

HIF-1 α -1790G>A polymorphism significantly increases the risk of digestive tract cancer: A meta-analysis

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Abstract

AIM: To investigate the association between hypoxia-inducible factor-1 α (HIF-1 α) polymorphisms (-1772C>T and -1790G>A) and the risk of digestive tract cancer.

METHODS: A total of 13 eligible studies were retrieved from PubMed, EMBASE, and the China

National Knowledge Infrastructure database. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of the associations.

RESULTS: By pooling the eligible studies, we found that the HIF-1 α -1772C>T polymorphism was not associated with the risk of developing digestive tract cancer (dominant comparison, OR: 1.156; 95%CI: 0.839-1.593; $P_{\text{heterogeneity}} = 0.007$), and no significant association was found in the Asian population or the Caucasian population. However, for the -1790G>A polymorphism, carriers of the variant -1790A allele had a significantly increased risk of digestive tract cancer compared with those with the wildtype -1790G allele (dominant comparison, OR: 3.252; 95%CI: 1.661-6.368; $P_{\text{heterogeneity}} < 0.001$). Additionally, this increased risk of digestive cancer was only detected in Asians; there was no significant association in Caucasians.

CONCLUSION: This meta-analysis demonstrates that the HIF-1 α -1790G>A polymorphism is associated with a significantly increased risk of digestive tract cancer, while the -1772C>T polymorphism is not.

Key words: Hypoxia-inducible factor-1 α ; Digestive tract cancer; Polymorphisms; Cancer risk; Meta-analysis

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Core tip: The functional polymorphisms of hypoxia-inducible factor-1 α (HIF-1 α) (-1772C>T and -1790G>A) have been extensively investigated; however, the relationship between HIF-1 α polymorphisms and digestive tract cancer has remained unclear. In this work, we found that the HIF-1 α -1772C>T polymorphism was not associated with the overall risk of developing digestive tract cancer (dominant comparison, OR: 1.156; 95%CI: 0.839-1.593; $P_{\text{heterogeneity}} = 0.007$). However, the variant -1790A allele significantly increased the risk of

digestive tract cancer (OR: 3.252; 95%CI: 1.661-6.368; $P_{\text{heterogeneity}} < 0.001$).

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INTRODUCTION

Genetic polymorphisms are natural DNA sequence variations that occur in the healthy population with an expected frequency higher than 1%^[1]. Common genetic polymorphisms include single nucleotide polymorphisms, insertions, deletions, minisatellites and microsatellites. Approximately 90% of DNA polymorphisms are single nucleotide polymorphisms (SNPs). Functional SNPs in gene regulatory or coding sequences can alter gene expression or affect the function of proteins. SNPs are associated with inter-individual variation and diversity and have recently been considered as principal genetic elements involved in the development of complex diseases, such as cancer^[2].

Hypoxia-inducible factor-1 (HIF-1) is a transcription factor complex that activates gene transcription, enhancing oxygen availability and allowing metabolic adaptation to hypoxia^[3]. HIF-1 is composed of two subunits, HIF-1 α and HIF-1 β . HIF-1 α plays a critical role in adjusting oxygen levels, and it is involved in the processes of angiogenesis^[4-6] and cell proliferation^[7,8]. HIF-1 α is expressed in many cancer cells as a result of oncogene expression and intratumoral hypoxia^[9,10]. Furthermore, it has been demonstrated that HIF-1 α is an unfavorable prognostic factor in a variety of digestive tract cancers, such as pancreatic cancer and hepatocellular carcinoma^[11-13].

The *HIF-1 α* gene is located on chromosome 14q21-24. Two common SNPs in the protein coding region of the *HIF-1 α* gene have been widely investigated: the C-to-T substitution at -1772 (-1772C>T, P582S, or rs11549465) and the G-to-A substitution at -1790 (-1790G>A, A588T, or rs11549467). The -1772C>T polymorphism leads to a proline-to-serine substitution, and the -1790G>A polymorphism leads to an alanine-to-threonine substitution. Both the -1772C>T and -1790G>A polymorphisms are functional and located in the oxygen-dependent degradation domain, which is closely related to the N-terminal transactivation domain of HIF-1 α ^[4,14]. Therefore, these functional SNPs may affect the stability and trans-activating capacity of HIF-1 α . Additionally, evidence also

suggests that these functional SNPs could alter the susceptibility to various types of cancer. However, current studies have yielded conflicting results about HIF-1 α polymorphisms and the risk of developing cancer of the digestive tract. For example, Kang *et al.*^[15] found that the -1772C>T polymorphism was associated with an increased risk of colorectal cancer; however, Li *et al.*^[16] did not find any significant association with gastric cancer risk. Thus, this meta-analysis was performed to ascertain the relationship between the HIF-1 α -1772C>T and -1790G>A polymorphisms and susceptibility to cancer of the digestive tract.

MATERIALS AND METHODS

Selection of eligible studies

The eligible studies were obtained by searching online databases. In order to identify as many related articles as possible, PubMed, EMBASE, and the China National Knowledge Infrastructure (CNKI) were searched. Combinations of medical subheadings and the key words "HIF-1 α " or "hypoxia-inducible factor 1, α subunit" or "HIF1A" or "HIF-1 α ", "polymorphism, single nucleotide" or "single nucleotide polymorphism" or "polymorphism" or "SNP", and "neoplasms" or "cancer" or "tumor" were used to search the databases. Alternative spellings of these key words were also considered. The most recent research was performed on July 15, 2013, and there was no limitation on the research.

Inclusion and exclusion criteria

Studies were selected according to the following inclusion criteria: (1) case-control studies; (2) investigation of the association of HIF-1 α polymorphisms (-1772C>T and -1790G>A) and the risk of developing digestive tract cancer; (3) cancer diagnosis by histopathology; and (4) studies providing detailed genotype frequencies. Studies without detailed genotype frequencies were excluded. The titles and abstracts of the records retrieved from the databases were screened, and the full-text papers were further evaluated to confirm eligibility. Two reviewers (Sun X and Liu YD) extracted the eligible studies independently according to the inclusion criteria. Disagreements between the two reviewers were discussed with another reviewer until a consensus was achieved.

Data extraction

Data from the eligible studies were independently extracted by the two reviewers using a predesigned data collection form. The following data were collected: name of first author, year of publication, country where the study was carried out, ethnicity, cancer types, the source of the controls, number of cases and controls, genotype frequency in the cases

Table 1 Baseline characteristics of eligible studies

Ref.	Year	Country	Ethnicity	Control	Cancer type	SNP	Cases	Controls
Alves <i>et al</i> ^[21]	2012	Brazil	Latin America	HB	Oral cancer	C1722T, G1790A	40	88
Ruiz-Tovar <i>et al</i> ^[22]	2012	Spain	Caucasian	PB	Pancreatic cancer	C1722T, G1790A	59	159
Wang <i>et al</i> ^[7]	2009	China	Asian	HB	Pancreatic cancer	C1722T, G1790A	263	271
Kang <i>et al</i> ^[15]	2011	Korea	Asian	HB	Colorectal cancer	C1722T	50	50
Shieh <i>et al</i> ^[24]	2010	China	Asian	HB	Oral cancer	C1722T, G1790A	305	96
Hsiao <i>et al</i> ^[25]	2010	China	Asian	HB	Hepatocellular carcinoma	C1722T, G1790A	102	347
Knechtel <i>et al</i> ^[17]	2010	Austria	Caucasian	HB	Colorectal cancer	C1722T, G1790A	381	1209
Chen <i>et al</i> ^[26]	2009	China	Asian	PB	Oral cancer	C1722T, G1790A	347	174
Li <i>et al</i> ^[16]	2009	China	Asian	HB	Gastric cancer	C1722T, G1790A	87	106
Muñoz-Guerra <i>et al</i> ^[27]	2009	Spain	Caucasian	PB	Oral cancer	C1722T, G1790A	155	139
Fransén <i>et al</i> ^[28]	2006	Sweden	Caucasian	HB	Colorectal cancer	C1722T, G1790A	198	258
Ling <i>et al</i> ^[29]	2005	China	Asian	PB	Esophageal cancer	C1722T	95	104
Kuwai <i>et al</i> ^[30]	2004	Japan	Asian	PB	Colorectal cancer	C1722T	100	100

HB: Hospital-based studies; PB: Population-based studies; SNP: Single nucleotide polymorphism.

and controls. Ethnicity was categorized as Asian, Caucasian, or Latin American (Table 1). According to the source of control, the eligible studies were defined as hospital-based (HB) and population-based (PB). The sample size in the eligible studies was classified as either large (> 500) or small (< 500). Hardy-Weinberg equilibrium (HWE) in the controls was tested using the χ^2 test for goodness of fit, and $P < 0.05$ was considered as the absence of HWE. Two reviewers reached consensus on each item.

Statistical analysis

The strength of the association between the HIF-1 α -1772C>T and -1790G>A polymorphisms and the risk of developing digestive tract cancer was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The estimates of the pooled ORs were obtained by calculating a weighted average of the ORs from each study. A 95%CI was used for the test of statistical significance, and a 95%CI without an OR of 1 indicated a significantly increased or reduced cancer risk. The pooled ORs were calculated for allele comparison (A vs a), heterozygote comparison (Aa vs aa), and dominance modeling (AA/Aa vs aa) (A: the mutant allele, a: the wildtype allele; the -1772T and -1790A alleles were considered as mutant alleles). The combined genotype was reported by Kang *et al*^[15] and Knechtel *et al*^[17]; thus, only dominant comparison models were calculated for these 2 studies. Subgroup analyses were also conducted according to ethnicity, cancer type, source of control, and sample size. A sub-group analysis was not performed for subgroups containing less than 2 studies. Sensitivity analyses were performed to identify each individual study's effect on the pooled results and test the reliability of the results.

The χ^2 test based on Q was used to check the statistical heterogeneity between studies, and the

heterogeneity was considered significant when $P < 0.10$. The fixed-effects model (based on the Mantel-Haenszel method) and random-effects model (based on the DerSimonian-Laird method) were used to pool the data from different studies. The fixed-effects model was used when there was no significant heterogeneity; otherwise, the random-effects model was applied^[18]. Meta-regression was performed to detect the source of heterogeneity. Publication bias was detected by Begg's funnel plot and Egger's linear regression test, and a $P < 0.05$ was considered significant^[19]. To test the influence of publication bias, the fail-safe number was also calculated for $P = 0.05$ ($N_{fs0.05}$) and $P = 0.01$ ($N_{fs0.01}$)^[20]. All statistical analyses were calculated with STATA software version 10.0 (Stata Corp., College Station, TX, USA), and all P values are two-sided.

RESULTS

Overview of eligible studies

According to our search strategy, 558 records were retrieved and screened. After primary screening, 16 full-text papers were retrieved for further assessment of eligibility. Finally, 13^[15-17,21-30] eligible studies were included and 3 studies were excluded because they were not related to cancer risk^[31,32] or the HIF-1 α -1772C>T and -1790G>A polymorphisms^[33]. The procedure for study selection is shown in Figure 1.

Of the 13 eligible studies, 2182 cancer patients and 3101 controls were enrolled. The baseline characteristics of the included studies are shown in Table 1. Six types of digestive tract cancer were investigated: oral cancer, esophageal cancer, gastric cancer, pancreatic cancer, hepatocellular carcinoma, and colorectal cancer. Most studies were carried out among Asian and Caucasian populations, while only one study was performed in Latin America. The -1772C>T polymorphism

Table 2 Meta-analysis results of -1772C>T polymorphism

	Dominant comparison		Allele comparison		Heterozygote comparison	
	OR (95%CI)	<i>P</i> _{het}	OR (95%CI)	<i>P</i> _{het}	OR (95%CI)	<i>P</i> _{het}
Overall	1.156 (0.839-1.593)	0.007	1.325 (0.846-2.076)	< 0.001	0.853 (0.502-1.450)	< 0.001
Ethnicity						
Caucasian	1.053 (0.842-1.317)	0.381	1.075 (0.795-1.454)	0.011	0.459 (0.174-1.211)	0.060
Asian	1.302 (0.748-2.266)	0.007	1.169 (0.667-2.049)	< 0.001	1.132 (0.628-2.040)	0.009
Source of control						
HB	1.314 (0.884-1.954)	0.014	1.661 (0.755-3.656)	< 0.001	1.153 (0.633-2.099)	0.009
PB	0.898 (0.498-1.620)	0.086	1.163 (0.698-1.938)	0.089	0.482 (0.166-1.405)	0.004
Cancer types						
OC	1.063 (0.643-1.757)	0.304	2.517 (0.705-8.980)	< 0.001	0.917 (0.444-1.895)	0.135
PC	1.388 (0.542-3.555)	0.032	1.753 (1.225-2.508) ¹	0.349	0.500 (0.018-14.015)	0.001
CRC	1.118 (0.573-2.182)	0.015	0.262 (0.011-6.380)	0.024	0.241 (0.011-5.509)	0.027
HWE						
No	0.777 (0.466-1.296)	0.832	3.221 (0.673-15.414)	< 0.001	0.250 (0.051-1.211)	0.139
Yes	1.260 (0.873-1.818)	0.007	1.149 (0.723-1.826)	0.009	1.091 (0.660-1.803)	0.005
Sample size						
Small	0.958 (0.621-1.479)	0.031	1.192 (0.680-2.089)	< 0.001	0.658 (0.362-1.197)	0.007
Large	1.569 (1.049-2.345) ¹	0.125	1.983 (1.325-2.969) ¹	0.867	1.994 (1.307-3.042) ¹	0.529

¹Significant association. *P*_{het}: *P* value of heterogeneity; HB: Hospital-based studies; PB: Population-based studies; OC: Oral cancer; PC: Pancreatic cancer; CRC: Colorectal cancer.

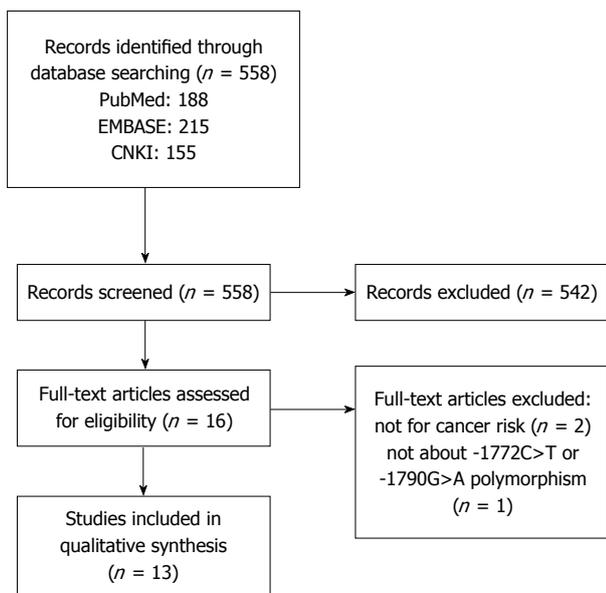


Figure 1 Flow chart of study selection.

was investigated in all studies, and the -1790G>A polymorphism was studied in 10 studies^[16,17,21-28]. For the -1772C>T polymorphism, the absence of HWE in controls was detected in 3 studies^[21,22,27]; however, no disequilibrium was detected for the -1790G>A polymorphism. In the control population, homozygotes for the variant -1772TT were detected in 4 studies^[20,23,26,27], while the -1790AA genotype was not detected among the cancer cases.

Meta-analysis results

-1772C>T polymorphism: By pooling all the

eligible studies, we found that the -1772C>T polymorphism was not associated with the risk of digestive tract cancer in any of the three comparison models (dominant comparison, OR: 1.156; 95%CI: 0.839-1.593; *P*_{heterogeneity} = 0.007; Figure 2). The meta-analysis results for the -1772C>T polymorphism are shown in Table 2. Sub-group analyses were performed, and no significant association with the risk of digestive tract cancer was found among Asians or Caucasians in the HB studies. Because the data from 3 studies were not inconsistent with HWE, we performed sub-group analyses according to HWE, and no statistical association was found in any of the groups. In terms of cancer types, we found that only the variant -1772T allele was associated with a significantly increased risk of pancreatic cancer (OR: 1.753; 95%CI: 1.225-2.508; *P*_{heterogeneity} = 0.349), while no significant association was observed with oral cancer or colorectal cancer. Notably, sample size had a significant influence on the pooled results. As shown in Table 2, large studies suggested an increased risk, while small studies revealed no significant association.

Begg’s funnel plot (*P* = 0.373; Figure 3) and Egger’s linear regression test (*P* = 0.813) suggested that no publication bias affected the results. A sensitivity analysis also confirmed the stability of our results because no individual study affected the pooled results significantly (Figure 4). Due to the significant heterogeneity among the studies, a meta-regression was performed to identify the source of heterogeneity (for the dominant model), and the results suggested that ethnicity (*P* = 0.021), sample size (*P* = 0.002), and HWE (*P* < 0.001) were the

Table 3 Meta-analysis results of -1790G>A polymorphism

	Dominant comparison		Allele comparison		Heterozygote comparison	
	OR (95%CI) ¹	<i>P</i> _{het}	OR (95%CI) ¹	<i>P</i> _{het}	OR (95%CI) ¹	<i>P</i> _{het}
Overall	3.252 (1.661-6.368) ¹	< 0.001	4.455 (1.938-10.241) ¹	< 0.001	2.677 (1.677-4.273) ¹	< 0.001
Ethnicity						
Caucasian	1.882 (0.627-5.644)	< 0.001	2.881 (0.943-8.807)	0.009	1.898 (0.411-8.761)	0.002
Asian	2.921 (1.909-4.470) ¹	0.163	2.793 (1.877-4.158) ¹	0.195	2.891 (1.890-4.422) ¹	0.165
Source of control						
HB	3.258 (1.331-7.977) ¹	< 0.001	4.904 (1.375-17.489) ¹	< 0.001	2.521 (1.526-4.167) ¹	0.094
PB	3.516 (1.340-9.229) ¹	0.026	3.923 (1.894-8.128) ¹	0.084	2.729 (0.823-9.053) ¹	0.011
Cancer types						
OC	7.919 (1.582-39.636) ¹	< 0.001	9.663 (1.312-71.149) ¹	< 0.001	3.165 (1.264-7.924) ¹	0.019
PC	2.499 (0.929-6.726)	0.098	3.030 (1.946-4.716) ¹	0.418	1.611 (0.241-10.760)	0.019
CRC	0.971 (0.571-1.650)	0.454				
Sample size						
Small	4.127 (1.511-11.267) ¹	< 0.001	4.976 (1.457-16.996) ¹	< 0.001	2.351 (1.180-4.682) ¹	0.007
Large	2.186 (0.863-5.537)	0.001	3.313 (2.214-4.959) ¹	0.969	3.492 (2.298-5.307) ¹	0.690

¹Significant association. OR: Odds ratio.

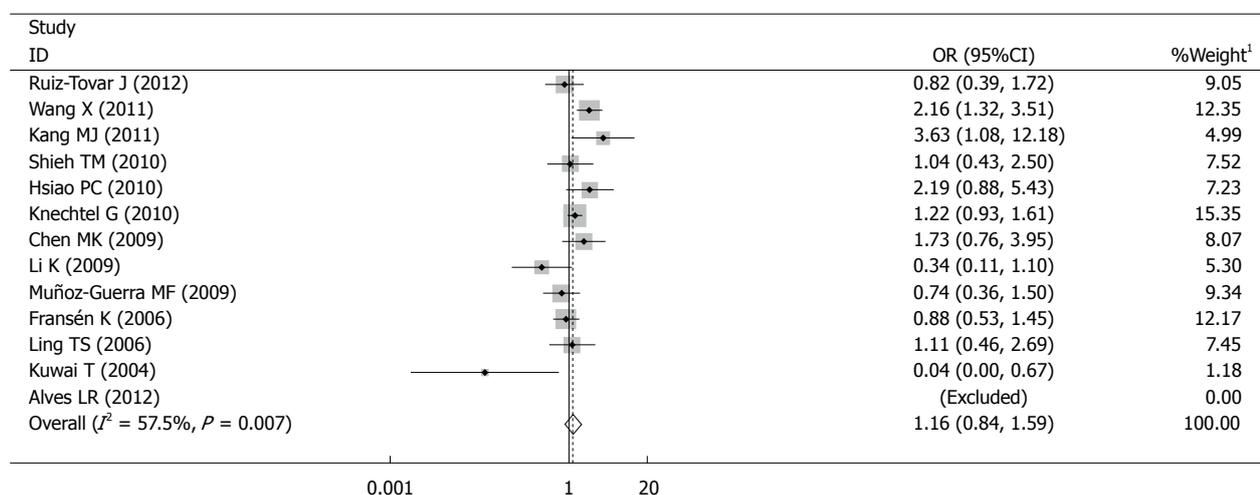


Figure 2 Forrest plot of the -1772C>T polymorphism and the risk of digestive tract cancer. ¹Weights are from random effects analysis. Dominant comparison: TT + CT vs CC. OR: Odds ratio.

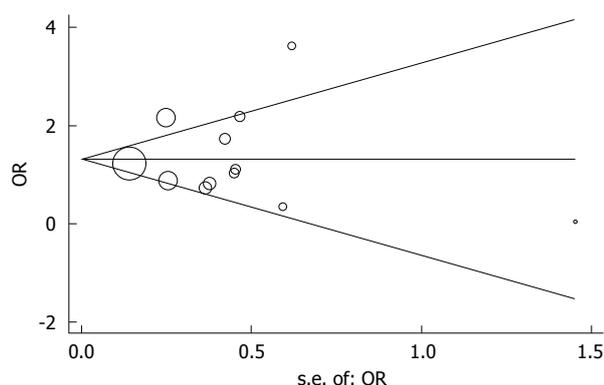


Figure 3 Begg's funnel plot with pseudo 95% confidence limits.

sources of heterogeneity between the studies.

-1790G>A polymorphism: The results of the meta-analysis of the -1790G>A polymorphism

are shown in Table 3. A pooled analysis of the 10 eligible studies revealed that the variant -1790A allele significantly increased the risk of digestive tract cancer, as observed in the dominant model (OR: 3.252; 95%CI: 1.661-6.368; $P_{\text{heterogeneity}} < 0.001$; Figure 5), the allele comparison (OR: 4.455; 95% CI: 1.938-10.241; $P_{\text{heterogeneity}} < 0.001$), and the heterozygote comparison. Next, stratified analyses were performed. As shown in Table 3, the source of controls and the sample size did have a significant effect on the results. However, we only found a significantly increased risk in Asians, not in Caucasians. In Asians, the -1790G>A polymorphism was associated with increased susceptibility to cancers of the digestive tract, while no significant association was observed in Caucasians. As for the cancer types, the -1790G>A polymorphism increased the risk of oral cancer and pancreatic cancer, but not the risk of colorectal cancer (Table 3).

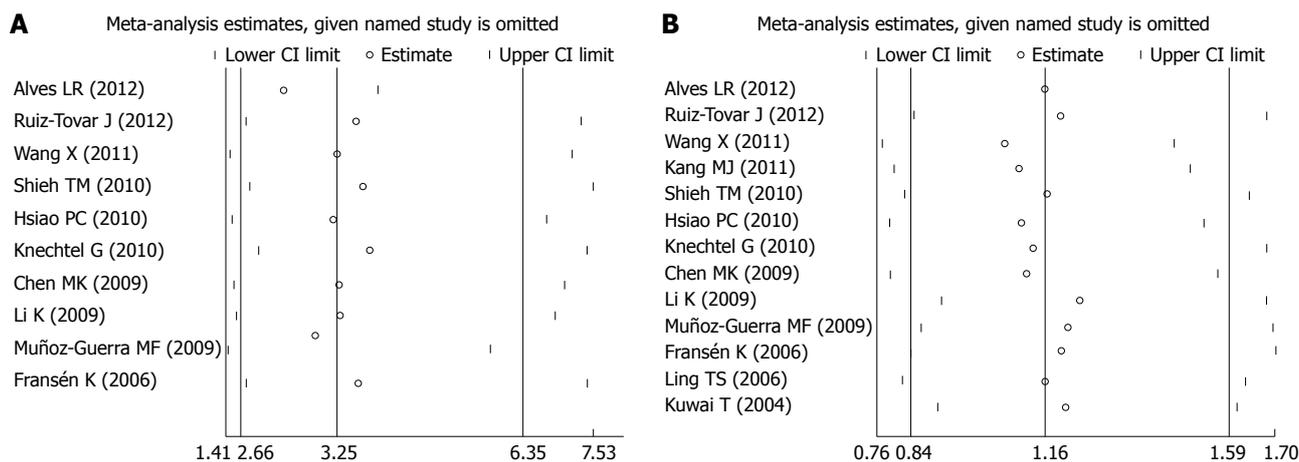


Figure 4 Meta-analysis estimates, with given named study omitted (A, B).

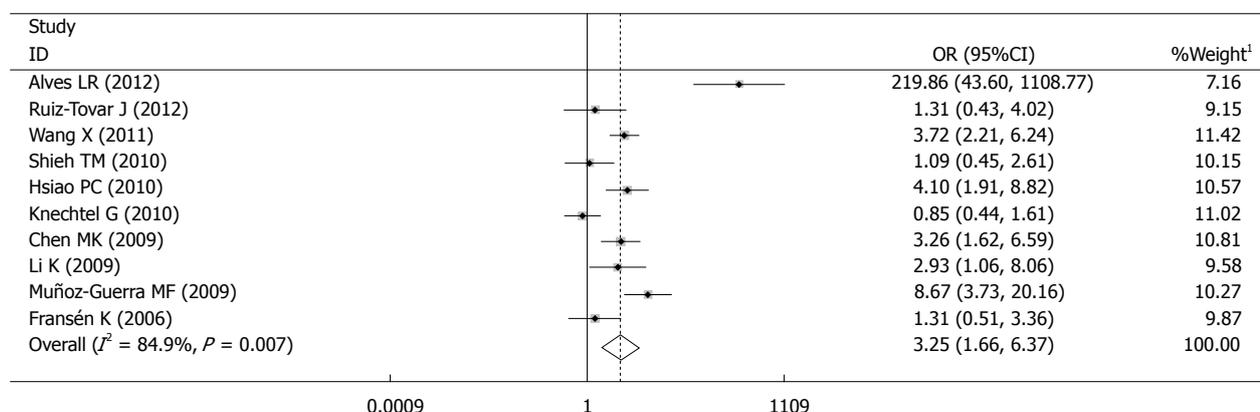


Figure 5 Forrest plot of the -1790G>A polymorphism and the risk of digestive tract cancer. [†]Weights are from random effects analysis. Dominant comparison: AA + GA vs GG.

The results of Begg’s test ($P = 0.05$) and Egger’s test ($P = 0.064$) indicated the presence of significant publication bias. Additionally, the stability of our results was confirmed by the sensitivity analysis (Figure 4B). The fail-safe number was calculated to estimate the influence of publication bias. The value of the fail-safe number was large ($Nfs_{0.05} = 359.34$, $Nfs_{0.01} = 172.98$), which suggested that the publication bias was low and our result was reliable. Due to the significant heterogeneity among the studies, a meta-regression was performed to identify the source of the heterogeneity (for the dominant model). The results suggested that sample size ($P = 0.002$) and HWE ($P < 0.001$) were the sources of heterogeneity between studies.

DISCUSSION

The results of the present meta-analysis suggest that the -1772C>T polymorphism of the *HIF-1 α* gene is not associated with the risk of digestive tract cancer; however, the -1790G>A polymorphism significantly increases the susceptibility to digestive tract cancer.

HIF-1 α is a critical gene involved in the cellular response to hypoxia. By activation of various genes that are related to the regulation of angiogenesis, cell survival, apoptosis, and the proliferative response, *HIF-1 α* has an important role in tumor progression and metastasis^[34,35]. In the presence of oxygen, *HIF-1 α* is hydroxylated and degraded by the proteasome^[36]; however, in a hypoxic microenvironment, the *HIF-1 α* protein accumulates^[37]. Studies have shown that *HIF-1 α* is overexpressed in various digestive tract tumors, such as colon cancer, pancreatic cancer, stomach cancer, and esophageal cancer^[9,38]. The functional -1772C>T and -1790G>A polymorphisms of *HIF-1 α* are associated with an increased trans-activation capacity of *HIF-1 α* under normoxic and hypoxic conditions^[4]. Thus, these two SNPs may alter the risk of digestive tract cancer.

In this meta-analysis, we identified 13 eligible studies^[15-17,21-30] and found that the -1772C>T polymorphism was not associated with the risk of digestive tract cancer. Stratified analyses according to ethnicity, source of controls, and HWE did not find any differences between the sub-groups. The results suggested that the -1772C>T did not alter

the overall risk of developing digestive tract cancer. However, the results of this meta-analysis did reveal that the -1790G>A polymorphism was associated with a significantly increased risk of digestive tract cancer, and an elevated susceptibility to cancer was also observed in the majority of the sub-groups. Specifically, we found that Asian carriers of the variant -1790A allele had an increased risk compared with Caucasians. The difference between ethnicities may be explained by differences in the genetic background, lifestyle, and environmental exposure between the groups^[39]. Additionally, the -1772C>T and -1790G>A polymorphisms had different impacts on the risk of developing a specific kind of cancer (Table 2 and Table 3), suggesting that HIF-1 α polymorphisms may exert cancer type-specific effects.

Notably, significant heterogeneity was detected in this meta-analysis. Meta-regression and subgroup analyses were carried out to detect the source of this heterogeneity. For both -1772C>T and -1790G>A, ethnicity was the source of the heterogeneity. For -1772C>T, sample size and HWE also contributed to the observed heterogeneity. On the other hand, the sensitivity analysis confirmed the reliability and stability of our results. Additionally, no evidence of significant publication bias was not found by Egger's test or Begg's test.

While we were conducting this meta-analysis, an updated meta-analysis of HIF-1 α polymorphisms was published^[40]. Compared with the updated meta-analysis, we focused exclusively on digestive tract cancer and included more eligible studies related to this type of cancer; Liu and Zhang^[40] only included studies before 2011. Because more eligible studies were included in our meta-analysis, we performed comprehensive sub-group analyses according to cancer type, sample size, HWE, and ethnicity. However, limitations of our meta-analysis should also be noted. First, although we performed a comprehensive meta-analysis, the number of relevant studies was limited and we could not perform sub-group analyses for each kind of digestive tract cancer. Second, the sample sizes in the included studies were relatively small. For the -1772C>T polymorphism, increased susceptibility was observed in large studies, while no significant association was found in small studies. Third, the genotype distribution of the controls was not in agreement with HWE in 3 studies on the -1772C>T polymorphism, although sub-group analysis demonstrated that the absence of HWE had no significant effect on the pooled results.

In summary, in this meta-analysis of 13 eligible studies, we found that the -1790G>A polymorphism of HIF-1 α significantly increases the susceptibility to digestive tract cancer, while the -1772C>T polymorphism is not associated with significant

risk. Further studies with larger sample sizes are warranted to validate these associations, particularly for the -1772C>T polymorphism.

COMMENTS

Background

Hypoxia-inducible factor-1 α (HIF-1 α) is a critical regulator of oxygen levels, and it is involved in the process of angiogenesis. The C-to-T substitution at -1772 (-1772C>T, rs11549465) and the G-to-A substitution at -1790 (-1790G>A, rs11549467) are two common single nucleotide polymorphisms of HIF-1 α .

Research frontiers

Previous association studies have reported the association between HIF-1 polymorphisms and the risk of digestive tract cancer. However, these studies have reported conflicting results, and the sample size was small in the majority of these studies. Therefore, we conducted this meta-analysis to address this issue.

Innovations and breakthroughs

Based on this meta-analysis, the HIF-1 α -1772C>T polymorphism was not associated with the overall risk of digestive tract cancer [odds ratio (OR): 1.156; 95%CI: 0.839-1.593]. However, the -1790G>A polymorphism significantly increased the risk of digestive tract cancer (OR: 3.252; 95% CI: 1.661-6.368).

Applications

These results highlighted that HIF-1 α -1790G>A plays a role in digestive tract cancer, indicating that this point mutation may affect the transcription of HIF-1 α . Further exploration of the mechanism will improve our understanding of the role and function of HIF-1 α -1790G>A.

Terminology

Genetic polymorphisms are natural DNA sequence variations that can occur in the healthy population. Functional polymorphisms in gene regulatory or coding sequences may alter gene expression or the function of the encoded proteins. The -1790G>A polymorphism leads to an alanine-to-threonine substitution in the oxygen-dependent degradation domain, which is critical for the function of HIF-1 α .

Peer-review

The Authors investigated the association of HIF-1 α polymorphisms and risk of digestive cancer. The meta-analysis of 13 studies showed that HIF-1 α -1790G>A polymorphism is associated with a significantly increased risk of digestive tract cancer.

REFERENCES

- 1 **Balasubramanian SP**, Brown NJ, Reed MW. Role of genetic polymorphisms in tumour angiogenesis. *Br J Cancer* 2002; **87**: 1057-1065 [PMID: 12402142 DOI: 10.1038/sj.bjc.6600625]
- 2 **Rannala B**. Finding genes influencing susceptibility to complex diseases in the post-genome era. *Am J Pharmacogenomics* 2001; **1**: 203-221 [PMID: 12083968]
- 3 **Le Mouél JL CJ**, Narteau C. Multiple scale dynamo. *Proc Natl Acad Sci USA* 1997; **94**: 5510-5514 [PMID: 11038547]
- 4 **Tanimoto K**, Yoshiga K, Eguchi H, Kaneyasu M, Ukon K, Kumazaki T, Oue N, Yasui W, Imai K, Nakachi K, Poellinger L, Nishiyama M. Hypoxia-inducible factor-1 α polymorphisms associated with enhanced transactivation capacity, implying clinical significance. *Carcinogenesis* 2003; **24**: 1779-1783 [PMID: 12919954 DOI: 10.1093/carcin/bgg132]
- 5 **Liang X**, Yang D, Hu J, Hao X, Gao J, Mao Z. Hypoxia inducible factor-1 α expression correlates with vascular endothelial growth factor-C expression and lymphangiogenesis/angiogenesis in oral squamous cell carcinoma. *Anticancer Res* 2008; **28**: 1659-1666 [PMID: 18630523]
- 6 **Burkitt K**, Chun SY, Dang DT, Dang LH. Targeting both HIF-1 and HIF-2 in human colon cancer cells improves tumor response to sunitinib treatment. *Mol Cancer Ther* 2009; **8**: 1148-1156 [PMID: 19435875 DOI: 10.1158/1535-7163.MCT-08-0944]
- 7 **Wang W**, Xu GL, Jia WD, Wang ZH, Li JS, Ma JL, Ge YS, Xie

- 8 SX, Yu JH. Expression and correlation of hypoxia-inducible factor-1 α , vascular endothelial growth factor and microvessel density in experimental rat hepatocarcinogenesis. *J Int Med Res* 2009; **37**: 417-425 [PMID: 19383236]
- 9 Sasabe E, Tatemoto Y, Li D, Yamamoto T, Osaki T. Mechanism of HIF-1 α -dependent suppression of hypoxia-induced apoptosis in squamous cell carcinoma cells. *Cancer Sci* 2005; **96**: 394-402 [PMID: 16053510 DOI: 10.1111/j.1349-7006.2005.00065.x]
- 10 Zhong H, De Marzo AM, Laughner E, Lim M, Hilton DA, Zagzag D, Buechler P, Isaacs WB, Semenza GL, Simons JW. Overexpression of hypoxia-inducible factor 1 α in common human cancers and their metastases. *Cancer Res* 1999; **59**: 5830-5835 [PMID: 10582706]
- 11 Koong AC, Mehta VK, Le QT, Fisher GA, Terris DJ, Brown JM, Bastidas AJ, Vierra M. Pancreatic tumors show high levels of hypoxia. *Int J Radiat Oncol Biol Phys* 2000; **48**: 919-922 [PMID: 11072146]
- 12 Hoffmann AC, Mori R, Vallbohmer D, Brabender J, Klein E, Drebbler U, Baldus SE, Cooc J, Azuma M, Metzger R, Hoelscher AH, Danenberg KD, Prenzel KL, Danenberg PV. High expression of HIF1 α is a predictor of clinical outcome in patients with pancreatic ductal adenocarcinomas and correlated to PDGFA, VEGF, and bFGF. *Neoplasia* 2008; **10**: 674-679 [PMID: 18592007]
- 13 Daskalou K, Pfander D, Weichert W, Rohwer N, Thelen A, Neuhaus P, Jonas S, Wiedenmann B, Benckert C, Cramer T. Distinct temporospatial expression patterns of glycolysis-related proteins in human hepatocellular carcinoma. *Histochem Cell Biol* 2009; **132**: 21-31 [PMID: 19350262 DOI: 10.1007/s00418-009-0590-4]
- 14 Couvelard A, O'Toole D, Leek R, Turley H, Sauvaget A, Degott C, Ruzsniwski P, Belghiti J, Harris AL, Gatter K, Pezzella F. Expression of hypoxia-inducible factors is correlated with the presence of a fibrotic focus and angiogenesis in pancreatic ductal adenocarcinomas. *Histopathology* 2005; **46**: 668-676 [PMID: 15910598 DOI: 10.1111/j.1365-2559.2005.02160.x]
- 15 Jiang BH, Zheng JZ, Leung SW, Roe R, Semenza GL. Transactivation and inhibitory domains of hypoxia-inducible factor 1 α . Modulation of transcriptional activity by oxygen tension. *J Biol Chem* 1997; **272**: 19253-19260 [PMID: 9235919]
- 16 Kang MJ, Jung SA, Jung JM, Kim SE, Jung HK, Kim TH, Shim KN, Yi SY, Yoo K, Moon IH. Associations between single nucleotide polymorphisms of MMP2, VEGF, and HIF1A genes and the risk of developing colorectal cancer. *Anticancer Res* 2011; **31**: 575-584 [PMID: 21378341]
- 17 Li K, Zhang Y, Dan Z, Wang Y, Ren ZC. Association of the hypoxia inducible factor-1 α gene polymorphisms with gastric cancer in Tibetans. *Biochem Genet* 2009; **47**: 625-634 [PMID: 19504235 DOI: 10.1007/s10528-009-9254-2]
- 18 Knechtel G, Szkandera J, Stotz M, Hofmann G, Langsenlehner U, Krippel P, Samonigg H, Renner W, Langner C, Dehchamani D, Gerger A. Single nucleotide polymorphisms in the hypoxia-inducible factor-1 gene and colorectal cancer risk. *Mol Carcinog* 2010; **49**: 805-809 [PMID: 20572162 DOI: 10.1002/mc.20655]
- 19 Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; **127**: 820-826 [PMID: 9382404]
- 20 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563]
- 21 Zhuo WL, Zhang YS, Wang Y, Zhuo XL, Zhu B, Cai L, Chen ZT. Association studies of CYP1A1 and GSTM1 polymorphisms with esophageal cancer risk: evidence-based meta-analyses. *Arch Med Res* 2009; **40**: 169-179 [PMID: 19427967 DOI: 10.1016/j.arcmed.2009.01.003]
- 22 Alves LR, Fraga CA, Oliveira MV, Sousa AA, Jorge AS, Marques-Silva L, Santos SH, Jones KM, de Paula AM, Guimarães AL. High HIF-1 α expression genotypes increase odds ratio of oral cancer. *Head Neck Oncol* 2012; **4**: 87 [PMID: 23296286]
- 23 Ruiz-Tovar J, Fernandez-Contreras ME, Martín-Perez E, Gamallo C. Association of thymidylate synthase and hypoxia inducible factor-1 α DNA polymorphisms with pancreatic cancer. *Tumori* 2012; **98**: 364-369 [PMID: 22825513 DOI: 10.1700/1125.12406]
- 24 Wang X, Liu Y, Ren H, Yuan Z, Li S, Sheng J, Zhao T, Chen Y, Liu F, Wang F, Huang H, Hao J. Polymorphisms in the hypoxia-inducible factor-1 α gene confer susceptibility to pancreatic cancer. *Cancer Biol Ther* 2011; **12**: 383-387 [PMID: 21709439]
- 25 Shieh TM, Chang KW, Tu HF, Shih YH, Ko SY, Chen YC, Liu CJ. Association between the polymorphisms in exon 12 of hypoxia-inducible factor-1 α and the clinicopathological features of oral squamous cell carcinoma. *Oral Oncol* 2010; **46**: e47-e53 [PMID: 20656543 DOI: 10.1016/j.oraloncology.2010.04.009]
- 26 Hsiao PC, Chen MK, Su SC, Ueng KC, Chen YC, Hsieh YH, Liu YF, Tsai HT, Yang SF. Hypoxia inducible factor-1 α gene polymorphism G1790A and its interaction with tobacco and alcohol consumptions increase susceptibility to hepatocellular carcinoma. *J Surg Oncol* 2010; **102**: 163-169 [PMID: 20648588 DOI: 10.1002/jso.21539]
- 27 Chen MK, Chiou HL, Su SC, Chung TT, Tseng HC, Tsai HT, Yang SF. The association between hypoxia inducible factor-1 α gene polymorphisms and increased susceptibility to oral cancer. *Oral Oncol* 2009; **45**: e222-e226 [PMID: 19717330 DOI: 10.1016/j.oraloncology.2009.07.015]
- 28 Muñoz-Guerra MF, Fernández-Contreras ME, Moreno AL, Martín ID, Herráez B, Gamallo C. Polymorphisms in the hypoxia inducible factor 1- α and the impact on the prognosis of early stages of oral cancer. *Ann Surg Oncol* 2009; **16**: 2351-2358 [PMID: 19449077 DOI: 10.1245/s10434-009-0503-8]
- 29 Fransén K, Fenech M, Fredrikson M, Dabrosin C, Söderkvist P. Association between ulcerative growth and hypoxia inducible factor-1 α polymorphisms in colorectal cancer patients. *Mol Carcinog* 2006; **45**: 833-840 [PMID: 16865676 DOI: 10.1002/mc.20209]
- 30 Ling TS, Shi RH, Zhang GX, Zhu H, Yu LZ, Ding XF. Common single nucleotide polymorphism of hypoxia-inducible factor-1 α and its impact on the clinicopathological features of esophageal squamous cell carcinoma. *Chin J Dig Dis* 2005; **6**: 155-158 [PMID: 16246222 DOI: 10.1111/j.1443-9573.2005.00223.x]
- 31 Kuwai T, Kitadai Y, Tanaka S, Kuroda T, Ochiuni T, Matsumura S, Oue N, Yasui W, Kaneyasu M, Tanimoto K, Nishiyama M, Chayama K. Single nucleotide polymorphism in the hypoxia-inducible factor-1 α gene in colorectal carcinoma. *Oncol Rep* 2004; **12**: 1033-1037 [PMID: 15492789]
- 32 Park SW, Chung NG, Hur SY, Kim HS, Yoo NJ, Lee SH. Mutational analysis of hypoxia-related genes HIF1 α and CUL2 in common human cancers. *APMIS* 2009; **117**: 880-885 [PMID: 20078552 DOI: 10.1111/j.1600-0463.2009.02550.x]
- 33 Koukourakis MI, Papazoglou D, Giatromanolaki A, Panagopoulos I, Maltezos E, Harris AL, Gatter KC, Sivridis E. C2028T polymorphism in exon 12 and dinucleotide repeat polymorphism in intron 13 of the HIF-1 α gene define HIF-1 α protein expression in non-small cell lung cancer. *Lung Cancer* 2006; **53**: 257-262 [PMID: 16837101 DOI: 10.1016/j.lungcan.2006.05.025]
- 34 Frank B, Hoffmeister M, Klopp N, Illig T, Chang-Claude J, Brenner H. Single nucleotide polymorphisms in Wnt signaling and cell death pathway genes and susceptibility to colorectal cancer. *Carcinogenesis* 2010; **31**: 1381-1386 [PMID: 20403915 DOI: 10.1093/carcin/bgq082]
- 35 Wang GL, Semenza GL. Purification and characterization of hypoxia-inducible factor 1. *J Biol Chem* 1995; **270**: 1230-1237 [PMID: 7836384]
- 36 Carmeliet P, Dor Y, Herbert JM, Fukumura D, Brusselmanns K, Dewerchin M, Neeman M, Bono F, Abramovitch R, Maxwell P, Koch CJ, Ratcliff P, Moons L, Jain RK, Collen D, Keshert E. Role of HIF-1 α in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. *Nature* 1998; **394**: 485-490 [PMID: 9697772 DOI: 10.1038/28867]
- 37 Carroll VA, Ashcroft M. Targeting the molecular basis for tumour hypoxia. *Expert Rev Mol Med* 2005; **7**: 1-16 [PMID: 15831177 DOI: 10.1017/S1462399405009117]
- 38 Dang CV, Semenza GL. Oncogenic alterations of metabolism. *Trends Biochem Sci* 1999; **24**: 68-72 [PMID: 10098401]

- 38 **Koukourakis MI**, Giatromanolaki A, Skarlatos J, Corti L, Blandamura S, Piazza M, Gatter KC, Harris AL. Hypoxia inducible factor (HIF-1a and HIF-2a) expression in early esophageal cancer and response to photodynamic therapy and radiotherapy. *Cancer Res* 2001; **61**: 1830-1832 [PMID: 11280732]
- 39 **Hirschhorn JN**, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. *Genet Med* 2003; **4**: 45-61 [PMID: 11882781]
- 40 **Liu J**, Zhang HX. 1790 G/A polymorphism, but not 1772 C/T polymorphism, is significantly associated with cancers: an update study. *Gene* 2013; **523**: 58-63 [PMID: 23583797 DOI: 10.1016/j.gene.2013.03.129]

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