Research Paper

Different polymorphisms in HIF-1α may exhibit different effects on cancer risk in Asians: evidence from nearly forty thousand participants

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Keywords: *HIF-1α*, polymorphism, cancer, expression, survival
Received: June 14, 2020 **Accepted:** July 21, 2020 **Published:** November 4, 2020

ABSTRACT

The effect of different SNPs in *HIF-1α* and cancer susceptibility remain indistinct. Here, we evaluated the association between all identified SNPs (rs11549465, rs11549467 and rs2057482) in *HIF-1α* and the overall risk of cancer in all case-control studies published before April 2020. A total of 54 articles including 56 case-control studies were included in this analysis. We found that variant genotypes of rs11549465 and rs11549467 were associated with a significantly increased overall cancer risk. In contrast, the variant T allele of rs2057482 showed a significantly reduced risk of overall cancer. In addition, variant genotypes of the three studied SNPs exhibited a significant association with cancer risk in Asians and specific cancer types. Meanwhile, *HIF-1α* was significantly highly expressed in head and neck squamous cell carcinoma and pancreatic cancer tissues. More importantly, survival analysis indicated that the high expression of *HIF-1α* was associated with a poor survival in patients with lung cancer. These findings further provided evidence that different SNPs in *HIF-1α* may exhibit different effects on overall cancer risk; these effects were ethnicity and type-specific. Further studies with functional evaluations are required to confirm the biological mechanisms underlying the role of *HIF-1α* SNPs in cancer development and progression.

INTRODUCTION

Cancer is one of the leading causes of death worldwide, according to the latest statistics. There were more than 16.9 million cancer cases in the United States in 2019, and that number is expected to rise to more than 22.1 million by 2030 [1]. In comparison, although China has a lower cancer incidence rate, the cancer-associated mortality in China is 30-40% higher than that in the USA. There is no denying that environment and lifestyle play critical roles in the development of cancer, contributing to about 40% of all cancer cases, compared to the other risk factors [2]. Genetic factors are also considered one of the principal factors of cancer [3], among which, heritability is an important genetic parameter defined as the proportion of phenotypic variance caused by any set of single nucleotide polymorphisms (SNPs) [4]. According to a long-term follow-up study among Nordic twins, the overall heritability of cancer is 33% [5].

Various classic pathways may result in the occurrence of tumorigeneses, such as autophagy [6], angiogenesis [7], and hippo signalling [8]. Besides, numerous studies

have indicated that the microenvironment at the centre of the tumour is hypoxic during tumour development [9]. Because of severe hypoxia, cancer cells are characterised by dysplasia as they proliferate, as well as structural and functional abnormalities during angiogenesis [10]. The activation of hypoxia-independent mechanisms of hypoxia-inducible factor (HIF) signalling pathway is a sign of cancer [11]. Hypoxia-inducible factor -1 (HIF-1) is an essential transcription factor that regulates cellular response to hypoxia [12]. Mounting evidence shows that the inhibition of HIF-1 activity can significantly inhibit tumour growth [13]. HIF-1 consists of HIF-1α and HIF-1β subunits [14]. It is known that HIF-1α regulates a series of physiologic cancer pathways, such as cell proliferation, apoptosis, and angiogenesis. Hypoxia can stabilise HIF-1α, inhibit its modifications, and also maintain its transcriptional activity [15].

Moreover, SNPs in *HIF-1α* that modify cancer susceptibility have been studied extensively. Most of these studies focused on three common *HIF-1α* SNPs (rs11549465, rs11549467 and rs2057482). However, the results have been indistinct, for instance, a study previously reported that variant T allele of rs11549465 significantly increases the risk of developing lung cancer [16]. In contrast, another study reported that the same variant exhibits no significant association with lung cancer risk, where the effect value was in the opposite direction relative to the previous study [17]. Meanwhile, although some meta-analyses have been performed to investigate the association between *HIF-1α* SNPs and cancer risk, most of these did not incorporate all previously published research. For example, the meta-analysis performed by Li et al. did not integrate three previously published articles and was flawed, which affects the authenticity and accuracy of the research conclusions [18]. There is currently no collective meta-analysis covering all available SNPs in *HIF-1α* together. Therefore, in this study, we aimed to ascertain the association between the different known *HIF-1α* SNPs (rs11549465, rs11549467 and rs2057482) and cancer susceptibility using a total of 54 previously published articles including 56 case-control studies; the pattern of the effects of these SNPs on cancer risk was also evaluated.

RESULTS

Characteristics of the published studies

Following the application of strict screening criteria, 54 articles, including 56 case-control studies with a total of 16,901 cases and 21,836 controls, were ultimately included in the quantitative analysis. General characteristics of the included studies are listed in Supplementary Table 1. Among these 54 articles, 28 had been carried out among Asian populations, and 26, among Caucasian populations. Among the articles that explored the relationships between *HIF-1α* SNPs and cancer risk, 4 focused on 3 SNPs (rs11549465, rs11549467 and rs2057482), and 33 focused on 2 SNPs, and the remaining 17 focused on 1 SNP. The distribution of genotypes and alleles of *HIF-1α* polymorphisms (rs11549465, rs11549467 and rs2057482) for each study is listed in Supplementary Tables 2–4.

Quantitative synthesis

The variant T allele of rs11549465 was associated with a significantly increased cancer risk (dominant model: OR = 1.18, 95% CI = 1.04-1.34) (Table 1). The variant A allele of rs11549467 was also correlated with a significantly increased cancer risk (dominant model: OR = 1.59, 95% CI = 1.20-2.12) (Table 2). On the contrary, the variant T allele of rs2057482 exhibited a significant association with decreased cancer risk (dominant model: OR = 0.87, 95% CI = 0.80-0.95) (Table 3).

Stratified analysis of ethnicity and cancer type

We evaluated the effect of the 3 SNPs on cancer risk among the subgroups. In the stratified analyses of ethnicity (Figure 1A–1C), the variant T allele of rs11549465 had a significant association with increased risk of cancer among Asian populations (dominant model: OR = 1.22, 95% CI = 1.05-1.43) (Table 1). At the same time, the association between the rs11549467 and the increased risk of cancer was also significant among Asians (dominant model: OR = 1.50, 95% CI = 1.15-1.96) (Table 2). The association between rs2057482 and decreased cancer risk was also significant among Asian populations (dominant model: OR = 0.84, 95% CI = 0.71-0.98) (Table 3). However, none of the 3 SNPs was significantly associated with cancer risk among Caucasians.

When stratified by cancer type, rs11549465 was significantly associated with the risk of pancreatic cancer (T versus C: OR = 1.77, 95% CI = 1.24-2.52) (Table 1). The rs11549467 was associated with the risk of lung cancer (dominant model: OR = 1.80, 95% CI = 1.39-2.33), head and neck cancer (dominant model: OR = 5.15, 95% CI = 1.26-21.12), pancreatic cancer (dominant model: OR = 3.14, 95% CI = 1.99-4.97) and prostate cancer (A versus G: OR = 1.45, 95% CI = 1.00-2.10) (Table 2). Besides, when we classified tumours in different parts of the body by the organ system, the variant A allele of rs11549467 was significantly associated with increased risk of digestive system

Table 1. Summary ORs of the *HIF-1α* rs11549465 polymorphism and cancer risk.

Variables	Studies	CT versus CC			T versus C			Dominant model		
		OR(95%CI)	P^a	I^2	OR (95%CI)	P^a	I^2	OR(95%CI)	P^a	I^2
Total	51	1.11(0.97-1.28)	<0.001	64.8%	1.24(1.09-1.42)	<0.001	73.8%	1.18(1.04-1.34)	<0.001	67.0%
Ethnicity										
Asians	26	1.15(0.98-1.34)	0.006	47.3%	1.25(1.07-1.46)	<0.001	56.9%	1.22(1.05-1.43)	0.001	53.1%
Caucasians	25	1.08(0.85-1.36)	<0.001	74.2%	1.26(1.03-1.56)	<0.001	80.8%	1.14(0.93-1.40)	<0.001	74.7%
Cancer type										
breast	8	1.05(0.90-1.23)	0.276	19.4%	1.12(0.98-1.29)	0.096	42.3%	1.09(0.94-1.27)	0.188	30.0%
prostate	7	1.25(0.94-1.67)	<0.001	82.7%	1.25(0.96-1.64)	<0.001	84.4%	1.27(0.95-1.69)	<0.001	83.9%
renal	5	0.80(0.44-1.44)	0.001	77.5%	1.01(0.69-1.48)	0.004	74.0%	0.80(0.43-1.46)	0.001	79.8%
colorectal	5	0.83(0.24-2.83)	0.005	81.4%	0.92(0.37-2.26)	0.019	74.6%	1.28(0.75-2.20)	0.013	68.3%
lung	4	1.19(0.78-1.82)	0.044	63.0%	1.23(0.69-2.20)	<0.001	84.3%	1.23(0.71-2.13)	0.002	79.1%
head and neck	5	1.05(0.68-1.62)	0.135	46.0%	2.18(0.83-5.71)	<0.001	83.2%	1.16(0.77-1.74)	0.325	13.5%
cervical	3	0.98(0.72-1.34)	0.084	59.7%	1.41(0.59-3.35)	<0.001	88.3%	1.32(0.61-2.87)	0.006	80.4%
endometrial	2	1.69(0.18-16.15)	0.003	88.5%	2.12(0.46-9.78)	0.001	90.3%	2.29(0.25-21.11)	0.001	90.1%
hepatocellular	2	0.96(0.17-5.29)	0.021	81.3%	1.14(0.59-2.22)	0.061	71.5%	1.06(0.24-4.68)	0.035	77.4%
pancreatic	2	0.50(0.02-14.02)	0.001	90.3%	1.77(1.24-2.52)	0.349	0.0%	1.39(0.54-3.56)	0.032	78.1%
System										
urinary[b]	6	0.80(0.44-1.44)	0.001	77.5%	1.00(0.69-1.48)	0.004	74.0%	0.88(0.54-1.42)	0.001	74.7%
female reproductive[c]	6	1.14(0.68-1.90)	0.011	66.2%	1.47(0.81-2.67)	<0.001	84.8%	1.37(0.75-2.49)	<0.001	77.8%
digestive[d]	16	0.96(0.63-1.46)	<0.001	68.9%	1.31(0.93-1.85)	<0.001	67.4%	1.20(0.91-1.57)	0.005	55.7%

[a] P for heterogeneity, random-effects model was used when *P* value for heterogeneity test < 0.05; otherwise, fixed-effect model was used

[b] The urinary system cancer includes renal cancer and bladder cancer

[c] The female reproductive system cancer includes cervical cancer, endometrial cancer and ovarian cancer

[d] The digestive system cancer includes colorectal cancer, esophagus cancer, gastric cancer, liver cancer, oral cancer, and pancreatic cancer

Table 2. Summary ORs of the *HIF-1α* rs11549467 polymorphism and cancer risk.

Variables	Studies	GA versus GG			A versus G			Dominant model		
		OR(95%CI)	P^a	I^2	OR (95%CI)	P^a	I^2	OR(95%CI)	P^a	I^2
Total	39	1.51(1.16-1.96)	<0.001	73.2%	1.74(1.28-2.36)	<0.001	84.5%	1.59(1.20-2.12)	<0.001	80.5%
Ethnicity										
Asians	21	1.53(1.19-1.97)	<0.001	66.7%	1.54(1.18-2.01)	<0.001	74.4%	1.50(1.15-1.96)	<0.001	72.3%
Caucasians	18	1.34(0.67-2.69)	<0.001	79.0%	2.06(0.91-4.67)	<0.001	89.2%	1.77(0.86-3.65)	<0.001	86.0%
Cancer type										
breast	6	1.26(0.95-1.68)	0.112	50.0%	1.29(0.99-1.68)	0.056	60.3%	1.28(0.97-1.70)	0.077	56.1%
lung	4	1.59(1.21-2.10)	0.652	0.0%	1.68(1.03-2.76)	0.042	63.4%	1.80(1.39-2.33)	0.177	39.2%
head and neck	5	2.49(1.06-5.85)	0.009	70.3%	6.08(1.06-34.73)	<0.001	94.7%	5.15(1.26-21.12)	<0.001	90.5%
renal	4	1.51(0.45-5.05)	<0.001	91.7%	1.53(0.60-3.92)	<0.001	89.0%	1.58(0.49-5.04)	<0.001	91.6%
cervical	3	0.78(0.52-1.19)	0.513	0.0%	0.74(0.49-1.10)	0.653	0.0%	0.76(0.50-1.14)	0.578	0.0%
colorectal	3	1.05(0.45-2.45)	0.304	5.5%	1.05(0.45-2.43)	0.307	4.2%	0.91(0.55-1.52)	0.534	0.0%
prostate	3	1.41(0.97-2.07)	0.365	0.7%	1.45(1.00-2.10)	0.330	9.9%	1.44(0.98-2.10)	0.340	7.2%
hepatocellular	2	1.42(0.17-11.54)	<0.001	93.1%	1.34(0.17-10.84)	<0.001	93.5%	1.39(0.16-11.81)	<0.001	93.5%
pancreatic	2	1.61(0.24-10.76)	0.019	81.9%	3.08(1.98-4.78)	0.418	0.0%	3.14(1.99-4.97)	0.098	63.4%
System										
urinary[b]	5	1.51(0.45-5.05)	<0.001	91.7%	1.53(0.60-3.92)	<0.001	89.0%	1.36(0.51-3.59)	<0.001	91.0%
female reproductive[c]	5	0.85(0.56-1.27)	0.190	39.8%	0.79(0.53-1.18)	0.200	37.8%	0.82(0.54-1.22)	0.194	39.1%
digestive[d]	13	2.11(1.28-3.46)	<0.001	72.6%	3.15(1.52-6.53)	<0.001	89.7%	2.54(1.39-4.65)	<0.001	85.3%

[a] P for heterogeneity, random-effects model was used when *P* value for heterogeneity test < 0.05; otherwise, fixed-effect model was used

[b] The urinary system cancer includes renal cancer and bladder cancer.

[c] The female reproductive system cancer includes cervical cancer, endometrial cancer and ovarian cancer

[d] The digestive system cancer includes colorectal cancer, esophagus cancer, gastric cancer, liver cancer, oral cancer, and pancreatic cancer

Table 3. Summary ORs of the *HIF-1α* rs2057482 polymorphism and cancer risk.

Variables	Studies	CT versus CC			T versus C			Dominant model		
		OR(95%CI)	P^a	I^2	OR (95%CI)	P^a	I^2	OR(95%CI)	P^a	I^2
Total	9	0.85(0.72-1.00)	0.006	63.1%	0.91(0.85-0.97)	0.201	27.4%	0.87(0.80-0.95)	0.055	47.4%
Ethnicity										
Asians	6	0.80(0.66-0.98)	0.002	74.4%	0.90(0.83-0.97)	0.075	50.1%	0.84(0.71-0.98)	0.018	63.5%
Caucasians	3	1.01(0.78-1.31)	0.836	0.0%	0.93(0.83-1.05)	0.701	0.0%	0.99(0.78-1.27)	0.899	0.0%
Cancer type										
multiple myeloma	1	0.94(0.59-1.51)			0.89(0.59-1.34)			0.91(0.58-1.43)		
lung	1	0.92(0.69-1.24)			1.00(0.79-1.28)			0.96(0.72-1.27)		
non-hodgkin lymphoma	1	0.98(0.67-1.44)			1.06(0.77-1.46)			1.02(0.71-1.48)		
colorectal	1	1.15(0.70-1.89)			0.92(0.80-1.04)			1.05(0.64-1.71)		
pancreatic	1	0.45(0.33-0.62)			0.76(0.60-0.96)			0.58(0.44-0.77)		
cervical	1	0.71(0.54-0.92)			0.73(0.59-0.90)			0.69(0.54-0.89)		
prostate	1	0.90(0.72-1.13)			0.86(0.72-1.03)			0.87(0.70-1.08)		
renal	1	0.99(0.78-1.26)			1.05(0.87-1.27)			1.02(0.81-1.29)		
breast	1	0.93(0.78-1.10)			0.95(0.82-1.09)			0.93(0.78-1.10)		

[a] P for heterogeneity, random-effects model was used when *P* value for heterogeneity test < 0.05; otherwise, fixed-effect model was used

cancers (dominant model: OR = 2.54, 95% CI = 1.39-4.65) (Table 2).

Sensitivity analysis and publication bias

We excluded studies that were not in Hardy Weinberg Equilibrium (HWE) to evaluate the stability of the previously acquired results. The results of the 3 SNPs were still statistically significant after omitting the studies that were not in HWE, which confirmed that the obtained results of the meta-analysis were stable and robust. We then utilised the funnel plot, Begg's test, and Egger's test to evaluate potential publication bias of the studied literature. The funnel plots were symmetrical in case of all the studied SNPs (Figure 2A–2C). Moreover, Begg's test and Egger's test provided further statistical evidence for the absence of publication bias in all the studied SNPs (dominant model: $P > 0.05$).

HIF-1α expression

Stratified analysis indicated that *HIF-1α* SNPs (rs11549465, rs11549467, or rs2057482) were mainly associated with the risk of pancreatic, lung, head and neck, and prostate cancers. We then quantified the expression levels of *HIF-1α* in the above four cancers using the GEPIA database. The expression levels of *HIF-1α* was significantly higher in head and neck

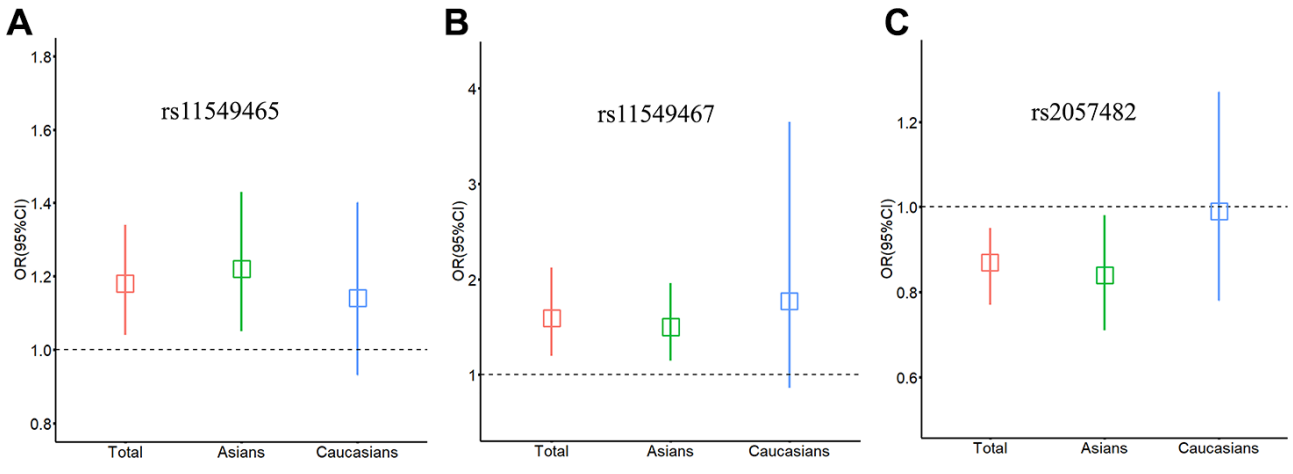

Figure 1. Relationship between *HIF-1α* SNPs and cancer risk stratified by ethnicity. (**A**) rs11549465; (**B**) rs11549467; (**C**) rs2057482. Squares represent the ORs and vertical lines represent the corresponding 95% CI.

squamous cell carcinoma (HNSC) and pancreatic adenocarcinoma (PAAD) tissues ($P < 0.05$), as shown in Figure 3. However, we did not observe any significant association for *HIF-1α* expression in lung adenocarcinoma (LUAD) and prostate adenocarcinoma (PRAD) tissues.

Survival analysis

To evaluate the function of *HIF-1α* in the survival rate of the above mentioned four cancer types, we conducted Kaplan-Meier analysis according to *HIF-1α* expression and cancer survival based on GEPIA database. As

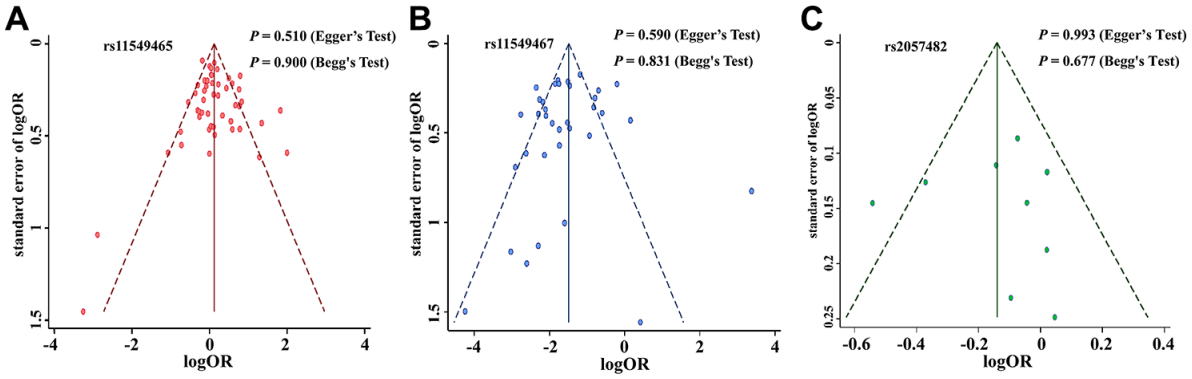

Figure 2. Funnel plot for publication bias of the *HIF-1α* SNPs and cancer risk. (**A**): rs11549465; (**B**): rs11549467; (**C**): rs2057482.

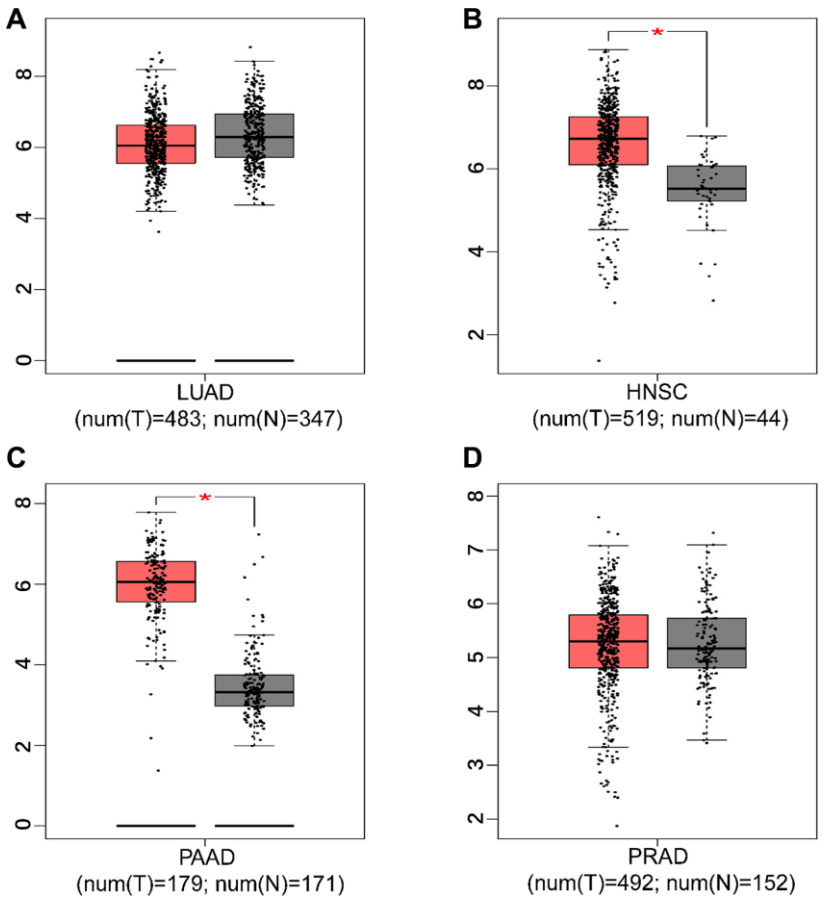

Figure 3. The expression level of *HIF-1α* in tumor tissues and adjacent non-tumor tissues. ((**A**) lung adenocarcinoma; (**B**) head and neck squamous cell carcinoma; (**C**) pancreatic adenocarcinoma; (**D**) prostate adenocarcinoma; * $P < 0.05$).

shown in Figure 4, high expression of *HIF-1α* was associated with poor survival in subjects with LUAD (*P* = 0.034). However, *HIF-1α* expression was not associated with the survival of subjects in the other three cancer types.

DISCUSSION

In this study, we conducted a meta-analysis of 54 articles including 56 case-control studies (up to a total of 16,901 cases and 21,836 controls). We demonstrated that both variant genotypes of rs11549465 and rs11549467 were associated with a significant increase in the overall cancer risk. In contrast, the variant T allele of rs2057482 showed a significantly reduced overall risk of cancer. Moreover, there was evidence of significantly high *HIF-1α* expression in HNSC and PAAD tissues. More importantly, survival analysis indicated that high expression of *HIF-1α* was associated with a poor prognosis in patients with LUAD.

It is well known that one of the characteristics of tumours is the dysregulation of cell proliferation [19]. During the growth of solid tumours, the cells are adequately oxygenated through angiogenesis and glycolytic activation, a process known as the Warburg effect [20]. This effect causes abnormalities in the structure and function of blood vessels, which in turn causes severe hypoxia [21]. HIF-1 is a key transcription factor that regulates oxygen in cells and the entire organism [22]. Many researchers have confirmed that HIF-1A regulates many vital functions, such as

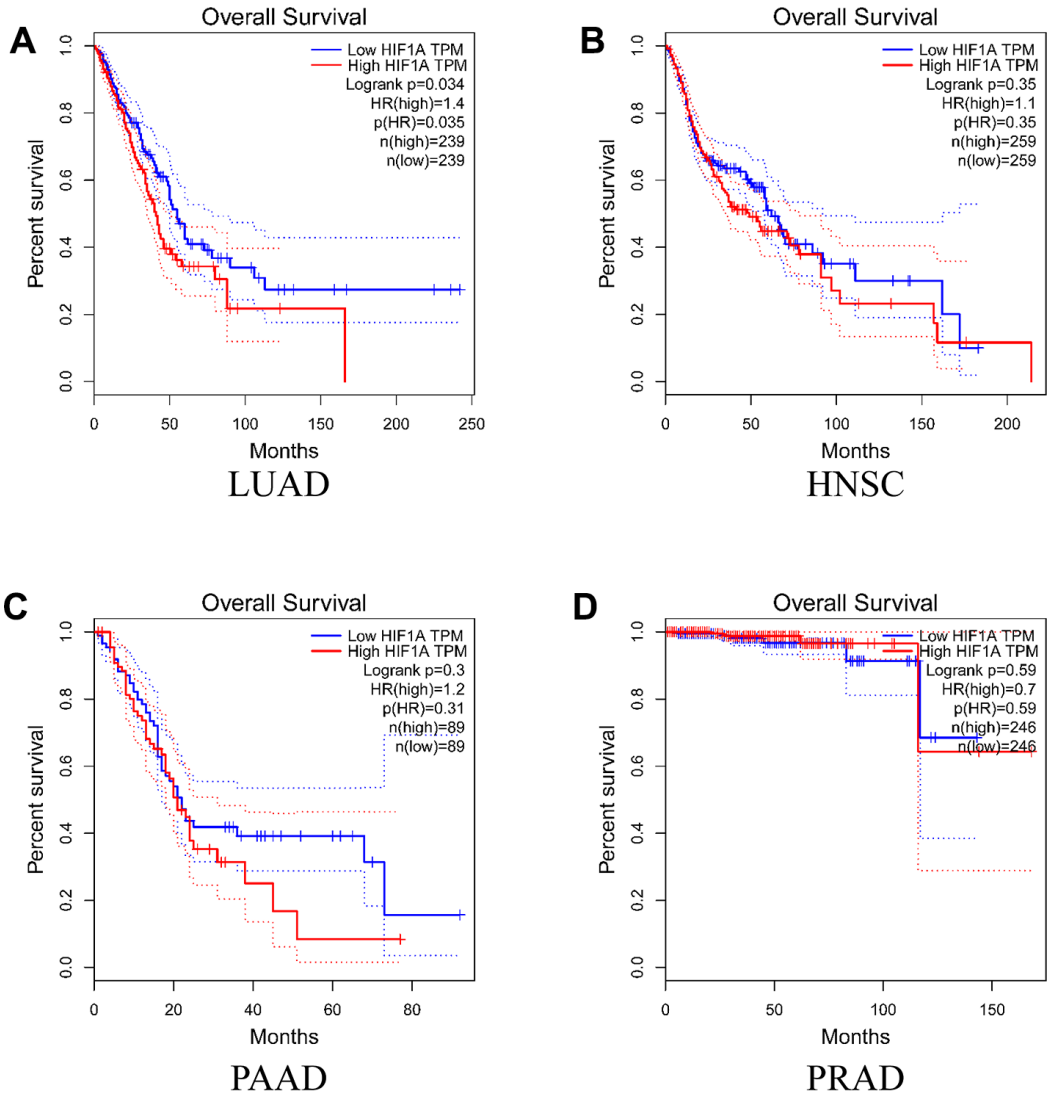

Figure 4. Overall survival time curves for different expression level of *HIF-1α*. (**A**) lung adenocarcinoma; (**B**) head and neck squamous cell carcinoma; (**C**) pancreatic adenocarcinoma; (**D**) prostate adenocarcinoma).

lymphatic regeneration [23]. Increasing evidence confirmed that HIF-1α is associated with the development and progression of multiple human cancers [24–26].

Using the GEPIA database, we found that *HIF-1α* was significantly highly expressed in HNSC and PAAD tissues, which hinted its function as an oncogene. A systematic review indicated that high expression of *HIF-1α* is often correlated with adverse clinical characteristics, including the disease stage and differentiation grade, which negatively influences the survival of patients with HNSC [27]. There is a similar study, which reported that oral epithelial dysplastic lesions with increased *HIF-1α* expression are at a high risk of malignant transformation to oral squamous cell carcinoma [28]. In addition, high expression of *HIF-1α*, which is regulated by the LncRNA PVT1/miR-519d-3p axis, promotes glycolysis and pancreatic ductal adenocarcinoma progression [29]. Survival analysis based on GEPIA database indicated that the high expression of *HIF-1α* was associated with a poor prognosis in patients with LUAD, which is consistent with a recent study [30]. It was also reported that proto-oncogene *HIF-1α*-regulated miR-1275 maintains stem cell-like phenotype and promotes the progression of LUAD through the activation of Wnt/β-catenin and Notch signalling pathways [31].

In our study, we interestingly revealed that different SNPs in the same gene might exhibit different effects on cancer risk. Variant genotypes of *HIF-1α* rs11549465 and rs11549467 SNPs were both associated with a significantly increased cancer risk. In contrast, the variant genotype of rs2057482 showed a significantly reduced risk of cancer. Coincidentally, both rs11549465 and rs11549467 are located in exon 12 of *HIF-1α*, and the two SNPs are not in linkage disequilibrium (r^2 = 0.005). Based on the DNase I hypersensitive site sequencing (DNase-seq) dataset, we found that exon 12 is within open chromatin regions associated with gene regulatory elements, further ChIP-Seq data from the ENCODE project showed that exon 12 locates in a region which may affect POLR2A transcription factors binding. More importantly, both of them are missense variants. PROVEAN and SIFT (http://provean.jcvi.org/) consistently predict that amino acid substitution resulted from rs11549465 is deleterious (damaging) that may affect protein function, while amino acid substitution resulted from the other SNP rs11549467 is neutral (tolerated). Thus, it is biologically plausible that an amino acid substitution in rs11549465 (Pro>Ser) may lead to the dysfunction of HIF-1α, hence increasing cancer susceptibility. However, the SNP rs2057482 is not located in the exon region; it is in the 3′ UTR region of *HIF-1α*. It is well known that miRNAs can directly mediate post-transcriptional gene silencing through binding to the 3′ UTR of the target gene, which is considered as the canonical mode of miRNA-mediated gene regulation [32, 33]. The target prediction database miRanda was used to identify miRNAs that may target *HIF-1α*, following strict screening criteria (score cutoff ≥ 145, energy cutoff ≤ -15 kcal/mol). Four miRNAs (miR-196a, miR-196b, miR-921 and miR-98) were identified that might bind to 3′ UTR of *HIF-1α*. Among which, a low miR-196b-5p expression is significantly associated with metastases and poor survival in patients with colorectal cancer, while miR-196b-5p inhibition leads to significantly increased colorectal cancer cell migration/invasion and metastases [34]. Also, the expression levels of miR-196b-5p are significantly down-regulated in breast cancer tumour samples compared to the matching normal tissues, while miR-196b-5p over-expression significantly inhibits the proliferation and migration of breast cancer cells [35]. Moreover, it was reported that mir-98-5p is down-regulated in lung cancer cell lines compared to healthy lung epithelial human BES-2B cells, while over-expression of miR-196b-5p inhibits the growth, migration, and invasion in lung cancer cells [36]. The above studies regarding different cancer types indicated that miR-196b and mir-98 might function as a tumour suppressor gene. Considering miRanda database revealed that miR-196b and miR-98 binding to *HIF-1α* is feasible in rs2057482 wild C allele. Thus, it is biologically plausible that the T allele variant of *HIF-1α* SNP rs2057482 might decrease the binding ability of miR-196b and miR-98 to *HIF-1α*, and the increase on miR-196b and miR-98 expressions might of a consequence of this. These miRNAs might hence be involved in the inhibition of cancer development.

It is worth mentioning that when we performed the stratified analysis of ethnicity, both variant genotypes of the studied SNPs exhibited significant association with cancer risk in Asians. However, none of the SNPs exhibited any significant association with cancer risk in Caucasians. There may be two major reasons for these inconsistent results. First, we could not exclude the possibility that genetic heterogeneity between different ethnicities, 28 articles from Asia were included, 85.71% (24/28) of which were from East Asia (China, Japan and Korea), and the genetic background among East Asian populations were relatively similar. Second, different types of cancers may involve random errors. For example, the rs11549465 exhibited no significant association with the risk of renal cancer in stratified analysis, and the effect value was in the opposite direction relative to the overall cancer risk. As expected, 80.0% of the articles that focused on renal

cancer (4/5) were in Caucasian populations, which may partly lead to the differences in findings between Caucasians and Asians. Nevertheless, further studies with large sample sizes are warranted to evaluate the relationship between the three studied SNPs and cancer risk in Caucasians.

The advantages of this meta-analysis are apparent. First of all, until now, no study has collectively reported a meta-analysis of all available SNPs in *HIF-1α*. In this study, we extensively reviewed all the available SNPs in *HIF-1α* and screened all possible reports. More importantly, it is encouraging that we arrived at an important conclusion that different SNPs in *HIF-1α* may exhibit different effects on cancer risk. Second, based on the different positions of three SNPs in *HIF-1α*, we explored the possible reasons why the three SNPs exhibit different effects on cancer risk in detail, which may shed light to further biological mechanism studies. Third, using the GEPIA database, we identified that *HIF-1α* might function as an oncogene in a cancer type-specific manner; high *HIF-1α* expression may influence survival in lung cancer patients. However, some limitation also need to be addressed in our study, since we could not extract the original genotyping data for each individual in each study, thus we could not explore the gender effect in the association with cancer types, meanwhile, we could not provide the haplotype analysis for variants rs11549465 and rs11549467.

CONCLUSION

This study provided new evidence showing that different SNPs in *HIF-1α* exhibit different effects on overall cancer risk. Furthermore, rs11549465, rs11549467 and rs2057482 in *HIF-1α* may modify cancer susceptibility in an ethnicity- and type-specific manner. Further studies with functional evaluations are required to confirm the biological mechanisms underlying the role of *HIF-1α* SNPs in cancer development and progression.

MATERIALS AND METHODS

Identification and eligibility criteria of relevant studies

A comprehensive literature search of research papers published before April 30, 2020, using PubMed and Web of Science databases was performed. We used the following keywords: ("polymorphism", "variation", "variant", or " mutation") and ("cancer", "carcinoma", " tumor", " tumour", or "neoplasm") and ("hif1a", "*HIF-1A*", "hif1-a", "hif1alpha", "*HIF-1A*lpha", "hif1-alpha", "hypoxia inducible factor 1 alpha", " hypoxia inducible factor-1alpha", "hypoxia inducible factor1-alpha", "hypoxia-inducible factor 1 alpha", "hypoxia-inducible factor-1alpha" or "hypoxia-inducible factor1-alpha"). The meta-analysis included only full-text articles available in English. In addition, to obtain all eligible publications, the references in the retrieved articles were reviewed. In this meta-analysis, studies meeting the following criteria were included: (1) involving *HIF-1α* polymorphisms and cancer risk; (2) designed as case-control studies; (3) at least two articles for each studied *HIF-1α* SNP; (4) containing available genotype frequencies of *HIF-1α* SNPs (e.g., rs11549465, rs11549467 and rs2057482). The exclusion criteria were as follows: Studies that (1) did not focus on cancer risk; (2) did not study *HIF-1α* SNPs (rs11549465, rs11549467 and rs2057482); (3) did not report relevant genotype frequency data; (4) were not published in English. Finally, 54 articles including 56 case-control studies were included in the meta-analysis (Figure 5).

Data extraction

Two authors (L.Y. and Z.X.) extracted the data independently. Each article contained the following information: The name of the first author, year of publication, country of origin, ethnicity, type of cancer and numbers of case/control. All disagreements were discussed and resolved, and a consensus was finally reached.

Functional annotation based on GEPIA

GEPIA (Gene Expression Profiling Interactive Analysis) (http://gepia.cancer-pku.cn) is a novel

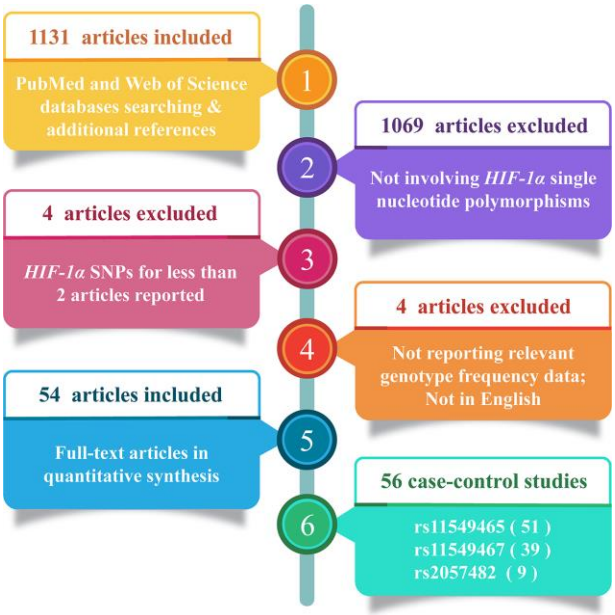

Figure 5. Flow diagram of the study selection process.

interactive web server that can be used to explore and analyze the RNA sequencing expression data, based on the 9,736 tumors and 8,587 normal samples from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) projects. More specifically, various customizable functions could be supplied by GEPIA database, including tumor/normal differential expression analysis, profiling according to cancer types or pathological stages, patient survival analysis, similar gene detection, correlation analysis, and dimensionality reduction analysis.

Statistical analysis

For each study, the odds ratio (OR) and 95% confidence interval (CI) were used to estimate the cancer risk associated with each *HIF-1α* polymorphism. Additionally, the heterogeneity was examined using a chi-square-based Q statistic test, where $P \leq 0.05$ was considered statistically significant. When heterogeneity between studies was absent, we pooled the results using fixed-effect models. Otherwise, a random-effects model was chosen. Subsequently, we evaluated the risks of the heterozygous genotype relative to the wild-type homozygous genotype and then assessed the risks of the combined heterozygous as well as variant homozygous genotypes relative to the wild-type homozygous genotype. We also assessed the allele model. Besides, we performed a stratified analysis based on ethnicity (divided into Asian and Caucasian), and cancer type. Funnel plot, Begg's test, and Egger's test were used to assess publication bias. All analyses were performed using Stata SE version 15.1 software (Stata Corporation, College Station, TX, USA).

AUTHOR CONTRIBUTIONS

Yichen Liu, Xiaoqi Zhu, and Xiaoyi Zhou designed the research, analyzed the data, and wrote the paper. Yueping Zhong and Minjie Chu participated in its design and coordination. Jingwen Cheng and Xiaoyu Fu contributed reagents, materials, and analysis tools. Jingsheng Xu and Yuya Wang prepared figures and tables. Yueping Zhong and Minjie Chu reviewed drafts of the paper.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This work was partially supported by the National Natural Science Foundation of China (81502876), Natural Science Foundation of Jiangsu Province (BK20191449). The funding sources had no role to play in the study design, the collection and interpretation of the data, writing of the report, or decision to submit this paper for publication.

REFERENCES

1. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, Jemal A, Kramer JL, Siegel RL. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019; 69:363–85. https://doi.org/10.3322/caac.21565 PMID:31184787

2. Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: good or bad news from the 2018 global cancer statistics? Cancer Commun (Lond). 2019; 39:22. https://doi.org/10.1186/s40880-019-0368-6 PMID:31030667

3. Meyskens FL Jr, Mukhtar H, Rock CL, Cuzick J, Kensler TW, Yang CS, Ramsey SD, Lippman SM, Alberts DS. Cancer prevention: obstacles, challenges and the road ahead. J Natl Cancer Inst. 2015; 108:djv309. https://doi.org/10.1093/jnci/djv309 PMID:26547931

4. Yang J, Zeng J, Goddard ME, Wray NR, Visscher PM. Concepts, estimation and interpretation of SNP-based heritability. Nat Genet. 2017; 49:1304–10. https://doi.org/10.1038/ng.3941 PMID:28854176

5. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, Graff RE, Holst K, Möller S, Unger RH, McIntosh C, Nuttall E, Brandt I, et al, and Nordic Twin Study of Cancer (NorTwinCan) Collaboration. Familial risk and heritability of cancer among twins in nordic countries. JAMA. 2016; 315:68–76. https://doi.org/10.1001/jama.2015.17703 PMID:26746459

6. Levine B, Kroemer G. Biological functions of autophagy genes: a disease perspective. Cell. 2019; 176:11–42. https://doi.org/10.1016/j.cell.2018.09.048 PMID:30633901

7. Aguilar-Cazares D, Chavez-Dominguez R, Carlos-Reyes A, Lopez-Camarillo C, Hernadez de la Cruz ON, Lopez-Gonzalez JS. Contribution of angiogenesis to inflammation and cancer. Front Oncol. 2019; 9:1399. https://doi.org/10.3389/fonc.2019.01399 PMID:31921656

8. Yu FX, Zhao B, Guan KL. Hippo pathway in organ size control, tissue homeostasis, and cancer. Cell. 2015; 163:811–28. https://doi.org/10.1016/j.cell.2015.10.044 PMID:26544935

9. Butturini E, Carcereri de Prati A, Boriero D, Mariotto S. Tumor dormancy and interplay with hypoxic tumor microenvironment. Int J Mol Sci. 2019; 20:4305.

https://doi.org/10.3390/ijms20174305
PMID:31484342

10. Semenza GL. Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. Trends Pharmacol Sci. 2012; 33:207–14. https://doi.org/10.1016/j.tips.2012.01.005 PMID:22398146

11. Hayashi Y, Yokota A, Harada H, Huang G. Hypoxia/pseudohypoxia-mediated activation of hypoxia-inducible factor-1α in cancer. Cancer Sci. 2019; 110:1510–17. https://doi.org/10.1111/cas.13990 PMID:30844107

12. Zhao T, Lv J, Zhao J, Nzekebaloudou M. Hypoxia-inducible factor-1alpha gene polymorphisms and cancer risk: a meta-analysis. J Exp Clin Cancer Res. 2009; 28:159. https://doi.org/10.1186/1756-9966-28-159 PMID:20035632

13. Chen C, Wang J, Liu R, Qian S. RNA interference of hypoxia-inducible factor-1 alpha improves the effects of transcatheter arterial embolization in rat liver tumors. Tumour Biol. 2012; 33:1095–103. https://doi.org/10.1007/s13277-012-0349-8 PMID:22407533

14. Ke Q, Costa M. Hypoxia-inducible factor-1 (HIF-1). Mol Pharmacol. 2006; 70:1469–80. https://doi.org/10.1124/mol.106.027029 PMID:16887934

15. Lal A, Peters H, St Croix B, Haroon ZA, Dewhirst MW, Strausberg RL, Kaanders JH, van der Kogel AJ, Riggins GJ. Transcriptional response to hypoxia in human tumors. J Natl Cancer Inst. 2001; 93:1337–43. https://doi.org/10.1093/jnci/93.17.1337 PMID:11535709

16. Kuo WH, Shih CM, Lin CW, Cheng WE, Chen SC, Chen W, Lee YL. Association of hypoxia inducible factor-1α polymorphisms with susceptibility to non-small-cell lung cancer. Transl Res. 2012; 159:42–50. https://doi.org/10.1016/j.trsl.2011.09.003 PMID:22153809

17. Konac E, Dogan I, Onen HI, Yurdakul AS, Ozturk C, Varol A, Ekmecki A. Genetic variations in the hypoxia-inducible factor-1alpha gene and lung cancer. Exp Biol Med (Maywood). 2009; 234:1109–16. https://doi.org/10.3181/0902-RM-49 PMID:19546348

18. Li HN, He T, Zha YJ, Du F, Liu J, Lin HR, Yang WZ. HIF-1α rs11549465 C>T polymorphism contributes to increased cancer susceptibility: evidence from 49 studies. J Cancer. 2019; 10:5955–63. https://doi.org/10.7150/jca.35716 PMID:31762805

19. Liu PC, Lu G, Deng Y, Wang CD, Su XW, Zhou JY, Chan TM, Hu X, Poon WS. Inhibition of NF-κB pathway and modulation of MAPK signaling pathways in glioblastoma and implications for lovastatin and tumor necrosis factor-related apoptosis inducing ligand (TRAIL) combination therapy. PLoS One. 2017; 12:e0171157. https://doi.org/10.1371/journal.pone.0171157 PMID:28135339

20. Seagroves TN, Ryan HE, Lu H, Wouters BG, Knapp M, Thibault P, Laderoute K, Johnson RS. Transcription factor HIF-1 is a necessary mediator of the pasteur effect in mammalian cells. Mol Cell Biol. 2001; 21:3436–44. https://doi.org/10.1128/MCB.21.10.3436-3444.2001 PMID:11313469

21. Vaupel P, Multhoff G. Fatal alliance of hypoxia-/HIF-1α-driven microenvironmental traits promoting cancer progression. Adv Exp Med Biol. 2020; 1232:169–76. https://doi.org/10.1007/978-3-030-34461-0_21 PMID:31893407

22. Sorathia N, Chawda N, Saraki K, Rajadhyaksha MS, Hejmadi M. hif-1 plays a role in hypoxia-induced gustatory plasticity of Caenorhabditis elegans. Int J Neurosci. 2019; 129:864–70. https://doi.org/10.1080/00207454.2019.1576662 PMID:30696318

23. Balamurugan K. HIF-1 at the crossroads of hypoxia, inflammation, and cancer. Int J Cancer. 2016; 138:1058–66. https://doi.org/10.1002/ijc.29519 PMID:25784597

24. Meka PB, Cingeetham A, Nanchari SR, Damineni S, Tipirisetti N, Gorre M, Jarjapu S, Annamaneni S, Digumarthi R, Satti V. HIF-1α (1772C>T) polymorphism as marker for breast cancer development. Tumour Biol. 2015; 36:3215–20. https://doi.org/10.1007/s13277-014-2949-y PMID:25510668

25. Wang JS, Jing CQ, Shan KS, Chen YZ, Guo XB, Cao ZX, Mu LJ, Peng LP, Zhou ML, Li LP. Semaphorin 4D and hypoxia-inducible factor-1α overexpression is related to prognosis in colorectal carcinoma. World J Gastroenterol. 2015; 21:2191–98. https://doi.org/10.3748/wjg.v21.i7.2191 PMID:25717256

26. Zhao X, Gao S, Ren H, Sun W, Zhang H, Sun J, Yang S, Hao J. Hypoxia-inducible factor-1 promotes pancreatic ductal adenocarcinoma invasion and metastasis by activating transcription of the actin-bundling protein fascin. Cancer Res. 2014; 74:2455–64. https://doi.org/10.1158/0008-5472.CAN-13-3009 PMID:24599125

27. Swartz JE, Pothen AJ, Stegeman I, Willems SM, Grolman W. Clinical implications of hypoxia biomarker expression in head and neck squamous cell carcinoma: a systematic review. Cancer Med. 2015; 4:1101–16. https://doi.org/10.1002/cam4.460 PMID:25919147

28. Patel NR, Jain L, Mahajan AM, Hiray PV, Shinde SS, Patel PA. An immunohistochemical study of HIF-1 alpha in oral epithelial dysplasia and oral squamous cell carcinoma. Indian J Otolaryngol Head Neck Surg. 2019; 71:435–41. https://doi.org/10.1007/s12070-019-01597-y PMID:31750100

29. Sun J, Zhang P, Yin T, Zhang F, Wang W. Upregulation of LncRNA PVT1 facilitates pancreatic ductal adenocarcinoma cell progression and glycolysis by regulating MiR-519d-3p and HIF-1A. J Cancer. 2020; 11:2572–79. https://doi.org/10.7150/jca.37959 PMID:32201527

30. Yan X, Jiao SC, Zhang GQ, Guan Y, Wang JL. Tumor-associated immune factors are associated with recurrence and metastasis in non-small cell lung cancer. Cancer Gene Ther. 2017; 24:57–63. https://doi.org/10.1038/cgt.2016.40 PMID:28084319

31. Jiang N, Zou C, Zhu Y, Luo Y, Chen L, Lei Y, Tang K, Sun Y, Zhang W, Li S, He Q, Zhou J, Chen Y, et al. HIF-1α-regulated miR-1275 maintains stem cell-like phenotypes and promotes the progression of LUAD by simultaneously activating Wnt/β-catenin and notch signaling. Theranostics. 2020; 10:2553–70. https://doi.org/10.7150/thno.41120 PMID:32194819

32. Pu M, Chen J, Tao Z, Miao L, Qi X, Wang Y, Ren J. Regulatory network of miRNA on its target: coordination between transcriptional and post-transcriptional regulation of gene expression. Cell Mol Life Sci. 2019; 76:441–51. https://doi.org/10.1007/s00018-018-2940-7 PMID:30374521

33. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009; 136:215–33. https://doi.org/10.1016/j.cell.2009.01.002 PMID:19167326

34. Stiegelbauer V, Vychytilova-Faltejskova P, Karbiener M, Pehserl AM, Reicher A, Resel M, Heitzer E, Ivan C, Bullock M, Ling H, Deutsch A, Wulf-Goldenberg A, Adiprasito JB, et al. miR-196b-5p regulates colorectal cancer cell migration and metastases through interaction with HOXB7 and GALNT5. Clin Cancer Res. 2017; 23:5255–66. https://doi.org/10.1158/1078-0432.CCR-17-0023 PMID:28533224

35. Zhu X, Rao X, Yao W, Zou X. Downregulation of MiR-196b-5p impedes cell proliferation and metastasis in breast cancer through regulating COL1A1. Am J Transl Res. 2018; 10:3122–32. PMID:30416655

36. Wu F, Mo Q, Wan X, Dan J, Hu H. NEAT1/hsa-mir-98-5p/MAPK6 axis is involved in non-small-cell lung cancer development. J Cell Biochem. 2019; 120:2836–46. https://doi.org/10.1002/jcb.26442 PMID:29095526

SUPPLEMENTARY MATERIALS

Supplementary Tables

Supplementary Table 1. Characteristics of literature included in the study.

Number	First Author	Year	Country	Ethnicity	Type of cancer	Case/Control	Genotyped SNPs		
							rs11549465	rs11549467	rs2057482
1	Clifford	2001	UK	Caucasian	renal	48/143	√	√	
2	Tanimoto	2003	Japan	Asian	head and neck	55/110	√	√	
3	KUWAI	2004	Japan	Asian	colorectal	100/100	√		
4	Ollerenshaw	2004	UK	Caucasian	renal	160/162(146/288) [a]	√	√	
5	LING	2005	China	Asian	esophageal	95/104	√		
6	Chau	2005	America	Caucasian	prostate	196/196	√		
7	Fransén	2006	Sweden	Caucasian	colorectal	198/258	√	√	
8	Konac	2007	Turkey	Caucasian	cervical	32/107	√	√	
8	Konac	2007	Turkey	Caucasian	endometrial	21/107	√	√	
8	Konac	2007	Turkey	Caucasian	ovarian	49/107	√	√	
9	Li	2007	America	Caucasian	prostate	1072/1271	√	√	
10	Orr-Urtreger	2007	Israel	Asian	prostate	402/300	√	√	
11	Nadaoka	2008	Japan	Asian	bladder	219/461	√	√	
12	Apaydin	2008	Turkey	Caucasian	breast	102/102	√	√	
13	KIM	2008	Korea	Asian	breast	90/102	√	√	
14	Lee	2008	Korea	Asian	breast	1599/1536	√		√
15	Horrée	2008	Netherlands	Caucasian	endometrial	58/559	√		
16	Jacobs	2008	USA	Caucasian	prostate	1420/1450	√		
17	NAIDU	2009	Malaysia	Asian	breast	410/275	√	√	
18	Li	2009	China	Asian	gastric	87/106	√	√	
19	Konac	2009	Turkey	Caucasian	lung	141/156	√	√	
20	Muñoz-Guerra	2009	Spain	Caucasian	head and neck	74/139	√	√	
21	Chen	2009	China	Asian	head and neck	174/347	√	√	
22	Foley	2009	Ireland	Caucasian	prostate	95/188	√		
23	MORRIS	2009	UK	Caucasian	renal	332/313	√	√	
24	Knechtel	2010	Austria	Caucasian	colorectal	381/2156	√	√	
25	Frank	2010	Germany	Caucasian	colorectal	1768/1794			√
26	HSIAO	2010	China	Asian	hepatocellular	102/347	√	√	
27	Shieh	2010	China	Asian	head and neck	305/96	√	√	
28	Kim	2011	Korea	Asian	cervical	199/214	√	√	
29	KANG	2011	Korea	Asian	colorectal	50/50	√		
30	Xu	2011	China	Asian	glioma	150/150	√		
31	PUTRA	2011	Japan	Asian	lung	83/110	√	√	
32	Wang	2011	China	Asian	pancreatic	263/271	√	√	
33	Zagouri	2012	Greece	Caucasian	breast	113/124	√		
34	KUO	2012	China	Asian	lung	285/300	√	√	
35	Alves	2012	Brazil	Caucasian	head and neck	40/88	√	√	
36	Ruiz-Tovar	2012	Spain	Caucasian	pancreatic	59/152	√	√	
37	Li	2012	China	Asian	prostate	662/716	√	√	√
38	Qin	2012	China	Asian	renal cell	620/623	√	√	√
39	RIBEIRO	2013	Portugal	Caucasian	breast	96/74	√	√	
40	Mera-Menéndez	2013	Spain	Caucasian	glottic	121/154	√	√	
41	Meka	2014	India	Asian	breast	348/320	√		
42	Sharma	2014	India	Asian	breast	200/200	√	√	
43	Fu	2014	China	Asian	cervical	518/553	√	√	√
44	Liu	2014	China	Asian	hepatocellular	157/173	√	√	

45	Fraga	2014	Portugal	Caucasian	prostate	754/736	√		
46	Lessi	2014	Italy	Caucasian	renal	117/1000	√		
47	Ni	2015	China	Asian	Multi [b]	267/275	√	√	
48	YAMAMOTO	2016	Japan	Asian	lung	462/379	√	√	√
49	Peckham-Gregory	2016	USA	Caucasian	non-hodgkin lymphoma	180/528			√
50	Wang	2016	China	Asian	pancreatic	410/490			√
51	Demirel	2017	Turkey	Caucasian	colorectal	92/101	√	√	
52	Shan	2018	China	Asian	breast	560/583		√	
53	Uslu	2018	Turkey	Caucasian	laryngeal	35/35	√		
54	Martina	2018	Czech	Caucasian	multiple myeloma	275/219		√	√

[a] 160/162 for rs11549465; 146/288 for rs11549467

[b] Including multi digestive tract cancers

Supplementary Table 2. Distribution of genotypes of *HIF-1α* rs11549465 polymorphism.

Number	First Author	Type of cancer	Frequency distributions of the genotypes					
			CC_case	CT_case	TT_case	CC_control	CT_control	TT_control
1	Nadaoka	bladder	197	22		419	42	
2	Sharma	breast	152	38	10	149	42	9
3	Meka	breast	245	94	9	229	89	2
4	RIBEIRO	breast	74	21	1	61	9	4
5	Zagouri	breast	98	15	0	107	17	0
6	NAIDU	breast	294	100	16	222	50	3
7	KIM	breast	81	8	1	93	9	0
8	Apaydin	breast	79	21	2	68	29	5
9	Lee	breast	1207	119	6	1245	123	1
10	Fu	cervical	467	49	2	492	60	1
11	Kim	cervical	177	22	0	187	27	0
12	Konac	cervical	10	14	8	68	37	2
13	Fransén	colorectal	167	28	3	213	43	2
14	KUWAI	colorectal	100	0	0	89	11	0
15	KANG	colorectal	38	12		46	4	
16	Demirel	colorectal	62	27	3	81	16	4
17	Knechtel	colorectal	291	77		1773	383	
18	Ni	Multi [a]	219	44	4	241	34	0
19	Horrée	endometrial	50	5	3	463	84	12
20	Konac	endometrial	4	12	5	68	37	2
21	LING	esophageal	84	11	0	93	11	0
22	Li	gastric	83	4	0	93	13	0
23	Xu	glioma	121	27	2	135	14	1
24	Mera-Menéndez	glottic	85	18	15	113	27	8
25	Liu	hepatocellular	152	4	1	162	11	0
26	HSIAO	hepatocellular	94	8	0	334	13	0
27	Tanimoto	head and neck	45	10	0	98	12	0
28	Uslu	laryngeal	28	7	0	28	7	0
29	YAMAMOTO	lung	405	55	2	341	37	1
30	KUO	lung	153	94	38	216	73	11
31	PUTRA	lung	74	9	0	98	12	0
32	Konac	lung	110	31	0	111	43	2
33	Muñoz-Guerra	head and neck	57	6	7	113	27	8
34	Chen	head and neck	163	10	1	334	13	0
35	Alves	head and neck	0	1	39	0	85	3

36	Shieh	head and neck	282	23	0	89	7	0
37	Konac	ovarian	34	14	1	68	37	2
38	Ruiz-Tovar	pancreatic	47	1	11	116	28	8
39	Wang	pancreatic	209	54	0	242	29	0
40	Fraga	prostate	579	164	11	566	156	14
41	Li	prostate	612	48	2	659	57	0
42	Foley	prostate	65	30	0	175	13	0
43	Li	prostate	818	209	14	995	221	18
44	Chau	prostate	161	29	6	179	14	3
45	Jacobs	prostate	1156	252	12	1138	284	28
46	Orr-Urtreger	prostate	287	99	16	217	80	3
47	MORRIS	renal	290	39	3	262	46	5
48	Lessi	renal	82	30	5	808	181	11
49	Qin	renal	572	46	2	578	43	2
50	Ollerenshaw	renal	16	54	90	1	90	71
51	Clifford	renal	42	6	0	110	27	6

[a] Including multi digestive tract cancers

Supplementary Table 3. Distribution of genotypes of *HIF-1α* rs11549467 polymorphism.

Number	First Author	Type of cancer	Frequency distributions of the genotypes					
			GG_case	GA_case	AA_case	GG_control	GA_control	AA_control
1	Nadaoka	bladder	204	15		421	40	
2	Shan	breast	501	55	4	544	37	2
3	Sharma	breast	200	0	0	200	0	0
4	RIBEIRO	breast	96	0	0	74	0	0
5	NAIDU	breast	332	72	6	232	41	2
6	KIM	breast	87	3	0	94	7	1
7	Apaydin	breast	102	0	0	98	4	0
8	Fu	cervical	489	29	0	510	42	1
9	Kim	cervical	187	12	0	200	13	1
10	Konac	cervical	32	0	0	107	0	0
11	Fransén	colorectal	189	9	0	247	9	0
12	Demirel	colorectal	91	1	0	98	3	0
13	Knechtel	colorectal	356	11		2080	76	
14	Ni	Multi [a]	221	41	5	259	16	0
15	Konac	endometrial	21	0	0	107	0	0
16	Li	gastric	74	13	0	100	6	0
17	Mera-Menéndez	glottic	107	4	0	130	9	0
18	Liu	hepatocellular	147	10	0	151	21	1
19	HSIAO	hepatocellular	87	15	0	333	14	0
20	Tanimoto	head and neck	51	4	0	101	9	0
21	YAMAMOTO	lung	407	53	2	343	32	4
22	KUO	lung	150	94	41	215	74	11
23	PUTRA	lung	72	9	2	101	9	0
24	Konac	lung	140	1	0	154	2	0
25	Martina	multiple myeloma	259	15	1	211	7	1
26	Muñoz-Guerra	head and neck	40	21	3	130	9	0
27	Chen	head and neck	153	20	1	333	14	0
28	Alves	head and neck	2	1	37	81	7	0
29	Shieh	head and neck	281	24	0	89	7	0
30	Konac	ovarian	47	2	0	107	0	0
31	Ruiz-Tovar	pancreatic	54	2	3	142	10	0

32	Wang	pancreatic	198	65	0	249	22	0
33	Li	prostate	614	47	1	685	31	0
34	Li	prostate	1053	13	0	1247	17	0
35	Orr-Urtreger	prostate	198	2	0	298	2	0
36	MORRIS	renal	313	10	2	294	15	0
37	Qin	renal	575	45	0	584	39	0
38	Ollerenshaw	renal	65	67	14	239	39	10
39	Clifford	renal	47	1	0	140	4	0

[a] Including multi digestive tract cancers

Supplementary Table 4. Distribution of genotypes of *HIF-1α* rs2057482 polymorphism.

Number	First Author	Type of cancer	Frequency distributions of the genotypes					
			CC_case	CT_case	TT_case	CC_control	CT_control	TT_control
1	Martina	multiple myeloma	225	47	3	176	39	4
2	YAMAMOTO	lung	302	138	22	244	121	14
3	Peckham-Gregory	non-hodgkin lymphoma	125	49	6	369	147	12
4	Wang	pancreatic	301	69	40	302	154	34
5	Fu	cervical	343	150	25	318	197	38
6	Li	prostate	418	212	32	428	241	47
7	Qin	renal	388	196	36	393	201	29
8	Frank	colorectal	32	477	1259	34	441	1319
9	Lee	breast	691	415	44	611	396	41