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Association of hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism with susceptibility to renal cell carcinoma/prostate cancer

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Key words: Renal cell carcinoma (RCC), Prostate cancer, Hypoxia-inducible factor-1α (HIF1α), 1772C/T gene polymorphism, Meta-analysis

Abstract: In this study, we used a meta-analysis method to evaluate the relationship between hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism (rs 11549465) and renal cell carcinoma (RCC)/prostate cancer risk. We searched for relevant studies (before March 1, 2019) on Cochrane Library, Embase, and PubMed. Studies meeting the inclusion criteria were recruited into this meta-analysis. The outcome of dichotomous data was showed in the way of odds ratios (OR), and 95% confidence intervals (CI) were also counted. In this investigation, there was no association between HIF1α 1772C/T gene polymorphism and susceptibility to RCC in Caucasians, Asians as well as overall populations. In addition, HIF1α 1772C/T gene polymorphism was not found to be relevant to the survival in RCC. Interestingly, the T allele was relevant to prostate cancer risk in all populations, but not in Caucasians and Asians. However, the TT genotype and the CC genotype were not related to prostate cancer susceptibility in Asian, Caucasian, and all populations. In conclusion, the T allele of the HIF1α 1772C/T gene polymorphism was related to prostate cancer risk in the overall populations.

Introduction

Renal cell carcinoma is one of the most common renal neoplasms, accounting for approximately 3.9% of new cancers, and its morbidity was also on the rise in the past two decades (Pan *et al.*, 2018; Hu *et al.*, 2017). Cancer prognosis is affected by the underlying tumor biology and also by the host inflammatory response to the disease (Chaves *et al.*, 2018). Surgery and other treatments like conventional chemotherapy and radiotherapy are applied to RCC, but it still has the highest mortality and recurrence rate among the genitourinary carcinomas (Pan *et al.*, 2018; Zhang *et al.*, 2018; Zhao *et al.*, 2018). Prostate cancer contributes the most to morbidity and mortality in men all over the world, while its morbidity has had a significant increase in recent years (Ramalho-Carvalho *et al.*, 2018; Bernal-Ramos *et al.*, 2017). In order to overcome the treatment resistance that occurs with recurrence, it is rather critical to developing more effective methods for early diagnosis and treatment for prostate cancer (Wang *et al.*, 2018b). The current evidence suggests that genetic factors contribute to the risk of RCC and prostate cancer.

HIF1α, a member of the HIF transcription factor family, controls various cellular pathways involved in embryonic development and many normal physiological processes such as cell apoptosis, response to hypoxia chemotaxis, and proliferation. HIF1α is also essential for cell survival, energy metabolism, angiogenesis, progression, and metastasis of tumors (Maybin *et al.*, 2018; Qian *et al.*, 2018; Wang *et al.*, 2018a; Wilkes *et al.*, 2018). HIF1α 1772C/T (rs11549465) gene polymorphism increases the risk of certain cancers (Wang *et al.*, 2018a; Kang *et al.*, 2011; Anam *et al.*, 2015; Li *et al.*, 2015). However, some investigations revealed that the HIF1α 1772C/T (rs 11549465) gene polymorphism was not related to the risk of other cancers like hepatocellular carcinoma and colorectal cancer (Liu *et al.*, 2014; Xu *et al.*, 2014). The available evidence is insufficient to justify the divergence and sparse data in the reported studies. This meta-analysis was performed to assess whether the gene polymorphism of HIF1α 1772C/T (rs 11549465) is related to the susceptibility to RCC and prostate cancer.

Methods

Search strategy

We searched Cochrane Library, Embase, and PubMed (from inception to March 1, 2019) to identify eligible studies using the search terms "hypoxia-inducible factor-1α" or "HIF1α"

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TABLE 1

Characteristics of studies evaluating the effects of hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism on renal cell carcinoma and prostate cancer risk

Cancer Types	Author, Year	Country	Ethnicity	Case			Control		
				TT	TC	CC	TT	TC	CC
Renal cell carcinoma									
	Clifford 2001	UK	Caucasian	0	6	42	6	27	110
	Ollerenshaw 2004	UK	Caucasian	90	54	16	71	90	1
	Morris 2009	Poland	Caucasian	3	39	290	5	46	262
	Qin 2012	China	Asian	2	46	572	2	43	578
Prostate cancer									
	Chau 2005	USA	Mix	6	29	161	3	14	179
	Li 2007	USA	Mix	14	209	818	18	221	995
	Orr-Urtreger 2007	Israel	Caucasian	16	99	287	3	80	217
	Foley 2009	Ireland	Caucasian	0	30	65	0	13	175
	Li 2012	China	Asian	2	48	612	0	57	659
	Fraga 2014	Portuguese	Caucasian	11	164	579	14	156	566

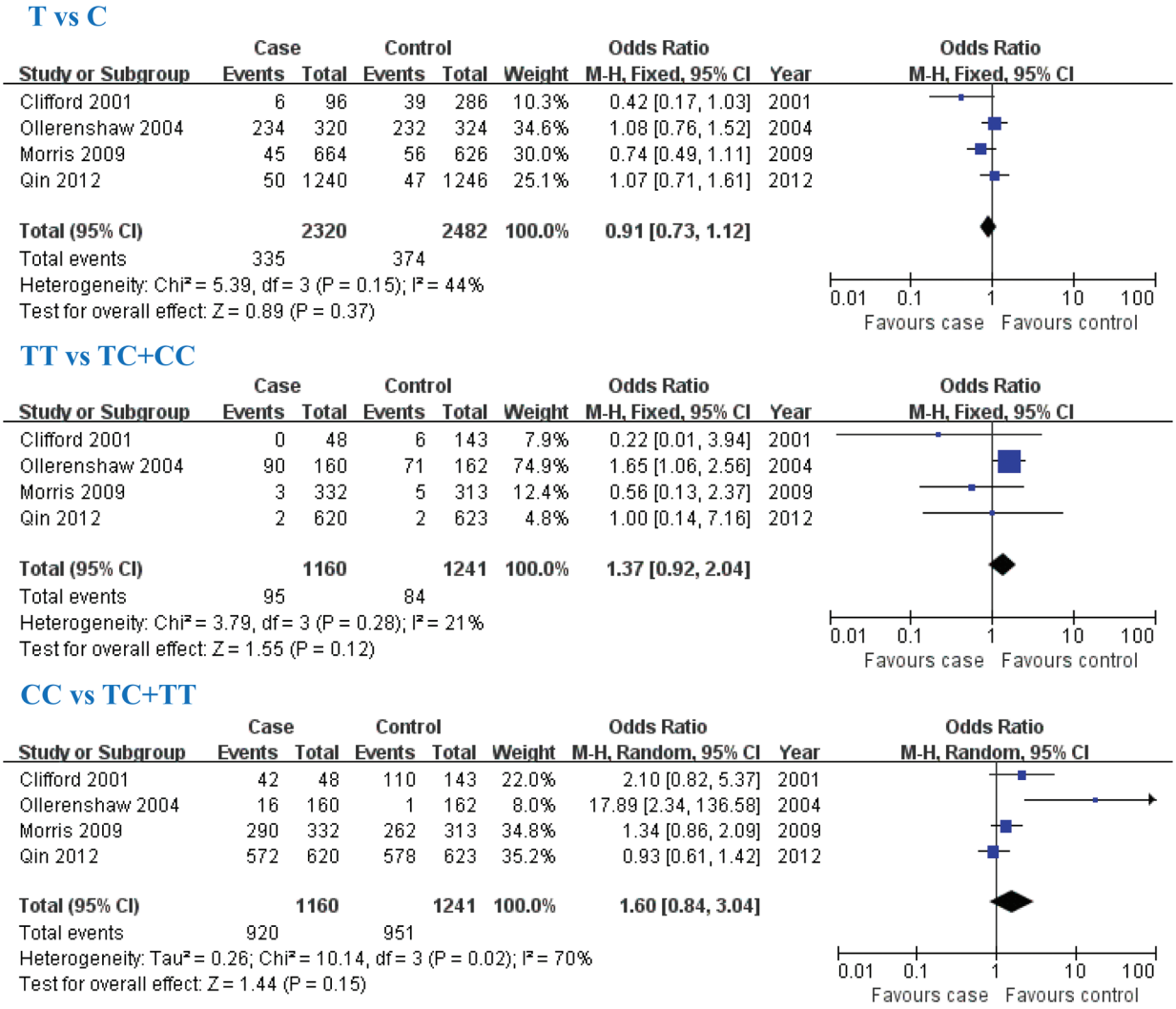

FIGURE 1. Association between hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism and renal cell carcinoma susceptibility in overall populations.

TABLE 2

Meta-analysis of the association of hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism with renal cell carcinoma and prostate cancer risk and renal cancer survival

Cancer Type	Group and subgroups	Studies Number	Q test *p*-value	Model selected	OR (95%CI)	P
Renal cell carcinoma						
T *vs.* C	Overall	4	0.15	Fixed	0.91 (0.73, 1.12)	0.37
	Caucasian	3	0.10	Fixed	0.85 (0.66, 1.10)	0.21
	Asian	1	–	Fixed	1.07 (0.71, 1.61)	0.74
TT *vs.* TC+CC	Overall	4	0.28	Fixed	1.37 (0.92, 2.04)	0.12
	Caucasian	3	0.16	Fixed	1.39 (0.92, 2.08)	0.11
	Asian	1	–	Fixed	1.00 (0.14, 7.16)	1.00
CC *vs.* TC+TT	Overall	4	0.02	Random	1.60 (0.84, 3.04)	0.15
	Caucasian	3	0.03	Random	2.47 (0.87, 6.97)	0.09
	Asian	1	–	Fixed	0.93 (0.61, 1.42)	0.73
Prostate cancer						
T *vs.* C	Overall	6	<0.0001	Random	1.38 (1.02, 1.87)	0.04
	Caucasian	3	<0.0001	Random	1.64 (0.86, 3.13)	0.13
	Asian	1	–	Fixed	0.99 (0.67, 1.45)	0.94
TT *vs.* TC+CC	Overall	6	0.13	Fixed	1.29 (0.84, 1.98)	0.24
	Caucasian	3	0.02	Random	1.65 (0.31, 8.71)	0.55
	Asian	1	–	Fixed	5.42 (0.26, 113.18)	0.28
CC *vs.* TC+TT	Overall	6	<0.00001	Random	0.71 (0.51, 1.00)	0.05
	Caucasian	3	<0.00001	Random	0.59 (0.28, 1.23)	0.16
	Asian	1	–	Fixed	1.06 (0.71, 1.57)	0.78
Survival of renal cell carcinoma						
T *vs.* C	Overall	2	0.08	Random	0.88 (0.07, 10.66)	0.92
TT *vs.* TC+CC	Overall	2	–	Fixed	2.80 (0.30, 25.92)	0.36
CC *vs.* TC+TT	Overall	2	0.07	Random	1.14 (0.08, 16.32)	0.92

and "renal cell carcinoma" or "renal cancer" or "RCC" or "prostate cancer".

Inclusion and exclusion criteria

Inclusion criteria: (1) the disease had to be renal cancer, prostate cancer; (2) two comparison groups (case group *vs.* control group) had to be included; (3) the detailed genotype distribution data should be provided.

Exclusion criteria: (1) editorials, case reports, and review articles; (2) when the main results did not include HIF1α 1772C/T and outcome; (3) the effect of HIF1α gene levels on disease was investigated and (4) when detailed genotype distribution of HIF1α 1772C/T was not provided.

Data extraction and synthesis

From every eligible investigation, we extracted the important information, which was the first author's surname, publication year, and number of patients with RCC, prostate cancer and control patients for HIF1α 1772C/T genotypes. The frequency of HIF1α 1772C/T in each control and case group was counted in accordance with the corresponding genotype distribution. Survival data of renal cell or prostate cancer was also extracted.

Statistical analysis

Each statistical analysis was conducted by means of the Cochrane Review Manager Version 5 (Cochrane Library, UK). The calculated statistics were summarized with the help of a fixed-effects model, but once the *p*-value of the heterogeneity test was under 0.1, a random-effects model (Der Simonian-Laird method) had to be used. The outcomes were expressed as the odds ratio (OR) of the binary data with 95% confidence intervals (CI). Statistical significance was found when the pooled OR had a $P < 0.05$. The heterogeneity test was tested by I^2-value among included studies.

Results

Study characteristics for relationship between the HIF1α 1772C/T gene polymorphism and susceptibility to RCC

In order to study the relationship between HIF1α 1772C/T gene polymorphism and RCC risk (Tab. 1), our meta-analysis recruited four studies (Clifford *et al.*, 2001; Ollerenshaw *et al.*, 2004; Morris *et al.*, 2009; Qin *et al.*, 2012), which contained 1160 case series and 1241 controls. And the relevant data was extracted by the first author's

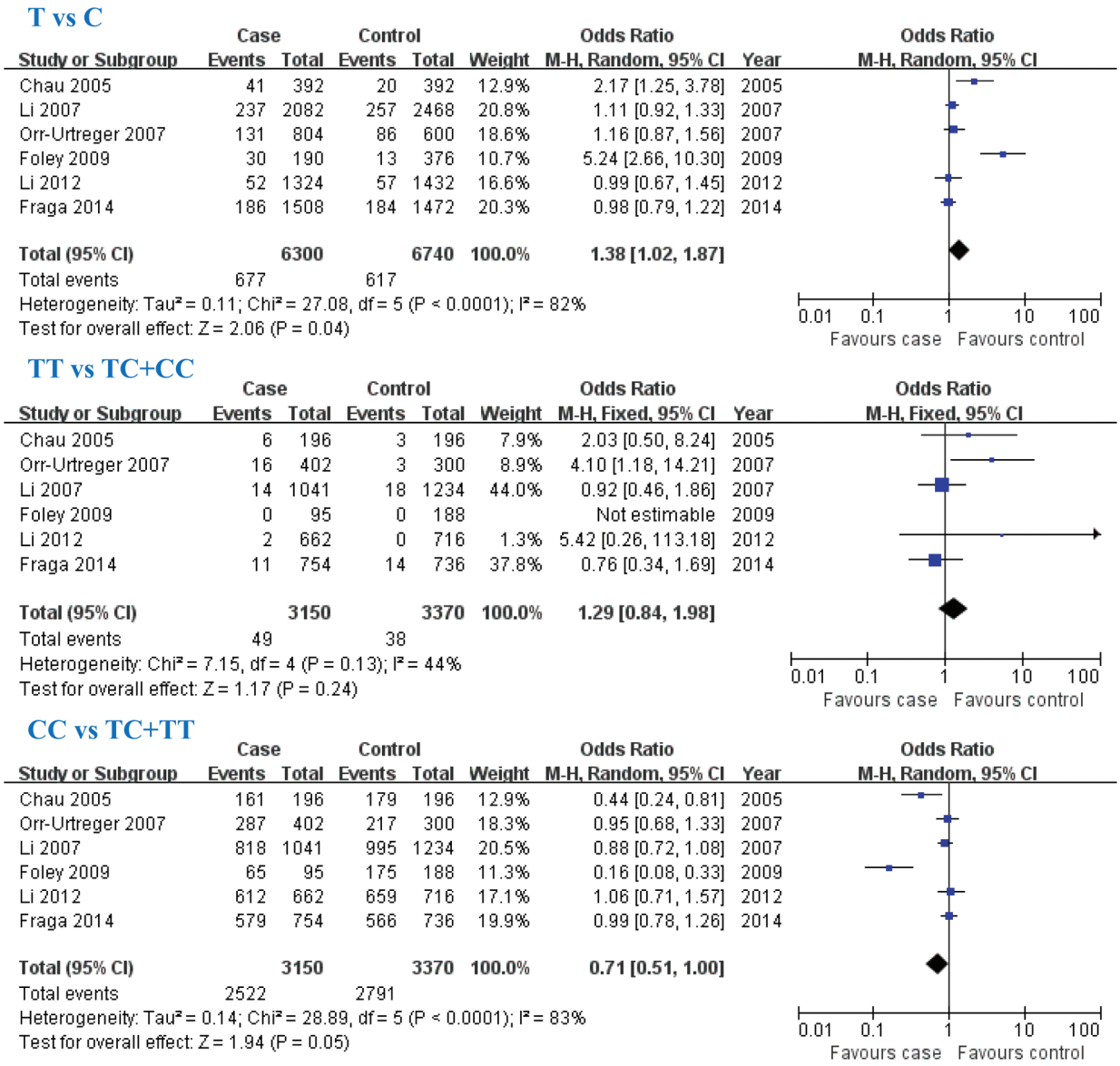

FIGURE 2. Association between hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism and prostate cancer susceptibility in overall populations.

surname, publication year, and the number of patients with RCC and controls for the HIF1α1772C/T genotype (Tab. 1).

Study characteristics for relationship between HIF1α 1772C/T gene polymorphism and susceptibility to prostate cancer

Six studies (Orr-Urtreger *et al.*, 2007; Li *et al.*, 2007, 2012; Foley *et al.*, 2009; Fraga *et al.*, 2014; Chau *et al.*, 2005) including 3150 case series and 3370 controls were included in our research to find the relationship between HIF1α 1772C/T gene polymorphism and the prostate cancer risk (Tab. 1).

Study characteristics for the relationship between the HIF1α 1772C/T gene polymorphism and the RCC survival

Two studies (Qin *et al.*, 2012; Ferreira *et al.*, 2017) were recruited into our research to find the association of the HIF1α 1772C/T gene polymorphism with the RCC survival.

Association of the HIF1α 1772C/T gene polymorphism with the susceptibility to renal cell carcinoma

This meta-analysis study revealed that HIF1α 1772C/T gene polymorphism was not related to renal cancer susceptibility in overall population (T: OR = 0.91, 95% CI: 0.73–1.12, P = 0.37; TT: OR = 1.37, 95% CI: 0.92–2.04, P = 0.12; CC: OR = 1.60, 95% CI: 0.84–3.04, P = 0.15; Fig. 1 and Tab. 2), Caucasians and Asians.

Association of the HIF1α 1772C/T gene polymorphism with prostate cancer susceptibility

T allele was relevant to the susceptibility to prostate cancer in the whole populations, but not in Asians or Caucasians (the whole populations: T: OR = 1.38, 95% CI: 1.02–1.87, P = 0.04; Fig. 2 and Tab. 2). TT genotype and CC genotype were not relevant to prostate cancer susceptibility in the overall population, Asians, and Caucasians (Overall: TT: OR = 1.29, 95% CI: 0.84–1.98, P = 0.24; CC: OR = 0.71, 95% CI: 0.51–1.00, P = 0.05; Fig. 2 and Tab. 2).

Association of the HIF1α 1772C/T gene polymorphism with the survival of RCC

HIF1α 1772C/T gene polymorphism is not related to RCC survival in the overall population (T: OR = 0.88, 95% CI:

0.07–10.66, $P = 0.92$; TT: OR = 2.80, 95% CI: 0.30–25.92, $P = 0.36$; CC: OR = 1.14, 95% CI: 0.86–16.32, $P = 0.92$; Tab. 2).

Discussion

In this study, we investigated the relationship between the HIF1α 1772C/T gene polymorphism (rs 11549465) and susceptibility to RCC/prostate cancer. We did not find a relationship between HIF1α 1772C/T gene polymorphism and RCC susceptibility or survival for the overall population, neither for Caucasians nor Asian populations individually. It was interesting to find that the T allele was related to prostate cancer risk in overall populations, but not in Caucasians and Asian populations. However, the TT and CC genotypes had no relationship with prostate cancer susceptibility in the whole populations, Asians, and Caucasians.

There were some other meta-analyses in previous papers from this group. Li *et al.* (2015) completed a meta-analysis on the association of HIF1α 1772C/T gene polymorphism with cancer risk, reporting that HIF1α 1772C/T gene polymorphism is not associated with susceptibility to renal cell carcinoma/prostate cancer. Li *et al.* (2013) made a meta-analysis reporting that HIF1α 1772C/T gene polymorphism was not either associated with susceptibility to renal cell carcinoma/prostate cancer. Anam *et al.* (2015) reported that the HIF1α 1772C/T gene polymorphism was not related to susceptibility to RCC/prostate cancer by means of a meta-analysis containing genome-wide association studies of HIF1α 1772C/T polymorphism with cancer risk. These meta-analyses mentioned above were not performed by ethnicity. Our results revealed that the HIF1α 1772C/T gene polymorphism was not related to the RCC risk among Caucasians, Asians, and overall populations. Additionally, there was no association between the HIF1α 1772C/T gene polymorphism and survival in RCC. Interestingly, the T allele was related to the risk of prostate cancer among all populations, but not among Caucasians and Asian populations. However, the TT genotype and the CC genotype were not related to prostate cancer susceptibility among Asians, Caucasians, and overall populations. These results add new information inferred by our further analysis considering the different ethnic groups.

Conclusion

This meta-analysis suggests that the T allele was related to the risk of prostate cancer in the overall populations, but not in Caucasians and Asians. However, additional correlation research is needed to further confirm their association.

Abbreviations: HIF1α: hypoxia-inducible factor-1α; OR: Odds ratios; CI: confidence intervals.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions: TBZ was in charge of conceiving and designing the study. TBZ, CLL and HYL were responsible for the collection of data and performing the statistical analysis and manuscript preparation. CLL and WJW were responsible for checking the data. All authors were responsible for drafting the manuscript, reading it, and approving the final version.

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