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Update meta-analysis on 1790G/A polymorphism and cancer risk: Evidence from 26 studies

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The results from the published studies on the association between hypoxia-inducible factor-1(Hif-1/HIF-1) polymorphisms and cancer risk are conflicting. The common 1790G/A rs11549467) genetic polymorphism has been reported to be functional and may contribute to genetic susceptibility to cancers. However, the association between 1790G/A (rs11549467) and cancer risk remains inconclusive.

To better understand the role of 1790G/A (rs11549467) polymorphism in cancer, we conducted this comprehensive meta-analysis encompassing 6337 cases and 9302 controls.

Overall, the 1790G/A (rs11549467) genetic polymorphism was associated with higher cancer risk. In the stratified analysis, significant associations were found between the Hif-1/HIF-1 1790G/A polymorphism and lung cancer, pancreatic cancer and oral squamous cell carcinoma. We also observed that the AA genotype might modulate lung cancer (OR=5.42[2.75-10.70]), pancreatic cancer (OR=9.30[1.12-77.61]) and oral squamous cell carcinoma (OSCC) (OR=13.32[1.57-112.75]) risk comparing with the GG genotype. Moreover, a significantly increased cancer risk was found in homozygote comparison (AA vs. GG) and recessive genetic model (AA vs. AG/GG) among Caucasian population. When stratified by study design, significantly elevated susceptibility to cancer was found among hospital-based studies.

These findings suggested that the 1790G/A (rs11549467) genetic polymorphism may contribute to the susceptibility of cancers except gynecologic cancer, especially in homozygote comparison and recessive genetic model among Caucasian population, and this SNP was significantly associated with the lung cancer, pancreatic cancer and oral squamous cell carcinoma (OSCC). The phenomenon also indicates that the SNP functions as a recessive mutation needs to be verified or linked with functional studies.

Key words: Hif-1/HIF-1, 1790G/A, cancer, genetic polymorphism, meta-analysis

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, resulting in rapid tumor cell proliferation and developing 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/HIF-1) plays an essential role in adaptive responses to reduced oxygen levels[5,6].

Hif-1/HIF-1 is a dimeric protein complex, consisting of α and β subunits. The activity of Hif-1/HIF-1 is regulated predominantly through the stability of the subunit [7]. Koshiji et al. demonstrated that Hif-1/HIF-1 (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 [9,10] [11,12]. These data support the concept that defective DNA repair pathways cause genomic instability within the tumor microenvironment. PASD8 (Hif-1/HIF-1) 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-1/HIF-1 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 [14-19]. The target genes of Hif-1/HIF-1 are particularly relevant to cancer, encoding angiogenic factors, proliferation/survival factors, glucose transporters and glycolytic enzymes [20]. 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/HIF-1 polymorphisms and cancer risk, but the results have been conflicting [21-38]. Thus, the association between the Hif-1/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 August.2013 in a meta-analysis to give a comprehensive picture of the role of Hif-1/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-1/HIF-1α 1790G/A (rs11549467) polymorphisms with all cancers, different kinds of cancers, and different kinds of populations.

Materials and 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 August,2013) was conducted using the search terms including "Hif-1/HIF-1α" or "hypoxia-inducible factor-1" or "1790G/A" or "rs11549467" or "A588T (Ala588Thr, G1790A, rs11549467)" , "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 1790G/A 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 1790G/A 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(Fig. 1). For each eligible study, the following information was recorded: the first author's name, the year of

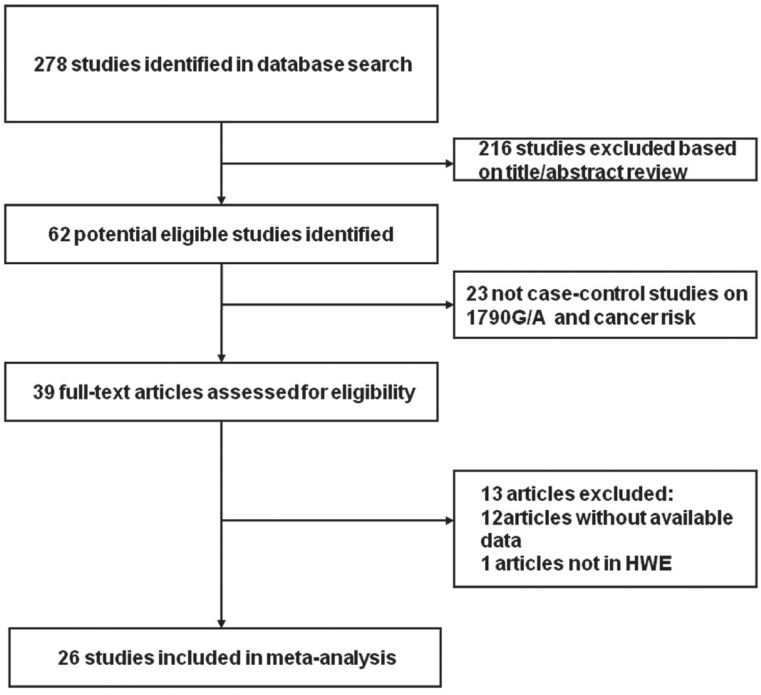

Figure 1. Flow diagram of study identification.

publication, patients, ethnicity, genotyping methods, sources of control, racial descent of the study population, genotype and allele distributions and main results of each study.

Statistical analysis. The strength of relationship between 1790G/A polymorphism and cancer was assessed by using crude OR with 95% CI. We examined the association between the 1790G/A polymorphism and cancer risk using the following genetic models: homozygote comparison (AA vs. GG), heterozygote comparison (AG vs. GG), dominant genetic model (AA/AG vs. GG), recessive genetic model (AA vs. AG/GG) and additive model (A vs. G). Firstly, we checked the Hardy-Weinberg equilibrium (HWE) in controls for each study. Then we performed Q-test for evaluating the heterogeneity [39]. Fixed effects model was used to pool the data when the P-value of Q-test ≥0.05; otherwise, random effects model was selected [40]. I^2 was also used to assess the heterogeneity in this meta-analysis. If I^2> 50%,the heterogeneity exists[41]. 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)[42]. All statistical analysis were performed using STATA 12.0 software and Review Manager 5.2.

Results

Eligible studies. Overall,26 relevant studies involving 6337 cases and 9302 controls were selected in this meta-analysis[21,26,27,29,30,32,43-62]. The main characteristics of these studies were shown in Table 1. Genotype and allele distributions of 1790G/A polymorphism among cancer cases and controls and *P* value of HWE in controls were shown in Table 1 and 2. All studies were case-control studies, including three oral squamous cell carcinoma (OSCC) studies [46,51,59], three prostate cancer studies[29,44,60], three renal cell carcinoma studies[21,49,57], three breast cancer studies[30,32,50], two gynecologic carcinoma studies[27,53], two colorectal studies[26,62], two pancreatic cancer studies[55,58], three lung cancer studies[47,54,56] and the others(including head and neck squamous cell carcinoma(HNSCC)[43], transitional cell carcinoma of the bladder[45], hepatocellular carcinoma[52], gastric cancer[52], glottic cancer[61]). Cancers were histological or pathological in most studies. There were fourteen studi es[32,43,45,46,48,50,52-57,60,61] of Asian descent, twelve studies[21,26,27,29,30,44,47,49,51,58,61,62] of Caucasian descent. Population-based controls were carried out in 9

Table1. 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	0.655
Munoz-Guerra 2009 OSCC	Spain	Caucasian	PCR-RFLP	Hospital	64/139	0.693
Li 2007 prostate cancer	USA	Caucasian	PCR-RFLP	Population	1066/1264	0.810
Orr-Urtreger 2007 prostate cancer	Israel	Caucasian	PCR-RFLP	Population	200/300	0.954
Clifford 2001 renal cell carcinoma	UK	Caucasian	PCR-Sequencing	Hospital	48/144	0.866
Apaydin 2008 breast cancer	Turkey	Caucasian	PCR-RFLP	Population	102/102	0.840
Kim 2008 breast cancer	Korea	Asian	PCR-Sequencing	Hospital	90/102	0.060
Konac 2007 gynecologic cancer	Turkey	Caucasian	PCR-RFLP	Hospital	102/107	—
Fransen 2006 colorectal cancer	Sweden	Caucasian	PCR-RFLP	Hospital	198/256	0.775
Naidu 2009 breast cancer	Malaysia	Asian	PCR-RFLP	Hospital	410/275	0.180
Ruiz-Tovar 2012 pancreatic cancer	Spain	Caucasian	PCR-RFLP	Hospital	59/152	0.675
Kuo 2012 non–small-cell lung cancer	China	Asian	PCR-RFLP	Hospital	285/300	0.154
Wang 2011 pancreatic cancer	China	Asian	PCR-Sequencing	Hospital	263/271	0.486
Hsiao 2010 hepatocellular carcinoma	China	Asian	PCR-RFLP	Hospital	102/347	0.701
Chen 2009 OSCC	China	Asian	PCR-RFLP	Population	174/347	0.701
Konac 2009 lung cancer	Turkey	Caucasian	PCR-RFLP	Hospital	141/156	0.936
Li 2009 gastric cancer	China	Asian	PCR-LDR	Hospital	87/106	0.764
Nadaoka 2008 bladder cnacer	Japan	Asian	PCR-RFLP	Hospital	219/461	0.330
Kim 2011 cervical cancer	Korea	Asian	SNaPShot	Hospital	199/214	0.136
Qin 2012 renal cell carcinoma	China	Asian	Taqman	Hospital	620/623	0.420
Morris 2009 renal cell carcinoma	Poland	Caucasian	Taqman	Population	325/309	0.662
Putra 2011 lung cancer	Japan	Asian	PCR-Sequencing	Hospital	83/110	0.655
Knechtel 2010 colorectal cancer	Austria	Caucasian	Taqman	Population	367/2156	0.405
Li 2012 prostate cancer	China	Asian	Taqman	Population	662/716	0.554
Mera-Menendez 2013 glottic cancer	Spain	Caucasian	PCR-RFLP	Population	111/139	0.693
Shieh 2010 OSCC	China	Asian	PCR-Sequencing	Hospital	305/96	0.711

p Value of Hardy-Weinberg equilibrium in controls.

Table 2. Distribution of 1790G/A(rs11549467) polymorphism and the main results of eligible studies.

Stuies(cancer type)	Case	Control	OR(95% CI)				
	(AA/AG/GG)	(AA/AG/GG)	AA vs.GG	AG vs.GG	AA/AG vs.GG	AA vs.AG/GG	A vs.G
Tanimoto 2003 HNSCC	55 (0/4/51)	110 (0/9/101)	—	0.88 (0.26-3.00)	0.88 (0.26-3.00)	—	0.88 (0.27-2.94)
Munoz-Guerra 2009 OSCC	64 (3/21/40)	139 (0/9/130)	22.56 (1.14-445.89)	7.58 (3.22-17.88)	8.67 (3.73-20.16)	15.88 (0.81-312.08)	7.99 (3.63-17.58)
Li 2007 prostate cancer	1066 (0/13/1053)	1264 (0/17/1247)	—	0.91 (0.44-1.87)	0.91 (0.44-1.87)	—	0.91 (0.44-1.87)
Orr-Urtreger 2007 prostate cancer	200 (0/2/198)	300 (0/2/298)	—	1.51 (0.21-10.77)	1.51 (0.21-10.77)	—	1.50 (0.21-10.71)
Clifford 2001 renal cell carcinoma	48 (0/1/47)	144 (0/4/140)	—	0.74 (0.08-6.83)	0.74 (0.08-6.83)	—	0.75 (0.08-6.77)
Apaydin 2008 breast cancer	102 (0/0/102)	102 (0/4/98)	—	0.11 (0.01-2.01)	0.11 (0.01-2.01)	—	0.11 (0.01-2.04)
Kim 2008 breast cancer	90 (0/3/87)	102 (1/7/94)	0.36 (0.01-8.95)	0.46 (0.11-1.85)	0.41 (0.10-1.58)	0.37 (0.02-9.29)	0.37 (0.10-1.38)
Konac 2007 gynecologic cancer	102 (0/2/47)	107 (0/0/107)	—	5.35 (0.25-112.76)	5.35 (0.25-112.76)	—	5.30 (0.25-110.99)
Fransen 2006 colorectal cancer	198 (0/9/189)	256 (0/9/247)	—	1.31 (0.51-3.36)	1.31 (0.51-3.36)	—	1.30 (0.51-3.31)
Naidu 2009 breast cancer	410 (6/72/332)	275 (2/41/232)	2.10 (0.42-10.48)	1.23 (0.81-1.86)	1.27 (0.84-1.91)	2.03 (0.41-10.12)	1.28 (0.88-1.87)
Ruiz-Tovar 2012 pancreatic cancer	59 (3/2/54)	152 (0/10/142)	18.30 (0.93-360.19)	0.53 (0.11-2.48)	1.31 (0.43-4.02)	18.89 (0.96-371.56)	2.14 (0.82-5.56)
Kuo 2012 non–small-cell lung cancer	285 (41/94/150)	300 (11/74/215)	5.34 (2.66-10.73)	1.82 (1.26-2.63)	2.28 (1.62-3.21)	4.41 (2.22-8.78)	2.35 (1.77-3.11)
Wang 2011 pancreatic cancer	263 (1/64/198)	271 (0/22/249)	3.77 (0.15-93.07)	3.66 (2.18-6.15)	3.72 (2.21-6.24)	3.10 (0.13-76.51)	3.39 (2.06-5.58)
Hsiao 2010 hepatocellular carcinoma	102 (0/15/87)	347 (0/14/333)	—	4.10 (1.91-8.82)	4.10 (1.91-8.82)	—	3.85 (1.83-8.13)
Chen 2009 OSCC	174 (1/20/153)	347 (0/14/333)	6.52 (0.26-160.91)	3.11 (1.53-6.32)	3.26 (1.62-6.59)	6.01 (0.24-148.26)	3.28 (1.83-8.13)
Konac 2009 lung cancer	141 (0/1/140)	156 (0/2/154)	—	0.55 (0.05-6.13)	0.55 (0.05-6.13)	—	0.55 (0.05-6.12)
Li 2009 gastric cancer	87 (0/13/74)	106 (0/6/100)	—	2.93 (1.06-8.06)	2.93 (1.06-8.06)	—	2.77 (1.03-7.45)
Nadaoka 2008 bladder cancer	219 (0/15/204)	461 (0/40/421)	—	0.77 (0.42-1.43)	0.77 (0.42-1.43)	—	0.78 (0.43-1.43)
Kim 2011 cervical cancer	199 (0/12/187)	214 (1/13/200)	0.36 (0.01-8.80)	0.99 (0.44-2.22)	0.92 (0.41-2.03)	0.36 (0.01-8.81)	0.86 (0.40-1.85)
Qin 2012 renal cell carcinoma	620(0/45/575)	623 (0/39/584)	—	1.17 (0.75-1.83)	1.17 (0.75-1.83)	—	1.17 (0.75-1.80)
Morris 2009 renal cell carcinoma	325 (2/10/313)	309 (0/15/294)	4.70 (0.22-98.24)	0.63 (0.28-1.42)	0.75 (0.35-1.63)	4.78 (0.23-100.04)	0.88 (0.42-1.85)
Putra 2011 lung cancer	83 (2/9/72)	110 (0/9/101)	7.00 (0.33-148.00)	1.40 (0.53-3.71)	1.71 (0.68-4.35)	6.78 (0.32-143.12)	1.99 (0.83-4.78)
Knechtel 2010 colorectal cancer	367 (0/11/356)	2156 (0/76/2080)	—	0.85 (0.44-1.61)	0.85 (0.44-1.61)	—	0.85 (0.45-1.60)
Li 2012 prostate cancer	662 (1/47/614)	716 (0/31/685)	3.35 (0.14-82.30)	1.69 (1.06-2.70)	1.73 (1.09-2.75)	3.25 (0.13-79.90)	1.74 (1.10-2.74)
Mera-Menendez 2013 glottic cancer	111 (0/4/107)	139 (0/9/130)	—	0.54 (1.16-1.80)	0.54 (0.16-1.80)	—	0.55 (0.17-1.80)
Shieh 2010 OSCC	305 (0/24/281)	96 (0/7/89)	—	1.09 (0.45-2.61)	1.09 (0.45-2.61)	—	1.08 (0.46-2.55)

studies, while hospital-based controls were carried out in 17 studies. All studies were reported in English. The genotyping methods contained the classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, PCR-sequencing, PCR-LDR, SnaPShot and Taqman. The genotype distributions of controls were all in agreement with HWE except for one studie not estimable [27].

Meta-analysis. Overall, as shown in Table 3, we observed that the 1790G/A(rs11549467) polymorphism increased the cancer risk in the homozygote (AA vs. GG, OR=4.37[2.61-7.33]) (Fig.2), heterozygote model (AG vs. GG, OR=1.39[1.06-1.82]) (Fig.3), dominant genetic model (OR=1.46[1.11-1.92]) (Fig.4), recessive model (OR=3.87[2.32-6.46]) (Fig.5) and additive model (A vs. G, OR=1.49[1.15-1.95]) (Fig.6) when all the eligible studies were pooled into the meta-analysis. In the heterozygote comparison, dominant 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 sensitivity 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 1790G/A(rs11549467) polymorphism according to specific cancer types, different ethnicities, different detection method and different sources of control. As shown in Table 3, we found that 1790G/A(rs11549467) polymorphism elevated oral squamous cell carcinoma (OSCC) risk and lung cancer risk in all the five models (AA vs. GG, AG vs. GG, AA/AG vs. GG, AA vs. AG/GG, A vs. G). For oral squamous cell carcinoma (OSCC), the ORs[95%CI] were 13.32[1.57-112.75], 2.96[1.05-8.31], 3.15[1.05-9.47], 10.70[1.25-91.51] and 3.09[1.07-8.93] respectively; for lung cancer, the ORs[95%CI] were 5.42[2.75-10.70], 1.72[1.22-2.42], 2.14[1.56-2.94], 4.52[2.31-8.83] and 2.26[1.74-2.95] respectively. For pancreatic cancer, significant association was found in the following models: AA vs. GG: OR=9.30[1.12-77.61]; AG vs. GG: OR=2.90[1.82-4.62]; AA vs. AG/GG: OR=8.65[1.04-71.65]; A vs. G: OR=3.12[2.01-4.84]. We also found significant association between 1790G/A (rs11549467) polymorphism and hepatocellular and gastric cancer in heterozygote, recessive and additive model. In the stratified analysis by ethnicity, significantly increased risks were found in Asian in all genetic models tested (Table 3). For Caucasian, significant associations were observed in homozygote comparison (AA vs. GG, OR=12.40[2.19-70.22]) and recessive model (AA vs. AG/GG, OR=11.37[2.02-63.93]). According to the source of controls, signification effects in all genetic models were observed in hospital-based studies; while in population-based studies, significant association was not observed in any genetic model. According to the detection method, signification effects in most genetic models were observed in PCR-RFLP subgroup; while in other subgroup, significant association was not observed in any genetic model.

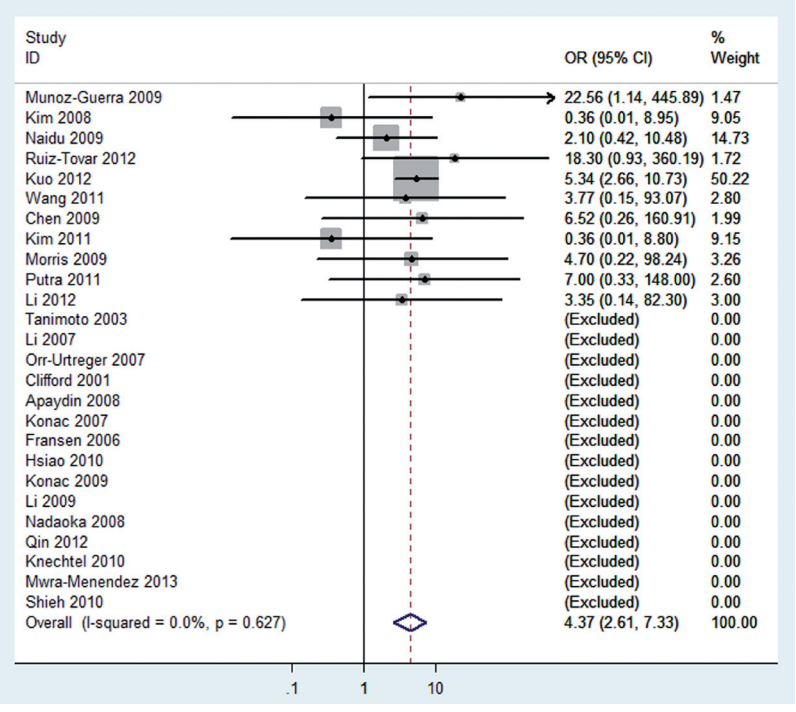

Figure 2. The forest plot of AA vs. GG of 1790G/A polymorphism and overall cancer risk(fixed model).
The overall OR is shown. The OR of each study is marked with a grey square. The %weight of OR is indicated by a shadow. The overall OR is indicated by blue diamond.

Table 3. Results of meta-analysis for 1790G/A(rs11549467) polymorphism and cancer risk.

Study Groups	NO.of	Case	Control	AA vs.GG		AG vs.GG		AA/AG vs.GG		AA vs.AG/GG		A vs.G	
	studies	(AA/AG/GG)	(AA/AG/GG)	OR(95% CI)	Pa;Pb;I^2(%)	OR(95% CI)	Pa;Pb;I^2(%)	OR(95% CI)	Pa;Pb;I^2(%)	OR(95% CI)	Pa;Pb;I^2(%)	OR(95% CI)	Pa;Pb;I^2(%)
All population	26	6337 (60/513/5764)	9302 (15/483/8804)	**4.37 (2.61-7.33)**	0.000;0.535;0,0%	**1.39 (1.06-1.82)**	0.017;0.000;63.8%	**1.46 (1.11-1.92)**	0.007;0.000;66.7%	**3.87 (2.32-6.46)**	0.000;0.714;0.0%	**1.49 (1.15-1.95)**	0.003;0.000;67.9%
Ethnicity													
Asian	14	3554 (52/437/3065)	4078 (15/326/3737)	**3.82 (2.21-6.61)**	0.000;0.556;0.0%	**1.59 (1.19-2.13)**	0.002;0.001;63.6%	**1.64 (1.21-2.22)**	0.001;0.000;68.1%	**3.37 (1.96-5.80)**	0.000;0.661;0.0%	**1.63 (1.21-2.19)**	0.001;0.000;69.9%
Caucasian	12	2783 (8/76/2699)	5224 (0/157/5067)	**12.40 (2.19-70.22)**	0.004;0.737;0.0%	1.04 (0.58-1.84)	0.900;0.003;61.5%	1.16 (0.66-2.05)	0.612;0.002;63.5%	**11.37 (2.02-63.93)**	0.006;0.790;0.0%	1.24 (0.71-2.19)	0.447;0.001;65.1%
Source of control													
Population	9	3062 (4/111/2947)	5443 (0/177/5266)	4.65 (0.75-28.82)	0.099;0.959;0.0%	1.07 (0.69-1.67)	0.764;0.023;55.1%	1.11 (0.71-1.73)	0.648;0.023;55.1%	4.53 (0.73-28.04)	0.104;0.964;0.0%	1.14 (0.74-1.76)	0.542;0.025;54.4%
Hospital	17	3275 (56/402/2817)	3859 (15/306/3538)	**4.35 (2.54-7.45)**	0.000;0.338;11.8%	**1.59 (1.13-2.22)**	0.007;0.000;66.7%	**1.68 (1.20-2.37)**	0.003;0.000;69.8%	**3.81 (2.23-6.51)**	0.000;0.427;0.2%	**1.71 (1.23-2.38)**	0.001;0.000;71.1%
Detection method													
PCR-Sequencing	6	844 (3/105/736)	833 (1/58/774)	2.21 (0.48-10.16)	0.309;0.391;0.0%	1.29 (0.63-2.63)	0.893;0.024;61.3%	1.30 (0.63-2.70)	0.476;0.009;67.1%	2.11 (0.45-9.88)	0.342;0.420;0.0%	1.30 (0.65-2.63)	0.459;0.010;66.7%
PCR-RFLP	14	3233 (54/270/2909)	4345 (13/245/4087)	**5.37 (2.96-9.75)**	0.000;0.580;0.0%	1.51 (0.99-2.31)	0.007;0.000;67.3%	**1.65 (1.08-2.53)**	0.022;0.000;71.4%	**4.59 (2.55-8.27)**	0.000;0.633;0.0%	**1.72 (1.14-2.58)**	0.009;0.000;72.5%
PCR-LDR	1	87 (0/13/74)	106 (0/6/100)	—	—	**2.93 (1.06-8.06)**	0.893;0.024;61.3%	**2.93 (1.06-8.06)**	0.038;-;-	—	—	**2.77 (1.03-7.45)**	0.043;-;-
SNaPShot	1	199 (0/12/187)	214 (1/13/200)	0.36 (0.01-8.80)	0.528;-;-	0.99 (0.44-2.22)	0.007;0.000;67.3%	0.92 (0.41-2.03)	0.831;-;-	0.36 (0.01-8.81)	0.529;-;-	**0.86 (0.40-1.85)**	0.693;-;-
Taqman	4	1974 (3/113/1858)	3804 (0/161/3643)	4.05 (0.45-36.53)	0.213;0.880;0.0%	1.10 (0.75-1.63)	0.893;0.024;61.3%	1.19 (0.80-1.64)	0.444;0.178;38.9%	4.04 (0.45-36.37)	0.213;0.863;0.0%	1.22 (0.94-1.58)	0.301;0.228;30.7%
Cancer type													
HNSCC	1	55 (0/4/51)	110 (0/9/101)	—	—	0.88 (0.26-3.00)	0.838;-;-	0.88 (0.26-3.00)	0.838;-;-	—	—	0.88 (0.27-2.94)	0.841;-;-
OSCC	3	543 (4/65/474)	582 (0/30/552)	**13.32 (1.57-112.75)**	0.017;0.577;0.0%	**2.96 (1.05-8.31)**	0.039;0.008;79.4%	**3.15 (1.05-9.47)**	0.041;0.004;82.2%	**10.70 (1.25-91.51)**	0.030;0.661;0.0%	**3.09 (1.07-8.93)**	0.038;0.003;82.3%
Prostate	3	1928 (1/62/1865)	2280 (0/50/2230)	3.35 (0.14-82.30)	0.460;-;-	1.41 (0.97-2.07)	0.082;0.365;0.7%	1.44 (0.98-2.10)	0.104;0.340;7.2%	3.25 (0.13-79.90)	0.471;-;-	1.45 (1.00-2.11)	0.109;0.330;9.9%
RCC	3	993 (2/56/935)	1076 (0/58/1018)	4.70 (0.22-98.24)	0.319;-;-	1.00 (0.69-1.47)	0.975;0.402;0.0%	1.04 (0.71-1.51)	0.841;0.595;0.0%	4.78 (0.23-100.04)	0.313;-;-	1.07 (0.74-1.55)	0.706;0.777;0.0%
Breast	3	602 (6/75/521)	479 (3/52/424)	1.44 (0.38-5.44)	0.595;0.336;0.0%	0.68 (0.23-2.05)	0.498;0.120;52.8%	0.63 (0.19-2.10)	0.451;0.081;60.2%	1.41 (0.37-5.37)	0.613;0.356;0.0%	0.59 (0.17-2.10)	0.419;0.058;65.0%
Gynecologic c	2	301 (0/14/287)	321 (1/13/307)	0.36 (0.01-8.80)	0.528;-;-	1.16 (0.54-2.48)	0.744;0.291;10.4%	1.08 (0.51-2.28)	0.791;0.270;18.0%	0.36 (0.01-8.81)	0.529;-;-	1.00 (0.48-2.08)	0.831;0.252;23.8%
Colorectal	2	565 (0/20/545)	2412 (0/85/2327)	—	—	0.97 (0.57-1.63)	0.912;0.454;0.0%	0.97 (0.57-1.63)	0.912;0.454;0.0%	—	—	0.97 (0.58-1.62)	0.914;0.459;0.0%
Pancreatic	2	322 (4/66/252)	423 (0/32/391)	**9.30 (1.12-77.61)**	0.039;0.478;0.0%	**2.90 (1.82-4.62)**	0.625;0.020;81.6%	2.50 (0.93-6.73)	0.070;0.098;63.4%	**8.65 (1.04-71.65)**	0.045;0.418;0.0%	**3.12 (2.01-4.84)**	0.000;0.400;0.0%
Lung	3	509 (43/104/362)	566 (11/85/470)	**5.42 (2.75-10.70)**	0.000;0.866;0.0%	**1.72 (1.22-2.41)**	0.002;0.571;0.0%	**2.14 (1.56-2.94)**	0.000;0.458;0.0%	**4.52 (2.31-8.83)**	0.000;0.788;0.0%	**2.26 (1.74-2.95)**	0.000;0.481;0.0%
Hepatocellular	1	102 (0/15/87)	347 (0/14/333)	—	—	**4.10 (1.91-8.82)**	0.000;-;-	**4.10(1.91-8.82)**	0.006;-;-	—	—	**3.85 (1.83-8.13)**	0.000;-;-
Gastric	1	87 (0/13/74)	106 (0/6/100)	—	—	**2.93 (1.06-8.06)**	0.038;-;-	**2.93 (1.06-8.06)**	0.038;-;-	—	—	**2.77 (1.03-7.45)**	0.043;-;-
Bladder	1	219 (0/15/204)	461 (0/40/421)	—	—	0.77 (0.42-1.43)	0.415;-;-	0.77 (0.42-1.43)	0.415;-;-	—	—	0.78 (0.43-1.43)	0.425;-;-
Glottic	1	111 (0/4/97)	139 (0/9/130)	—	—	0.54 (0.16-1.80)	0.316;-;-	0.54 (0.16-1.80)	0.316;-;-	—	—	0.55 (0.17-1.80)	0.323;-;-

a,P value for Z test. b,P value for Q test for between-study heterogeneity. c,Ovarian,cervical and endometrial cancer.

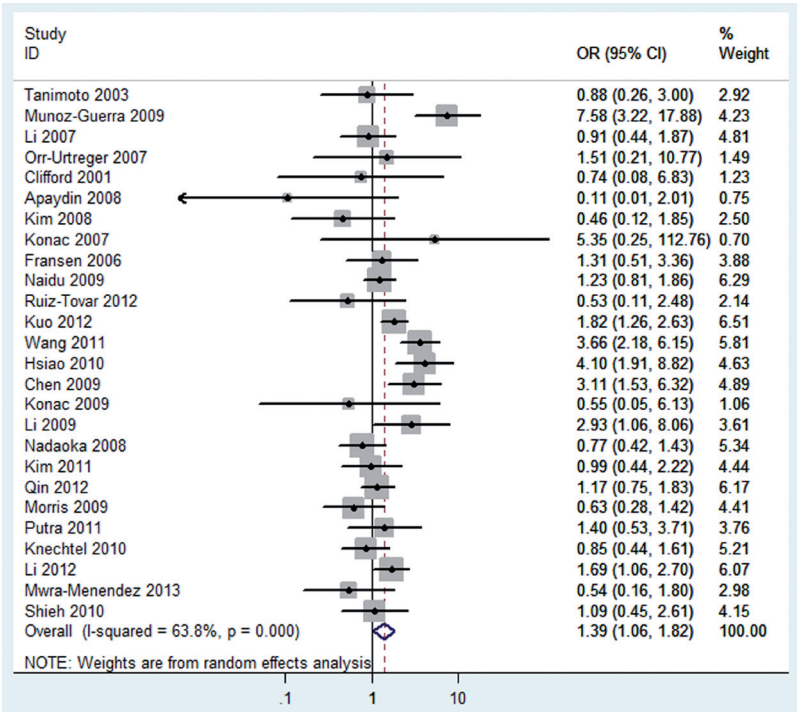

Figure 3. The forest plot of AG vs. GG of 1790G/A polymorphism and overall cancer risk(random model).
The overall OR is shown. The OR of each study is marked with a grey square. The %weight of OR is indicated by a shadow. The overall OR is indicated by blue diamond.

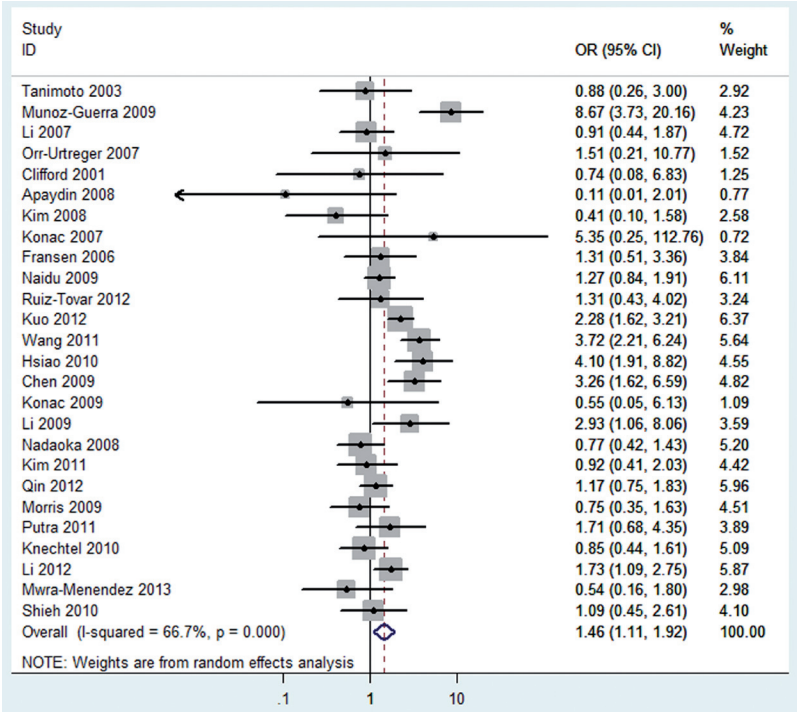

Figure 4. The forest plot of AA/AG vs. GG of 1790G/A polymorphism and overall cancer risk(random model).
The overall OR is shown. The OR of each study is marked with a grey square. The %weight of OR is indicated by a shadow. The overall OR is indicated by blue diamond.

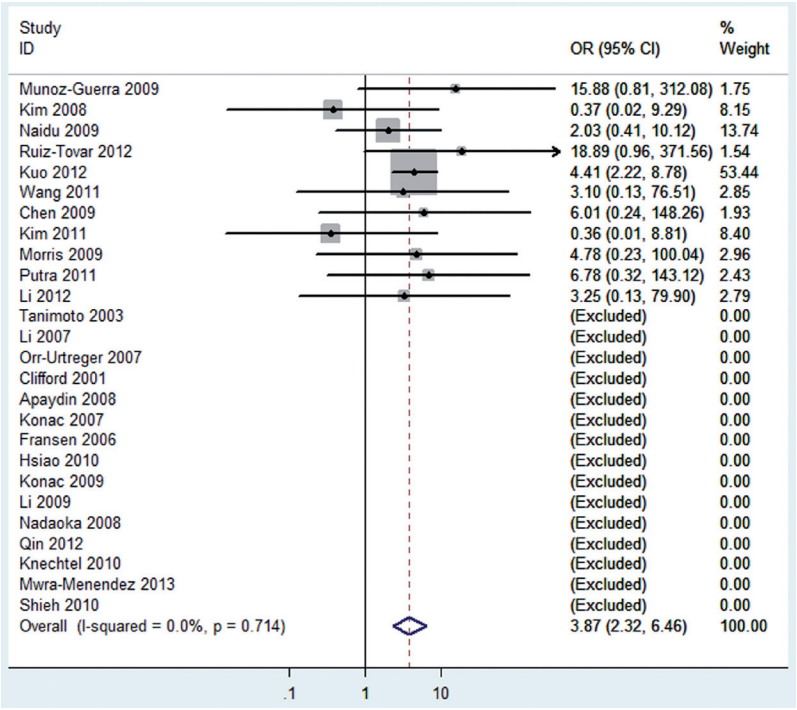

Figure 5. The forest plot of AA vs. AG/GG of 1790G/A polymorphism and overall cancer risk(fixed model).
The overall OR is shown. The OR of each study is marked with a grey square. The %weight of OR is indicated by a shadow. The overall OR is indicated by blue diamond.

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 (AA vs.GG. *P*=0.533; AG vs. GG. *P*=0.271; AA/AG vs.GG, *P*=0.243; AA vs. AG/GG, *P*=0.658; A vs. G. *P*=0.183).

Discussion

This meta-analysis of 26 studies involving 6337 cases and 9302 controls was conducted in order to yield a valid conclusion concerning the potential association between 1790G/A (rs11549467) 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, cell survival, and energy metabolism [63,64]. The Hif-1/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/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 1790 of the exon 12 of the Hif-1/HIF-1. Because a study by Tanimoto [64] showed both of the substitutions displayed an increased transactivation capacity of Hif-1/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/HIF-1 polymorphism with cancer susceptibility had controversial conclusions[21,26,27,29,30,32,43-59]. 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 oral squamous cell carcinoma (OSCC) risk under the homozygote model. Patients carrying the A allele at position 1790 of the exon 12 of the Hif-1/HIF-1 had more cancer risk than did patients homozygous for the G allele. Besides, for oral squamous cell carcinoma (OSCC), pancreatic cancer and lung cancer, the associations were more significant in the recessive model than in the dominant model. These results suggested that homozygous AA had stronger effects on an individual's phenotype than heterozygous AG. So individuals with AA genotype could have higher risk of the three cancer type than that with AG genotype. The pooled effects for homozygote comparison and dominant model comparison suggested a significant association between the 1790G/A

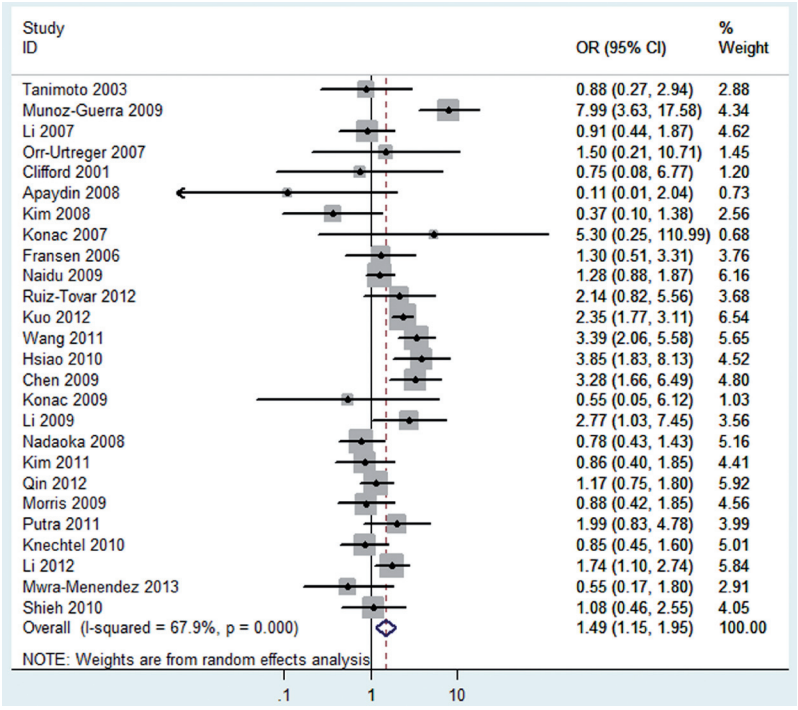

Figure 6. The forest plot of A vs. G of 1790G/A polymorphism and overall cancer risk(random model).
The overall OR is shown. The OR of each study is marked with a grey square. The %weight of OR is indicated by a shadow. The overall OR is indicated by blue diamond.

(rs11549467) polymorphism and a decreased gynecologic cancer risk. Furthermore, We found that Caucasian with AA genotype had higher risk of cancer compared to Asian under the homozygote and recessive 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 which may lead to various degrees of cancer susceptibility. In our meta-analysis, we also observed inconsistent results between hospital-based studies and population-based studies. Our results show that 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 results. It might be difficult to get a concrete conclusion if the number of included studies in subgroup was few. Besides, 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 Hif-1/HIF-1 1790G/A(rs11549467) genetic polymorphism may contribute to the susceptibility of cancers except gynecologic cancer, especially in homozygote comparison (AA vs. GG) and recessive genetic model (AA vs. AG/GG) among Caucasian population, and this SNP was significantly associated with the lung cancer, pancreatic cancer and oral squamous cell carcinoma (OSCC). The phenomenon also indicates that the SNP functions as a recessive mutation, which needs to be verified or linked with functional studies. Large well designed epidemiological studies are needed to validate our findings.

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