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Common Polymorphisms in the *USF1* Gene and Cancer Susceptibility: A Meta-Analysis

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Abstract

Upstream transcription factor 1(*USF1*) has been identified to be implicated in the development of many cancer categories. In view of recent studies, several polymorphisms in *USF1* gene appeared to exert diverse influence on cancer susceptibility. However, the association between *USF1* polymorphisms and cancer susceptibility remains inconclusive due to the finite relevant published discoveries. Therefore, we conducted a meta-analysis by pooling all available published data on the susceptibility of *USF1* (rs2516838, rs2516839, rs2774276 and rs3737787) polymorphisms to cancer. The pooled odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. Finally, nine independent case-control studies comprising of 1,927 cases and 4,037 controls were enrolled in the present study. An increased susceptibility was identified inrs2516839 polymorphism and rs3737787 polymorphism, whereas no association was identified in rs2516838 andrs2774276.In addition, a statistically significant association between the *USF1*2516839 polymorphism and HCC was revealed. Nonetheless, more individual studies with higher quality are required for further elucidation.

Keywords

USF1, Polymorphism, Cancer, Meta-analysis

Introduction

The etiology of cancer is obscure because of the involvement of multiple risk factors including complicated gene-gene and gene-environment interactions. Hepatocellular carcinoma (HCC) is one of the most occurring cancers and a leading cause of cancer-related deaths worldwide, especially in China [1]. Currently, the well-recognized risk factors for HCC include chronic viral hepatitis (HBV, HCV), smoking, alcohol consumption, aflatoxin exposure and liver cirrhosis [2,3]. Among these reasons, chronic inflammation plays a crucial role in the development of cancer [4,5]. Increasing evidence suggests that single nucleotide polymorphisms (SNPs) in genes are responsible for key elements of chronic inflammation development and progression, which may lead to HCC as well as papillary thyroid cancer (PTC) [6,7]. SNP is one of the most common types of genetic abnormalities. Recently, polymorphisms have become a hot spot of research, which is expected to be the molecular markers for predicting disease susceptibility and ponderable in individual treatment. Increasing attention has been paid to genetic susceptibility and several candidate genes have been identified in recent years.

Upstream transcription factor 1 (*USF1*), which is located on chromosome 1q22-23, is an important transcription factor in human genome. It belongs to the helix-loop-helix leucine zipper family. *USF1* functions as a ubiquitously expressed transcription factor that regulates gene transcription by binding to the E-box motif of target genes [8]. It is engaged in the transcription activation of various functional genes implicated in different physiological processes, such as lipid and glucose metabolism [9,10], stress response [11], immune response [12,13], cell cycle control [14] and tumor suppression [15]. Accordingly, genetic variations of *USF1* may be correlated with some metabolic syndromes and cardiovascular diseases such as familial combined hyperlipidemia (FCHL) [16,17] high plasma triglyceride

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[18], low-density lipoprotein (LDL) level [19], atherosclerosis lesions [20], coronary artery calcifications [21], and low APOE expression [16].

As for the risk of cancer, some case-control studies in *USF1* were performed among Chinese population. According to the previous studies, two polymorphisms in *USF1* (rs2516839 and rs3737787) have been demonstrated to be associated with HCC susceptibility in Chinese [22,23]. While in another research three polymorphisms in *USF1* (rs2516838, rs3737787 and rs2516839) showed significant association with PTC susceptibility in Chinese population [24]. Nonetheless, the association of *USF1* polymorphisms and cancer susceptibility remains an issue due to inconclusive findings in currently published case-control studies. Therefore, the present study was carried out to investigate the effect of *USF1* polymorphisms on cancer susceptibility by pooling all currently available data.

Materials and methods

Search strategy

A comprehensive literature search was performed in PubMed, Embase, Web of Science databases (up to 15 June 2015) to collect all eligible studies on the relevance between polymorphisms of *USF1* (rs2516838, rs2516839, rs2774276 and rs3737787) and cancer susceptibility by using the following search strategy: ("*USF1*"or "upstream transcription factor 1") and ("polymorphism "or" mutation") and ("cancer "or" tumor"). Moreover, studies were identified by a manual search of the reference lists of eligible reviews and retrieved studies for additional studies.

Inclusion criteria

The articles adopted in our current meta-analysis met the following criteria: (a) studies that evaluated the relevance between the polymorphisms in *USF1* and cancer susceptibility; (b) case-control study; (c) an OR with a 95% can be obtained from all the cases and controls. We excluded studies which were: (a) case-only studies and Reviews; (b) insufficient raw statistics to calculate odds ratios (ORs) with 95% confidence intervals (CIs); (c) duplicated publications; (d) studies based on families.

Data extraction

Three investigators (M.Zhang, J.Bai and J.J. Huang) extracted the data independently from adopted studies and a consensus was reached on every item. Any disagreement was settled according to the description above. The following statistics was collected: first author's surname, publication year, ethnic population, sample size of cases and control, source of controls, and genotype or allele distribution in cases and controls.

Statistical analysis

ORs and 95% CIs in the case-control studies were employed to assess the association between the *USF1* polymorphisms and cancer susceptibility. The pooled ORs were performed under the allele contrast(C vs. T), dominant (CC+TC vs. TT), and recessive (CC vs. TC+TT) models. Comparisons were made in heterozygote (TC vs. TT) and homozygote (CC vs. TT). The P values of HWE for the genotype distribution in controls were calculated by χ^2 test. The meta-analyses were conducted using the STATA 12.0 (Stata Corporation, College Station, Texas). A chi-square based Q-statistic test was conducted for the heterogeneity of studies within the case-control studies [25]. If the Q test ($P > 0.1$) presented homogeneity in studies, we would applied the fixed effects model [26]; Otherwise, the random effects model was selected [27]. The inconsistency index was also adopted to evaluate the heterogeneity across studies ($I^2 >$ 50%: significant heterogeneity; I^2=25–50%: moderate heterogeneity; $I^2 <$ 25%: no heterogeneity). Stratification analyses were performed by cancer type and source of control. Sensitivity analysis was conducted by extracting a study each time to evaluate the stability of the results. Begg's funnel plot and Egger's regression test were applied to assess

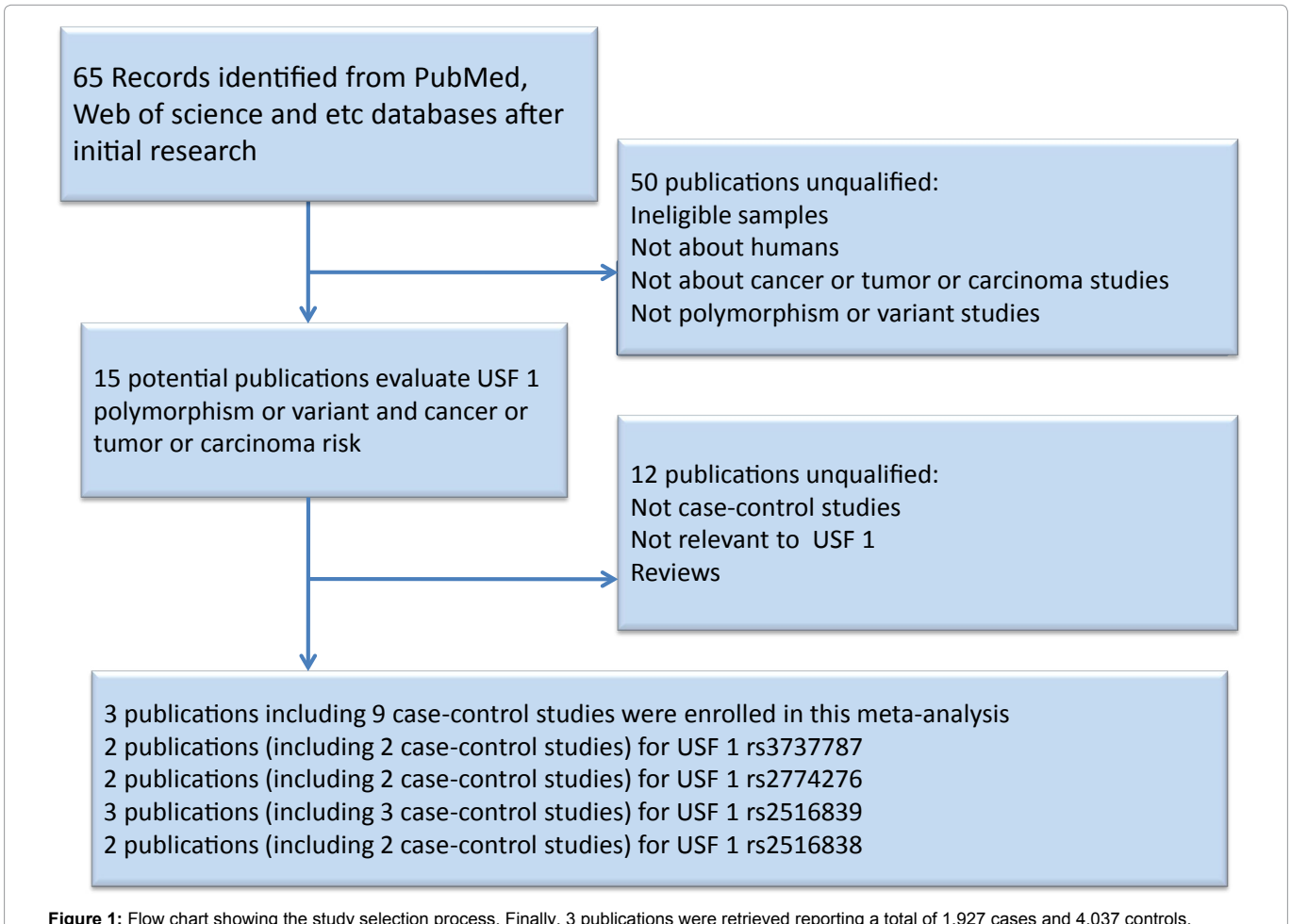

Figure 1: Flow chart showing the study selection process. Finally, 3 publications were retrieved reporting a total of 1,927 cases and 4,037 controls.

Table 1: Polymorphisms and characteristics of studies involved in this meta-analysis

SNP	First Author	Year	Ethnicity	Genotyping Method	Source of Control	Cancer type	Case			Control			
							TT	TC	CC	TT	TC	CC	P(HWE)
rs2516838	Zhao*et al.*	2015	Chinese	Taqman	HB	HCC	33	49	12	47	43	10	0.971
	Yuan*et al.*	2015	Chinese	PCR	HB	TC	261	65	8	628	191	35	**0.000**
rs2516839	Zhou*et al.*	2014	Chinese	PCR	PB	HCC	35	76	43	52	78	30	0.937
	Zhao*et al.*	2015	Chinese	Taqman	HB	HCC	45	22	27	63	25	12	**0.001**
	Mu*et al.*	2015	Chinese	PCR	HB	TC	88	154	92	281	387	187	**0.014**
rs2774276	Zhao*et al.*	2015	Chinese	Taqman	HB	HCC	59	32	3	65	32	3	0.692
	Mu*et al.*	2015	Chinese	PCR	HB	TC	160	152	22	377	395	82	0.141
rs3737787	Zhou*et al.*	2014	Chinese	PCR	PB	HCC	63	72	20	89	54	17	0.052
	Mu*et al.*	2015	Chinese	PCR	HB	TC	147	144	43	453	303	98	**0.000**

HWE: Hardy-Weinberg equilibrium; HB: Hospital-based, PB: Population-based, HCC: Hepatocellular Carcinoma, TC: Thyroid cancer

Table 2: Results of meta-analysis for polymorphisms in USF1 and cancer susceptibility

Variables (rs2516839)	**Case/Control**	**C vs. T**			**CC vs. TT**			**TC vs. TT**		
		OR (95% CI)	**P[a]**	**I² (%)**	**OR (95% CI)**	**P[a]**	**I²**	**OR (95% CI)**	**P[a]**	**I²**
Total	582/1115	1.392(1.203-1.612)*	0.113	29.3	1.837(1.386-2.433)*	0.243	8.6	1.301(1.017-1.665)*	0.904	0.0
Source of control										
HB	428/955	1.373(1.164-1.620)*	0.040	58.4	1.771(1.293-2.424)*	0.110	37.0	1.264(0.958-1.669)	0.936	0.0
Cancer Type										
HCC	248/260	1.655(1.284-2.135)*	0.192	17.0	2.496(1.529-4.074)*	0.445	0.0	1.363(0.895-2.077)	0.717	0.0
	Case/Control	**CC+TC vs. TT**			**CC vs. TC+TT**					
		OR (95% CI)	**P[a]**	**I²**	**OR (95% CI)**	**P[a]**	**I²**			
Total	582/1115	1.486(1.185-1.863)*	0.594	0.0	1.548(1.219-1.965)*	0.155	21.4			
Source of control										
HB	428/955	1.450(1.125-1.869)	0.352	0.0	1.515(1.160-1.979)*	0.058	52.1			
Cancer Type										
HCC	248/260	1.727(1.184-2.519)*	0.749	0.0	2.037(1.324-3.134)*	0.228	9.7			
Variables (rs2516838)	**Case/Control**	**C vs. T**			**CC vs.** TT			**CT vs. TT**		
		OR (95% CI)	**P[a]**	**I² (%)**	**OR (95% CI)**	**P[a]**	**I² (%)**	**OR (95% CI)**	**P[a]**	**I² (%)**
Total	428/954	1.004(0.564-1.788)	0.020	66.6	0.938(0.309-2.850)	0.070	48.3	1.096(0.565-2.127)	0.049	54.9
	Case/Control	**CC+CT vs. TT**			**CC vs. CT+TT**					
		OR (95% CI)	**P[a]**	**I² (%)**	**OR (95% CI)**	**P[a]**	**I² (%)**			
Total	428/954	1.082(0.523-2.237)	0.025	64.3	0.801(0.455-1.412)	0.168	22.4			
Variables (rs2774276)	**Case/Control**	**C vs. T**			**CC vs. TT**			**CT vs.TT**		
		OR (95% CI)	**P[a]**	**I² (%)**	**OR (95% CI)**	**P[a]**	**I²**	**OR (95% CI)**	**P[a]**	**I²**
Total	428/954	0.914(0.804-1.040)	0.430	0.0	0.701(0.460-1.068)	0.560	0.0	0.966(0.851-1.096)	0.597	0.0
	Case/Control	**CC+CT vs. TT**			**CC vs. CT+TT**					
		OR (95% CI)	**P[a]**	**I²**	**OR (95% CI)**	**P[a]**	**I²**			
Total	428/954	0.947(0.846-1.062)	0.510	0.0	0.708(0.459-1.094)	0.600	0.0			
Variables (rs3737787)	**Case/Control**	**Cvs. T**			**CC vs. TT**			**TC vs. TT**		
		OR (95% CI)	**P[a]**	**I² (%)**	**OR (95% CI)**	**P[a]**	**I²**	**OR (95% CI)**	**P[a]**	**I²**
Total	428/954	1.210(1.082-1.354)*	0.421	0.0	1.325(1.003-1.751)*	0.622	0.0	1.277(1.124-1.450)*	0.380	0.0
	Case/Control	**CC+CTvs. TT**			**CC vs. TC+TT**					
		OR (95% CI)	**P[a]**	**I² (%)**	**OR (95% CI)**	**P[a]**	**I²**			
Total	428/954	1.227(1.105-1.362)*	0.362	0.0	1.143(0.852-1.534)	0.823	0.0			

I²: 0–25, means no heterogeneity, 25–50 means modest heterogeneity, >50 means high heterogeneity, PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism, P[a]: P value of Q test for heterogeneity test, * means statistically significant (P<0.05).

the possibility of publication bias.

Results

The identification and characteristics of eligible studies

After a systematic literature search in the databases of PubMed, Embase and Web of Science on the association between *USF1* polymorphisms and cancer including nine independent case-control studies. A total of 1,927 cases and 4,037controls were enrolled in our meta-analysis [22-24]. We presented a flow chart of the studies screening process in Figure 1.They were published between 2014 and 2015. Table 1 shows the characteristics of all eligible studies [22-24]. Among the eligible nine case-control studies, three are TaqMan assay, while six are performed by PCR. In addition, two of these case-control studies are population-based and seven are hospital-based. The ethnicity in these case-control studies is Chinese.

Association between *USF1* polymorphisms and cancer susceptibility

We summarized the main results of the present meta-analysis and the heterogeneity test in Table 2. By pooling ORs and 95% CIs, it demonstrated that neither *USF1* rs2516838 nor *USF1* rs2516838 polymorphisms was associated with the susceptibility of cancer. Nevertheless, we identified an increased susceptibility in the polymorphism of *USF1*rs2516839 (C vs. T: OR=1.392, 95%CI=1.203-1.612, $P_{heterogeneity}$ = 0.113; CC vs. TT: OR = 1.837, 95%CI = 1.386-2.433, $P_{heterogeneity}$ = 0.243; TC vs. TT: OR = 1.301, 95% CI = 1.017-1.665, $P_{heterogeneity}$ = 0.904; CC/TC vs. TT: OR = 1.486, 95% CI = 1.185-1.863, $P_{heterogeneity}$ = 0.594; CC vs. TC/TT: OR = 1.548, 95% CI = 1.219-1.965, $P_{heterogeneity}$ = 0.155), as well as the polymorphism of *USF1* rs3737787 (C vs. T: OR = s1.210, 95%CI = 1.082-1.354, p = 0.421; CC vs. TT : OR = 1.325, 95% CI = 1.003-1.751, $P_{heterogeneity}$ = 0.622; TC vs. TT: OR = 1.277 95% CI = 1.124-1.450, $P_{heterogeneity}$ = 0.380; CC/TC vs. TT: OR = 1.227, 95% CI = 1.105-1.362, $P_{heterogeneity}$ = 0.362). When we stratified the analysis by types of cancer, the polymorphism of *USF1* rs2516839 was revealed to contribute to HCC cancer susceptibility and the pooled results were statistically significant (C vs. T: OR = 1.655, 95% CI = 1.284-2.135, $P_{heterogeneity}$ = 0.192; CC vs. TT: OR = 2.496, 95% CI = 1.529-4.074, $P_{heterogeneity}$ = 0.445; CC/TC vs. TT: OR = 1.727, 95% CI = 1.184-2.519, $P_{heterogeneity}$ = 0.749; CC vs. TC/TT: OR = 2.037, 95% CI = 1.324-3.134, $P_{heterogeneity}$ = 0.04). Additionally, a significant association

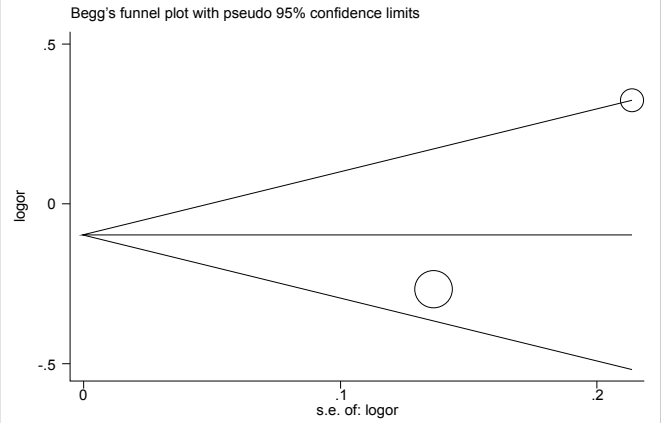

Figure 2a: Publication bias in studies of the association between the *USF1 rs2516838* polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test (C vs T). Log (OR): the natural logarithm of the odds ratio.

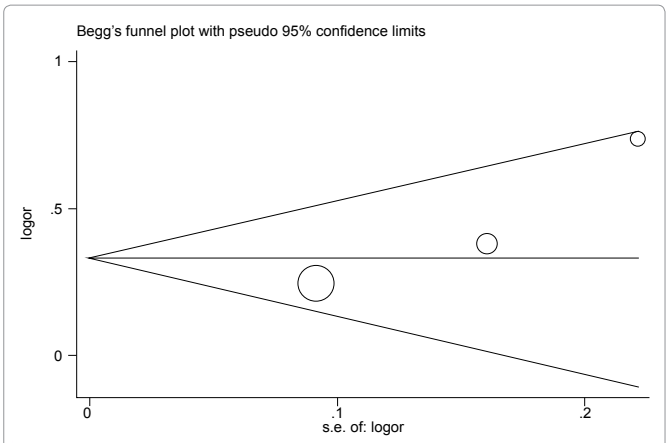

Figure 2b: Publication bias in studies of the association between the *USF1* rs2516839 polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test (C vs. T). Log (OR): the natural logarithm of the odds ratio.

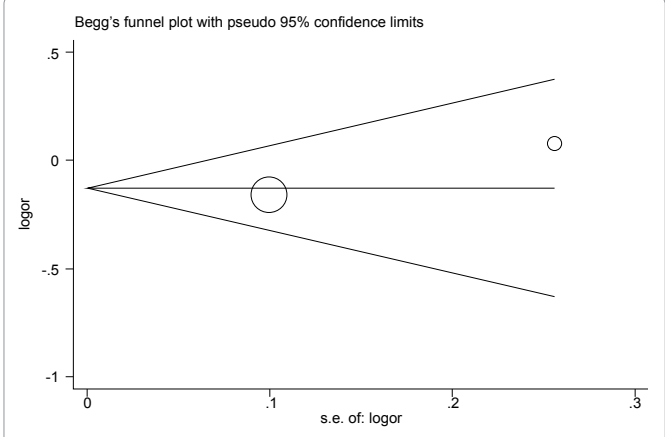

Figure 2c: Publication bias in studies of the association between the *USF1* rs2774276 polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test (C vs. T). Log (OR): the natural logarithm of the odds ratio.

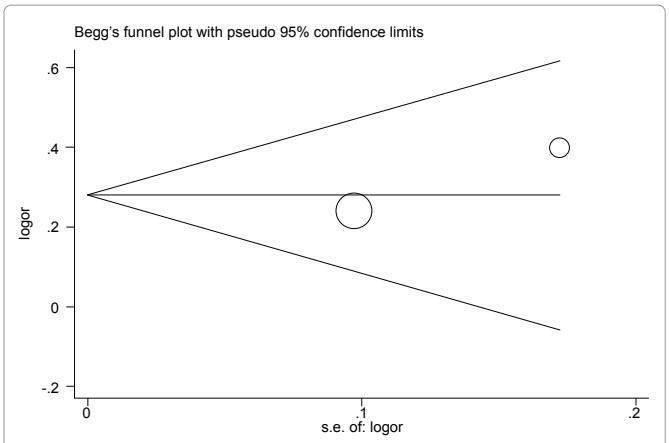

Figure 2d: Publication bias in studies of the association between the *USF1* rs3737787 polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test (C vs. T). Log (OR): the natural logarithm of the odds ratio.

of the polymorphism of *USF1* rs2516839 was found in hospital-based subgroup. (C vs. T: OR = 1.373, 95% CI = 1.164-1.1620, $P_{heterogeneity}$ = 0.192; CC vs. TT: OR = 1.771, 95% CI = 1.293-2.424, $P_{heterogeneity}$ = 0.110; CC vs. TC/TT: OR = 1.515, 95% CI = 1.160-1.979, $P_{heterogeneity}$ = 0.058)

Heterogeneity analysis and publication bias risk

According to the results of heterogeneity analysis, no separate study shows influence on the pooled OR. Begg's funnel plot and Egger's test which were carried out to evaluate the publication bias risk. No publication bias was shown (Figure 2a, Figure 2b, Figure 2c and Figure 2d).

Discussion

A wide variety of genes are direct targets of *USF*, including genes involved in the immune response [28], glucid and lipid pathways [29], cell cycle [30,31], cell proliferation [32], and carcinogenesis [33-36]. Upstream transcription factors 1(*USF1*) is a member of the basic helix-loop-helix transcription factor family. It functions as a ubiquitous expressed transcription factor that regulates gene transcription by binding to the E-box motif of target genes [8,37]. According to plenty of studies, *USF1* is one of the critical components within signal transduction path ways. Via regulating the expression of various genes they are involved in various aspects of cellular functions including regulation of cell growth and cell death. Therefore, disturbances within the proper function of *USF1* may be related to tumorigenesis and cancer [38].

In a current study, Zhao *et al.* demonstrated that *USF1* rs2516839 were an increased susceptibility of developing HCC in Chinese [22]. In addition, the other study conducted by Zhou *et al.* draw a similar conclusion. However, Zhou's study also demonstrated that *USF1* rs3737787 is contributed to adding susceptibility of HCC [23]. While Yuan *et al.* proved that the *USF1* alleles (rs2516838, rs3737787 and rs2516839) were all associated with HCC cancer susceptibility among Chinese [24]. Considering the inconsistent conclusions, we collect all the case-control studies currently published for a pooled analysis. In the present meta-analysis, we analyzed nine independent case–control studies with a sum of 1,927 cases and 4,037 controls. The pooled results illustrated that there is no evident association between the polymorphisms (rs2516838 and rs2774276) of *USF1*and cancer susceptibility. However, the polymorphisms (rs2516839 and rs3737787) were regarded as a risk factor separately. Moreover, in the stratified analysis, we found that the HCC cancer susceptibility is relevant with the polymorphism of *USF1* rs2516839.

Although our present study have conducted a comprehensive retrieve for all the eligible studies, the pool results should be interpreted with caution due to several drawbacks in our meta-analysis. Firstly, the currently available case-control studies enrolled in our study were limited. Secondly, our study was conducted only in Chinese population, so the results may not be applied in other ethnicities. Thirdly, there was only one study in discussing the genetic predisposition of *USF1* polymorphisms to PTC. We cannot evaluate any polymorphism of *USF1*on PTC susceptibility since eligible case-control studies that were currently published were insufficient for a pooled analysis. Finally, the effect of *USF1*polymorphisms on cancer susceptibility might be affected by some complex factors, such as age, gender, histological types of cancer, and matching criteria and so on. Therefore, more case-control studies are required to further assess gene association in cancer susceptibility.

To sum up, our work has revealed that *USF1* rs2516839 and rs3737787polymorphisms alter the susceptibility of cancer. When considering a certain type of cancer, HCC appeared to be related to the

*USF1*2516839 polymorphism. A well-designed research may be needed to further explicit the relation between *USF1* polymorphisms and cancer.

Declared of Interest

None

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