b; I^2 (%)
All population	28	7807 (120/1131/6556)	8633 (55/1100/7478)	**2.15 (1.19-3.88)**	0.011; 0.010; 52.0%	1.15 (0.96-1.36)	0.127; 0.000; 63.8%	1.19 (0.99-1.42)	0.071; 0.000; 69.1%	**2.21 (1.60-3.05)**	0.010; 0.028; 45.5%	**1.20 (1.01-1.44)**	0.043; 0.000; 71.8%
Ethnicity													
Asian	19	5281 (68/619/4594)	5851 (18/571/5262)	**4.17 (2.48-7.01)**	0.000; 0.913; 0.0%	1.19 (0.97-1.47)	0.097; 0.003; 53.7%	1.24 (0.99-1.55)	0.063; 0.000; 60.7%	**3.70 (2.21-6.19)**	0.000; 0.936; 0.0%	**1.26 (1.01-1.57)**	0.041; 0.000; 63.2%
Caucasian	9	2526 (52/512/1962)	2782 (37/529/2216)	1.34 (0.55-3.31)	0.521; 0.012; 63.5%	1.09 (0.79-1.50)	0.613; 0.000; 76.3%	1.12 (0.80-1.56)	0.503; 0.000; 78.9%	1.36 (0.57-3.21)	0.489; 0.019; 60.4%	1.13 (0.83-1.54)	0.432; 0.000; 80.6%
Source of control													
Population	11	4390 (44/596/3750)	4883 (32/616/4235)	1.39 (0.88-2.20)	0.158; 0.067; 49.0%	1.12 (0.84-1.50)	0.430; 0.000; 73.4%	1.14 (0.86-1.52)	0.360; 0.000; 74.0%	1.40 (0.89-2.22)	0.148; 0.073; 47.9%	1.15 (0.88-1.49)	0.302; 0.000; 73.3%
Hospital	17	3417 (76/535/2806)	3750 (23/484/3243)	**3.75 (2.34-6.01)**	0.000; 0.326; 13.3%	1.17 (0.94-1.46)	0.164; 0.005; 53.3%	1.21 (0.95-1.55)	0.121; 0.000; 63.1%	**3.36 (2.10-5.37)**	0.000; 0.455; 0.0%	1.23 (0.97-1.57)	0.090; 0.000; 68.0%
Detection method													
PCR-Sequencing	7	991 (1/134/856)	977 (0/93/884)	3.44 (0.14-85.66)	0.451; -; -	1.51 (0.78-2.94)	0.000; 0.001; 75.0%	1.54 (0.80-2.97)	0.198; 0.001; 74.5%	3.44 (0.14-85.40)	0.452; -; -	1.53 (0.84-2.79)	0.000; 0.002; 71.3%
PCR-RFLP	15	3584 (106/719/2759)	4315 (47/698/3570)	**2.31 (1.12-4.73)**	0.000; 0.005; 61.6%	1.15 (0.95-1.40)	0.012; 0.010; 51.9%	1.21 (0.97-1.52)	0.098; 0.000; 66.0%	**2.21 (1.13-4.30)**	0.020; 0.016; 55.8%	1.24 (0.98-1.56)	0.000; 0.000; 73.2%
SNP-ITTM	1	1332 (6/119/1207)	1369 (1/123/1245)	6.19 (0.74-51.48)	0.092; -; -	1.00 (0.77-1.30)	0.988; -; -	1.04 (0.80-1.35)	0.769; -; -	6.19 (0.74-51.49)	0.092; -; -	1.08 (0.84-1.39)	0.543; -; -
Taqman	3	1614 (7/133/1474)	1652 (7/146/1499)	0.97 (0.35-2.66)	0.950; 0.397; 0.0%	0.91 (0.71-1.17)	0.477; 0.562; 0.0%	0.92 (0.72-1.17)	0.488; 0.486; 0.0%	0.99 (0.36-2.71)	0.842; 0.407; 0.0%	0.92 (0.73-1.16)	0.502; 0.415; 0.0%
PCR-LDR	1	87 (0/4/83)	106 (0/13/93)	-	-	0.34 (0.11-1.10)	0.072; -; -	0.34 (0.11-1.10)	0.072; -; -	-	-	0.36 (0.12-1.13)	0.079; -; -
SNaPShot	1	199 (0/22/177)	214 (0/27/187)	-	-	0.86 (0.47-1.57)	0.624; -; -	0.86 (0.47-1.57)	0.624; -; -	-	-	0.87 (0.49-1.55)	0.635; -; -
Cancer type													
HNSCC	1	55 (0/10/45)	110 (0/12/98)	-	-	1.81 (0.73-4.51)	0.199; -; -	1.81 (0.73-4.51)	0.199; -; -	-	-	1.73 (0.72-4.15)	0.217; -; -
Prostate	4	2200 (32/386/1782)	2438 (21/371/2046)	2.02 (0.60-6.83)	0.117; 0.090; 58.5%	1.42 (0.84-2.40)	0.062; 0.000; 87.7%	1.46 (0.89-2.40)	0.031; 0.000; 86.9%	2.03 (0.58-7.16)	0.124; 0.077; 60.9%	1.43 (0.93-2.21)	0.017; 0.000; 85.0%
Prostate in Asian	1	662 (2/48/612)	716 (0/57/659)	5.38 (0.26-112.36)	0.278; -; -	0.91 (0.61-1.35)	0.631; -; -	0.94 (0.64-1.40)	0.777; -; -	5.42 (0.26-113.18)	0.275; -; -	0.99 (0.67-1.45)	0.943; -; -
Prostate in Caucasian	3	1538 (30/338/1170)	1722 (21/313/1387)	1.78 (0.43-7.40)	0.427; 0.045; 75.2%	1.71 (0.83-3.51)	0.144; 0.000; 91.2%	1.75 (0.89-3.47)	0.107; 0.000; 90.7%	1.78 (0.41-7.74)	0.443; 0.038; 76.8%	1.68 (0.94-3.02)	0.081; 0.000; 89.5%
Breast	5	2047 (25/263/1759)	1972 (9/228/1735)	2.16 (0.52-8.85)	0.031; 0.084; 54.8%	1.07 (0.88-1.29)	0.516; 0.188; 35.0%	1.07 (0.76-1.50)	0.254; 0.061; 55.6%	**2.27 (1.06-4.87)**	0.035; 0.120; 48.6%	1.09 (0.76-1.55)	0.106; 0.022; 64.9%
Breast in Asian	3	1832 (23/227/1582)	1746 (4/182/1560)	**4.38 (1.58-12.12)**	0.004; 0.932; 0.0%	1.14 (0.92-1.41)	0.228; 0.211; 35.6%	1.26 (0.89-1.79)	0.198; 0.132; 50.7%	**4.16 (1.51-11.48)**	0.006; 0.911; 0.0%	1.32 (0.93-1.86)	0.115; 0.109; 54.9%
Breast in Caucasian	2	215 (2/36/177)	226 (5/46/175)	0.34 (0.06-1.83)	0.211; -; -	0.75 (0.46-1.22)	0.251; 0.388; 0.0%	0.72 (0.44-1.16)	0.178; 0.309; 3.2%	0.39 (0.07-2.05)	0.265; -; -	0.71 (0.45-1.14)	0.156; 0.286; 12.3%

Gynecologic[c]	2	301 (14/62/225)	321 (2/64/255)	**9.92 (2.15-45.66)**	0.003; -; -	1.16 (0.77-1.75)	0.488; 0.176; 45.4%	1.31 (0.58-2.94)	0.152; 0.048; 74.5%	**8.35 (1.85-37.75)**	0.006; -; -	1.38 (0.58-3.29)	0.020; 0.018; 82.2%
Gynecologic in Asian	1	199 (0/22/177)	214 (0/27/187)	-	-	0.86 (0.47-1.57)	0.624; -; -	0.86 (0.47-1.57)	0.624; -; -	-	-	**0.87 (0.49-1.55)**	0.635; -; -
Gynecologic in Caucasian	1	102 (14/40/48)	107 (2/37/68)	**9.92 (2.15-45.66)**	0.003; -; -	1.53 (0.86-2.74)	0.150; -; -	**1.96 (1.13-3.41)**	0.017; -; -	**8.35 (1.85-37.75)**	0.006; -; -	**2.11 (1.35-3.30)**	0.001; -; -
Colorectal	3	348 (3/32/313)	408 (2/66/340)	**1.91 (0.32-11.58)**	0.480; -; -	0.34 (0.09-1.34)	0.009; 0.030; 71.5%	0.34 (0.08-1.41)	0.016; 0.023; 73.4%	1.97 (0.33-11.90)	0.460; -; -	0.38 (0.09-1.50)	0.035; 0.021; 74.0%
Colorectal in Asian	2	150 (0/4/146)	150 (0/13/127)	-	-	0.15 (0.02-1.01)	0.051; 0.182; 43.8%	0.15 (0.02-1.01)	0.051; 0.182; 43.8%	-	-	0.16 (0.02-1.15)	0.069; 0.169; 47.1%
Colorectal in Caucasian	1	198 (3/28/167)	258 (2/43/213)	1.91 (0.32-11.58)	0.480; -; -	0.83 (0.50-1.39)	0.482; -; -	0.88 (0.53-1.45)	0.612; -; -	1.97 (0.33-11.90)	0.460; -; -	0.94 (0.59-1.49)	0.783; -; -
ESCC	1	95 (0/11/84)	104 (0/11/93)	-	-	1.11 (0.46-2.69)	0.822; -; -	1.11 (0.46-2.69)	0.822; -; -	-	-	1.10 (0.47-2.60)	0.827; -; -
Lung	3	509 (38/134/337)	566 (13/128/425)	1.41 (0.07-30.44)	0.000; 0.044; 75.3%	1.13 (0.59-2.19)	0.067; 0.018; 75.2%	1.19 (0.51-2.76)	0.003; 0.001; 85.6	1.38 (0.09-22.18)	0.000; 0.065; 70.6%	1.19 (0.50-2.86)	0.000; 0.000; 88.9%
Lung in Asian	2	368 (38/103/227)	410 (11/85/314)	**4.88 (2.42-9.84)**	0.000; -; -	1.56 (0.94-2.61)	0.088; 0.230; 30.6%	1.67 (0.79-3.54)	0.183; 0.107; 61.5%	**4.04 (2.02-8.08)**	0.000; -; -	1.68 (0.77-3.64)	0.191; 0.084; 66.4%
Lung in Caucasian	1	141 (0/31/110)	156 (2/43/111)	0.20 (0.01-4.25)	0.303; -; -	0.73 (0.43-1.24)	0.241; -; -	0.70 (0.41-1.18)	0.177; -; -	0.22 (0.01-4.59)	0.327; -; -	0.70 (0.43-1.13)	0.144; -; -
Pancreatic	1	263 (0/54/209)	271 (0/29/242)	-	-	**2.16 (1.32-3.51)**	0.002; -; -	**2.16 (1.32-3.51)**	0.002; -; -	-	-	**2.02 (1.27-3.23)**	0.003; -; -
Glioma	1	150 (2/27/121)	150 (1/14/135)	2.23 (0.20-24.92)	0.514; -; -	**2.15 (1.08-4.29)**	0.030; -; -	**2.16 (1.10-4.21)**	0.025; -; -	2.01 (0.18-22.45)	0.569; -; -	**2.05 (1.09-3.83)**	0.025; -; -
Hepatocellular	1	102 (0/8/94)	347 (0/13/334)	-	-	2.19 (0.88-5.43)	0.092; -; -	2.19 (0.88-5.43)	0.092; -; -	-	-	2.14 (0.87-5.23)	0.096; -; -
OSCC	2	479 (1/33/445)	443 (0/20/423)	6.14 (0.25-151.49)	0.267; -; -	1.28 (0.69-2.38)	0.432; 0.501; 0.0%	1.35 (0.73-2.49)	0.334; 0.403; 0.0%	6.01 (0.24-148.26)	0.273; -; -	1.41 (0.78-2.56)	0.257; 0.323; 0.0%
Gastric	1	87 (0/4/83)	106 (0/13/93)	-	-	0.34 (0.11-1.10)	0.072; -; -	0.34 (0.11-1.10)	0.072; -; -	-	-	0.36 (0.12-1.13)	0.079; -; -
Bladder	1	219 (0/22/197)	461 (0/2/419)	-	-	1.11 (0.65-1.92)	0.697; -; -	1.11 (0.65-1.92)	0.697; -; -	-	-	1.11 (0.65-1.88)	0.704; -; -
RCC	2	952 (5/85/862)	936 (7/89/840)	0.67 (0.21-2.15)	0.498; 0.616; 0.0%	0.92 (0.67-1.26)	0.599; 0.283; 13.1%	0.90 (0.67-1.22)	0.509; 0.235; 29.2%	0.69 (0.22-2.17)	0.521; 0.640; 0.0%	0.89 (0.67-1.19)	0.432; 0.207; 37.1%
RCC in Asian	1	620 (2/46/572)	623 (2/43/578)	1.01 (0.14-7.20)	0.992; -; -	1.08 (0.70-1.66)	0.724; -; -	1.08 (0.71-1.65)	0.728; -; -	1.00 (0.14-7.16)	0.996; -; -	1.07 (0.71-1.61)	0.738; -; -
RCC in Caucasian	1	332 (3/39/290)	313 (5/46/262)	0.54 (0.13-2.29)	0.405; -; -	0.77 (0.48-1.21)	0.254; -; -	0.74 (0.48-1.16)	0.189; -; -	0.56 (0.13-2.37)	0.432; -; -	0.74 (0.49-1.11)	0.149; -; -

[a]P value for Z test. [b]P value for Q test for between-study heterogeneity. [c]Ovarian, cervical and endometrial cancer. The numbers in parentheses represent 95% confidence interval [CI]. The bold numbers mean that the OR values for the contrast models are significant.

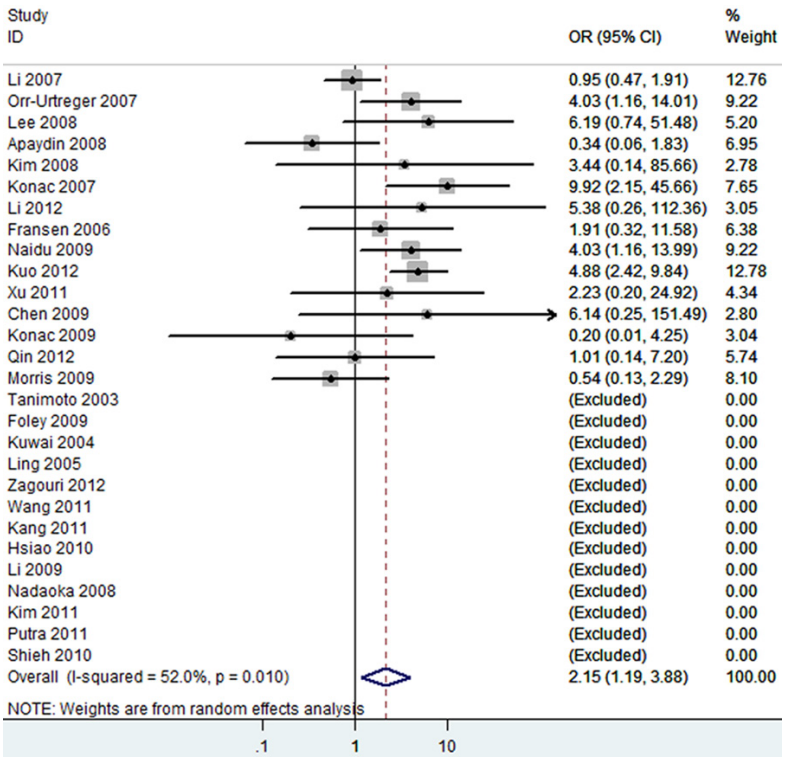

Figure 2. The forest plot of TT vs. CC of rs11549465 polymorphism and overall cancer risk (Random model). The overall OR is shown. The OR of each study is marked with a black dot. The overall OR is indicated by blue diamond.

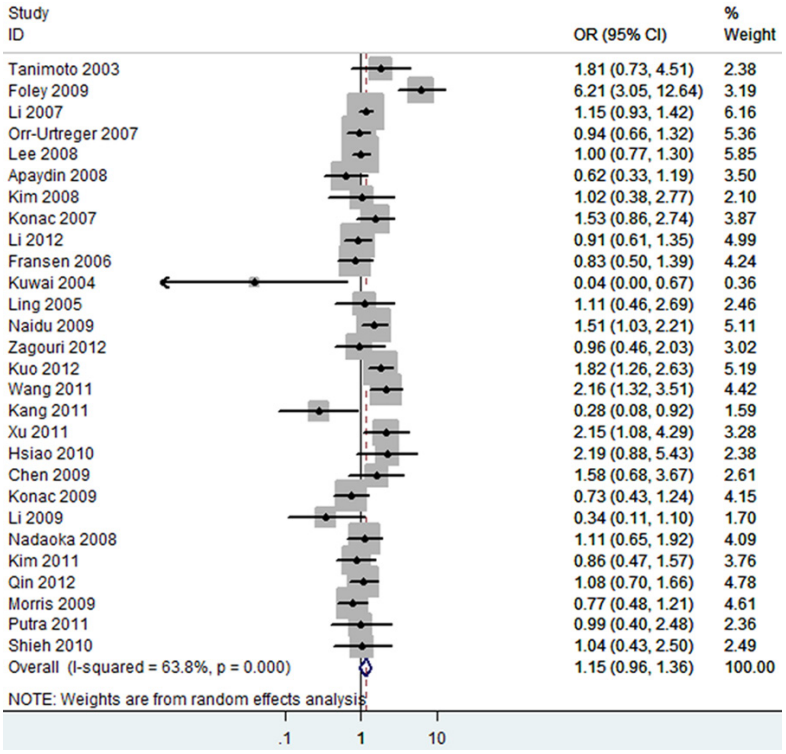

Figure 3. The forest plot of TC vs. CC of rs11549465 polymorphism and overall cancer risk (Random model). The overall OR is shown. The OR of each study is marked with a black dot. The overall OR is indicated by blue diamond.

meta-analysis [20, 24, 27, 28, 30, 31, 33, 34, 39, 44-62]. The main characteristics of these studies were shown in **Table 1**. Genotype and allele distributions of rs11549465 polymorphism among cancer cases and controls and *P* value of HWE in controls were shown in **Tables 1** and **2**. All studies were case-control studies, including four prostate cancer studies [20, 30, 45, 52], three colorectal cancer studies [24, 27, 54], two gynecologic carcinoma studies [28, 55] , five breast cancer studies [31, 33, 34, 51, 61], two oral squamous cell carcinoma (OSCC) studies [47, 62], three lung cancer studies [48, 56, 59], two renal cell carcinoma studies [50, 60] and the others (including esophageal squamous cell carcinoma (ESCC) [39], head and neck squamous cell carcinoma (HNSCC) [44], transitional cell carcinoma of the bladder [46], gastric cancer [49], hepatocellular carcinoma [53], pancreatic cancer [57] and glioma [58]). Cancers were diagnosed histopathologically in most studies. There were nineteen studies [20, 24, 30, 33, 34, 39, 44, 46, 47, 49, 51, 53-60, 62] of Asian descent, nine studies [27, 28, 30, 31, 45, 48, 50, 52, 61] of Caucasian descent. Population-based controls were carried out in 11 studies, while hospital-based controls were carried out in 17 studies. All studies were reported in English and the genotyping methods contained the classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, PCR-sequencing, SNP-ITTM, PCR-LDR, SnaPShot and Taqman. The genotype distributions of controls were all in agreement with HWE.

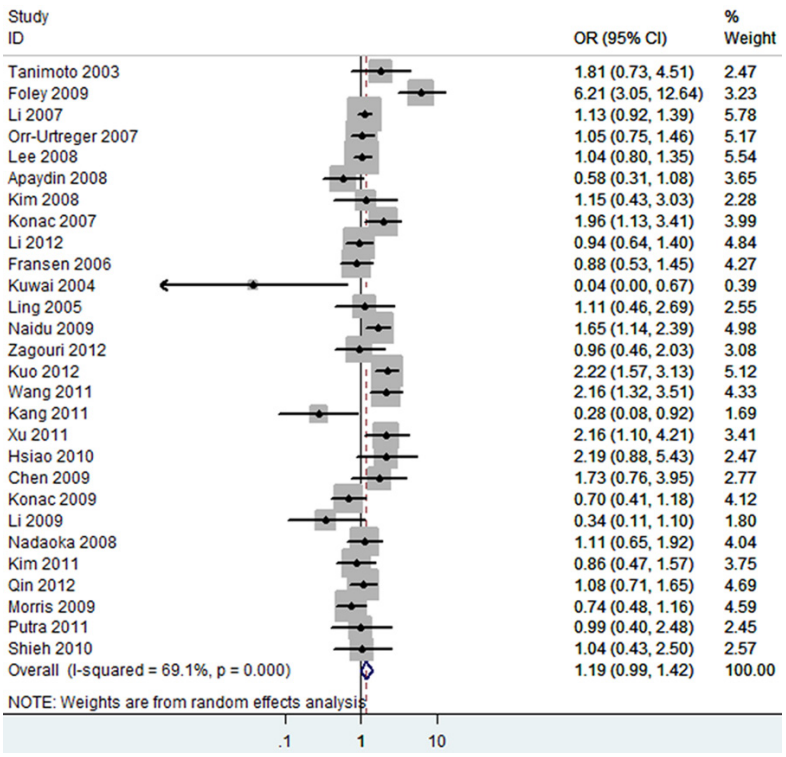

Figure 4. The forest plot of TT/TC vs. CC of rs11549465 polymorphism and overall cancer risk (Random model). The overall OR is shown. The OR of each study is marked with a black dot. The overall OR is indicated by blue diamond.

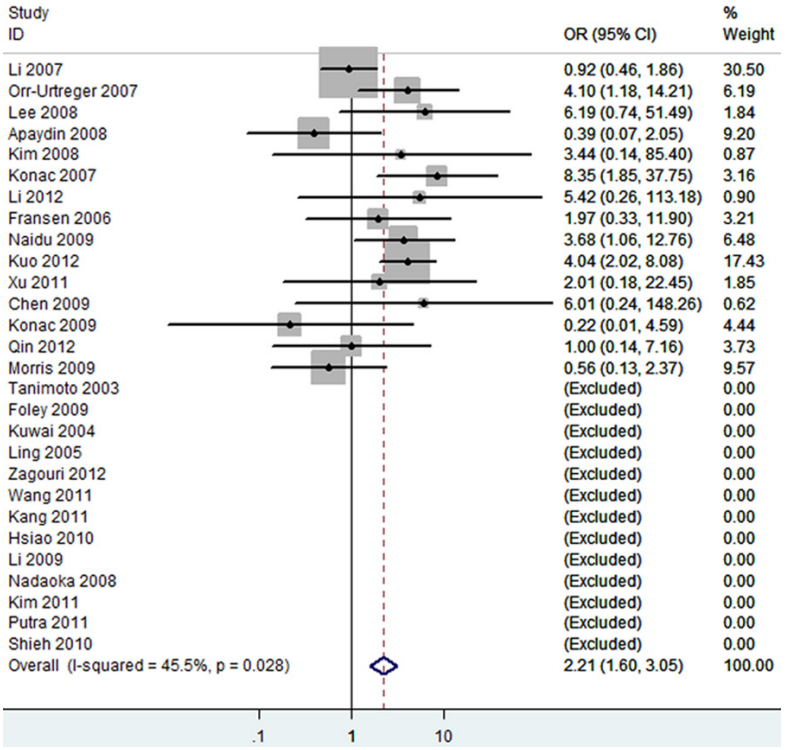

Figure 5. The forest plot of TT vs. TC/CC of rs11549465 polymorphism and overall cancer risk (Fixed model). The overall OR is shown. The OR of each study is marked with a black dot. The overall OR is indicated by blue diamond.

Meta-analysis

Overall, as shown in **Table 3**, we observed that the rs-11549465 (1772C/T) polymorphism increased the cancer risk in the homozygote (TT vs. CC, OR=2.15 [1.19-3.88]) (**Figure 2**), heterozygote model (TC vs. CC, OR=1.15 [0.96-1.36]) (**Figure 3**), dominant genetic model (OR=1.19 [0.99-1.42]) (**Figure 4**), recessive model (OR=2.21 [1.60-3.05]) (**Figure 5**) and additive model (T vs. C, OR=1.20 [1.01-1.44]) (**Figure 6**) when all the eligible studies were pooled into the meta-analysis. In the homozygote comparison, heterozygote comparison, dominant genetic, recessive genetic and additive models, all the *P* values of Q-test were lower than 0.05 and I^2 values were higher than 50%. So we performed the sensitive analysis by deleting one single study from overall pooled analysis each time to check the influence of the removed data. However, the results revealed that no extreme sensitive study changed the between-study heterogeneities.

We then evaluated the effects of the rs11549465 (1772C/T) polymorphism according to specific cancer types, different ethnicities, different detection methods and different sources of control. The results of stratified analyses were listed out in **Table 3**. Subgroup analyses for cancer types indicated that the pooled ORs for the homozygote (TT vs. CC, OR=9.92 [2.15-45.66]), heterozygote model (TC vs. CC, OR=1.53 [0.86-2.74]), dominant genetic model (OR=1.96 [1.13-3.41]), recessive model (OR=8.35 [1.85-37.75]) and additive model (T vs. C, OR=2.11 [1.35-3.30]) (**Table 3**)

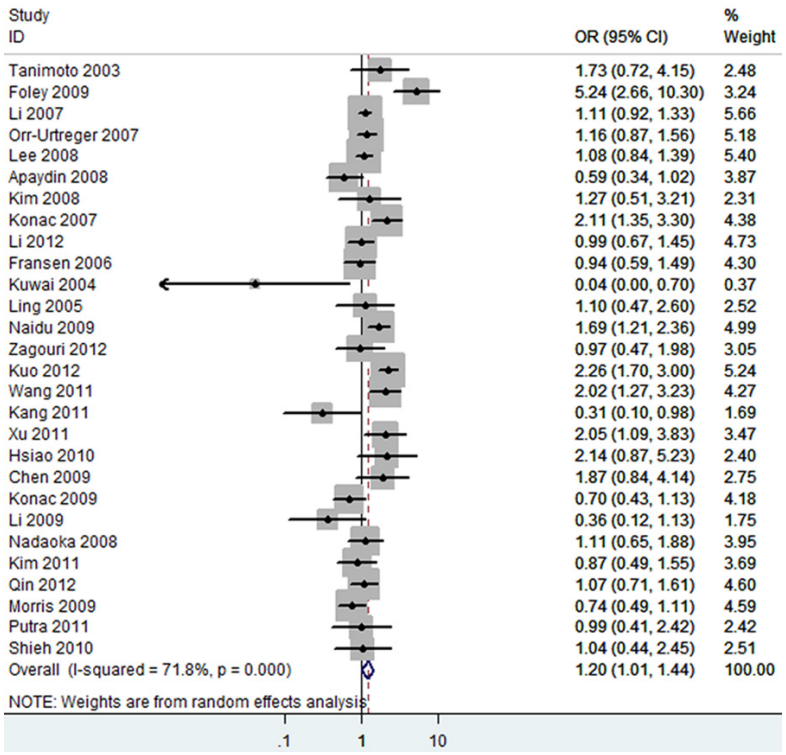

Figure 6. The forest plot of T vs. C of rs11549465 polymorphism and overall cancer risk (Random model). The overall OR is shown. The OR of each study is marked with a black dot. The overall OR is indicated by blue diamond.

suggested the rs11549465 polymorphism was significantly associated with an increased gynecologic cancer risk in Caucasian. A marginal significant association between the rs11549465 polymorphism and increased lung cancer risk was detected in Asians under homozygote comparison (TT vs. CC, OR=4.88 [2.42-9.84]) and recessive genetic model (TT vs. TC/CC, OR=4.04 [2.02-8.08]) (**Table 3**) and the pooled ORs for all genetic models tested suggested that rs11549465 polymorphism was significantly associated with a decreased lung cancer risk in Caucasian (**Table 3**). A marginal significant association between the rs11549465 polymorphism and increased breast cancer risk was detected in Asians under homozygote comparison (TT vs. CC, OR=4.38 [1.58-12.12]) (**Figure 7**) and recessive genetic model (TT vs. TC/CC, OR=4.16 [1.51-11.48]) (**Figure 8**) and the pooled ORs for all genetic models tested suggested that rs11549465 polymorphism was significantly associated with a decreased breast cancer risk in Caucasian (**Table 3**). For pancreatic cancer and glioma, significant associations were observed in heterozygote comparison (TC vs. CC), dominant genetic model (TT/TC vs. CC) and additive model (T vs. C) (**Table 3**). Significant association was not observed for head and neck squamous cell carcinoma (HNSCC), prostate cancer, colorectal cancer, esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma, oral squamous cell carcinoma (OSCC), Gastric cancer, transitional cell carcinoma of the bladder and renal cell carcinoma in all genetic models tested. In the stratified analysis by ethnicity, significantly increased risks were found in Asian in almost all genetic models tested (**Table 3**). The remaining polled ORs from this analysis were not significant (**Table 3**). Significant association was not observed for different detection methods. According to the source of controls, signification effects in two genetic models were observed in hospital-based studies; while in population-based studies, significant association was not observed in any genetic model.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis. Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not present any obvious evidence of publication bias (TT vs. CC. P=0.908; TC vs. CC. P=0.660; TT/TC vs. CC, P=0.627; TT vs. TC/CC, P=0.992; T vs. C. P=0.516).

Discussion

This meta-analysis of 28 studies involving 7807 cases and 8633 controls was conducted in order to yield a valid conclusion concerning the potential association between rs11549465 (1772C/T) polymorphism and cancer risk. HIF-1 plays a major role in cancer progression and metastasis through activation of various genes that are linked to regulation of angiogenesis,

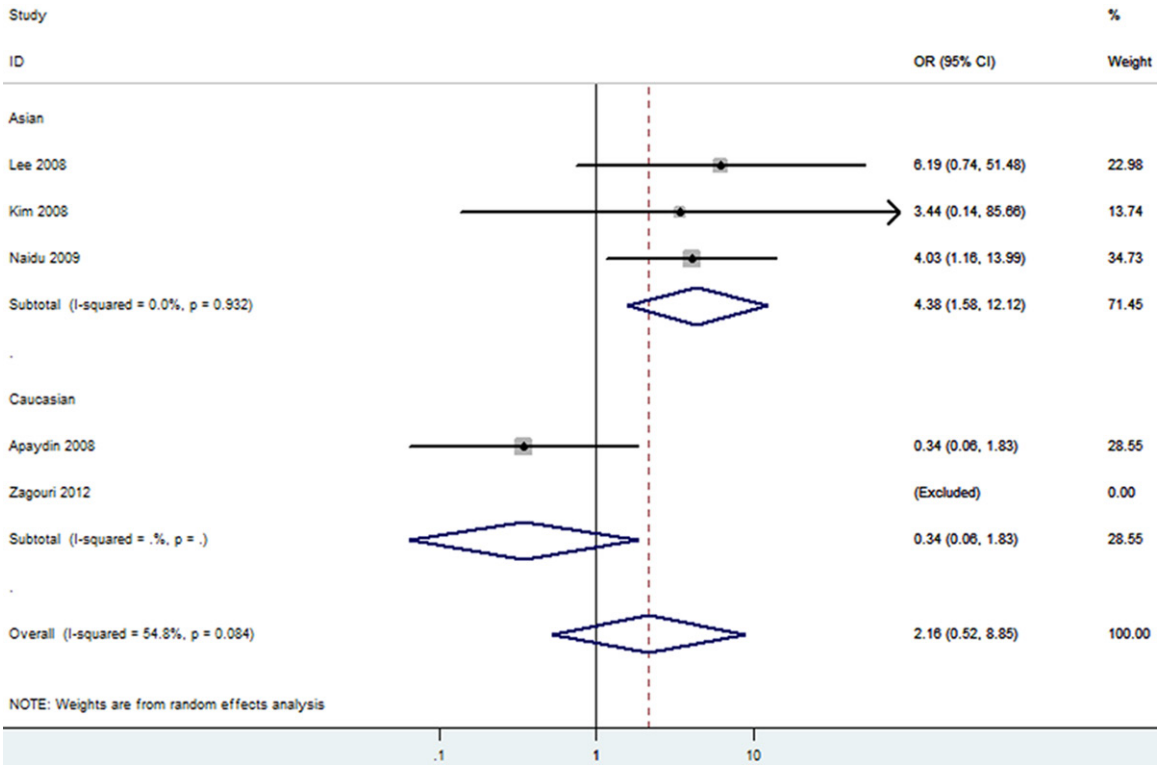

Figure 7. The forest plot of T vs. C of rs11549465 polymorphism and breast cancer risk (Random model). The overall OR is shown. The OR of each study is marked with a black dot. The overall OR is indicated by blue diamond.

cell survival, and energy metabolism [63, 64]. The HIF-1 was previously found to be implicated in the development and progression of cancer [63, 64]. In 2009, Zhao T *et al*. [65] have done a meta-analysis on the relationship between HIF-1 and cancers, but their study only referred to the case-control studies before 2009. The polymorphisms analyzed in the present study consist of G to A nucleotide substitutions at positions 1772 of the exon 12 of the HIF-1. Because a study by Tanimoto [64] showed both of the substitutions displayed an increased transactivation capacity of HIF-1α in vitro, the presence of the variant alleles might be associated with increased cancer susceptibility. However, studies focusing on the association of the HIF-1 polymorphism with cancer susceptibility had controversial conclusions [20, 22, 27, 28, 30, 31, 33, 44-51, 53, 55-57, 59, 60, 62, 66, 67]. The lack of concordance across many of these studies reflects limitation in the studies, such as small sample sizes, ethnic difference and research methodology and so on. Meta-analysis is a powerful tool for summarizing the results from different studies by producing a single estimate of the major effect with enhanced precision.

In our analysis, there was significant association between this polymorphism and increased gynecologic cancer risk in Caucasian. Patients carrying the T allele at position 1772 of the exon 12 of the HIF-1 had more cancer risk than did patients homozygous for the C allele. A marginal significant association between the rs11549465 polymorphism and increased lung and breast cancer risk was detected in Asians under homozygote comparison and recessive genetic model. The pooled effects for all genetic models tested suggested a significant association between the rs11549465 (1772C/T) polymorphism and a decreased lung and breast cancer risk in Caucasian. Furthermore, We found that Asians with TT genotype had higher risk of cancer compared to Caucasians under the homozygote, recessive and additive models. Inconsistency between the two ethnicities can be explained by the possibility that different ethnic groups live with multiple life styles and environmental factors. And different populations carry different genotype and/or allele frequencies of this locus polymorphism may lead to various degrees of cancer susceptibility. In our meta-analysis, we also observed inconsistent results between hospi-

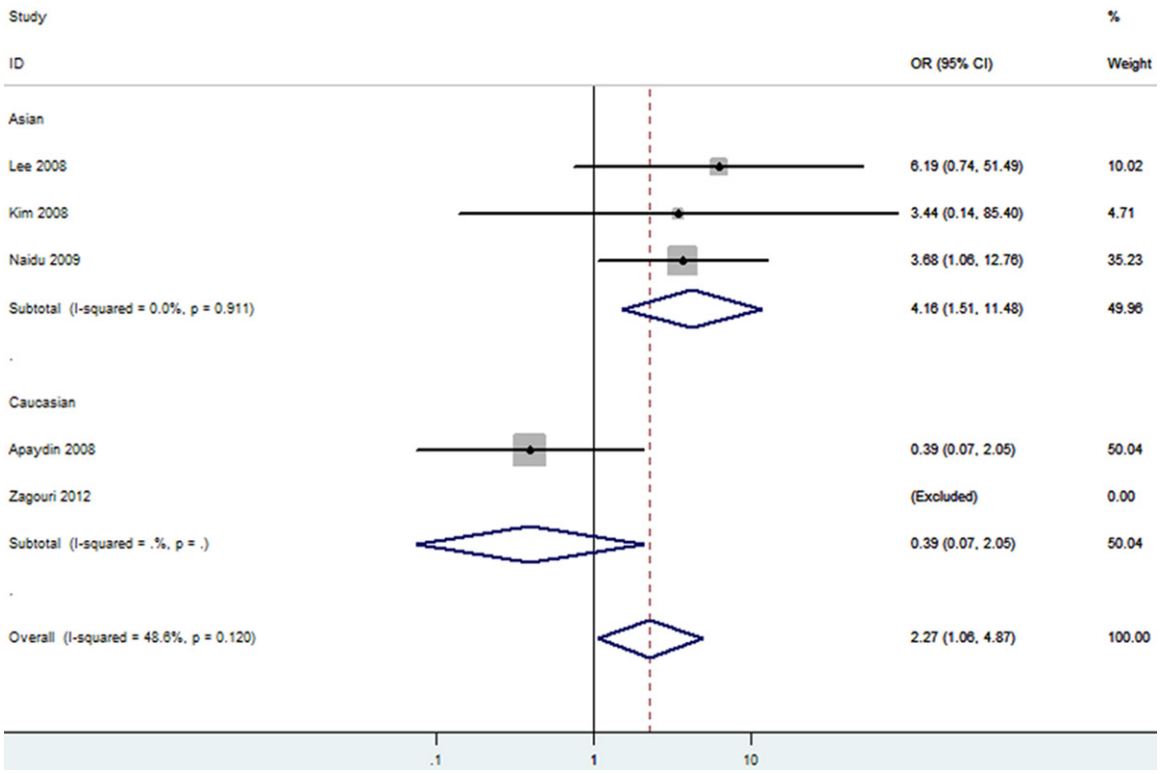

Figure 8. The forest plot of TT vs. TC/CC of rs11549465 polymorphism and breast cancer risk (Fixed model). The overall OR is shown. The OR of each study is marked with a black dot. The overall OR is indicated by blue diamond.

tal-based studies and population-based studies. Controls in hospital-based studies are more representative of general population than controls from population-based studies. Several factors such as environmental factors and genetic backgrounds might contribute to the discrepancy.

There were some limitations in our meta-analysis. First, sample size in any given cancer was not sufficiently large, which could increase the probability of false positive or false negative. It might be difficult to get a concrete conclusion if the number of included studies in subgroup was few. Besides, the sample size was not large enough, studies involved in different ethnicities were warranted to estimate the effects of this functional polymorphism on cancer risk. Second, due to the original data of the eligible studies was unavailable, it was difficult for us to evaluate the roles of some special environmental factors and lifestyles such as diet, alcohol consumption, and smoking status in developing cancer. Third, the influence of bias in the present analysis could not be completely excluded because positive results are supposed to be published much more quickly than articles with "negatives" results.

Conclusions

Our meta-analysis suggested that the rs11549465 (1772C/T) genetic polymorphism is significantly associated with higher breast and lung cancer risk among Asian population, and this SNP is significantly associated with decreased breast and lung cancer risk among Caucasian population, but this SNP was significantly associated with the gynecologic cancer among Caucasian population. The effect of the rs11549465 polymorphism on cancer especially exists in Asians. Large well designed epidemiological studies are needed to validate our findings.

Disclosure of conflict of interest

None for all authors.

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