Review Article

Hypoxia-inducible factors in cancer: an overview of major findings from meta-analyses

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Abstract: This paper aims to systematically review the major findings from meta-analyses regarding the impact of hypoxia-inducible factors (HIFs) in various human cancers. A total of 56 eligible meta-analysis papers were identified via the PubMed and EMBASE databases. The associations of HIF-1α gene polymorphism and/or HIF-1α and HIF-2α protein expression with the risk, clinicopathological features, and/or survival were explored in head and neck cancer (n=4), glioma (n=2), oral cancer (n=10), oropharyngeal cancer (n=1), nasopharyngeal cancer (n=1), lung cancer (n=12), breast cancer (n=17), esophageal cancer (n=5), gastric cancer (n=8), colorectal cancer (n=15), pancreatic cancer (n=8), hepatocellular carcinoma (n=5), prostate cancer (n=13), renal cancer (n=13), bladder cancer (n=3), ovarian cancer (n=3), cervical cancer (n=10), endometrial cancer (n=1), and osteosarcoma (n=1). Based on the current evidence, the impact of HIFs should be heterogeneous on various human cancers.

Keywords: Cancer; risk; survival; hypoxia-inducible (HIF); meta-analysis; systematic review

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Introduction

Hypoxia, which refers to a low oxygen condition, is closely associated with the development and progression of cancer (1-3). Hypoxia-inducible factors (HIFs) are important proteins for the regulation of molecular response on hypoxia (4). *HIFs* consist of two subunits (i.e., α and β). The α subunit is expressed according to the oxygen conditions and determines the transcriptional activity of HIF. In details, the degradation of *HIF-1α* is enhanced and suppressed in the normoxic and hypoxic conditions, respectively; and high and low expression of *HIF-1α* increases and decreases the HIF activity, respectively. *HIF-1α* family contains 3 members (*HIF-1α*, *HIF-2α*, and *HIF-3α*) (5-8). By comparison, the β subunit is constitutively expressed in the nucleus.

Among the *HIF-1α* family members, *HIF-1α* is the most widely studied in human cancer (9,10). *HIF-1α* gene, which is located at the chromosome 14q21-24, consists of 15 exons and 14 introns, codes the cDNA of 3,919 bps, and produces the protein of 826 amino acids. *HIF-1α* can transactivate more than 70 target genes and is a master regulator of erythropoiesis, blood vessel formation, cell metabolism, and genetic stability. There are two major *HIF-1α* gene polymorphisms (*C1772T* and *G1790A*). Both of them are located at the exon 12 of the *HIF-1α* gene within the oxygen-dependent degradation domain. *HIF-1α C1772T* (*rs11549465*) mutation refers to an amino acid substitution

from proline to serine at codon 582 (Pro582Ser or P582S). *HIF-1α G1790A* (*rs11549467*) mutation refers to an amino acid substitution from alanine to threonine at codon 588 (Ala588Thr or A588T).

To the best of our knowledge, numerous studies and meta-analyses have explored the role of *HIF-1α* gene polymorphism and protein expression in cancer. By comparison, less evidence has been accumulated regarding the role of *HIF-2α* and *HIF-3α* in cancer. In this paper, we have conducted an overview of meta-analyses to provide more comprehensive recognition of evidence regarding the role of HIFs in cancer.

Methods

Registration

Our study protocol was registered in PROSPERO database. The registration number was CRD42016037401.

Search strategy

We identified the relevant meta-analysis papers via the PubMed and EMBASE databases. We also manually identified the relevant meta-analysis papers. Search items were: "(hypoxia inducible factor) OR *HIF*" AND "(((cancer) OR tumor) OR neoplasm) OR carcinoma" AND "(meta analysis)". The last search date was April 6, 2016.

Eligibility criteria

Only meta-analysis papers regarding the role of *HIF* in cancer were eligible for our study. Duplicates, comments or editorials, narrative reviews, original articles, and irrelevant meta-analysis papers were excluded. Publication language or date was not limited.

Data extraction

We primarily extracted the data from the eligible meta-analysis papers, as follows: first author, publication year, journal, country, databases which were employed for each meta-analysis, date when each meta-analysis was conducted, type of cancer, *HIF* gene polymorphism or protein expression, number of studies which were included in each meta-analysis, and results of each meta-analysis. If the statistical analyses were performed by using both fixed- and random-effects models, only the results by a random-effects model would be considered.

Evaluation of heterogeneity

If the results were heterogeneous among two or more meta-analyses, we would further identify the reliability according to the following criteria.

First, the number of eligible studies should be considered. A meta-analysis with a larger number of eligible studies would be more reliable.

Second, if the number of eligible studies was similar among them, the number of participants would be considered. A meta-analysis with a larger number of participants would be more reliable.

Third, if the eligible studies were completely overlapped among them, the methods of meta-analysis would be considered. A meta-analysis using a random-effect model would be more reliable.

Fourth, if the controversy or uncertainty remained according to the above-mentioned criteria, the original studies would be extracted and a meta-analysis might be updated. We might also contact with the authors or journal editors, if necessary.

Results

After excluding the irrelevant papers, a total of 55 meta-analysis papers were included in our study (*Figure 1*). Among them, 53 papers were written by Chinese researchers, 1 paper by UK researchers, and 1 paper by Bangladeshi researchers. The last search date for each meta-analysis ranged from 2009 to 2016. Results of meta-analyses were summarized according to the location of cancer.

Overall cancer

A total of 13 meta-analysis papers explored the role of *HIF* in overall cancer regardless of location of cancer (11-23) (*Table S1*). Among them, 5 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (11,13,15,18,22), 5 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (12,14,17,19,21), and 3 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,20,23).

Risk

Nine papers explored the association of *HIF-1α rs11549465*

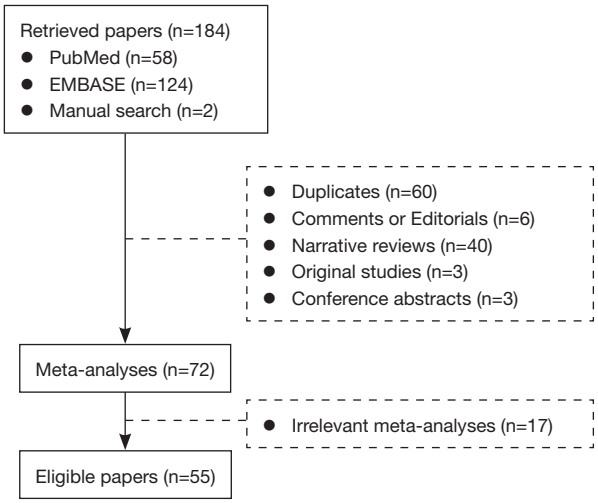

Figure 1 The flowchart of inclusion.

(*1772 C/T*) polymorphism with the risk of overall cancer (11,12,14,15,17-19,21,22). All of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of overall cancer (11,12,14,15,17-19,21,22).

Seven papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of overall cancer (11,15,16,18,20,22,23). Six of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of overall cancer (11,15,16,18,20,23). But another paper did not show any significant association between them (22). The meta-analyses by Liu P (16) and Zhou Y (23) had a larger number of included studies than those by Yang X (18), Ye Y (20), Anam MT (11), Zhao T (22), and Liu J (15) (26 and 26 versus 24, 21, 19, 12, and 6). Thus, we should support a significant association between *HIF-1α rs11549467* (*1790 G/A*) polymorphism and the risk of overall cancer.

Clinicopathological features

One paper explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the clinicopathological features of overall cancer (13). It demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the lymph node metastasis and histological grade of overall cancer, but not the tumor size or stage (13).

One paper explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the clinicopathological features of overall cancer (13). It demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the lymph node metastasis and tumor size of overall cancer, but not the histological grade or tumor stage (13).

Head and neck cancer

A total of 4 meta-analysis papers explored the role of *HIF* in head and neck cancer (12,14,16,23) (*Table S2*). Among them, 2 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (12,14), and another 2 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,23).

Risk

Two papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of head and neck cancer (12,14). One of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of head and neck cancer (12). But another paper did not show any significant association between them (14). The meta-analysis by He P (12) had a larger number of included studies than that by Li Y (14) (5 versus 1). Thus, we should support a significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of head and neck cancer.

Two papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of head and neck cancer (16,23). One of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was

significantly associated with the risk of head and neck cancer (23). But another paper did not show any significant association between them (16). The meta-analysis by Zhou Y (23) had a larger number of included studies than that by Liu P (16) (6 versus 1). Thus, we should support a significant association between *HIF-1α rs11549467* (*1790 G/A*) polymorphism and the risk of head and neck cancer.

Glioma

A total of two meta-analysis papers explored the role of HIF in glioma (14,24) (*Table S3*). Among them, one paper explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (14), and another paper explored HIF-1α expression alone (24).

Risk

One paper explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of glioma (14). It demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of glioma (14).

Clinicopathological features

One paper explored the association of *HIF-1α* expression with the clinicopathological features of glioma (24). It demonstrated that *HIF-1α* expression was significantly associated with the tumor stage of glioma (24).

Oral cancer

A total of ten meta-analysis papers explored the role of *HIF* in oral cancer (14,16,18-20,25-29) (*Table S4*). Among them, four papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (18,27-29), three papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (14,19,25), two papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,20), and one paper explored both *HIF-1α* and *HIF-2α* protein expressions (26).

Risk

Seven papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of oral cancer (14,18,19,25,27-29). All of them did not show any significant association between them (14,18,19,25,27-29).

Six papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of oral cancer (16,18,20,27-29). Four of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of oral cancer (16,20,27,28). But another two papers did not show any significant association between them (18,29). The meta-analyses by Sun X (27) and Yan Q (28) had a larger number of included studies than those by Liu P (16), Yang X (*Plos One*, 2013) (18), Yang X (*Tumour Biol*, 2014) (29), and Ye Y (20). Thus, we should support a significant association between *HIF-1α rs11549467* (*1790 G/A*) polymorphism and the risk of oral cancer.

Prognosis

One paper explored the association of *HIF-1α* and *HIF-2α* protein expression with the prognosis of oral cancer (26). It demonstrated that neither *HIF-1α* nor *HIF-2α* protein expression was significantly associated with the survival of oral cancer (26).

Oropharyngeal cancer

Only one paper explored the role of *HIF* in oropharyngeal cancer (30) (*Table S5*). It explored the association of *HIF-1α* expression with the prognosis of oropharyngeal cancer (30). It demonstrated that *HIF-1α* expression was significantly associated with the survival of oropharyngeal cancer (30).

Nasopharyngeal cancer

Only one paper explored the role of *HIF* in nasopharyngeal cancer (31) (*Table S6*). It explored the association of *HIF-1α* expression with the risk and clinicopathological features of nasopharyngeal cancer (31). It demonstrated that *HIF-1α* expression was significantly associated with the risk, lymph node metastasis, and clinical stage of nasopharyngeal cancer (31).

Lung cancer

A total of 12 meta-analysis papers explored the role of *HIF* in lung cancer (11,12,14,16,18,23,25,28,32-35) (*Table S7*). Among them, 4 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (11,18,28,33), 3 papers explored *HIF-1α rs11549465* (*1772*

C/T) polymorphism alone (12,14,25), 2 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,23), 1 paper explored both *HIF-1α* and *HIF-2α* protein expressions (32), and 2 papers explored *HIF-1α* protein expression alone (34,35).

Risk

Seven papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of lung cancer (11,12,14,18,25,28,33). Four of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of lung cancer (11,18,28,33). But another 3 papers did not show any significant association between them (12,14,25). The meta-analyses by He P (12), Hu X (25), Li Y (14), Yan Q (28), and Yang X (18) had a larger number of included studies than those by Anam MT (11) and Liao S (33) (3, 3, 3, 3, and 3 versus 2 and 2). Among the meta-analyses by He P (12), Hu X (25), Li Y (14), Yan Q (28), and Yang X (18), the included studies were completely identical (*Table S8*). Only the meta-analysis by Yang X employed a random-effect model (18). Thus, we should support a significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of lung cancer.

Six papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of lung cancer (11,16,18,23,28,33). All of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of lung cancer (11,16,18,23,28,33).

Clinicopathological features

One paper explored the association of *HIF-1α* protein expression with the clinicopathological features of lung cancer (34). It demonstrated that *HIF-1α* protein expression was significantly associated with the stage, pathological type, diameter, lymph node metastasis, and differentiation of lung cancer (34).

Prognosis

Three papers explored the association of *HIF-1α* protein expression with the prognosis of lung cancer (32,34,35). All of them demonstrated that *HIF-1α* protein expression was significantly associated with the survival of lung cancer (32,34,35).

One paper explored the association of *HIF-2α* protein expression with the prognosis of lung cancer (32). It demonstrated that *HIF-2α* protein expression was significantly associated with the survival of lung cancer (32).

Breast cancer

A total of 17 meta-analysis papers explored the role of *HIF* in breast cancer (11-14,16-20,22,23,25,28,36-39) (*Table S9*). Among them, 5 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and rs11549467 (1790 G/A) polymorphisms (11,18,22,28,39), 7 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (12-14,17,19,25,36), 3 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,20,23), and 2 papers explored *HIF-1α* protein expression alone (37,38).

Risk

Eleven papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of breast cancer (11,12,14,17-19,22,25,28,36,39). Three of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of breast cancer (14,18,39). But another 8 papers did not show any significant association between them (11,12,17,19,22,25,28,36). The meta-analyses by He P (12), Ren HT (36), Wu G (17), and Yan Q (28) had a larger number of included studies than those by Hu X (*Tumour Biol*, 2014) (25), Li Y (14), Yang X (18), Ye Y (19), Zhao T (22), and Anam MT (11) (6, 6, 6, and 6 versus 5, 5, 5, 3, 3, and 2). An abstract paper by Yin W did not report the number of included studies (39). Thus, we should not support any significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of breast cancer.

Eight papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of breast cancer (11,16,18,20,22,23,28,39). Two of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of breast cancer (11,22). But another 6 papers did not show any significant association between them (16,18,20,23,28,39). The meta-analysis by Yan Q (28) had a larger number of included studies than those by Liu P (16), Yang X (18), Zhou Y (23), Anam MT (11), Ye Y (20), and Zhao T (22) (4 versus 3, 3, 3, 2, 2, and 2). An abstract paper by Yin W did not report the number of included studies (39). Thus, we should not support any significant association between *HIF-1α rs11549467* (*1790 G/A*) polymorphism and the risk of

breast cancer.

Clinicopathological features

One paper explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the clinicopathological features of breast cancer (13). It did not show any significant association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the lymph node metastasis or histological grade of breast cancer (13).

One paper explored the association of *HIF-1α* protein expression with the clinicopathological features of breast cancer (37). It demonstrated that *HIF-1α* protein expression was significantly associated with the pathological differentiation, regional invasive extension, axillary lymph node status, and clinical stage of breast cancer (37).

Prognosis

Two papers explored the association of *HIF-1α* protein expression with the prognosis of breast cancer (37,38). Both of them demonstrated that *HIF-1α* protein expression was significantly associated with the survival of breast cancer (37,38).

Digestive cancer

A total of 33 meta-analysis papers explored the role of *HIF* in digestive cancer (*Table S10*). Among them, 6 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (15,27-29,40,41), 11 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (11-14,17-19,22,25,42,43), 3 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,20,23), 1 paper explored both *HIF-1α* and *HIF-2α* protein expressions (44), 10 papers explored *HIF-1α* protein expression alone (45-54), and 2 papers explored *HIF-2α* protein expression alone (55,56).

Overall digestive cancer

A total of 8 meta-analysis papers explored the role of *HIF* in overall digestive cancer regardless of location of digestive cancer (17,20,27,29,40-43) (*Table S10*). Among them, 4 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (27,29,40,41), 3 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (17,42,43), and 1 paper explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (20).

Risk

Seven papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of overall digestive cancer (17,27,29,40-43). Four of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of overall digestive cancer (29,40,42,43). But another 3 papers did not show any significant association between them (17,27,41). The meta-analysis by Sun X (27) had a larger number of included studies than those by Yang X (29), Ni Z (40), Wu G (17), Xu JJ (*Genet Mol Res*, 2014) (41), Xu J (*Genet Mol Res*, 2014) (43), and Xu J (*Genet Test Mol Biomarkers*, 2013) (42) (13 versus 12, 10, 9, 8, 6, and 6). Thus, we should not support any significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of overall digestive cancer.

Five papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of overall digestive cancer (20,27,29,40,41). All of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of overall digestive cancer (20,27,29,40,41).

Esophageal cancer

A total of 5 meta-analysis papers explored the role of *HIF* in esophageal cancer (14,42,47,49,50) (*Table S10*). Among them, 2 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (14,42) and 3 papers explored *HIF-1α* protein expression alone (47,49,50).

Risk

Two papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of esophageal cancer (14,42). Both of them did not show any significant association between them (14,42).

Two papers explored the association of *HIF-1α* protein expression with the risk of esophageal cancer (47,50). Both of them demonstrated that *HIF-1α* protein expression was significantly associated with the risk of esophageal cancer (47,50).

Clinicopathological features

Three papers explored the association of *HIF-1α* protein expression with the clinicopathological features of esophageal cancer (47,49,50). All of them demonstrated that *HIF-1α* protein expression was significantly associated with the lymphoma node metastasis of esophageal cancer (47,49,50).

Prognosis

Two papers explored the association of *HIF-1α* protein expression with the prognosis of esophageal cancer (47,49). Both of them demonstrated that *HIF-1α* protein expression was significantly associated with the survival of esophageal

cancer (47,49).

Gastric cancer

A total of 8 meta-analysis papers explored the role of *HIF* in gastric cancer (14,16,42,46,48,52,54) (*Table S10*). Among them, 2 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (14,42), 1 paper explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16), 4 papers explored *HIF-1α* protein expression alone (46,48,52,54), and 1 paper explored *HIF-2α* expression alone (56).

Risk

Two papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of gastric cancer (14,42). One of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of gastric cancer (42). But another paper did not show any significant association between them (14). The number of included studies was similar between the two meta-analysis papers by Li Y (14) and Xu J (42) (1 versus 1). The included study was also identical between the two meta-analysis papers (*Table S11*). After learning the results from the original study (Li K, *et al. Biochem Genet*, 2009) (57), we should not support any significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of gastric cancer.

One paper explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of gastric cancer (16). It demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of gastric cancer (16).

Clinicopathological features

Three papers explored the association of *HIF-1α* protein expression with the clinicopathological features of gastric cancer (46,48,54). All of them demonstrated that *HIF-1α* protein expression was significantly associated with the depth of invasion, lymphatic invasion, vascular invasion, and TNM stage of gastric cancer (46,48,54).

One paper explored the association of *HIF-2α* protein expression with the clinicopathological features of gastric cancer (56). It demonstrated that *HIF-2α* protein expression was significantly associated with the tumor infiltration, lymphatic metastasis, and TNM stage of gastric cancer (56).

Prognosis

Four papers explored the association of *HIF-1α* protein expression with the prognosis of gastric cancer (46,48,52,54). All of them demonstrated that *HIF-1α* protein expression was significantly associated with the survival of gastric cancer (46,48,52,54).

One paper explored the association of *HIF-2α* protein expression with the prognosis of gastric cancer (56). It demonstrated that *HIF-2α* protein expression was significantly associated with the survival of gastric cancer (56).

Colorectal cancer

A total of 15 meta-analysis papers explored the role of *HIF* in colorectal cancer (11-16,18,19,22,25,27-29,42,44) (*Table S10*). Among them, 4 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (15,27-29), 9 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (11-14,18,19,22,25,42), 1 paper explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16), and 1 paper explored both *HIF-1α* and *HIF-2α* protein expressions (44).

Risk

Twelve papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of colorectal cancer (11,12,14,15,18,19,22,25,27-29,42,55). All of them did not show any significant association between them (11,12,14,15,18,19,22,25,27-29,42).

Four papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of colorectal cancer (16,27-29). All of them did not show any significant association between them (16,27-29).

Clinicopathological features

One paper explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the clinicopathological features of colorectal cancer (13). It did not show any significant association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the lymph node metastasis and histological grade of colorectal cancer (13).

One paper explored the association of *HIF-1α* protein expression with the clinicopathological features of colorectal cancer (44). It demonstrated that *HIF-1α* protein expression was significantly associated with the Dukes' stages, lymph node status, depth of invasion, metastasis, and UICC stage of colorectal cancer, but not the differentiation grade (44).

One paper explored the association of *HIF-2α* protein expression with the clinicopathological features of colorectal cancer (44). It demonstrated that *HIF-2α* protein expression was significantly associated with the differentiation grade of colorectal cancer, but not the Dukes' stages, lymph node status, or depth of invasion (44).

Prognosis

One paper explored the association of *HIF-1α* protein

expression with the prognosis of colorectal cancer (44). It demonstrated that *HIF-1α* protein expression was significantly associated with the survival of colorectal cancer (44).

One paper explored the association of *HIF-2α* protein expression with the prognosis of colorectal cancer (44). It demonstrated that *HIF-2α* protein expression was significantly associated with the survival of colorectal cancer (44).

Pancreatic cancer

A total of 8 meta-analysis papers explored the role of *HIF* in pancreatic cancer (12,14,16,23,27-29,51) (*Table S10*). Among them, 2 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (27,29), 2 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (12,14), 3 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,23,28), and 1 paper explored *HIF-1α* protein expression alone (51).

Risk

Four papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of pancreatic cancer (12,14,27,29). All of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of pancreatic cancer (12,14,27,29).

Five papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of pancreatic cancer (16,23,27-29). All of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*)polymorphism was significantly associated with the risk of pancreatic cancer (16,23,27-29).

Clinicopathological features

One paper explored the association of *HIF-1α* protein expression with the clinicopathological features of pancreatic cancer (51). It demonstrated that *HIF-1α* protein expression was significantly associated with the lymph node metastasis and tumor stage of pancreatic cancer, but not the tumor size (51).

Prognosis

One paper explored the association of *HIF-1α* protein expression with the prognosis of pancreatic cancer (51). It demonstrated that *HIF-1α* protein expression was significantly associated with the survival of pancreatic cancer (51).

Hepatocellular carcinoma

A total of 5 meta-analysis papers explored the role of *HIF* in hepatocellular carcinoma (14,16,45,53,55) (*Table S10*). Among them, 1 paper explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (14), 1 paper explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16), 2 papers explored *HIF-1α* protein expression alone (45,53), and 1 paper explored *HIF-2α* protein expression alone (55).

Risk

One paper explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of hepatocellular carcinoma (14). It did not show any significant association between them (14).

One paper explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of hepatocellular carcinoma (16). It demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of hepatocellular carcinoma (16).

Clinicopathological features

One paper explored the association of *HIF-1α* protein expression with the clinicopathological features of hepatocellular carcinoma (46). It demonstrated that *HIF-1α* protein expression was significantly associated with the vascular invasion of hepatocellular carcinoma, but not the tumor size or differentiation, liver cirrhosis, or capsule formation (46).

One paper explored the association of *HIF-2α* protein expression with the clinicopathological features of hepatocellular carcinoma (55). It demonstrated that *HIF-2α* protein expression was significantly associated with the vein invasion, histological grade, and capsule infiltration of hepatocellular carcinoma, but not the tumor size or liver cirrhosis (55).

Prognosis

Two papers explored the association of *HIF-1α* protein expression with the prognosis of hepatocellular carcinoma (46,53). Both of them demonstrated that *HIF-1α* protein expression was significantly associated with the survival of hepatocellular carcinoma (46,53).

One paper explored the association of *HIF-2α* protein expression with the prognosis of hepatocellular carcinoma (55). It did not show any significant association between *HIF-2α* protein expression and the survival of hepatocellular carcinoma (55).

Urinary cancer

A total of 15 meta-analysis papers explored the role of *HIF* in urinary cancer (11,12,14,16-20,22,23,25,28,58-60) (*Table S12*). Among them, 5 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (11,18,22,28,59), 5 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone

(12,14,17,19,25), 3 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,20,23), 1 paper explored both *HIF-1α* and *HIF-2α* protein expressions (58), and 1 paper explored HIF-1α protein expression alone (60).

Overall urinary cancer

One meta-analysis paper explored the association of *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms with the risk of overall urinary cancer (59) (*Table S12*). It demonstrated that neither of them was significantly associated with the risk of overall urinary cancer (59).

Prostate cancer

A total of 13 meta-analysis papers explored the role of HIF in prostate cancer (11,12,14,16-20,22,23,25,28,59) (*Table S12*). Among them, 5 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (11,18,22,28,59), 5 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (11,18,22,28,59), and 3 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,20,23).

Risk

Ten papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of prostate cancer (11,12,14,17-19,22,25,59). Five of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of prostate cancer (14,18,19,22,25). Another 5 papers did not show any significant association between them (11,12,17,28,59). The meta-analyses by Anam MT (11), He P (12), Li D (59), Wu G (17), and Yan Q (28) had a larger number of included studies than those by Hu X (25), Yang X (18), Ye Y (19), Li Y (14), and Zhao T (22) (6, 6, 6, 6, and 6 versus 5, 5, 5, 4, and 4). Thus, we should not support any significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of prostate cancer.

Eight papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of prostate cancer (11,16,18,20,22,23,28,59). One of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of prostate cancer (59). Another 7 papers did not show any significant association between them (11,16,18,20,22,23,28). The meta-analysis by Li D (59) had a larger number of included studies than those by Anam MT (11), Liu P (16), Yan Q (28), Ye Y (20), Yang X (18), Zhou Y (23), and Zhao T (22) (4 versus 3, 3, 3, 3, 3, 3, and 2). Thus, we should support a significant association between *HIF-1α rs11549467* (*1790 G/A*) polymorphism and the risk of prostate cancer.

Renal cancer

A total of 13 meta-analysis papers explored the role of *HIF* in renal cancer (11,12,14,16,17,19,20,23,25,28,58-60) (*Table S12*). Among them, 3 papers explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (11,28,59), 5 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (12,14,17,19,25), 3 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,20,23), 1 paper explored both *HIF-1α* and *HIF-2α* nuclear and cytoplasmic expressions (58), and 1 paper explored *HIF-1α* protein expression alone (60).

Risk

Eight papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of renal cancer (11,12,14,17,19,25,28,59). Two of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of renal cancer (11,12). Another 6 papers did not show any significant association between them (14,17,19,25,28,59). The meta-analyses by Hu X (25), Li D (59), Wu G (17), and Yan Q (28) had a larger number of included studies than those by Anam MT (11), He P (12), Ye Y (19), and Li Y (14) (4, 4, 4, and 4 versus 3, 3, 3, and 2). Thus, we should not support any significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of renal cancer.

Six papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of renal cancer (11,16,20,23,28,59). Three of them demonstrated that *HIF-1α rs11549467* (*1790 G/A*) polymorphism was significantly associated with the risk of renal cancer (11,23,28). Another 3 papers did not show any significant association between them (16,19,59). The meta-analyses by Anam MT (11), Li D (59), and Yan Q (28) had a larger number of included studies than those by Liu P (16), Zhou Y (23), and Ye Y (20) (4, 4, and 4 versus 3, 3, and 2). The included studies were completely identical among the 3 meta-analyses by Anam MT (11), Li D (59), and Yan Q (28) (*Table S13*). Notably, some statistical results (AA + AG *vs.* GG and A allele *vs.* G allele) were completely identical among them (11,28,59). However, the meta-analyses by Anam MT (11) and Yan Q (28) had more statistical results

(AA *vs.* GG, GA *vs.* GG, and AA *vs.* GA + GG) than that by Li D (59). Thus, we should support a significant association between *HIF-1α rs11549467* (*1790 G/A*) polymorphism and the risk of renal cancer.

Clinicopathological features

One paper explored the association of *HIF-1α* protein expression with the clinicopathological features of renal cancer (60). It demonstrated that *HIF-1α* protein expression was significantly associated with the lymph node metastasis and clinical and pathological stage of renal cancer (60).

Prognosis

One paper explored the association of *HIF-1α* and *HIF-2α* nuclear and cytoplasmic expressions with the prognosis of renal cancer (58). It demonstrated that neither *HIF-1α* nor *HIF-2α* nuclear and cytoplasmic expression was significantly associated with the survival of renal cancer (58).

Bladder cancer

A total of 3 meta-analysis papers explored the role of *HIF* in bladder cancer (14,16,25) (*Table S12*). Among them, 2 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (14,25), and 1 paper explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16).

Risk

Two papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of bladder cancer (14,25). Neither of them demonstrated any significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of bladder cancer (14,25).

One paper explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of bladder cancer (16). It did not show any significant association between them (16).

Gynecological cancer

A total of 12 meta-analysis papers explored the role of HIF in gynecological cancer (12-14,16,19,20,25,28,61-64) (*Table S14*). Among them, 1 paper explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (28), 8 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (12-14,19,25,64), 2 papers explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16,20), and 1 paper explored *HIF-1α* protein expression alone (61-63,65).

Overall gynecological cancer

A total of 3 meta-analysis papers explored the role of HIF in overall gynecological cancer (14,16,65) (*Table S14*). Among them, 1 paper explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (14), 1 paper explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (16), and 1 paper explored *HIF-1α* protein expression alone (65).

Risk

One paper explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of overall gynecological cancer (14). It demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of overall gynecological cancer (14).

One paper explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of overall gynecological cancer (16). It did not show any significant association between them (16).

Clinicopathological features

One paper explored the association of *HIF-1α* protein expression with the clinicopathological features of overall gynecological cancer (65). It demonstrated that *HIF-1α* protein expression was significantly associated with the pathological and histological type, FIGO stage, and lymph node metastasis of overall gynecological cancer (65).

Prognosis

One paper explored the association of *HIF-1α* protein expression with the prognosis of overall gynecological cancer (65). It demonstrated that *HIF-1α* protein expression was significantly associated with the survival of overall gynecological cancer (65).

Ovarian cancer

A total of 3 meta-analysis papers explored the role of *HIF* in ovarian cancer (62,63,65). All of them explored *HIF-1α* protein expression alone (62,63,65) (*Table S14*).

Risk

One paper explored the association of *HIF-1α* protein expression with the risk of ovarian cancer (63). It demonstrated that *HIF-1α* protein expression was significantly associated with the risk of ovarian cancer (63).

Clinicopathological features

Three papers explored the association of *HIF-1α* protein expression with the lymph node metastasis of ovarian cancer (62,63,65). All of them demonstrated that *HIF-1α* protein expression was significantly associated with the lymph node metastasis of ovarian cancer (62,63,65).

Three papers explored the association of *HIF-1α* protein expression with the pathological type of ovarian cancer (62,63,65). Two of them demonstrated *HIF-1α* protein expression was significantly associated with the pathological

type of ovarian cancer (62,65). But another paper did not show any significant association between them (63). The meta-analyses by Jin Y (*Tumour Biol*, 2014) (62) and Jin Y (*PLoS One*, 2015) (65) had a larger number of included studies than that by Sun C (63) (13 and 13 versus 4). Thus, we should support a significant association between *HIF-1α* protein expression and the pathological type of ovarian cancer.

Two papers explored the association of *HIF-1α* protein expression with the FIGO stage of ovarian cancer (62,65). Both of them demonstrated that *HIF-1α* protein expression was significantly associated with the FIGO stage of ovarian cancer (62,65).

Prognosis

Two papers explored the association of *HIF-1α* protein expression with the prognosis of ovarian cancer (62,65). Both of them demonstrated that *HIF-1α* protein expression was significantly associated with the survival of ovarian cancer (62,65).

Cervical cancer

A total of 10 meta-analysis papers explored the role of *HIF* in cervical cancer (12,13,18-20,25,28,61,64,65) (*Table S14*). Among them, 1 paper explored both *HIF-1α rs11549465* (*1772 C/T*) and *rs11549467* (*1790 G/A*) polymorphisms (28), 6 papers explored *HIF-1α rs11549465* (*1772 C/T*) polymorphism alone (12,13,18,19,25,64), 1 paper explored *HIF-1α rs11549467* (*1790 G/A*) polymorphism alone (20), and 2 papers explored *HIF-1α* protein expression alone (61,65).

Risk

Six papers explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the risk of cervical cancer (12,18,19,25,28,64). Five of them demonstrated that *HIF-1α rs11549465* (*1772 C/T*) polymorphism was significantly associated with the risk of cervical cancer (12,18,25,28,64). But another paper did not show any significant association between them (19). The meta-analysis by Zhu J (64) had a larger number of included studies than those by He P (12), Hu X (25), Yan Q (28), Yang X (18), and Ye Y (19) (4 versus 3, 3, 3, 3, and 3). Thus, we should support a significant association between *HIF-1α rs11549465* (*1772 C/T*) polymorphism and the risk of cervical cancer.

Two papers explored the association of *HIF-1α rs11549467* (*1790 G/A*) polymorphism with the risk of cervical cancer (20,28). Neither of them showed any significant association between *HIF-1α rs11549467* (*1790 G/A*) polymorphism and the risk of cervical cancer (20,28).

Clinicopathological features

One paper explored the association of *HIF-1α rs11549465* (*1772 C/T*) polymorphism with the lymph node metastasis of cervical cancer (13). It did not show any significant association between them (13).

Two papers explored the association of *HIF-1α* protein expression with the FIGO stage of cervical cancer (61,65). Both of them demonstrated that *HIF-1α* protein expression was significantly associated with the FIGO stage of cervical cancer (61,65).

Two papers explored the association of *HIF-1α* protein expression with the histological type and lymph node metastasis of cervical cancer (61,65). One of them demonstrated that *HIF-1α* protein expression was significantly associated with the histological type and lymph node metastasis of cervical cancer (65). But another paper did not show any significant association between them (61). As for the histological type, the meta-analysis by Jin Y (65) had a larger number of included studies than that by Huang M (61) (6 versus 4). As for the lymph node metastasis, the meta-analysis by Jin Y (65) had a larger number of included studies than that by Huang M (61) (8 versus 5). Thus, we should support a significant association between *HIF-1α* protein expression and the histological type and lymph node metastasis of cervical cancer.

Prognosis

Two papers explored the association of *HIF-1α* protein expression with the prognosis of cervical cancer (61,65). Both of them demonstrated that *HIF-1α* protein expression was significantly associated with the survival of cervical cancer (61,65).

Endometrial cancer

Only one paper explored the association of *HIF-1α* protein expression with the clinicopathological features and prognosis of endometrial cancer (65) (*Table S14*). It demonstrated that *HIF-1α* protein expression was significantly associated with the pathological and histological type, FIGO stage, and lymph node metastasis of endometrial cancer, but not the survival (65).

Osteosarcoma

Only one paper explored the association of *HIF-1α* protein expression with the clinicopathological features and prognosis of osteosarcoma (66) (*Table S15*). It demonstrated that *HIF-1α* protein expression was significantly associated with the metastasis, pathologic and tumor grade, and

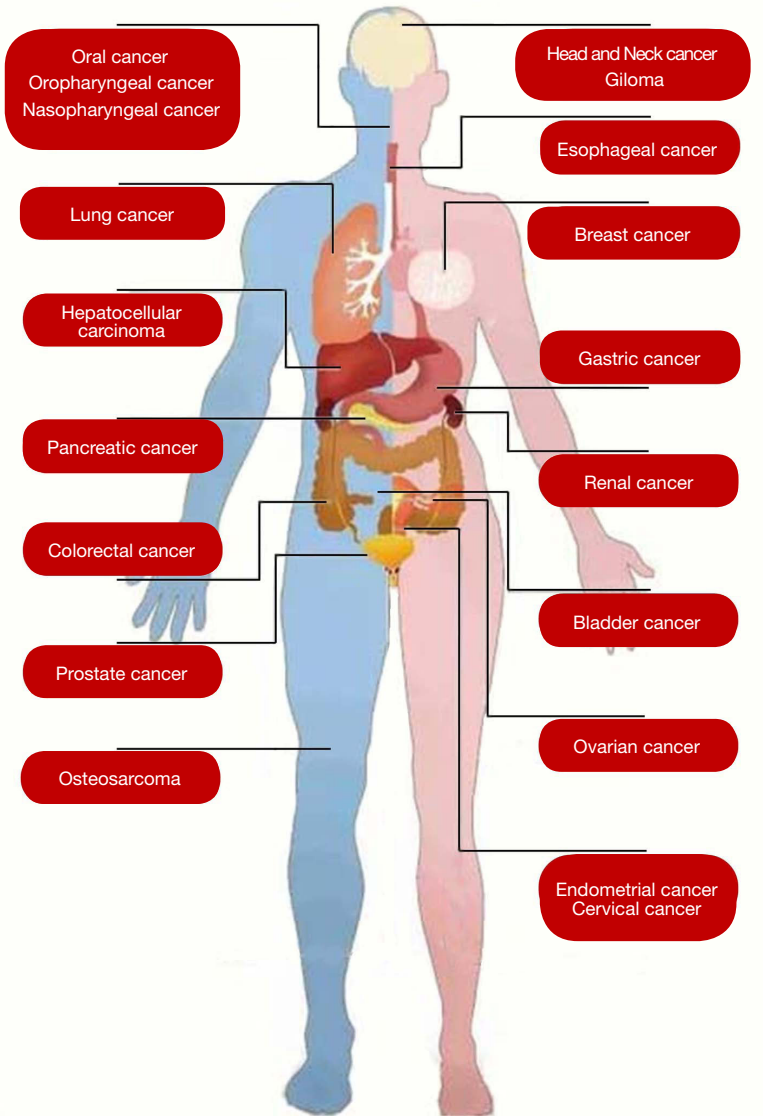

Figure 2 A schematic diagram of various human cancers in which the role of HIFs has been explored by meta-analyses. HIFs, hypoxia-inducible factors.

survival of osteosarcoma, but not the histopathology, tumor size, or tumor site (66).

Conclusions

Based on our systematic search strategy, numerous meta-analyses have explored the role of *HIF* gene polymorphism and protein expression in various human cancers, including head and neck cancer, glioma, oral cancer, oropharyngeal cancer, nasopharyngeal cancer, lung cancer, breast cancer, esophageal cancer, gastric cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, prostate cancer, renal cancer, bladder cancer, ovarian cancer, cervical cancer, endometrial cancer, and osteosarcoma (*Figure 2*).

Based on the current evidence, major findings were summarized in *Table 1*.

First, the evidence regarding the association of *HIF-1α* gene polymorphism with risk of cancer suggested the following: (I) both *HIF-1α rs11549465* (*1772 C/T*) and *HIF-1α rs11549467* (*1790 G/A*) polymorphisms should be associated with the risk of head and neck cancer and lung cancer; (II) *HIF-1α rs11549465* (*1772 C/T*) polymorphism,

Table 1 Summary of major evidence

Cancer	Risk		Lymph node metastasis/ tumor stage		Survival	
	HIF-1α rs11549465 (*1772 C/T*) polymorphism	*HIF-1α rs11549467* (*1790 G/A*) polymorphism	*HIF-1α* expression	*HIF-2α* expression	*HIF-1α* expression	*HIF-2α* expression
Head and neck cancer	Y	Y				
Glioma	Y		Y			
Oral cancer	N	Y			N	N
Oropharyngeal cancer					Y	
Nasopharyngeal cancer			Y			
Lung cancer	Y	Y	Y/Y		Y	Y
Breast cancer	N	N	Y		Y	
Esophageal cancer	N		Y		Y	
Gastric cancer	N	Y	Y/Y	Y/Y	Y	Y
Colorectal cancer	N	N	Y/Y	N/N	Y	Y
Pancreatic cancer	Y	Y	Y/Y		Y	
Hepatocellular carcinoma	N	Y			Y	N
Prostate cancer	N	Y				
Renal cancer	N	Y	Y/Y		N	N
Bladder cancer	N	N				
Ovarian cancer			Y/Y		Y	
Cervical cancer	Y	N			Y	
Endometrial cancer					N	
Osteosarcoma			Y		Y	

Y, There is a significant correlation; N, There is no significant correlation.

rather than *HIF-1α rs11549467* (*1790 G/A*) polymorphism, should be associated with the risk of cervical cancer; (III) *HIF-1α rs11549467* (*1790 G/A*) polymorphism, rather than *HIF-1α rs11549465* (*1772 C/T*) polymorphism, should be associated with the risk of oral cancer, gastric cancer, hepatocellular carcinoma, prostate cancer, and renal cancer; and (IV) neither *HIF-1α rs11549465* (*1772 C/T*) nor *HIF-1α rs11549467* (*1790 G/A*) polymorphism should be associated with the risk of breast cancer, colorectal cancer, and bladder cancer.

Second, the evidence regarding the association of *HIF-1α* protein expression with the lymph node metastasis of cancer suggested the following: (I) both *HIF-1α* and *HIF-2α* expression were associated with the lymph node metastasis of gastric cancer; and (II) *HIF-1α* expression, rather than *HIF-2α* expression, was associated with the lymph node metastasis of colorectal cancer.

Third, the evidence regarding the association of *HIF-1α* protein expression alone with the lymph node metastasis of cancer suggested that *HIF-1α* expression was associated with the lymph node metastasis of glioma, nasopharyngeal cancer, lung cancer, breast cancer, esophageal cancer, gastric cancer, pancreatic cancer, renal cancer, ovarian cancer, and osteosarcoma.

Fourth, the evidence regarding the association of *HIF-1α* protein expression with the survival of cancer suggested the following: (I) both *HIF-1α* and *HIF-2α* expressions were associated with the survival of lung cancer, gastric

cancer, and colorectal cancer; (II) *HIF-1α* expression, rather than *HIF-2α* expression, was associated with the survival of hepatocellular carcinoma; and (III) neither *HIF-1α* nor *HIF-2α* expression was associated with the survival of renal cancer.

Fifth, the evidence regarding the association of *HIF-1α* protein expression alone with the survival of cancer suggested that *HIF-1α* expression was associated with the survival of oropharyngeal cancer, breast cancer, esophageal cancer, pancreatic cancer, ovarian cancer, cervical cancer, and osteosarcoma, but not that of endometrial cancer.

Collectively, the impact of *HIFs* on the risk, clinicopathological features, and survival of various human cancers should be heterogeneous. The potential explanation might be attributed to the heterogeneity in the cancer biological behavior and effect of hypoxia across the different types of human cancers. Further studies should uncover the potential mechanisms.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.04.08). Xingshun Qi serves as an Editor-in-Chief of AME Medical Journal. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 HIF in overall cancer

First author	Journal [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Anam MT	*Biomark Res* [2015]	Bangladesh	PubMed, PubMed Central, Google Scholar	2014.12	Overall cancer	*HIF-1α rs11549465* (*1772 C/T*) polymorphism	22	Risk:
								TT *vs.* CC: OR =1.52, 95% CI: 0.73–3.18, P=0.2648
								CT *vs.* CC: OR =1.23, 95% CI: 1.00–1.53, P=0.0536
								TT + CT *vs.* CC: OR =1.30, 95% CI: 1.06–1.59, P=0.0115
								TT *vs.* CT + CC: OR =1.64, 95% CI: 0.94–2.85, P=0.0832
								T allele *vs.* C allele: OR =1.32, 95% CI: 1.07–1.63, P=0.0098
					Overall cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	19	Risk:
								AA *vs.* GG: OR =5.10, 95% CI: 3.12–8.33, P<0.0001
								GA *vs.* GG: OR =1.74, 95% CI: 1.20–2.52, P=0.0033
								AA *vs.* GA + GG: OR =3.79, 95% CI: 2.34–6.15, P<0.0001
								AA + GA *vs.* GG: OR =1.82, 95% CI: 1.26–2.62, P=0.0014
								A allele *vs.* G allele: OR =1.82, 95% CI: 1.31–2.52, P=0.0003
He P	*PLoS One* [2013]	China	PubMed, Embase, CNKI	2013.8.23	Overall cancer	*HIF-1α rs11549465* (*1772 C/T*) polymorphism		Risk:
							36	Dominant model (TT + CT *vs.* CC): OR =1.23, 95% CI: 1.03–1.47
							26	Recessive model (TT *vs.* CT + CC): OR =2.51, 95% CI: 1.54–4.09
							25	Homozygote comparison (TT *vs.* CC): OR =2.02, 95% CI: 1.21–3.39
							36	Heterozygote comparison (CT *vs.* CC): OR =1.16, 95% CI: 0.97–1.38
Hu X	*Tumour Biol* [2013]	China	PubMed, Embase, CNKI	2013.2	Overall cancer	*HIF-1α rs11549465* (*1772 C/T*) polymorphism	15	Lymph node metastasis:
								OR =1.38, 95% CI: 1.13–1.68, P=0.002
							7	Distant metastasis:
								OR =1.39, 95% CI: 0.96–2.02, P=0.082
							9	Tumor size:
								T2–4 *vs.* T1: OR =1.09, 95% CI: 0.83–1.45, P=0.530
								T3–4 *vs.* T1–2: OR =1.29, 95% CI: 0.93–1.80, P=0.128
							5	Stage:
								OR =0.93, 95% CI: 0.66–1.31, P=0.43
							9	Histological grade:
								Grades G3 *vs.* G1: OR =1.07, 95% CI: 0.71–1.60, P=0.759
								Grades G3 *vs.* G2: OR =1.51, 95% CI: 1.08–2.13, P=0.017
								Grades G2 *vs.* G1: OR =0.67, 95% CI: 0.46–0.97, P=0.035
						HIF-1α rs11549467 (1790 G/A) polymorphism	8	Lymph node metastasis:
								OR =1.33, 95% CI: 1.00–1.78, P=0.050
							4	Distant metastasis:
								OR =0.97, 95% CI: 0.58–1.62, P=0.893
							5	Tumor size:
								T2–4 *vs.* T1: OR =1.04, 95% CI: 0.65–1.65, P=0.871
								T3–4 *vs.* T1–2: OR =1.64, 95% CI: 1.04–2.58, P=0.033
							4	Stage:
								OR =1.00, 95% CI: 0.65–1.52, P=0.987
							5	Histological grade:
								Grades G3 *vs.* G1: OR =0.93, 95% CI: 0.56–1.55, P=0.789
								Grades G3 *vs.* G2: OR =1.12, 95% CI: 0.73–1.70, P=0.609
								Grades G2 *vs.* G1: OR =0.88, 95% CI: 0.57–1.36, P=0.556
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Overall cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	28	Risk:
								TT *vs.* CC: OR =2.15, 95% CI: 1.19–3.88, P=0.011
								CT *vs.* CC: OR =1.15, 95% CI: 0.96–1.36, P=0.127
								TT/CT *vs.* CC: OR =1.19, 95% CI: 0.99–1.42, P=0.071
								TT *vs.* CT/CC: OR =2.21, 95% CI: 1.60–3.05, P=0.010
								T allele *vs.* C allele: OR =1.20, 95% CI: 1.01–1.44, P=0.043
Liu J	*Gene* [2013]	China	PubMed, Embase	2012.3	Overall cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism		Risk:
							8	Allele: OR =1.177, 95% CI=1.011–1.369, P=0.035
							7	Genotype: OR =0.975, 95% CI=0.868–1.055, P=0.373
						HIF-1α rs11549467 (1790 G/A) polymorphism		Risk:
							6	Allele: OR =1.254, 95% CI=0.77–2.043, P=0.362
							5	Genotype: OR =0.736, 95% CI=0.595–0.910, P=0.005
Liu P	*Neoplasma* [2014]	China	PubMed, Embase, Web of Knowledge, Google Scholar	2013.8	Overall cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	26	Risk:
								AA *vs.* GG: OR =4.37, 95% CI: 2.61–7.33, p<0.001
								GA *vs.* GG: OR =1.39, 95% CI: 1.06–1.82, P=0.017
								AA + GA *vs.* GG: OR =1.46, 95% CI: 1.11–1.92, P=0.007
								AA *vs.* GA + GG: OR =3.87, 95% CI: 2.32–6.46, P<0.001
								A allele *vs.* G allele: OR =1.49, 95% CI: 1.15–1.95, P=0.003
Wu G	*Tumour Biol* [2014]	China	PubMed, Embase, Google Scholar, Wanfang	2013.6.10	Overall cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	38	Risk:
								TT + CT *vs.* CC: OR =1.18, 95% CI: 1.00–1.38, P=0.048
							35	TT *vs.* CT + CC: OR =1.22, 95% CI: 1.05–1.41, P=0.01
Yang X	*PLoS One* [2013]	China	PubMed, Embase	2013.6.26	Overall cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	34	Risk:
								TT *vs.* CC: OR =2.45, 95% CI: 1.52–3.96
								CT *vs.* CC: OR =1.15, 95% CI: 0.92–1.45
								TT + CT *vs.* CC: OR =1.27, 95% CI: 1.05–1.55
								TT *vs.* CT + CC: OR =3.18, 95% CI: 1.92–5.29
								T allele *vs.* C allele: OR =1.42, 95% CI: 1.18–1.70
						HIF-1α rs11549467 (1790 G/A) polymorphism	24	Risk:
								AA *vs.* GG: OR =4.74, 95% CI: 1.78–12.6
								GA *vs.* GG: OR =1.35, 95% CI: 0.82–2.21
								AA + GA *vs.* GG: OR =1.65, 95% CI: 1.05–2.60
								AA *vs.* GA + GG: OR =4.39, 95% CI: 1.61–11.9
								A allele *vs.* G allele: OR =1.83, 95% CI: 1.13–2.96
Ye Y	*Cancer Invest* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Overall cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	29	Risk:
								TT + CT *vs.* CC: OR =1.28, 95% CI: 1.06–1.54, P=0.009
Ye Y	*Tumori* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Overall cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	21	Risk:
								TT + CT *vs.* CC: OR =1.79, 95% CI: 1.12–2.86, P=0.01
Zhang Q	*PLoS One* [2013]	China	PubMed, Embase	2012.12.1	Overall cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism		Risk:
							15	TT+CT *vs.* CC: OR =1.39, 95% CI: 1.13–1.71, P=0.002
							5	TT *vs.* CT+CC: OR =1.93, 95% CI: 0.86–4.36, P=0.11
							15	T allele *vs.* C allele: OR =1.36, 95% CI: 1.12–1.64, P=0.002
Zhao T	*J Exp Clin Cancer Res* [2009]	China	PubMed	2009.6	Overall cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	18	Risk:
								T allele *vs.* C allele: OR =1.29, 95% CI: 1.01–1.65, P=0.04
								TT *vs.* CT + CC: OR =2.18, 95% CI: 1.32–3.62, P=0.003
								TT + CT *vs.* CC: OR =1.19, 95% CI: 0.88–1.59, P=0.26
						HIF-1α rs11549467 (1790 G/A) polymorphism	12	Risk:
								A allele *vs.* G allele: OR =1.61, 95% CI: 0.75–3.45, P=0.22
								AA + GA *vs.* GG: OR =1.56, 95% CI: 0.66–3.65, P=0.31
Zhou Y	*Cancer Cell Int* [2014]	China	PubMed, Embase, CNKI	2013.12.13	Overall cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism		Risk:
							25	AA + GA *vs.* GG: OR =1.85, 95% CI: 1.27–2.69
							26	AA *vs.* GA + GG: OR =5.69, 95% CI: 3.87–8.37
							12	AA *vs.* GG: OR =6.63, 95% CI: 4.49–9.79
							11	GA *vs.* GG: OR =2.39, 95% CI: 1.53–3.75

Table S2 HIF in head and neck cancer

First author	Journal (year)	Country	Databases	Search date	Cancer	HIF	No. studies	Results
He P	*PLoS One* [2013]	China	PubMed, Embase, CNKI	2013.8.23	Head and neck cancer	*HIF-1α rs11549465* (*1772 C/T*) polymorphism		Risk:
							5	Dominant model (TT + CT *vs.* CC): OR =1.20, 95% CI: 0.87–1.67
							4	Recessive model (TT *vs.* CT + CC): OR =11.29, 95% CI: 1.24–103.02
							3	Homozygote comparison (TT *vs.* CC): OR =2.24, 95% CI: 1.14–4.39
							5	Heterozygote comparison (CT *vs.* CC): OR =1.03, 95% CI: 0.69–1.62
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Head and neck squamous cell carcinoma	*HIF-1α rs11549465* (*1772 C/T*) polymorphism	1	Risk:
								CT *vs.* CC: OR =1.81, 95% CI: 0.73–4.51, P=0.199
								TT /CT *vs.* CC: OR =1.81, 95% CI: 0.73–4.51, P=0.199
								T allele *vs.* C allele: OR =1.73, 95% CI: 0.72–4.15, P=0.217
Liu P	*Neoplasma* [2014]	China	PubMed, Embase, Web of Knowledge, Google Scholar	2013.8	Head and neck squamous cell carcinoma	*HIF-1α rs11549467 (1790 G/A)* polymorphism	1	Risk:
								GA *vs.* GG: OR =0.88, 95% CI: 0.26–3.00, P=0.838
								AA + GA *vs.* GG: OR =0.88, 95% CI: 0.26–3.00, P=0.838
								A allele *vs.* G allele: OR =0.88, 95% CI: 0.27–2.94, P=0.841
Zhou Y	*Cancer Cell Int* [2014]	China	PubMed, Embase, CNKI	2013.12.13	Head and neck cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism		Risk:
							6	AA + GA *vs.* GG: OR =3.57, 95% CI: 0.98–12.99
							3	AA *vs.* GA + GG: OR =58, 95% CI: 1.75–1,924.88
							3	AA *vs.* GG: OR =101.38, 95% CI: 22.09–65.29
							3	GA *vs.* GG: OR =12.53, 95% CI: 2.42–64.76

Table S3 HIF in glioma

First author	Journal [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Glioma	*HIF-1α rs11549465* (*1772 C/T*) polymorphism	1	Risk:
								TT *vs.* CC: OR =2.23, 95% CI: 0.20–24.92, P=0.514
								CT *vs.* CC: OR =2.15, 95% CI: 1.08–4.29, P=0.030
								TT/CT *vs.* CC: OR =2.16, 95% CI: 1.10–4.21, P=0.025
								TT *vs.* CT/CC: OR =2.01, 95% CI: 0.18–22.45, P=0.569
								T allele *vs.* C allele: OR =2.05, 95% CI: 1.09–3.83, P=0.025
Liu Q	*Int J Clin Exp Med* [2015]	China	PubMed, Embase, Wanfang, CNKI	2015	Glioma	*HIF-1α* expression	24	IV + III *vs.* II+I:
								OR =8.59, 95% CI: 6.56–11.24, P<0.00001
							14	IV *vs.* III:
								OR =2.51, 95% CI: 1.43–4.42, P=0.001
							11	IV *vs.* II:
								OR =9.18, 95% CI: 5.18–16.28, P<0.00001
							9	IV *vs.* I:
								OR = 24.23, 95% CI: 12.21–48.09, P<0.00001
							12	III *vs.* II:
								OR =4.59, 95% CI: 2.96–7.12, P<0.00001
							10	III *vs.* I:
								OR =13.34, 95% CI: 7.53–23.62, P<0.00001
							11	II *vs.* I:
								OR =4.19, 95% CI: 2.59–6.77, P<0.00001

Table S4 HIF in oral cancer

First author	Journal [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Hu X	*Tumour Biol* [2014]	China	PubMed, Embase, CNKI	2013.7	Oral cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	4	Risk: T allele *vs.* C allele: OR =2.52, 95% CI: 0.71–8.98 TT *vs.* CC: OR =1.97, 95% CI: 0.72–5.39 CT *vs.* CC: OR =0.92, 95% CI: 0.44–1.89 TT + CT *vs.* CC: OR =1.06, 95% CI: 0.64–1.76 TT *vs.* CT + CC: OR =22.82, 95% CI: 0.28–1,887.72
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Oral squamous cell carcinoma	*HIF-1α rs11549465 (1772 C/T)* polymorphism	2	Risk: TT *vs.* CC: OR =6.14, 95% CI: 0.25–151.49, P=0.267 CT *vs.* CC: OR =1.28, 95% CI: 0.69–2.38, P=0.432 TT/CT *vs.* CC: OR =1.35, 95% CI: 0.73–2.49, P=0.334 TT *vs.* CT/CC: OR =6.01, 95% CI: 0.24–148.26, P=0.273 T allele *vs.* C allele: OR =1.41, 95% CI: 0.78–2.56, P=0.257
Liu P	*Neoplasma* [2014]	China	PubMed, Embase, Web of Knowledge, Google Scholar	2013.8	Oral squamous cell carcinoma	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk: AA *vs.* GG: OR =13.32, 95% CI: 1.57–112.75, P=0.017 GA *vs.* GG: OR =2.96, 95% CI: 1.05–8.31, P=0.039 AA + GA *vs.* GG: OR =3.15, 95% CI: 1.05–9.47, P=0.041 AA *vs.* GA + GG: OR =10.70, 95% CI: 1.25–91.51, P=0.030 A allele *vs.* G allele: OR =3.09, 95% CI: 1.07–8.93, P=0.038
Qian J	*Tumour Biol* [2016]	China	PubMed, Web of Knowledge, Web of Science	2016.1.12	Oral squamous cell carcinoma	*HIF-1α* expression	12	OS: RR =1.18, 95 % CI: 0.66–2.11
						HIF-2α expression	2	OS: RR =1.40; 95 % CI: 0.93–2.09
Sun X	*World J Gastroenterol* [2015]	China	PubMed, Embase, CNKI	2013.7.15	Oral cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	4	Risk: CT *vs.* CC: OR =0.917, 95% CI: 0.444–1.895 TT + CT *vs.* CC: OR =1.063, 95% CI: 0.643–1.757 T allele *vs.* C allele: OR =2.517, 95% CI: 0.705–8.980
					Oral cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	4	Risk: CT *vs.* CC: OR =3.165, 95% CI: 1.264–7.924 TT + CT *vs.* CC: OR =7.919, 95% CI: 1.582–39.636 T allele *vs.* C allele: OR =9.663, 95% CI: 1.312–71.149
Yan Q	*BMC Cancer* [2014]	China	PubMed, Web of Science	2013.9.20	Oral cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	4	Risk: TT *vs.* CC: OR =2.01, 95% CI: 0.75–5.41 CT *vs.* CC: OR =0.90, 95% CI: 0.55–1.47 TT + CT *vs.* CC: OR =1.04, 95% CI: 0.66–1.64 TT *vs.* CT + CC: OR =22.82, 95% CI: 0.28–1,887.72 T allele *vs.* C allele: OR =2.52, 95% CI: 0.71–8.98
						HIF-1α rs11549467 (1790 G/A) polymorphism	4	Risk: AA *vs.* GG: OR =72.11, 95% CI: 2.08–2,502.44 GA *vs.* GG: OR =3.17, 95% CI: 1.26–7.92 AA + GA *vs.* GG: OR =7.92, 95% CI: 1.58–39.64 AA *vs.* GA + GG: OR =58.05, 95% CI: 1.70–1,985.77 A allele *vs.* G allele: OR =9.66, 95% CI: 1.31–71.15
Yang X	*PLoS One* [2013]	China	PubMed, Embase	2013.6.26	Oral cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk: TT *vs.* CC: OR =2.01, 95% CI: 0.75–5.41 CT *vs.* CC: OR =0.85, 95% CI: 0.24–2.97 TT + CT *vs.* CC: OR =1.04, 95% CI: 0.61–1.78 TT *vs.* CT + CC: OR =22.8, 95% CI: 0.28–1,888 T allele *vs.* C allele: OR =3.93, 95% CI: 0.61–25.4
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk: AA *vs.* GG: OR =20.7, 95% CI: 0.10–4519 GA *vs.* GG: OR =2.21, 95% CI: 0.18–26.9 AA + GA *vs.* GG: OR =7.81, 95% CI: 0.27–224 AA *vs.* GA + GG: OR =17.5, 95% CI: 0.10–3,257 A allele *vs.* G allele: OR =9.34, 95% CI: 0.23–388
Yang X	*Tumour Biol* [2014]	China	PubMed, Medline, Embase	2013.7	Oral cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk; Homozygote codominant: OR =2.01, 95% CI: 0.75–5.41 Heterozygote codominant: OR =0.85, 95% CI: 0.24–2.97 Dominant model: OR =1.04, 95% CI: 0.61–1.78 Recessive model: OR =22.8, 95% CI: 0.28–1,887
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk: Homozygote codominant: OR =20.7, 95% CI: 0.10–4519 Heterozygote codominant: OR =2.21, 95% CI: 0.18–26.9 Dominant model: OR =7.81, 95% CI: 0.27–225 Recessive model: OR =17.6, 95% CI: 0.10–3,257
Ye Y	*Cancer Invest* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Oral carcinoma	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk: TT + CT *vs.* CC: OR =1.04, 95% CI: 0.60–1.80, P=0.9
Ye Y	*Tumori* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Oral cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk: TT + CT *vs.* CC: OR =3.15, 95% CI: 1.05–9.47, P=0.04

Table S5 HIF in oropharyngeal cancer

First author	Journal [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Rainsbury JW	*Head & Neck* [2013]	UK	Cochrane, Medline, Zetoc, National Cancer Trials databases, Proquest Dissertations, Theses database, Conference Proceedings Citation Index	2010.7	Oropharyngeal squamous cell carcinoma	*HIF-1α* expression	2	OS: RR =1.27, 95% CI: 0.91–1.77

Table S6 HIF in nasopharyngeal cancer

First author	Journal [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Jing S	*Chinese Journal of Cancer Prevention and Treatment* [2015]; Article in Chinese	China	PubMed, Embase, Cochrane, CBM, CNKI	2014.1.30	Nasopharyngeal carcinoma	*HIF-1α* expression	6	Risk: OR =0.052 ,95% CI: 0.012–0.219, P<0.001
							8	Sex: OR =1.460, 95% CI: 0.939–2.268, P>0.05
							6	Age: OR =1.046, 95%CI: 0.389–2.812, P>0.05
							5	T1 + T2 *vs.* T3 + T4: OR =0.680, 95% CI: 0.423–1.092, P>0.05
							7	Lymph node metastasis: OR =0.296, 95% CI: 0.170–0.516, P<0.001
							8	Clinical stage: OR =0.298, 95% CI: 0.187–0.474, P<0.001

Table S7 HIF in lung cancer

First author	Journal [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Anam MT	*Biomark Res* [2015]	Bangladesh	PubMed, PubMed Central, Google Scholar	2014.12	Lung cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	2	Risk:
								TT *vs.* CC: OR =4.88, 95% CI: 2.42–9.84, P<0.0001
								CT *vs.* CC: OR =1.56, 95% CI: 0.94–2.61, P=0.088
								TT + CT *vs.* CC: OR =1.67, 95% CI: 0.79–3.54, P=0.1832
								TT *vs.* CT + CC: OR =4.04, 95% CI: 2.02–8.08, P<0.0001
								T allele *vs.* C allele: OR =1.68, 95% CI: 0.77–3.64, P=0.1908
					Lung cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	2	Risk:
								AA *vs.* GG: OR =5.41, 95% CI: 2.74–10.69, P<0.0001
								GA *vs.* GG: OR =1.76, 95% CI: 1.25–2.49, P=0.0013
								AA *vs.* GA + GG: OR =4.51, 95% CI: 2.31–8.81, P<0.0001
								AA + GA *vs.* GG: OR =2.20, 95% CI: 1.60–3.03, P<0.0001
								A allele *vs.* G allele: OR =2.31, 95% CI: 1.77–3.02, P<0.0001
He P	*PLoS One* [2013]	China	PubMed, Embase, CNKI	2013.8.23	Lung cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism		Risk:
							3	Dominant model (TT + CT *vs.* CC): OR = 1.19, 95% CI: 0.51–2.76
							2	Recessive model (TT *vs.* CT + CC): OR =1.39, 95% CI: 0.09–21.85
							2	Homozygote comparison (TT *vs.* CC): OR =1.42, 95% CI: 0.07–29.73
							3	Heterozygote comparison (CT *vs.* CC): OR =1.13, 95% CI: 0.59–2.19
Hu X	*Tumour Biol* [2014]	China	PubMed, Embase, CNKI	2013.7	Lung cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk:
								T allele *vs.* C allele: OR =1.19, 95% CI: 0.50–2.86
								TT *vs.* CC: OR =1.41, 95% CI: 0.07–30.44
								CT *vs.* CC: OR =1.13, 95% CI: 0.59–2.19
								TT + CT *vs.* CC: OR =1.19, 95% CI: 0.51–2.76
								TT *vs.* CT + CC: OR = 1.38, 95% CI: 0.09–22.18
Li C	*Asian Pac J Cancer Prev* [2013]	China	PubMed	2012.12.20	Non-small cell lung cancer	*HIF-1α* expression	7	OS: HR=1.50, 95% CI: 1.07–2.10
						HIF-2α expression	3	OS: HR=2.02, 95% CI: 1.47–2.77
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Lung cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk:
								TT *vs.* CC: OR =1.41, 95% CI: 0.07–30.44*
								CT *vs.* CC: OR =1.13, 95% CI: 0.59–2.19*
								TT/CT *vs.* CC: OR =1.19, 95% CI: 0.51–2.76*
								TT *vs.* CT/CC: OR =1.38, 95% CI: 0.09–22.18*
								T allele *vs.* C allele: OR =1.19, 95% CI: 0.50–2.86*
Liao S	*J Recept Signal Transduct Res* [2015]	China	PubMed, Cochrane	2014.9.1	Lung cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	2	Risk:
								CC *vs.* CT+TT: OR =0.50, 95% CI: 0.36–0.69, P<0.0001
								TT *vs.* CT + CC: OR =4.04, 95% CI: 2.02–8.08, P<0.0001
								T allele *vs.* C allele: OR =1.68, 95% CI: 0.77–3.64, P=0.19
						HIF-1α rs11549467 (1790 G/A) polymorphism	2	Risk:
								GG *vs.* GA+AA: OR =0.45, 95% CI: 0.33–0.63, P<0.00001
								AA *vs.* GA+GG: OR =4.52, 95% CI: 2.31–8.83, P<0.0001
								A allele *vs.* G allele: OR =2.31, 95% CI: 1.77–3.02, P<0.00001
Liu P	*Neoplasma* [2014]	China	PubMed, Embase, Web of Knowledge, Google Scholar	2013.8	Lung cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk:
								AA *vs.* GG: OR =5.42, 95% CI: 2.75–10.70, P<0.001
								GA *vs.* GG: OR =1.72, 95% CI: 1.22–2.41, P=0.002
								AA + GA *vs.* GG: OR =2.41, 95% CI: 1.56–2.94, P<0.001
								AA *vs.* GA + GG: OR =4.52, 95% CI: 2.31–8.83, P<0.001
								A allele *vs.* G allele: OR =2.26, 95% CI: 1.74–2.95, P<0.001
Ren W	*Swiss Med Wkly* [2013]	China	Cochrane, PubMed, Embase, CNKI, CBM, VIP, WanFang	2012.5	Lung cancer	*HIF-1α* expression	4	5–year survival rates: OR = 0.13, 95% CI: 0.03–0.47, P=0.002
							7	OS: RR= 1.68, 95% CI: 1.12–2.50, P=0.01
							16	Tumor *vs.* benign tissues: OR =19.00, 95% CI: 12.12–29.78, P=0.00001
							20	Male *vs.* female: OR = 1.00, 95% CI: 0.80–1.26, P=0.99
							12	Age (≥60 *vs.* <60 years): OR = 1.14, 95% CI: 0.85–1.52, P=0.38
							7	Diameter (≥5 *vs.* <5 cm): OR = 1.84, 95% CI: 1.00–3.39, P=0.05
							4	Smoking *vs.* no smoking: OR = 2.16, 95% CI: 0.77–6.05, P=0.14
							18	Adenocarcinomas *vs.* squamous cell carcinoma: OR = 0.78, 95% CI: 0.63–0.98, P=0.03
							4	Non-small cell lung cancer *vs.* small cell lung cancer: OR = 0.24, 95% CI: 0.07–0.77, P=0.02
							21	Stage (I–II *vs.* III–IV): OR = 0.23, 95% CI: 0.14–0.36, P=0.00001
							22	Lymph node metastasis (yes *vs.* no): OR = 3.72, 95% CI: 2.38–5.80, P=0.00001
							18	Differentiation (well *vs.* poorly): OR = 0.47, 95% CI: 0.31–0.70, P=0.0002
Wang Q	*Gene* [2014]	China	PubMed, Embase, Web of Science	2013.8.31	Non-small cell lung cancer	*HIF-1α* expression	13	OS: HR=1.60, 95% CI: 1.14–2.25, P=0.007
Yan Q	*BMC Cancer* [2014]	China	PubMed, Web of Science	2013.9.20	Lung cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk:
								TT *vs.* CC: OR = 1.41, 95% CI: 0.07–30.44
								CT *vs.* CC: OR =1.13, 95% CI: 0.59–2.19
								TT + CT *vs.* CC: OR =1.19, 95% CI: 0.51–2.76
								TT *vs.* CT + CC: OR =3.27, 95% CI: 1.73–6.17
								T allele *vs.* C allele: OR =1.19, 95% CI: 0.50–2.86
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk:
								AA *vs.* GG: OR =5.42, 95% CI: 2.74–10.70
								GA *vs.* GG: OR =1.72, 95% CI: 1.22–2.41
								AA + GA *vs.* GG: OR =2.14, 95% CI: 1.56–2.94
								AA *vs.* GA + GG: OR =4.52, 95% CI: 2.31–8.83
								A allele *vs.* G allele: OR =2.27, 95% CI: 1.74–2.95
Yang X	*PLoS One* [2013]	China	PubMed, Embase	2013.6.26	Lung cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk:
								TT *vs.* CC: OR =1.41, 95% CI: 0.07–30.4
								CT *vs.* CC: OR =1.13, 95% CI: 0.59–2.19
								TT + CT *vs.* CC: OR =1.50, 95% CI: 1.15–1.96
								TT *vs.* CT + CC: OR =3.27, 95% CI: 1.73–6.17
								T allele *vs.* C allele: OR =1.19, 95% CI: 0.50–2.86
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk:
								AA *vs.* GG: OR =5.42, 95% CI: 2.75–10.7
								GA *vs.* GG: OR =0.26, 95% CI: 0.01–7.10
								AA + GA *vs.* GG: OR =0.82, 95% CI: 0.56–1.19
								AA *vs.* GA + GG: OR =7.11, 95% CI: 3.61–14.0
								A allele *vs.* G allele: OR =1.48, 95% CI: 1.09–2.00
Zhou Y	*Cancer Cell Int* [2014]	China	PubMed, Embase, CNKI	2013.12.13	Lung cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk:
								AA + GA *vs.* GG: OR =2.14, 95% CI: 1.56–2.95
							2	AA *vs.* GA + GG: OR =4.5, 95% CI: 2.3–8.81
							2	AA *vs.* GG: OR =5.42, 95% CI: 2.74–10.7
							2	GA *vs.* GG: OR =3.02, 95% CI: 1.48–6.16

Notes: *In the study by Li Y, based on the 95% CI of OR, the statistical difference should not be significant.

Table S8 Characteristics of studies regarding HIF-1α rs11549465 (1772 C/T) polymorphism with the risk of lung cancer

First author	Journal (year)	No. studies	Included studies	No. Case	No. Control	Results	Model
He P	*PLoS One* [2013]	3	Kuo WH, *et al. Transl Res* [2012]	285	300	TT *vs.* CT + CC: OR =1.39, 95% CI: 0.09–21.85; P value for heterogeneity =0.07	A fixed-effect model was used when P heterogeneity <0.05, otherwise a random effect model was used
			Putra AC, *et al. Respirology* [2011]	83	110		
			Konac E, *et al. Exp Biol Med (Maywood)* [2009]	141	156		
Hu X	*Tumour Biol* [2014]	3	Kuo WH, *et al. Transl Res* [2012]	285	300	TT *vs.* CT + CC: OR =1.38, 95% CI: 0.09–22.18; P value for heterogeneity =0.065	A P value of more than 0.05 for the Q test indicated a lack of heterogeneity, and the fixed-effects model (the Mantel-Haenszel method) was subsequently used to calculate the summary ORs. Otherwise, the random-effects model (the DerSimonian and Laird method) was applied
			Putra AC, *et al. Respirology* [2011]	83	110		
			Konac E, *et al. Exp Biol Med (Maywood)* [2009]	141	156		
Li Y	*Int J Clin Exp Med* [2015]	3	Kuo WH, *et al. Transl Res* [2012]	285	300	TT *vs.* CT/CC: OR =1.38, 95% CI: 0.09-22.18; P value for heterogeneity =0.065	Fixed effects model was used to pool the data when the P value of Q-test ≥0.05; otherwise, random effects model was selected
			Putra AC, *et al. Respirology* [2011]	83	110		
			Konac E, *et al. Exp Biol Med (Maywood)* [2009]	141	156		
Yan Q	*BMC Cancer* [2014]	3	Kuo WH, *et al. Transl Res* [2012]	285	300	TT *vs.* CT + CC: OR =3.27, 95% CI: 1.73–6.17; P value for heterogeneity =0.07	When P > 0.05, the effects were assumed to be homogenous, and the fixed-effect model (the Mantel-Haenszel method) was used. When P<0.05, the random-effect model (the DerSimonian and Laird method) was more appropriate
			Putra AC, *et al. Respirology* [2011]	83	110		
			Konac E, *et al. Exp Biol Med (Maywood)* [2009]	141	156		
Yang X	*PLoS One* [2013]	3	Kuo WH, *et al. Transl Res* [2012]	285	300	TT *vs.* CT + CC: OR =3.27, 95% CI: 1.73–6.17; P value for heterogeneity =0.065	A random-effects model was used when the significant Q statistic (P<0.1) indicated the presence of heterogeneity in the studies. Otherwise, a fixed-effects model was selected
			Putra AC, *et al. Respirology* [2011]	83	110		
			Konac E, *et al. Exp Biol Med (Maywood)* [2009]	141	156		

Table S9 HIF in breast cancer

First author	Journal (year)	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Anam MT	*Biomark Res* [2015]	Bangladesh	PubMed, PubMed Central, Google Scholar	2014.12	Breast cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	2	Risk:
								TT *vs.* CC: OR =5.18, 95% CI: 0.88–30.38, P=0.0683
								CT *vs.* CC: OR =1.00, 95% CI: 0.77–1.29, P=0.9964
								TT + CT *vs.* CC: OR =1.05, 95% CI: 0.81–1.35, P=0.7221
								TT *vs.* CT + CC: OR =5.18, 95% CI: 0.88–30.36, P=0.0684
								T allele *vs.* C allele: OR =1.09, 95% CI: 0.86–1.39, P=0.4701
					Breast cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	2	Risk:
								AA *vs.* GG: OR =0.36, 95% CI: 0.01–8.95, P=0.5332
								GA *vs.* GG: OR =0.35, 95% CI: 0.10–1.24, P=0.1045
								AA *vs.* GA + GG: OR =0.37, 95% CI: 0.02–9.29, P=0.5484
								AA + GA *vs.* GG: OR =0.32, 95% CI: 0.09–1.10, P=0.0702
								A allele *vs.* G allele: OR =0.30, 95% CI: 0.09–1.00, P=0.0495
He P	*PLoS One* [2013]	China	PubMed, Embase, CNKI	2013.8.23	Breast cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism		Risk:
							6	Dominant model (TT + CT *vs.* CC): OR =1.12, 95% CI: 0.87–1.52
							5	Recessive model (TT *vs.* CT + CC): OR =1.64, 95% CI: 0.56–4.77
							5	Homozygote comparison (TT *vs.* CC): OR =1.69, 95% CI: 0.56–5.14
							6	Heterozygote comparison (CT *vs.* CC): OR =1.10, 95% CI: 0.83–1.46
Hu X	T*umour Biol* [2013]	China	PubMed, Embase, CNKI	2013.2	Breast cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	4	Lymph node metastasis: OR =1.31, 95% CI: 0.98–1.75, P=0.069
							3	Histological grade:
								Grades G3 *vs.* G1: OR =1.41, 95% CI: 0.70–2.85, P=0.336
								Grades G3 *vs.* G2: OR =1.42, 95% CI: 0.91–2.20, P=0.121
								Grades G2 *vs.* G1: OR =1.12, 95% CI: 0.56–2.24, P=0.745
Hu X	*Tumour Biol* [2014]	China	PubMed, Embase, CNKI	2013.7	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	5	Risk:
								T allele *vs.* C allele: OR =1.09, 95% CI: 0.76–1.55
								TT *vs.* CC: OR =2.16, 95% CI: 0.52–8.85
								CT *vs.* CC: OR =1.05, 95% CI: 0.79–1.39
								TT + CT *vs.* CC: OR =1.07, 95% CI: 0.76–1.50
								TT *vs.* CT + CC: OR =2.15, 95% CI: 0.57–8.01
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	5	Risk:
								TT *vs.* CC: OR =2.16, 95% CI: 0.52–8.85, P=0.031
								CT *vs.* CC: OR =1.07, 95% CI: 0.88–1.29, P=0.516
								TT/CT *vs.* CC: OR =1.07, 95% CI: 0.76–1.50, P=0.254
								TT *vs.* CT/CC: OR =2.27, 95% CI: 1.06–4.87, P=0.035
								T allele *vs.* C allele: OR =1.09, 95% CI: 0.76–1.55, P=0.106
Liu P	*Neoplasma* [2014]	China	PubMed, Embase, Web of Knowledge, Google Scholar	2013.8	Breast cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk:
								AA *vs.* GG: OR =1.44, 95% CI: 0.38–5.44, P=0.595
								GA *vs.* GG: OR =0.68, 95% CI: 0.23–2.05, P=0.498
								AA + GA *vs.* GG: OR =0.63, 95% CI: 0.19–2.10, P=0.451
								AA *vs.* GA + GG: OR =1.41, 95% CI: 0.37–5.37, P=0.613
								A allele *vs.* G allele: OR =0.59, 95% CI: 0.17–2.10, P=0.419
Ren HT	*Med Sci Monit* [2014]	China	PubMed	2013.6	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	6	Risk:
								TT *vs.* CC: OR =1.64, 95% CI: 0.85–3.19, P=0.14
								CT *vs.* CC: OR =1.05, 95% CI: 0.87–1.27, P=0.58
								TT + CT *vs.* CC: OR =1.13, 95% CI: 0.94–1.36, P=0.19
								TT *vs.* CT + CC: OR =1.62, 95% CI: 0.83–3.15, P=0.16
								T allele *vs.* C allele: OR =1.10, 95% CI: 0.93–1.30, P=0.28
Sun G	*Breast J* [2014]	China	NA	2009	Breast cancer	*HIF-1α* protein expression	12	Cancer *vs.* normal tissues: OR =23.11, 95% CI: 10.07–53.03, P<0.05
							12	Pathological differentiation: OR =3.77, 95% CI: 2.78–5.11, P<0.05
							7	Regional invasive extension (T3–4 *vs.* T1–2): OR =1.21, 95% CI: 0.87–1.87, P>0.05
							10	Axillary lymph node status (positive *vs.* negative): OR =3.03, 95% CI: 1.76–5.22, P<0.05
							9	Clinical stage: OR =2.82, 95% CI: 1.94–4.10, P<0.05
							7	VEGF expression: OR =1.21, 95% CI: 0.87–1.87, P<0.05
							4	Overall survival: OR =0.54, 95% CI: 0.35–0.83, P<0.05
Wang W	*Clinica Chimica Acta* [2014]	China	PubMed, Embase, Web of Science	2013.4.1	Breast cancer	*HIF-1α* expression	7	OS: HR=1.46, 95% CI: 1.12–1.92, P=0.006
							8	DFS: HR=1.91, 95% CI: 1.43–2.57, P<0.001
							3	DMFS: HR=2.17, 95% CI: 1.16–4.05, P=0.015
							3	RFS: HR=1.33, 95% CI: 1.09–1.61, P=0.005
Wu G	*Tumour Biol* [2014]	China	PubMed, Embase, Google Scholar, Wanfang	2013.6.10	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism		Risk:
							6	TT + CT *vs.* CC: OR =0.99, 95% CI: 0.72–1.36, P=0.951
							6	TT *vs.* CT + CC: OR =1.05, 95% CI: 0.88–1.25, P=0.561
Yan Q	*BMC Cancer* [2014]	China	PubMed, Web of Science	2013.9.20	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	6	Risk:
								TT *vs.* CC: OR =1.41, 95% CI: 0.34–5.75
								CT *vs.* CC: OR =1.01, 95% CI: 0.91–1.33
								TT + CT *vs.* CC: OR =1.13, 95% CI: 0.94–1.36
								TT *vs.* CT + CC: OR =1.38, 95% CI: 0.35–5.46
								T allele *vs.* C allele: OR =1.09, 95% CI: 0.80–1.48
						HIF-1α rs11549467 (1790 G/A) polymorphism	4	Risk:
								AA *vs.* GG: OR =1.44, 95% CI: 0.38–5.44
								GA *vs.* GG: OR =1.03, 95% CI: 0.70–1.52
								AA + GA *vs.* GG: OR =1.05, 95% CI: 0.72–1.53
								AA *vs.* GA + GG: OR =1.41, 95% CI: 0.37–5.40
								A allele *vs.* G allele: OR =1.07, 95% CI: 0.76–1.52
Yang X	*PLoS One* [2013]	China	PubMed, Embase	2013.6.26	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	5	Risk:
								TT *vs.* CC: OR =2.30, 95% CI: 1.08–4.91
								CT *vs.* CC: OR =1.07, 95% CI: 0.88–1.29
								TT + CT *vs.* CC: OR =1.12, 95% CI: 0.92–1.35
								TT *vs.* CT + CC: OR =2.27, 95% CI: 1.06–4.87
								T allele *vs.* C allele: OR =1.09, 95% CI: 0.76–1.55
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk:
								AA *vs.* GG: OR =1.44, 95% CI: 0.38–5.44
								GA *vs.* GG: OR =1.03, 95% CI: 0.70–1.52
								AA + GA *vs.* GG: OR =1.05, 95% CI: 0.72–1.53
								AA *vs.* GA + GG: OR =1.41, 95% CI: 0.37–5.37
								A allele *vs.* G allele: OR =1.07, 95% CI: 0.75–1.52
Ye Y	*Cancer Invest* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk: TT + CT *vs.* CC: OR =0.91, 95% CI: 0.62–1.32, P=0.51
Ye Y	*Tumori* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Breast cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	2	Risk: TT + CT *vs.* CC: OR =0.32, 95% CI: 0.09–1.10, P=0.07
Ye Y	*Tumori* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Breast cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	2	Risk: TT + CT *vs.* CC: OR =0.32, 95% CI: 0.09–1.10, P=0.07
Yin W	*Cancer Res* (abstract) [2011]	China	NA	NA	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	NA	Risk:
								Recessive model: OR =2.273, 95% CI: 1.061–4.872, P=0.035
								Dominant model: OR =1.075, 95% CI: 0.717–1.613, P=0.725
						HIF-1α rs11549467 (1790 G/A) polymorphism	NA	Risk:
								Recessive model: not significant
								Dominant model: not significant
Zhao T	*J Exp Clin Cancer Res* [2009]	China	PubMed	2009.6	Breast cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk:
								T allele *vs.* C allele: OR =0.99, 95% CI: 0.79–1.23, P=0.9
								TT *vs.* CT + CC: OR =1.51, 95% CI: 0.55–4.11, P=0.42
								TT + CT *vs.* CC: OR =0.96, 95% CI: 0.76–1.21, P=0.75
						HIF-1α rs11549467 (1790 G/A) polymorphism	2	Risk:
								A allele *vs.* G allele: OR =0.28, 95% CI: 0.08–0.90, P=0.03
								AA + GA *vs.* GG: OR =0.29, 95% CI: 0.09–0.97, P=0.04
Zhou Y	*Cancer Cell Int* [2014]	China	PubMed, Embase, CNKI	2013.12.13	Breast cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism		Risk:
							3	AA + GA *vs.* GG: OR =0.63, 95% CI: 0.19–2.08
							2	AA *vs.* GA + GG: OR =1.44, 95% CI: 0.34–6.08
							2	AA *vs.* GG: OR =1.43, 95% CI: 0.37–5.44
							2	GA *vs.* GG: OR =1.45, 95% CI: 0.34–6.17

Table S10 *ITGF in digestive cancer*

First author	Journal (year)	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Aram MT	*Biomark Res* [2015]	Bangladesh	PubMed, PubMed Central, Google Scholar	2014.12	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	3	Risk: TT vs. CC: OR =1.91, 95% CI: 0.32–11.58, P=0.480 CT vs. CC: OR =0.83, 95% CI: 0.59–1.35, P=0.4617 TT + CT vs. CC: OR =1.24, 95% CI: 0.77–2.01, P=0.3756 TT vs. CT + CC: OR =1.97, 95% CI: 0.33–11.90, P=0.4603 T allele vs. C allele: OR =0.94, 95% CI: 0.69–1.49, P=0.7833
Cao S	*Clin Res Hepatol Gastroenterol* [2014]	China	PubMed, Embase	2013.8	Hepatocellular carcinoma	*HIF-1α* protein expression	4	DFS: OR =2.10, 95% CI: 1.89–2.97
							3	Capsule formation: OR =1.25, 95% CI: 0.93–1.69
							4	Cirrhosis: OR =1.00, 95% CI: 0.76–1.30
							6	Tumor size: OR =0.92, 95% CI: 0.74–1.14
							3	Tumor differentiation: OR =0.89, 95% CI: 0.65–1.21
							3	Vascular invasion: OR =2.04, 95% CI: 1.31–3.18
							5	HCC tissue vs. paraneoplastic tissue: OR =2.50, 95% CI: 0.98–6.36
Chen J	*PLoS One* [2014]	China	PubMed, Embase, Cochrane, CNKI	2013.6	Gastric cancer	*HIF-1α* protein expression	10	5-year OS: RR=1.508, 95% CI: 1.318–1.725, P<0.001
							9	Depth of invasion (T3 and T4 vs. T1 and T2): OR =3.550, 95% CI: 2.067–4.501, P<0.001
							11	Lymph node status: OR =3.486, 95% CI: 2.737–4.440, P<0.001
							5	Distant metastasis: OR =6.635, 95% CI: 1.855–23.736, P=0.004
							10	TNM stage (stage III and IV vs. stage I and II): OR =2.782, 95% CI: 1.941–3.942, P<0.001
							6	Vascular invasion: OR =2.368, 95% CI: 1.725–3.252, P<0.001
							10	Histological differentiation: OR =2.112, 95% CI: 1.410–3.163, P<0.001
							5	Size: OR =1.921, 95% CI: 1.394–2.647, P<0.001
							7	Sex: OR =0.905, 95% CI: 0.679–1.205, P=0.495
							11	Age: OR =0.846, 95% CI: 0.667–1.072, P=0.166
Chen Z	*PLoS One* [2013]	China	PubMed, Wanfang, Web of Science	NA	Colorectal cancer	*HIF-1α* protein expression	9	DFS: HR=2.64, 95% CI: 1.87–4.31
							11	OS: HR=2.01, 95% CI: 1.55–2.6
							15	Differentiation grade: OR =0.97, 95% CI: 0.67–1.39, P=0.864
							5	Duke' stages: OR =2.39, 95% CI: 0.17–6.88, P=0.025
							15	Lymph node status: OR =0.49, 95% CI: 0.32–0.73, P=0.001
							9	Depth of invasion: OR =5.71, 95% CI: 0.51–0.98, P=0.045
							5	Metastasis: OR =3.29, 95% CI: 0.11–8.41, P=0.018
							9	UICC stage: OR =5.42, 95% CI: 0.3–0.58, P<0.001
						HIF-2α protein expression	4	OS: HR=2.07, 95% CI: 1.51–4.26
							2	Differentiation grade: OR =0.66, 95% CI: 0.289–0.812, P=0.006
							2	Dukes' stages: OR =3.9, 95% CI: 0.197–4.168, P=0.3
							3	Lymph node status: OR =0.45, 95% CI: 0.419–2.16, P=0.904
							2	Depth of invasion: OR =0.379, 95% CI: 0.038–3.798, P=0.409
He P	*PLoS One* [2013]	China	PubMed, Embase, CNKI	2013.8.23	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism		Risk:
							2	Dominant model (TT + CT vs. CC): OR =0.25, 95% CI: 0.01–5.09
							1	Recessive model (TT vs. CT + CC): OR =1.97, 95% CI: 0.33–11.90
							1	Homozygote comparison (TT vs. CC): OR =1.91, 95% CI: 0.32–11.58
							2	Heterozygote comparison (CT vs. CC): OR =0.23, 95% CI: 0.01–4.69
					Pancreatic cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism		Risk:
							2	Dominant model (TT + CT vs. CC): OR = 1.39, 95% CI: 0.54 –3.56
							1	Recessive model (TT vs. CC): OR =4.13, 95% CI: 1.57–10.86
							1	Homozygote comparison (TT vs. CC): OR =3.39, 95% CI: 1.28–8.97
							2	Heterozygote comparison (CT vs. CC): OR =0.51, 95% CI: 0.02–11.53
Hu X	*Tumour Biol* [2013]	China	PubMed, Embase, CNKI	2013.2	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	2	Lymph node metastasis: OR =1.23, 95% CI: 0.73–2.07, P=0.429
							2	Histological grade: Grades G2 vs. G1: OR =0.58, 95% CI: 0.13–2.53, P=0.47 Grades G3 vs. G1: OR =1.24, 95% CI: 0.32–4.86, P=0.757 Grades G2 vs. G1: OR =0.52, 95% CI: 0.25–1.10, P=0.086
Hu X	*Tumour Biol* [2014]	China	PubMed, Embase, CNKI	2013.7	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	4	Risk: T allele vs. C allele: OR =0.26, 95% CI: 0.01–6.38 TT vs. CC: OR =1.91, 95% CI: 0.32–11.58 CT vs. CC: OR =0.24, 95% CI: 0.01–5.51 TT + CT vs. CC: OR =1.17, 95% CI: 0.62–2.22 TT vs. CT + CC: OR =1.97, 95% CI: 0.33–11.90
Jing S	*Chin J Pathol* [2014]	China	PubMed, Embase, Cochrane, CBM, CNKI	2014.7.30	Esophageal squamous cell carcinoma	*HIF-1α* protein expression	8	Risk: OR =0.088, 95% CI: 0.047–0.129, P<0.001
	Article in Chinese						10	Tumor differentiation: OR =1.267, 95% CI: 0.850–1.831, P=0.161
							4	Histological grade: OR =1.194, 95% CI: 0.307–4.642, P=0.798
							8	T1 + T2 vs. T3 + T4: OR =0.421, 95% CI: 0.320–0.566, P<0.008
							14	Lymph node metastasis: OR =0.387, 95% CI: 0.207–0.725, P=0.003
							8	Tumor stage: OR =0.535, 95% CI: 0.2361–1.11, P=0.116
							5	Lymphatic vessels invasion: OR =0.085, 95% CI: 0.219–1.431, P=0.226
							5	Vascular invasion: OR =0.971, 95% CI: 0.667–1.413, P=0.877
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	3	Risk: TT vs. CC: OR =1.91, 95% CI: 0.32–11.58 CT vs. CC: OR =0.34, 95% CI: 0.09–1.34* TT/CT vs. CC: OR =0.34, 95% CI: 0.09–1.41* TT vs. CT/CC: OR =1.97, 95% CI: 0.33–11.90* T allele vs. C allele: OR =0.38, 95% CI: 0.09–1.50*
					Esophageal squamous cell carcinoma	*HIF-1α* rs11549465 (1772 C/T) polymorphism	1	Risk: CT vs. CC: OR =1.11, 95% CI: 0.46–2.68, P=0.822 TT/CT vs. CC: OR =1.11, 95% CI: 0.48–2.68, P=0.822 T allele vs. C allele: OR =1.16, 95% CI: 0.47–2.80, P=0.847
					Pancreatic cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	1	Risk: CT vs. CC: OR =2.16, 95% CI: 1.32–3.51, P=0.002 TT/CT vs. CC: OR =2.16, 95% CI: 1.32–3.51, P=0.002 T allele vs. C allele: OR =2.02, 95% CI: 1.27–3.23, P=0.003
					Hepatocellular carcinoma	*HIF-1α* rs11549465 (1772 C/T) polymorphism	1	Risk: CT vs. CC: OR =2.15, 95% CI: 0.88–5.43, P=0.092 TT/CT vs. CC: OR =2.15, 95% CI: 0.88–5.43, P=0.092 T allele vs. C allele: OR =2.14, 95% CI: 0.87–5.23, P=0.096
					Gastric cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	1	Risk: CT vs. CC: OR =0.34, 95% CI: 0.11–1.10, P=0.072 TT/CT vs. CC: OR =0.34, 95% CI: 0.11–1.10, P=0.072 T allele vs. C allele: OR =0.36, 95% CI: 0.12–1.13, P=0.079
Lin S	*World J Gastroenterol* [2014]	China	PubMed, Embase, Web of Science	2013.8	Gastric cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	5	5-year OS rate: OR =0.35, 95% CI: 0.27–0.64, P=0.0004
							6	Tumor differentiation: OR =0.38, 95% CI: 0.23–0.64, P=0.0003
							7	Depth of invasion: OR =0.42, 95% CI: 0.32–0.57, P<0.00001
							9	Lymph node metastasis: OR =0.23, 95% CI: 1.46–3.48, P=0.0002
							5	Lymphatic invasion: OR =2.50, 95% CI: 1.46–4.28, P=0.0009
							5	Vascular invasion: OR =1.80, 95% CI: 1.29–2.51, P=0.0003
							6	TNM stages III + IV: OR =0.31, 95% CI: 0.15–0.60, P=0.0006
Liu J	*Gene* [2013]	China	PubMed, Embase	2012.3	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	NA	Risk: OR =1.239, 95% CI: =0.895–1.508, P=0.067
						HIF-1α rs11549467 (1790 G/A) polymorphism	NA	Risk: OR =0.867, 95% CI: =0.492–1.328, P=0.622
Liu P	*Neoplasma* [2014]	China	PubMed, Embase, Web of Knowledge, Google Scholar	2013.8	Colorectal cancer	*HIF-1α* rs11549467 (1790 G/A) polymorphism	2	Risk: GA vs. GG: OR =0.97, 95% CI: 0.577–1.63, P=0.912 AA + GA vs. GG: OR =0.97, 95% CI: 0.57–1.63, P=0.912 A allele vs. G allele: OR =0.97, 95% CI: 0.58–1.62, P=0.914
					Pancreatic cancer	*HIF-1α* rs11549467 (1790 G/A) polymorphism	2	Risk: AA vs. GG: OR =9.30, 95% CI: 1.12–77.01, P=0.039 GA vs. GG: OR =2.90, 95% CI: 1.82–4.62, P=0.625 AA + GA vs. GG: OR =2.50, 95% CI: 0.93–6.73, P=0.070 AA vs. GA + GG: OR =8.65, 95% CI: 1.04–71.65, P=0.045 A allele vs. G allele: OR =3.12, 95% CI: 2.01–4.84, P<0.001
					Hepatocellular carcinoma	*HIF-1α* rs11549467 (1790 G/A) polymorphism	1	Risk: GA vs. GG: OR =4.15, 95% CI: 1.81–9.82, P=0.001 AA + GA vs. GG: OR =4.15, 95% CI: 1.81–9.82, P=0.096 A allele vs. G allele: OR =3.85, 95% CI: 1.83–8.13, P=0.001
					Gastric cancer	*HIF-1α* rs11549467 (1790 G/A) polymorphism	1	Risk: GA vs. GG: OR =2.93, 95% CI: 1.06–8.06, P=0.038 AA + GA vs. GG: OR =2.93, 95% CI: 1.06–8.06, P=0.038 A allele vs. G allele: OR =2.77, 95% CI:1.00–7.45, P=0.043
Ni Z	*Genes Genom* [2015]	China	NA	NA	Overall digestive tract cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	10	Risk: Allele model: OR =1.292, 95% CI =1.107–1.507, P=0.001 Dominant model: OR =1.277, 95% CI:1.051–1.45, P=0.043
						HIF-1α rs11549467 (1790 G/A) polymorphism	9	Risk: Allele model: OR =1.920, 95% CI: =1.213–3.039, P=0.005 Dominant model: OR =1.957, 95% CI: =1.219–3.142, P=0.005
Peng W	*Tumour Biol* [2014]	China	PubMed, Medline, Embase, Cochrane, Web of Science, CBM	2013.9.10	Esophageal squamous cell carcinoma	*HIF-1α* expression	10	OS: HR=1.84, 95% CI: 1.36–2.50, P<0.001
							2	DFS: HR=1.230, 95% CI: 1.05–0.78, P=0.003
							2	Gender (male vs. female): HR= 0.82, 95% CI: 0.50–1.35, P=0.429
							8	Stage (stage III/IV vs. stage I/II): HR=2.80, 95% CI: 1.90–4.44, P<0.001
							11	Lymph node metastasis (yes vs. no): HR=1.95, 95% CI: 1.50–2.76, P<0.001
							7	Depth of invasion (T3/T4 vs. T1/T2): HR=2.45, 95% CI: 1.24–4.86, P=0.01
							5	Lymphatic invasion (yes vs. no): HR=2.25, 95% CI: 1.3–3.75, P=0.002
							5	Vascular invasion (yes vs. no): HR=1.36, 95% CI: 0.79–2.26, P=0.271
							8	Histological grade (poor vs. well/moderate): HR=1.25, 95% CI: 0.70–2.07, P=0.507
							5	Distant metastasis: HR=3.65, HR=1.97, 95% CI: 1.19–3.53, P=0.022
							4	Vascular endothelial growth factor (high vs. low): HR=3.67, 95% CI: 1.81–7.46, P<0.001
Sun G	*J Chin Oncol* [2012] Article in Chinese	China	PubMed, Cochrane	2011.12	Esophageal squamous cell carcinoma	*HIF-1α* protein expression	7	Risk: OR =33.111, 95% CI: 11.912–92.040, P<0.001
							11	2-year OS rate: RR=0.320, 95% CI: 0.115–0.897, P=0.0004
							3	Tumor differentiation: OR =1.185, 95% CI: 0.659–1.835, P=0.3
							8	Clinical stage: OR =0.421, 95% CI: 0.222–0.798, P=0.008
							13	Lymphoma node metastasis: OR =2.003, 95% CI: 1.319–4.344, P=0.003
							9	Depth of invasion: OR =1.751, 95% CI: 1.145–4.710, P=0.226
Sun K	*World J Gastroenterol* [2015]	China	PubMed, Embase, CNKI	2013.7.15	Overall digestive tract cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	13	Risk: CT vs. CC: OR =0.853, 95% CI: 0.630–1.493 TT + CT vs. CC: OR =1.156, 95% CI: 0.839–1.593 T allele vs. C allele: OR =1.325, 95% CI: 0.846–2.076
						HIF-1α rs11549467 (1790 G/A) polymorphism	10	Risk: GA vs. GG: OR =2.677, 95% CI: 1.677–4.273 AA + GA vs. GG: OR =3.252, 95% CI: 1.661–6.368 A allele vs. G allele: OR =4.455, 95% CI: 1.938–10.241
					Pancreatic cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	2	Risk: CT vs. CC: OR =0.500, 95% CI: 0.018–14.015 TT + CT vs. CC: OR =1.388, 95% CI: 0.540–3.555 T allele vs. C allele: OR =1.753, 95% CI: 1.225–2.508
						HIF-1α rs11549467 (1790 G/A) polymorphism	2	Risk: CT vs. CC: OR =1.611, 95% CI: 0.241–10.760 TT + CT vs. CC: OR =2.466, 95% CI: 0.929–6.726 T allele vs. C allele: OR =3.050, 95% CI: 1.949–4.716
					Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	4	Risk: CT vs. CC: OR =0.241, 95% CI: 0.011–5.509 TT + CT vs. CC: OR =1.118, 95% CI: 0.573–2.182 T allele vs. C allele: OR =0.282, 95% CI: 0.011–6.380
						HIF-1α rs11549467 (1790 G/A) polymorphism	2	Risk: TT + CT vs. CC: OR =0.971, 95% CI: 0.571–1.650
Wu G	*Tumour Biol* [2014]	China	PubMed, Embase, Google Scholar, Wanfang	2013.8.10	Overall digestive tract cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	9	Risk: TT + CT vs. CC: OR =1.17, 95% CI: 0.78–1.75, P=0.441
							7	TT vs. CT + CC: OR =1.04, 95% CI: 0.63–1.71, P=0.879
Xu J	*Genet Mol Res* [2014]	China	DSCOV, CRAHN, Web of Science, PubMed, Google Scholar, EBSCO, Cochrane, CBM	2013.5.1	Overall digestive tract cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	6	Risk: TT + CT vs. CC: OR =2.04, 95% CI: 1.06–3.92 T allele vs. C allele: OR =1.36, 95% CI: 1.11–1.62
Xu J	*Genet Test Mol Biomarkers* [2013]	China	PubMed, Embase, Web of Science, Cochrane, CBM	2013.5.1	Overall digestive tract cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	6	Risk: C allele vs. T allele: OR =1.36, 95% CI: 1.11–1.62, P<0.001 CC vs. TT + CT: OR =2.04, 95% CI: 1.06–3.92, P<0.001
					Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	4	Risk: C allele vs. T allele: OR =0.27, 95% CI: 0.01–5.45, P=0.395 CC vs. TT + CT: OR =1.12, 95% CI: 0.58–2.17, P=0.738
					Esophageal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	1	Risk: C allele vs. T allele: OR =1.10, 95% CI: 0.47–2.60, P=0.827 CC vs. TT + CT: OR =1.11, 95% CI: 0.46–2.68, P=0.822
					Gastric cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	1	Risk: C allele vs. T allele: OR =5.17, 95% CI: 1.73–15.26, P=0.003 CC vs. TT+CT: OR =5.79, 95% CI: 1.91–17.35, P=0.002
Xu JJ	*Genet Mol Res* [2014]	China	PubMed, Embase, Web of Science, Cochrane, CBM	2013.5.1	Overall digestive tract cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	8	Risk: TT vs. CC: OR =1.91, 95% CI: 0.32–11.58, P=0.480 TT vs. CT: OR =2.30, 95% CI: 0.36–14.67, P=0.377 TT + CT vs. CC: OR =1.23, 95% CI: 0.79–1.91, P=0.367 TT vs. CT + CC: OR =1.97, 95% CI: 0.33–11.9, P=0.460 T allele vs. C allele: OR =1.03, 95% CI: 0.56–1.89, P=0.920
						HIF-1α rs11549467 (1790 G/A) polymorphism	5	Risk: AA + GA vs. GG: OR =2.19, 95% CI: 1.12–4.29, P=0.022 A allele vs. G allele: OR =2.89, 95% CI: 1.91–4.37, P<0.001
Yan Q	*BMC Cancer* [2014]	China	PubMed, Web of Science	2013.9.20	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	4	Risk: CT vs. CC: OR =0.24, 95% CI: 0.01–5.51 CT+ vs. CC: OR =1.12, 95% CI: 0.57–2.18 T allele vs. C allele: OR =0.26, 95% CI: 0.01–6.38
						HIF-1α rs11549467 (1790 G/A) polymorphism	2	Risk: AA + GA vs. GG: OR =2.67, 95% CI: 0.51–1.63
					Pancreatic cancer	*HIF-1α* rs11549467 (1790 G/A) polymorphism	2	Risk: GA vs. GG: OR =1.61, 95% CI: 0.24–10.76 AA + GA vs. GG: OR =3.14, 95% CI: 1.99–4.97 A allele vs. G allele: OR =3.38, 95% CI: 1.80–4.78
Yang X	*PLoS One* [2013]	China	PubMed, Embase	2013.8.26	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	4	Risk: TT vs. CC: OR =1.91, 95% CI: 0.32–11.6 CT vs. CC: OR =0.24, 95% CI: 0.01–5.51 TT + CT vs. CC: OR =1.10, 95% CI: 0.57–1.39 TT vs. CT + CC: OR =1.97, 95% CI: 0.33–11.9 T allele vs. C allele: OR =1.36, 95% CI: 0.68–2.70
Yang X	*Tumour Biol* [2014]	China	PubMed, Medline, Embase	2013.7	Overall digestive tract cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	12	Risk: Homozygote comparison: OR =2.51, 95% CI: 1.31–4.81 Heterozygote comparison: OR =0.81, 95% CI: 0.45–1.48 Dominant model: OR =1.16, 95% CI: 0.67–1.64 Recessive model: OR =8.73, 95% CI: 1.33–57.1
						HIF-1α rs11549467 (1790 G/A) polymorphism	9	Risk: Homozygote comparison: OR =14.6, 95% CI: 0.70–305 Heterozygote comparison: OR =2.26, 95% CI: 0.91–5.59 Dominant model: OR =3.17, 95% CI: 1.21–8.25 Recessive model: OR =12.8, 95% CI: 0.65–252
					Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	3	Risk: Homozygote comparison: OR =1.91, 95% CI: 0.32–11.6 Heterozygote comparison: OR =0.24, 95% CI: 0.01–5.51 Dominant model: OR =1.12, 95% CI: 0.57–2.18 Recessive model: OR =1.97, 95% CI: 0.33–11.9
						HIF-1α rs11549467 (1790 G/A) polymorphism	2	Risk: Heterozygote codominant: OR =1.31, 95% CI: 0.51–3.36 Dominant model: OR =0.97, 95% CI: 0.57–1.63
					Pancreatic cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	2	Risk: Homozygote codominant: OR =3.39, 95% CI: 1.28–8.97 Heterozygote codominant: OR =0.50, 95% CI: 0.02–14.0 Dominant model: OR =1.39, 95% CI: 0.54–3.56 Recessive model: OR =4.13, 95% CI: 1.57–10.9
						HIF-1α rs11549467 (1790 G/A) polymorphism	2	Risk: Homozygote codominant: OR =9.35, 95% CI: 1.12–77.8 Heterozygote codominant: OR =1.60, 95% CI: 0.24–10.52 Dominant model: OR =3.14, 95% CI: 1.99–4.97 Recessive model: OR =8.65, 95% CI: 1.09–71.6
Yao Q	*Saudi Med J* [2015]	China	PubMed, Embase, Web of Science, Elsevier Science Direct, CBM, CNKI	2014.2.28	Hepatocellular carcinoma	*HIF-2α* expression	5	OS: HR=1.640, 95% CI: 0.648–4.151
							5	Tumor size: OR =2.173, 95% CI: 0.553–8.533, P=0.226
							4	Capsule infiltration: OR =2.738, 95% CI: 1.784–4.065, P<0.001
							3	Vein invasion: OR =2.458, 95% CI: 1.053–5.734, P=0.038
							4	Liver cirrhosis: OR =1.179, 95% CI: 0.520–2.647, P=0.694
							5	Histological grade: OR =0.172, 95% CI: 0.042–0.713, P=0.015
							3	Necrosis: OR =2.362, 95% CI: 0.472–11.815, P=0.295
Ye LY	*Pancreatology* [2014]	China	Medline, Embase, Web of Science, Manual search	NA	Pancreatic cancer	*HIF-1α* expression	6	OS: HR=1.88, 95% CI: 0.39–2.56, P=0.05
							6	Lymph node metastasis: OR =3.16, 95% CI: 1.90–5.11, P<0.05
							4	Tumor size: OR =1.58, 95% CI: 0.66–5.47, p<0.05
							3	Tumor staging (I–II vs. III–IV): OR =3.56, 95% CI: 2.01–6.69, P<0.05
Ye Y	*Cancer Invest* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	3	Risk: TT + CT vs. CC: OR =0.88, 95% CI: 0.46–1.66, P=0.7
Ye Y	*Tumour* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Overall digestive tract cancer	*HIF-1α* rs11549467 (1790 G/A) polymorphism	5	Risk: TT + CT vs. CC: OR =2.20, 95% CI: 1.12–4.34, P=0.02
Zhang ZG	*Asian Pac J Cancer Prev* [2013]	China	Cochrane, PubMed, EMBASE, Web of Science, CBM	2013.2	Gastric cancer	*HIF-1α* expression	10	OS: HR =1.54, 95% CI: 1.13–1.58, P=0.0009
Zhao T	*J Exp Clin Cancer Res* [2009]	China	PubMed	2009.6	Colorectal cancer	*HIF-1α* rs11549465 (1772 C/T) polymorphism	5	DFS: HR =1.87, 95% CI: 0.99–2.82, P=0.06
							2	Risk: T allele vs. C allele: OR =0.26, 95% CI: 0.01–6.38, P=0.41 TT vs. CT + CC: OR =1.97, 95% CI: 0.33–11.90, P=0.46 TT + CT vs. CC: OR =0.25, 95% CI: 0.01–5.06, P=0.39
Zheng F	*Medicine* [2016]	China	PubMed, Cochrane, EBSCO	NA	Gastric cancer	*HIF-2α* expression	6	5-year OS rate: OR =2.56, 95% CI: 1.21–5.38, P=0.0006
							4	Tumor infiltration (T3 and T4 vs. T2 and T1): OR =3.08, 95% CI: 1.18–8.04, P=0.022
							5	Lymphatic metastasis: OR =3.23, 95% CI: 1.19–8.83, P=0.033
							5	TNM stage: OR =2.61, 95% CI: 1.40–4.84, P=0.002
Zheng SS	*PLoS One* [2013]	China	PubMed, Elsevier, Web of Science	2013.2	Hepatocellular carcinoma	*HIF-1α* protein expression	3	Tumor differentiation: OR =2.0, 95% CI: 0.73–5.64, P=0.173
							4	DFS: HR=2.14, 95% CI: 0.29–2.29
Zhou Y	*Cancer Cell Int* [2014]	China	PubMed, Embase, CNKI	2013.12.13	Pancreatic cancer	*HIF-1α* rs11549467 (1790 G/A) polymorphism	6	OS: HR=1.65, 95% CI: 1.38–1.97
							2	Risk: AA + GA vs. GG: OR =2.5, 95% CI: 0.93–6.72
							1	AA vs. GA + GG: OR =18.8, 95% CI: 0.96–371.55
							1	AA vs. GG: OR =19.3, 95% CI: 0.93–360.19
							1	GA vs. GG: OR =29.4, 95% CI: 1.12–772.37
Zhu C	*Mol Biol Rep* [2013]	China	PubMed, Embase, Web of Science	2012.12.1	Gastric cancer	*HIF-1α* expression	9	Overall mortality risk: HR=2.14, 95% CI: 1.32–3.48
							4	TNM stage: OR =1.85, 95% CI: 0.80–4.25
							6	Depth of invasion: OR =2.49, 95% CI: 1.28–4.83
							7	Lymph node metastasis: OR =2.15, 95% CI: 1.27–3.66
							3	Distant metastasis: OR =3.29, 95% CI: 0.17–61.42
							6	Grade of differentiation: OR =1.87, 95% CI: 0.95–3.66
							5	Vascular invasion: OR =2.23, 95% CI: 1.20–4.14

Notes: *In the study by Li Y, based on the 95% CI of OR, the statistical difference should not be significant.

Table S11 Characteristics of studies regarding *HIF-1α rs11549465 (1772 C/T)* polymorphism with the risk of gastric cancer

First author	Journal (Year)	No. studies	Included studies	No. Case	No. Control	Results	Model
Li Y	*PLoS One* [2013]	1	Li K, *et al.* Biochem Genet [2009]	87	106	CT *vs.* CC: OR =0.34, 95% CI: 0.11–1.10, P=0.072 TT/CT *vs.* CC: OR =0.34, 95% CI: 0.11–1.10, P=0.072 T allele *vs.* C allele: OR =0.36, 95% CI: 0.12–1.13, P=0.079	A fixed-effect model was used when P heterogeneity <0.05, otherwise a random effect model was used
Xu J	*Genet Test Mol Biomarkers* [2013]	1	Li K, *et al.* Biochem Genet [2009]	87	106	C allele *vs.* T allele: OR =5.17, 95% CI: 1.75–15.26, P=0.003 CC *vs.* TT + CT: OR =5.75, 95% CI: 1.91–17.35, P=0.002	When a significant Q-test with P<0.05 or I^2>50% indicated that heterogeneity among studies existed, the random effects model (DerSimonian Laird method) was conducted for the meta-analysis; otherwise, the fixed effects model (Mantel–Haenszel method) was used

Table S12 HIF in urinary cancer

First author	Journal [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Anam MT	*Biomark Res* [2015]	Bangladesh	PubMed, PubMed Central, Google Scholar	2014.12	Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	6	Risk: TT *vs.* CC: OR =0.84, 95% CI: 0.47–1.49, P=0.5449 CT *vs.* CC: OR =1.34, 95% CI: 0.95–1.87, P=0.0913 TT + CT *vs.* CC: OR =1.33, 95% CI: 0.95–1.87, P=0.0982 TT *vs.* CT + CC: OR =0.81, 95% CI: 0.47–1.40, P=0.4535 T allele *vs.* C allele: OR =1.29, 95% CI: 0.94–1.76, P=0.1178
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk: AA *vs.* GG: OR =3.35, 95% CI: 0.14–82.30, P=0.4597 GA *vs.* GG: OR =1.41, 95% CI: 0.96–2.08, P=0.0822 AA *vs.* GA + GG: OR =3.25, 95% CI: 0.13–79.90, P=0.4707 AA + GA *vs.* GG: OR =1.41, 95% CI: 0.93–2.15, P=0.1043 A allele *vs.* G allele: OR =1.42, 95% CI: 0.93–2.17, P=0.1093
					Renal cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk: TT *vs.* CC: OR =0.27, 95% CI: 0.08–0.90, P=0.0335 CT *vs.* CC: OR =0.40, 95% CI: 0.12–1.34, P=0.1369 TT + CT *vs.* CC: OR =0.43, 95% CI: 0.15–1.20, P=0.1082 TT *vs.* CT + CC: OR =1.08, 95% CI: 0.44–2.64, P=0.8703 T allele *vs.* C allele: OR =0.84, 95% CI: 0.58–1.22, P=0.3548
						HIF-1α rs11549467 (1790 G/A) polymorphism	4	Risk: AA *vs.* GG: OR =5.11, 95% CI: 2.24–11.66, P=0.0001 GA *vs.* GG: OR =1.51, 95% CI: 0.45–5.05, P=0.5038 AA *vs.* GA + GG: OR =3.05, 95% CI: 1.36–6.84, P=0.0068 AA + GA *vs.* GG: OR =1.58, 95% CI: 0.49–5.03, P=0.442 A allele *vs.* G allele: OR =1.53, 95% CI: 0.60–3.92, P=0.3747
Fan Y	*Medicine* [2015]	China	PubMed, Embase, Web of Science, Cochrane, EBSCO, CINAHL, Biological Abstracts	2015.8.15	Renal cell carcinoma	HIF-1α nuclear and cytoplasmic expression	5	OS: HR =1.637, 95% CI: 0.898–2.985, P=0.108
							6	Cancer-specific survival: HR=1.110, 95% CI: 0.595–2.069, P=0.744
							4	PFS: HR =1.113, 95% CI: 0.675–1.836, P=0.674
						HIF-2α nuclear and cytoplasmic expression	4	Cancer-specific survival: HR=1.597, 95% CI: 0.667–3.824, P=0.293
							3	PFS: HR =0.847, 95% CI: 0.566–1.266, P=0.417
He P	*PLoS One* [2013]	China	PubMed, Embase, CNKI	2013.8.23	Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	6	Risk: Dominant model (TT + CT *vs.* CC): OR =1.36, 95% CI: 0.95–1.96
							5	Recessive model (TT *vs.* CT + CC): OR =1.31, 95% CI: 0.54–3.18
							5	Homozygote comparison (TT *vs.* CC): OR =1.34, 95% CI: 0.54–3.30
							6	Heterozygote comparison (CT *vs.* CC): OR =1.34, 95% CI: 0.93–1.92
					Renal cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism		Risk:
							3	Dominant model (TT + CT *vs.* CC): OR = 0.46, 95% CI: 0.13–1.60
							3	Recessive model (TT *vs.* CT + CC): OR =1.55, 95% CI: 1.02–2.37
							3	Homozygote comparison (TT *vs.* CC): OR =0.29, 95% CI: 0.06–1.45
							3	Heterozygote comparison (CT *vs.* CC): OR =0.44, 95% CI: 0.11–1.69
Hu X	*Tumour Biol* [2014]	China	PubMed, Embase, CNKI	2013.7	Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	5	Risk: T allele *vs.* C allele: OR =1.54, 95% CI: 1.04–2.30 TT *vs.* CC: OR =1.91, 95% CI: 0.82–4.47 CT *vs.* CC: OR =1.54, 95% CI: 0.95–2.49 TT + CT *vs.* CC: OR =1.58, 95% CI: 1.00–2.49 TT *vs.* CT + CC: OR =1.88, 95% CI: 0.79–4.47
					Renal cell carcinoma	*HIF-1α rs11549465 (1772 C/T)* polymorphism	4	Risk: T allele *vs.* C allele: OR =0.92, 95% CI: 0.70–1.19 TT *vs.* CC: OR =0.37, 95% CI: 0.12–1.12 CT *vs.* CC: OR =0.64, 95% CI: 0.32–1.29 TT + CT *vs.* CC: OR =0.65, 95% CI: 0.35–1.23 TT *vs.* CT + CC: OR =1.31, 95% CI: 0.77–2.24
					Bladder cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	2	Risk: TT + CT *vs.* CC: OR =1.12, 95% CI: 0.65–1.92
Li D	*PLoS One* [2013]	China	PubMed	2012.11.25	Overall urinary cancers	HIF-1a gene P582S polymorphism		Risk:
							11	TT *vs.* CT + CC: OR = 1.17, 95% CI: 0.67–2.05, P=0.57
							11	TT + CT *vs.* CC: OR =1.10, 95% CI: 0.83–1.45, P=0.52
							11	T allele *vs.* C allele: OR =1.13, 95% CI: 0.90–1.41, P=0.30
						HIF-1a gene A588T polymorphism		Risk:
							9	AA + AG *vs.* GG: OR =1.40, 95% CI: 0.76–2.58, P=0.28
							8	A allele *vs.* G allele: OR =1.57, 95% CI: 0.89–2.76, P=0.12
					Prostate cancer	HIF-1a gene P582S polymorphism		Risk:
							6	TT *vs.* CT + CC: OR = 1.31, 95% CI: 0.54–3.20, P=0.55
							6	TT + CT *vs.* CC: OR =1.36, 95% CI: 0.95–1.96, P=0.09
							6	T allele *vs.* C allele: OR =1.35, 95% CI: 0.96–1.89, P=0.08
						HIF-1a gene A588T polymorphism		Risk:
							4	AA + AG *vs.* GG: OR =1.45, 95% CI: 1.00–2.12, P=0.05
							4	A allele *vs.* G allele: OR =1.46, 95% CI: 1.01–2.12, P=0.04
					Renal cancer	HIF-1a gene P582S polymorphism		Risk:
							4	TT *vs.* CT + CC: OR = 1.37, 95% CI: 0.92–2.04, P=0.12
							4	TT + CT *vs.* CC: OR =0.62, 95% CI: 0.33–1.19, P=0.15
							4	T allele *vs.* C allele: OR =0.91, 95% CI: 0.73–1.12, P=0.37
						HIF-1a gene A588T polymorphism		Risk:
							4	AA + AG *vs.* GG: OR =1.58, 95% CI: 0.49–5.03, P=0.44
							4	A allele *vs.* G allele: OR =1.53, 95% CI: 0.60–3.92, P=0.38
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	4	Risk: TT *vs.* CC: OR =2.02, 95% CI: 0.60–6.83, P=0.117 CT *vs.* CC: OR =1.42, 95% CI: 0.84–2.40, P=0.062 TT/CT *vs.* CC: OR =1.46, 95% CI: 0.89–2.40, P=0.031 TT *vs.* CT/CC: OR =2.03, 95% CI: 0.58–7.16, P=0.124 T allele *vs.* C allele: OR =1.43, 95% CI: 0.93–2.21, P=0.017
					Renal cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	2	Risk: TT *vs.* CC: OR =0.67, 95% CI: 0.21–2.15C0.498 CT *vs.* CC: OR =0.92, 95% CI: 0.67–1.26, P=0.599 TT/CT *vs.* CC: OR =0.90, 95% CI: 0.67–1.22, P=0.509 TT *vs.* CT/CC: OR =0.69, 95% CI: 0.22–2.17, P=0.521 T allele *vs.* C allele: OR =0.89, 95% CI: 0.67–1.19, P=0.432
					Bladder cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	1	Risk: CT *vs.* CC: OR =1.11, 95% CI: 0.65–1.92, P=0.697 TT/CT *vs.* CC: OR =1.11, 95% CI: 0.65–1.92, P=0.697 T allele *vs.* C allele: OR =1.11, 95% CI: 0.65–1.88, P=0.704
Liu P	*Neoplasma* [2014]	China	PubMed, Embase, Web of Knowledge, Google Scholar	2013.8	Prostate cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk: AA *vs.* GG: OR =3.35, 95% CI: 0.14–82.30, P=0.460 GA *vs.* GG: OR =1.41, 95% CI: 0.97–2.07, P=0.082 AA + GA *vs.* GG: OR =1.44, 95% CI: 0.98–2.10, P=0.104 AA *vs.* GA + GG: OR =3.25, 95% CI: 0.13–79.90, P=0.471 A allele *vs.* G allele: OR =1.45, 95% CI: 1.00–2.11, P=0.109
					Renal cell carcinoma	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3	Risk: AA *vs.* GG: OR =4.70, 95% CI: 0.22–98.24, P=0.319 GA *vs.* GG: OR =1.00, 95% CI: 0.69–1.47, P=0.975 AA + GA *vs.* GG: OR =1.04, 95% CI: 0.71–1.51, P=0.841 AA *vs.* GA + GG: OR =4.78, 95% CI: 0.23–100.04, P=0.313 A allele *vs.* G allele: OR =1.07, 95% CI: 0.74–1.55, P=0.706
Tian Y	*Chinese Journal of Evidence-Based Medicine* [2015] Article in Chinese	China	Cochrane, PubMed, Embase, Ovid, CNKI, VIP, CBM, WanFang	2015.6	Renal cell cancer	HIF-1α expression	7	Risk: OR =16.76, 95% CI: 8.53–32.92, p<0.00001
							7	Lymph node metastasis: (yes *vs.* no): OR =4.33, 95% CI: 2.53–7.39, p<0.00001
							5	Clinical stage I–II *vs.* stage III–IV: OR =0.3, 95% CI: 0.18–0.51, p<0.0001
							4	Pathological stage G1+G2 *vs.* G3+G4: OR =0.54, 95% CI: 0.29–0.98, P=0.04
							3	Age (≥50 *vs.* <50): OR =1.09, 95% CI: 0.54–2.19, P=0.82
							6	Male *vs.* Female: OR =0.77, 95% CI: 0.48–1.25, P=0.29
Wu G	*Tumour Biol* [2014]	China	PubMed, Embase, Google Scholar, Wanfang	2013.6.10	Renal carcinoma	*HIF-1α rs11549465 (1772 C/T)* polymorphism		Risk:
							4	TT + CT *vs.* CC: OR =0.62, 95% CI: 0.33–1.19, P=0.15
							4	TT *vs.* CT + CC: OR =0.96, 95% CI: 0.76–1.20, P=0.706
					Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism		Risk:
							6	TT + CT *vs.* CC: OR =1.36, 95% CI: 0.95–1.96, P=0.094
							6	TT *vs.* CT + CC: OR =1.27, 95% CI: 0.93–1.73, P=0.126
Yan Q	*BMC Cancer* [2014]	China	PubMed, Web of Science	2013.9.20	Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	6	Risk: TT *vs.* CC: OR =1.34, 95% CI: 0.54–3.31 CT *vs.* CC: OR =1.34, 95% CI: 0.93–1.92 TT + CT *vs.* CC: OR =1.36, 95% CI: 0.95–1.96 TT *vs.* CT + CC: OR =1.31, 95% CI: 0.54–3.20 T allele *vs.* C allele: OR =1.35, 95% CI: 0.96–1.89
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk: GA *vs.* GG: OR =1.42, 95% CI: 0.97–2.07 AA + GA *vs.* GG: OR =1.44, 95% CI: 0.98–2.10 A allele *vs.* G allele: OR =1.45, 95% CI: 0.99–2.11
					Renal cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	4	Risk: TT *vs.* CC: OR =0.28, 95% CI: 0.12–1.28 CT *vs.* CC: OR =0.62, 95% CI: 0.31–1.24 TT + CT *vs.* CC: OR =0.62, 95% CI: 0.33–1.18 TT *vs.* CT + CC: OR =1.37, 95% CI: 0.92–2.04 T allele *vs.* C allele: OR =0.91, 95% CI: 0.73–1.12
						HIF-1α rs11549467 (1790 G/A) polymorphism	4	Risk: AA *vs.* GG: OR =5.10, 95% CI: 2.21–11.73 GA *vs.* GG: OR =1.51, 95% CI: 0.45–5.05 AA + GA *vs.* GG: OR =1.58, 95% CI: 0.49–5.04 AA *vs.* GA + GG: OR =3.09, 95% CI: 1.38–6.92 A allele *vs.* G allele: OR =1.53, 95% CI: 0.60–3.92
Yang X	*PLoS One* [2013]	China	PubMed, Embase	2013.6.26	Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	5	Risk: TT *vs.* CC: OR =3.68, 95% CI: 1.58–8.55 CT *vs.* CC: OR =2.02, 95% CI: 1.01–4.07 TT + CT *vs.* CC: OR =2.10, 95% CI: 1.08–4.09 TT *vs.* CT + CC: OR =3.52, 95% CI: 1.52–8.16 T allele *vs.* C allele: OR =2.06, 95% CI: 1.15–3.68
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk: AA *vs.* GG: OR =3.35, 95% CI: 0.14–82.3 GA *vs.* GG: OR =1.41, 95% CI: 0.97–2.07 AA + GA *vs.* GG: OR =1.44, 95% CI: 0.98–2.10 AA *vs.* GA + GG: OR =3.25, 95% CI: 0.13–79.9 A allele *vs.* G allele: OR =1.45, 95% CI: 1.00–2.11
Ye Y	*Cancer Invest* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	5	Risk: TT + CT *vs.* CC: OR =1.59, 95% CI: 1.11–2.28, P=0.01
					Renal cell carcinoma	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk: TT + CT *vs.* CC: OR =1.06, 95% CI: 0.41–2.73, P=0.9
Ye Y	*Tumori* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Prostate cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	3*	Risk: TT + CT *vs.* CC: OR =0.98, 95% CI: 0.55–1.76, P=0.95*
					Renal cell carcinoma	*HIF-1α rs11549467 (1790 G/A)* polymorphism	2	Risk: TT + CT *vs.* CC: OR =2.47, 95% CI: 0.21–28.92, P=0.47
Zhao T	*J Exp Clin Cancer Res* [2009]	China	PubMed	2009.6	Prostate cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	4	Risk: T allele *vs.* C allele: OR =1.78, 95% CI: 1.07–2.94, P=0.03 TT *vs.* CT + CC: OR =1.53, 95% CI: 0.90–2.60, P=0.11 TT + CT *vs.* CC: OR =1.85, 95% CI: 1.04–3.31, P=0.04
						HIF-1α rs11549467 (1790 G/A) polymorphism	2	Risk: A allele *vs.* G allele: OR =0.96, 95% CI: 0.49–1.90, P=0.91 AA + GA *vs.* GG: OR =0.96, 95% CI: 0.49–1.90, P=0.91
Zhou Y	*Cancer Cell Int* [2014]	China	PubMed, Embase, CNKI	2013.12.13	Prostate cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism		Risk:
							3	AA + GA *vs.* GG: OR =1.41, 95% CI: 0.93–2.14
							1	AA *vs.* GA + GG: OR =3.24, 95% CI: 0.13–79.9
							1	AA *vs.* GG: OR =3.34, 95% CI: 0.13–82.30
							1	GA *vs.* GG: OR =1.98, 95% CI: 0.07–50.4
					Renal cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism		Risk:
							3	AA + GA *vs.* GG: OR =0.94, 95% CI: 0.16–5.29
							2	AA *vs.* GA + GG: OR =2.69, 95% CI: 1.20–6.03
							2	AA *vs.* GG: OR =2.71, 95% CI: 1.52–7.99
							1	GA *vs.* GG: OR =0.81, 95% CI: 0.33–2

Notes: *In the study by Ye Y (Tumori, 2014), the number of included studies regarding prostate cancer should be 3, but not 4. Accordingly, the statistical results should not be reliable.

Table S13 Characteristics of studies regarding *HIF-1α rs11549467 (1790 G/A)* polymorphism with the risk of renal cancer

First author	Journal [year]	No. studies	Included studies	No. Case	No. Control	Results	Model
Anam MT	*Biomark Res* [2015]	4	Qin C, *et al. Ann Oncol* [2012]	620	623	AA *vs.* GG: OR =5.11, 95% CI: 2.24–11.66, P=0.0001; GA *vs.* GG: OR =1.51, 95% CI: 0.45–5.05, P=0.5038; AA *vs.* GA + GG: OR =3.05, 95% CI: 1.36–6.84, P=0.0068; AA + GA *vs.* GG: OR =1.58, 95% CI: 0.49–5.03, P=0.442; A allele *vs.* G allele: OR =1.53, 95% CI: 0.60–3.92, P=0.3747	Maybe a random-effects model was employed according to the forest plots
			Morris MR, *et al. Anticancer Res* [2009]	325	309		
			Ollerenshaw M, *et al. Cancer Genet Cytogenet* [2004]	146	288		
			Clifford SC, *et al. Oncogene* [2001]	48	144		
Li D	*PLoS One* [2013]	4	Qin C, *et al. Ann Oncol* [2012]	620	623	AA + AG *vs.* GG: OR =1.58, 95% CI: 0.49–5.03, P=0.44; A allele *vs.* G allele: OR =1.53, 95% CI: 0.60–3.92, P=0.38	The random-effects model (the Dersimonian-Laird method) would be used if the test of heterogeneity was significant; otherwise the fixed-effects model (the Mantel-Haenszel method) would be applied in the analysis
			Morris MR, *et al. Anticancer Res* [2009]	325	309		
			Ollerenshaw M, *et al. Cancer Genet Cytogenet* [2004]	146	288		
			Clifford SC, *et al. Oncogene* [2001]	48	144		
Yan Q	*BMC Cancer* [2014]	4	Qin C, *et al. Ann Oncol* [2012]	620	623	AA *vs.* GG: OR =5.10, 95% CI: 2.21–11.73; GA *vs.* GG: OR =1.51, 95% CI: 0.45–5.05; AA *vs.* GA + GG: OR =3.09, 95% CI: 1.38–6.92; AA + GA *vs.* GG: OR =1.58, 95% CI: 0.49–5.04; A allele *vs.* G allele: OR =1.53, 95% CI: 0.60–3.92	When P>0.05, the effects were assumed to be homogenous, and the fixed-effect model (the Mantel-Haenszel method) was used. When P<0.05, the random-effect model (the DerSimonian and Laird method) was more appropriate
			Morris MR, *et al. Anticancer Res* [2009]	325	309		
			Ollerenshaw M, *et al. Cancer Genet Cytogenet* [2004]	146	288		
			Clifford SC, *et al. Oncogene* [2001]	48	144		

Table S14 HIF in gynecological cancer

First author	*Journal* [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
He P	*PLoS One* [2013]	China	PubMed, Embase, CNKI	2013.8.23	Cervical cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism		Risk:
							3	Dominant model (TT + CT *vs.* CC): OR =1.81, 95% CI: 0.79–4.10
							2	Recessive model (TT *vs.* CT + CC): OR =8.80, 95% CI: 2.31–33.52
							2	Homozygote comparison (TT *vs.* CC): OR =11.49, 95% CI: 2.21–59.67
							3	Heterozygote comparison (CT *vs.* CC): OR =1.47, 95% CI: 0.79–2.74
Hu X	*Tumour Biol* [2013]	China	PubMed, Embase, CNKI	2013.2	Cervical cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	2	Lymph node metastasis: OR =1.32, 95% CI: 0.60–2.90, P=0.493
Hu X	*Tumour Biol* [2014]	China	PubMed, Embase, CNKI	2013.7	Cervical cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk:
								T allele *vs.* C allele: OR =1.89, 95% CI: 0.84–4.26
								TT *vs.* CC: OR =11.49, 95% CI: 2.18–60.52
								CT *vs.* CC: OR =1.47, 95% CI: 0.79–2.74
								TT + CT *vs.* CC: OR =1.81, 95% CI: 0.79–4.11
								TT *vs.* CT + CC: OR =8.80, 95% CI: 2.30–33.70
Huang M	*Int J Gynecol Cancer* [2014]	China	Medline, PubMed, Embase, Web of Science	2013.1	Cervical cancer	*HIF-1α* expression	7	DFS: HR =1.98, 95% CI: 1.22–3.21, P=0.006
							7	OS: HR =2.58, 95% CI: 1.86–3.56, P<0.001
							5	Lymph node metastasis (yes vs no): OR =2.58, 95% CI: 1.86–3.56, P=0.167
							3	Tumor grade (grade 3 *vs.* grade 1/2): OR =0.99, 95% CI: 0.54–1.82, P=0.969
							5	Tumor size (size≥4 cm *vs.* size <4 cm): OR =2.04, 95% CI: 1.24–3.34, P=0.005
							4	FIGO stage (advanced stage *vs.* earlier stage): OR =1.52, 95% CI: 0.87–2.69, P=0.145
							4	Histology type (other type *vs.* SCC): OR =1.63, 95% CI: 0.85–3.13, P=0.139
							3	Anemia (yes *vs.* no): OR =2.04, 95% CI: 1.07–3.88, P=0.030
Jin Y	*Tumour Biol* [2014]	China	PubMed, Cochrane, Web of Science, CNKI	2014.2	Epithelial ovarian cancer	*HIF-1α* expression	3	5-year survival rate: OR =11.46, 95% CI: 3.43–38.29, P<0.0001
								Pathological type:
							13	Cancer *vs.* benign: OR =9.73, 95% CI: 4.90–19.32, P<0.00001
							10	Cancer *vs.* borderline: OR =2.31, 95% CI: 1.04–5.09, P=0.04
							9	Borderline *vs.* benign: OR =6.29, 95% CI: 2.69–14.73, P<0.0001
							NA	Histological type:
								Serous *vs.* others: OR =1.02, 95% CI: 0.79–1.31, P=0.88
								Serous *vs.* others: OR =1.37, 95% CI: 0.78–2.42, P=0.28
							17	FIGO (III–IV *vs.* I–II): OR =3.01, 95% CI: 1.92–4.74, P<0.00001
							10	Histological grade:
								Grades G3 *vs.* G1: OR =4.52, 95% CI: 2.79–7.31, P<0.00001
								Grades G3 *vs.* G2: OR =2.02, 95% CI: 1.27–3.19, P=0.003
								Grades G2 *vs.* G1: OR =2.43, 95% CI: 1.65–3.59, P<0.0001
							9	Lymph node metastasis: OR =5.20, 95% CI: 2.10–12.89, P=0.0004
Jin Y	*PLoS One* [2015]	China	PubMed, Cochrane, Web of Knowledge, clinical trial registries	2014.1	Overall gynecological cancer	*HIF-1α* expression	9	5–year DFS rate: OR =2.93, 95% CI: 1.43–6.01, P=0.003
							8	5–year OS rate: OR =5.53, 95% CI: 2.48–12.31, P<0.0001
								Pathological type:
							21	Cancer *vs.* Borderline: OR =2.70, 95% CI: 1.69–4.31, P<0.0001
							26	Cancer *vs.* Normal: OR =9.59, 95% CI: 5.97–15.39, P<0.00001
							19	Borderline *vs.* Normal: OR =4.13, 95% CI: 2.43–7.02, P<0.00001
							32	FIGO stage: OR =2.66, 95% CI: 1.87–3.79, P<0.00001
								Histological type:
							22	G3 *vs.* G1: OR =3.77, 95% CI: 2.76–5.16, P<0.00001
							22	G3 *vs.* G2: OR =1.62, 95% CI: 1.20–2.19, P=0.002
							22	G2 *vs.* G1:OR =2.34, 95% CI: 1.82–3.00, P<0.00001
							21	Lymph node metastasis: OR =3.98, 95% CI: 2.10–12.89, P<0.0001
					Endometrial cancer	HIF-1α expression	4	5-year DFS rate: OR =1.56, 95% CI: 0.36–6.83, P=0.55
							2	5-year OS rate: OR =3.67, 95% CI: 0.52–25.63, P=0.19
								Pathological type:
							4	Cancer *vs.* Borderline: OR =4.45, 95% CI: 2.57–7.71, P<0.00001
							6	Cancer *vs.* Normal: OR =11.03, 95% CI: 6.55–18.58, P<0.00001
							3	Borderline *vs.* Normal: OR =3.48, 95% CI: 0.75–16.15, P=0.11
							11	FIGO stage: OR =2.76, 95% CI: 1.25–6.09, P=0.01
								Histological type:
							6	G3 *vs.* G1: OR =2.65, 95% CI: 1.53–4.59, P=0.0005
							6	G3 *vs.* G2: OR =1.15, 95% CI: 0.65–2.01, P=0.63
							6	G2 *vs.* G1: OR =2.19, 95% CI: 1.43–3.37, P=0.0003
							4	Lymph node metastasis: OR =4.02, 95% CI: 1.32–12.26, P=0.01
					Cervical cancer	*HIF-1α* expression	3	5-year DFS rate: OR =5.28, 95% CI: 2.90–9.63, P<0.00001
							3	5-year OS rate: OR =3.28, 95% CI: 1.63–6.60, P=0.008
								Pathological type:
							7	Cancer *vs.* borderline: OR =2.36, 95% CI: 1.04–5.38, P=0.04
							7	Cancer *vs.* normal: OR =8.17, 95% CI: 2.80–23.85, P=0.0001
							7	Borderline *vs.* normal: OR =2.40, 95% CI: 1.52–3.78, P=0.0002
							4	FIGO stage:
								OR =1.76, 95% CI: 1.03–2.99, P=0.04 (fixed-effect model)
								OR =1.69, 95% CI: 0.90–3.15, P=0.10 (random-effect model)
								Histological type:
							6	G3 *vs.* G1: OR =4.29, 95% CI: 2.26–8.14, P<0.00001
							6	G3 *vs.* G2: OR =1.62, 95% CI: 0.91–2.90, P=0.10
							6	G2 *vs.* G1: OR =2.40, 95% CI: 1.46–3.93, P=0.0005
							8	Lymph node metastasis: OR =2.94, 95% CI: 1.19–7329, P=0.02
					Ovarian cancer	*HIF-1α* expression	2	5-year DFS rate: OR =2.42, 95% CI: 0.80–7.36, P=0.12
							3	5-year OS rate: OR =11.46, 95% CI: 3.43–38.29, P<0.0001
								Pathological type:
							10	Cancer *vs.* borderline: OR =2.31, 95% CI: 1.04–5.09, P=0.04
							13	Cancer *vs.* normal: OR =9.73, 95% CI: 4.90–19.32, P<0.00001
							9	Borderline *vs.* normal: OR =6.29, 95% CI: 2.69–14.73, P<0.0001
							17	FIGO stage: OR =3.01, 95% CI: 1.92–4.74, P<0.00001
								Histological type:
							10	G3 *vs.* G1: OR =4.52, 95% CI: 2.79–7.31, P<0.00001
							10	G3 *vs.* G2: OR =2.02, 95% CI: 1.27–3.19, P=0.003
							10	G2 *vs.* G1: OR =2.43, 95% CI: 1.65–3.59, P<0.00001
							9	Lymph node metastasis: OR =5.20, 95% CI: 2.10–12.89, P=0.0004
Li Y	*Int J Clin Exp Med* [2015]	China	PubMed, Web of Knowledge, Medline, Embase, Google Scholar	2014.7	Gynecological cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	2	Risk:
								TT *vs.* CC: OR =9.92, 95% CI: 2.15–45.66, P=0.003
								CT *vs.* CC: OR =1.16, 95% CI: 0.77–1.75, P=0.488
								TT/CT *vs.* CC: OR =1.31, 95% CI: 0.58–2.94, P=0.152
								TT *vs.* CT/CC: OR =8.35, 95% CI: 1.85–37.75, P=0.006
								T allele *vs.* C allele: OR =1.38, 95% CI: 0.58–3.29, P=0.020
Liu P	*Neoplasma* [2014]	China	PubMed, Embase, Web of Knowledge, Google Scholar	2013.8	Gynecological cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	2	Risk:
								AA *vs.* GG: OR =0.36, 95% CI: 0.01–8.80, P=0.528
								GA *vs.* GG: OR =1.16, 95% CI: 0.54–2.48, P=0.744
								AA + GA *vs.* GG: OR =1.08, 95% CI: 0.51–2.28, P=0.791
								AA *vs.* GA + GG: OR =0.36, 95% CI: 0.01–8.81, P=0.529
								A allele *vs.* G allele: OR =1.00, 95% CI: 0.48–2.08, P=0.831
Sun C	*Ai Zheng. Ji Bian. Tu Bian.* [2015]; Article in Chinese	China	CNKI, CBM	2014.3.10	Epithelial ovarian cancer	HIF-1α protein expression	6	Risk: OR =0.036, 95% CI: 0.010–0.135, P<0.001
							3	Lymph node: OR =0.080, 95% CI: 0.029–0.220, P<0.001
							6	Clinical stage: OR =0.258, 95% CI: 0.136–0.490, P<0.001
							4	Pathological type: OR =1.779, 95% CI: 0.876–3.616, P=0.111
							6	Pathological stage: OR =0.327, 95% CI: 0.084–1.268, P=0.106
							3	Age: OR =1.331, 95% CI: 0.341–5.196, P=0.681
Yan Q	*BMC Cancer* [2014]	China	PubMed, Web of Science	2013.9.20	Cervical cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk:
								TT *vs.* CC: OR =10.11, 95% CI: 2.55–40.05
								CT *vs.* CC: OR =0.98, 95% CI: 0.72–1.34
								TT + CT *vs.* CC: OR =1.32, 95% CI: 0.61–2.87
								TT *vs.* CT + CC: OR =8.55, 95% CI: 2.28–32.13
								T allele *vs.* C allele: OR =1.41, 95% CI: 0.59–3.35
						HIF-1α rs11549467 (1790 G/A) polymorphism	3	Risk:
								AA *vs.* GG: OR =0.35, 95% CI: 0.04–3.39
								GA *vs.* GG: OR =0.62, 95% CI: 0.40–0.98
								AA + GA *vs.* GG: OR =0.60, 95% CI: 0.38–0.94
								AA *vs.* GA + GG: OR =0.36, 95% CI: 0.04–3.450
								A allele *vs.* G allele: OR =0.59, 95% CI: 0.38–0.91
Yang X	*PLoS One* [2013]	China	PubMed, Embase	2013.6.26	Cervical cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk:
								TT *vs.* CC: OR =10.1, 95% CI: 3.12–32.6
								CT *vs.* CC: OR =1.37, 95% CI: 0.92–2.02
								TT + CT *vs.* CC: OR =1.63, 95% CI: 1.12–2.37
								TT *vs.* CT + CC: OR =8.26, 95% CI: 2.64–25.9
								T allele *vs.* C allele: OR =1.89, 95% CI: 0.84–4.26
Ye Y	*Cancer Invest* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Cervical cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	3	Risk: TT + CT *vs.* CC: OR =1.78, 95% CI: 0.76, 4.18, P=0.18
Ye Y	*Tumori* [2014]	China	Medline, Embase, Web of Science	2012.2.20	Cervical cancer	*HIF-1α rs11549467 (1790 G/A)* polymorphism	2	Risk: TT + CT *vs.* CC: OR =0.92, 95% CI: 0.41–2.03, P=0.83
Zhu J	*Int J Clin Exp Pathol* [2014]	China	PubMed, Embase	2014.1.10	Cervical cancer	*HIF-1α rs11549465 (1772 C/T)* polymorphism	4	Risk:
								TT *vs.* CC: OR =6.32, 95% CI: 2.28–17.55
								CT *vs.* CC: OR =1.05, 95% CI: 0.80–1.38
								TT + CT *vs.* CC: OR =1.13, 95% CI: 0.87–1.47
								TT *vs.* CT + CC: OR =5.86, 95% CI: 2.13–16.11

Table S15 HIF in osteosarcoma

First author	Journal [year]	Country	Databases	Search date	Cancer	HIF	No. studies	Results
Ren HY	*Onco Targets Ther* [2016]	China	PubMed, Embase, Web of Science	2015.8.1	Osteosarcoma	*HIF-1α* expression	2	OS: HR=3.0, 95% CI: 1.46–6.15, P=0.003
							3	DFS: HR=2.23, 95% CI: 1.26–3.92, P=0.006
							5	Metastasis (yes *vs.* no): OR =5.06, 95% CI: 2.87–8.92, P<0.00001
							2	Pathologic grade (high *vs.* low): OR =21.33, 95% CI: 4.60-98.88, P<0.0001
							4	Tumor stage (high *vs.* low): OR =10.29, 95% CI: 3.55-29.82, P<0.0001
							2	Chemotherapy response (poor *vs.* good): OR =9.68, 95% CI: 1.87–50.18, P=0.007
							4	Tumor size (large *vs.* small): OR =1.12, 95% CI: 0.22–5.76, P=0.89
							3	Tumor site (tibia or femur *vs.* elsewhere): OR =2.02, 95% CI: 0.10–39.71, P=0.46
							2	Histopathology (osteoblastic *vs.* other types): OR =0.70, 95% CI: 0.28–1.73, P=0.46