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ORIGINAL RESEARCH

The association of HIF-1α expression with clinicopathological significance in prostate cancer: a meta-analysis

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Background: Hypoxia-inducible factor-1α (HIF-1α) plays an important role in tumor growth, invasion, and metastasis. The aim of this study was to perform a meta-analysis to explore the association of HIF-1α expression with clinicopathological significance in patients with prostate cancer (PCa).

Methods: A detailed literature search was made in PubMed, Embase, Cochrane Library, China Biology Medicine disc (CBM), and China National Knowledge Infrastructure (CNKI) up to August 21, 2017. Odds ratios (ORs) with 95% CIs were calculated to evaluate the strength of the correlations. Analysis of pooled data was performed using Review Manager 5.3 software.

Results: Eventually, 14 studies were identified and involved in this meta-analysis. The rate of HIF-1α protein expression was significantly higher in PCa than in nonmalignant prostate tissues (OR=12.01, 95% CI: 8.22–17.55, $P<0.00001$). Similar results were found in different subgroups. There were significant differences between HIF-1α expression and clinicopathological significance. The expression of HIF-1α protein was significantly associated with Gleason score (Gleason ≥7 vs Gleason <7: OR=3.58, 95% CI: 2.35–5.46, $P<0.00001$). The frequency of HIF-1α protein expression was significantly higher in T3–T4 stages than in T1–T2 stages of PCa (OR=3.70, 95% CI: 1.53–8.96, $P=0.004$). The expression of HIF-1α protein was significantly associated with the presence of lymph node and/or bone metastasis of PCa (metastasis positive vs negative: OR=7.07, 95% CI: 4.08–12.25, $P<0.00001$).

Conclusion: Taken together, our findings have demonstrated the certain associations of HIF-1α expression with an increased risk and clinicopathological significance in PCa patients, indicating that HIF-1α may serve as a valuable biomarker for diagnosing PCa and monitoring the progression.

Keywords: HIF-1α, prostate cancer, clinicopathological significance, meta-analysis

Introduction

Prostate cancer (PCa) seriously threatens psychological and physical health worldwide. It remains the most common malignancy diagnosed and the third highest cause of leading cancer-related death in males in the USA. An estimation of 2017 cancer statistics revealed 161,360 new cases and 26,730 newly related deaths assigned to PCa.[1] Currently, although there are different treatment options for PCa including surgery, local radiotherapy, castration, and chemotherapy, the molecular mechanisms for the emergence and progression of PCa remain research focus in recent years.[2,3] Especially, molecular biomarkers that predict the progression and clinical outcome would allow

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earlier and more appropriate therapeutic approaches for PCa. Therefore, new progressive and prognostic indicators for PCa are urgently required.

Hypoxia is a reduction in the normal concentration of tissue oxygen which occurs in many diseases including cancer. A key effect of hypoxia is the induction of genetic alterations and angiogenic stimulation, leading to a more aggressive cell phenotype and malignant progression.[4] Hypoxia-inducible factor (HIF) is a DNA-binding transcription factor, which responds to hypoxia. Recent advances have pointed to the critical role of HIF-1α in cell development, progression, and the metastasis of PCa.[5,6] However, the clinical relevance of the expression of HIF-1α in PCa remains controversial, and the association of HIF-1α expression with clinicopathological features is inconclusive due to the relatively small sample sizes in the included study. Meta-analysis can obtain a relatively precise and accurate estimation through incorporating all available evidences using statistical software.[7] Thus, we conducted a meta-analysis to assess the possible correlations between HIF-1α expression and clinicopathological significance in PCa, hoping to provide evidences for exploring molecular mechanisms and some novel potential biomarkers of PCa.

Methods

Ethics statement

No patient's privacy or clinical samples were involved in this study; hence, ethical approval was not required.

Search strategy

Literature resources including PubMed, Embase, Cochrane Library, CBM, and China National Knowledge Infrastructure (CNKI) were searched for eligible literatures, using the terms ("hypoxia-inducible factor or hypoxia-inducible factor-1 or hypoxia-inducible factor-1α or hypoxia-inducible factor-1A or HIF or HIF-1 or HIF-1α OR HIF-1A") and ("prostatic cancer" or "prostate cancer" or "prostatic carcinoma" or "prostate carcinoma" or "PCa"). Last search of current investigation was updated on August 21, 2017. Additionally, the publication language was only limited to English and Chinese. In case of omission, we identified the reference lists of relevant articles and review articles to seek for potentially relevant studies. We did not contact the corresponding authors if the relevant data were unavailable.

Inclusion and exclusion criteria

Studies which satisfied the following criteria were included in our study: 1) clinical study about the association of HIF-1α expression with PCa risk, 2) studies which contained relevant available data, and 3) PCa was histologically confirmed. Studies were excluded if they met the following criteria: 1) the available data about associations were absent, 2) similar or duplicate study (when the same or similar cohort was applied, after careful examination, the most complete information was included), 3) other type of article including review or abstract, and 4) studies involving cells lines or animal models.

Data extraction

Based on the inclusion and exclusion criteria, we extracted the relevant information from each eligible publication. Any disagreements were resolved by discussion between authors (Meng Huang and Hexi Du) or reviewed by a third author (Hong Che). The data on first author, publication year, study country, ethnicity, age, sample source, test method, control source, the HIF-1α cutoff value, T stage, Gleason score, TNM stage, lymph node, and/or bone metastasis status were extracted.

Statistical analyses

We explored the association of HIF-1α expression with PCa risk by applying Review Manager software (RevMan 5, The Cochrane Collaboration, Oxford, UK). Odds ratios (ORs) with 95% CIs were calculated for assessing the concrete relationships between HIF-1α expression and PCa risk. Meanwhile, the heterogeneity has been assessed via chi-square-based Q and I^2 tests across studies (no heterogeneity I^2<25%, moderate heterogeneity I^2=25%–50%, and extreme heterogeneity I^2>50%).[8] In case of extreme heterogeneity (I^2>50% or P<0.01 for Q test), we used random-effects (DerSimonian and Laird method) model.[9] Otherwise, fixed-effects (Mantel–Haenszel method) model was introduced.[10] One-way sensitivity analyses that individually removed publications in meta-analysis were conducted to assess the stability of the results. It mainly explored the impact of a specific study upon mixed OR. Funnel plots were performed to evaluate the publication bias. P-value <0.05 indicated that there was a bias of study.[11]

Results

Characteristics of eligible studies

As a result, a total of 14 studies consisting of 1,342 PCa samples satisfied the eligible studies (Figure 1).[12–25] Among them, six were written in English and eight were published in Chinese. The principal characteristics of the included studies are summarized in Table 1. Of these studies, four studies were

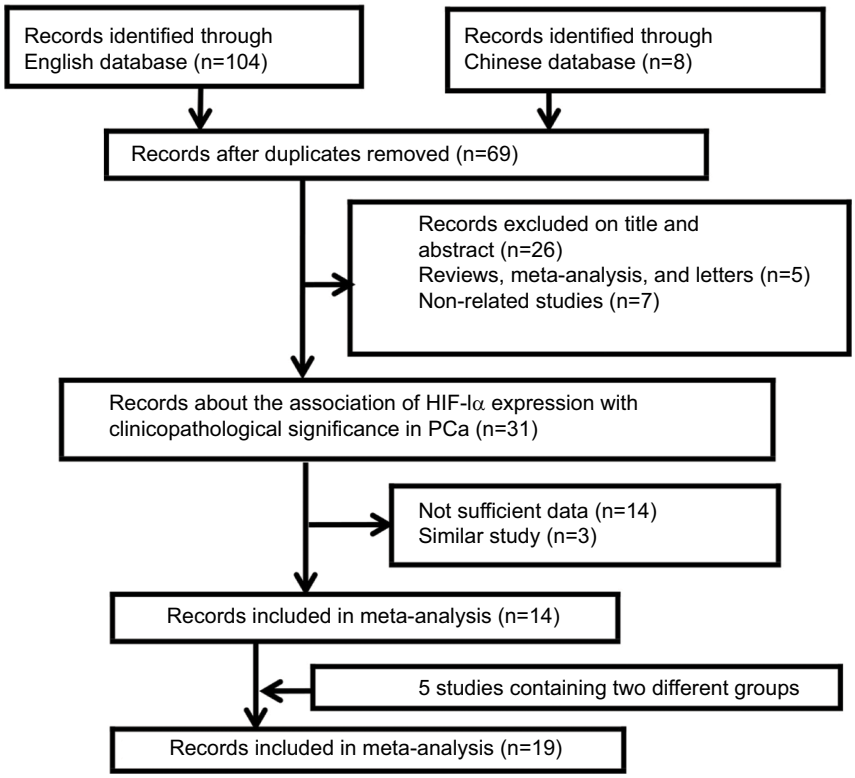

Figure 1 Flow diagram of the study selection process in the meta-analysis.
Abbreviations: HIF-1α, hypoxia-inducible factor-1α; PCa, prostate cancer.

involved in two control sources that originated from nonmalignant prostate tissues including normal prostate tissue (NP) and benign prostatic hyperplasia (BPH).[12,20,23,24] One study explored the association of HIF-1α expression with lymph node and bone metastasis, respectively.[18] We enrolled these independently into the meta-analysis, and this meta-analysis was eventually established based on 19 studies.

Quantitative synthesis

Seventeen studies were performed to detect the association between the paired groups. As shown in Figure 2, the rate of HIF-1α protein expression was significantly higher in PCa than in nonmalignant prostate tissues (OR=12.01, 95% CI: 8.22–17.55, $P<0.00001$). Additionally, different subgroups analyses regarding country, ethnicity, sample size, and control source were conducted. A similar result was found in different subgroups (Table 2).

In addition, eight, three, six, and two studies were extracted to explore the association of HIF-1α expression with Gleason score, T stage, the presence of metastasis, and TNM stage, respectively. Consequently, the association of HIF-1α expression with clinicopathological significance in PCa was detected. The expression of HIF-1α protein was significantly associated with Gleason score (Gleason ≥7 vs Gleason <7: OR=3.58, 95% CI: 2.35–5.46, $P<0.00001$) (Figure 3). The frequency of HIF-1α protein expression was significantly higher in T3–T4 stages than in T1–T2 stages of PCa (OR=3.70, 95% CI: 1.53–8.96, $P=0.004$) (Figure 4). The expression of HIF-1α protein was significantly associated with the presence of lymph node and/or bone metastasis of PCa (metastasis positive vs negative: OR=7.07, 95% CI: 4.08–12.25, $P<0.00001$) (Figure 5). The expression of HIF-1α protein was significantly associated with TNM stage (III+IV vs I+II: OR=6.85, 95% CI: 2.96–15.87, $P<0.001$).

Sensitivity analysis

Each study was deleted one at a time to assess the specific effect of the individual data on the pooled ORs, and one-way sensitivity analyses suggested that pooled results were relatively stable.

Publication bias evaluation

The funnel plots were largely symmetric (Figure 6), suggesting there were no publication biases in the meta-analysis of HIF-1α protein expression and clinicopathological features.

Table 1 The characteristics of included studies

Study	Year	Country	Ethnicity	Age (years), median (range)	Sample size	Test method	Sample source	Control source	Cutoff value
Wu et al[12]	2016	China	Asian	–	14	IHC	FFPE	NP/BPH	>10%
Bao et al[13]	2015	China	Asian	71 (59–82)	100	IHC	FFPE	BPH	>0%
Guo et al[14]	2014	China	Asian	68 (47–86)	128	IHC	FFPE	BPH	≥10%
Ranasinghe et al[15]	2013	Australia	White	66.6	100	IHC	FFPE	–	>0%
Li et al[16]	2013	China	Asian	67.4 (42–79)	124	IHC	FFPE	BPH	≥10%
Huang et al[17]	2012	China	Asian	70 (45–88)	144	IHC	FFPE	NP	>10%
Li et al[18]	2012	China	Asian	65 (55–76)	140	IHC	FFPE	BPH	>0%
Shi et al[19]	2007	China	Asian	68.7 (53–86)	172	IHC	FFPE	BPH	≥1%
Wang et al[20]	2006	China	Asian	72 (56–86)	64	IHC	FFPE	NP/BPH	≥5%
Lekas et al[21]	2006	Greece	White	67.8	170	IHC	FFPE	BPH	>0%
Ping et al[22]	2004	China	Asian	–	84	IHC	FFPE	NP	>0%
Zhong et al[23]	2004	USA	White	–	68	IHC	FFPE	NP/BPH	≥5%
Du et al[24]	2003	Japan	Asian	65 (57–71)	12	IHC	FFPE	NP/BPH	>10%
Zhong et al[25]	1999	USA	White	–	22	IHC	FFPE	NP	>1%

Abbreviations: BPH, benign prostatic hyperplasia; FFPE, formalin-fixed and paraffin-embedded; IHC, immunohistochemistry; NP, normal prostate tissue.

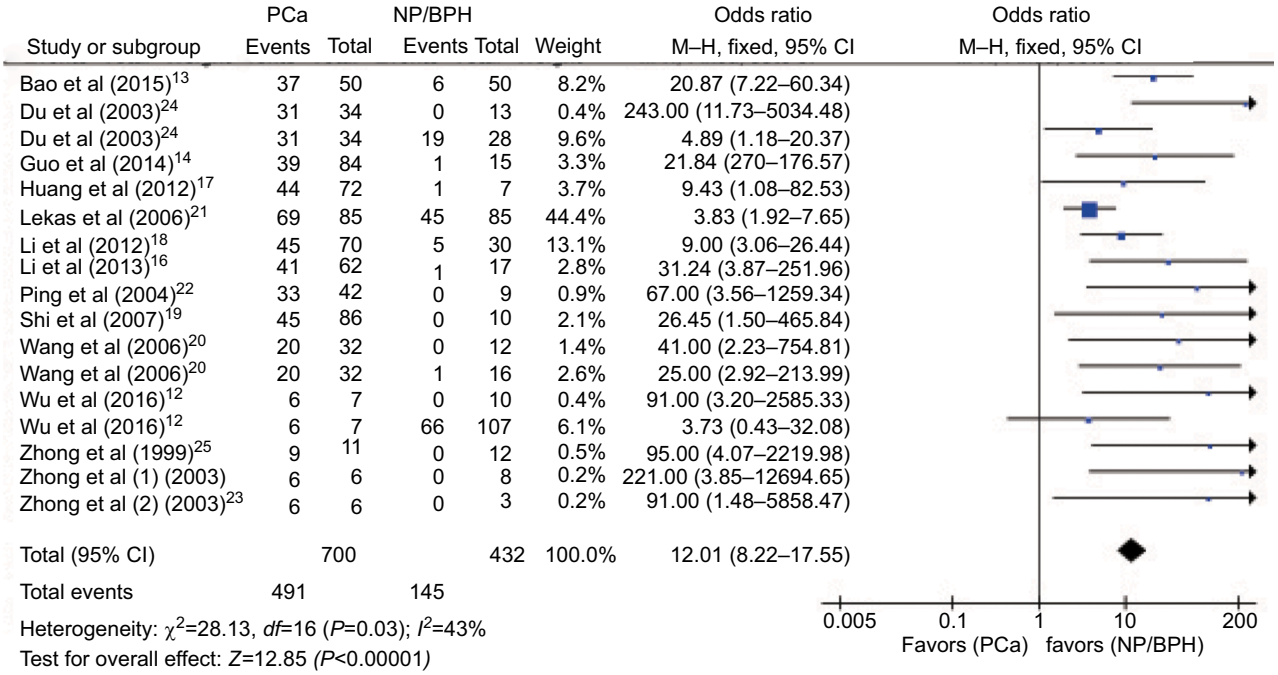

Figure 2 Forest plot for HIF-1α protein expression in PCa and nonmalignant prostate tissue.
Abbreviations: BPH, benign prostatic hyperplasia; HIF-1α, hypoxia-inducible factor-1α; NP, normal prostate tissue; PCa, prostate cancer.

Discussion

PCa is one of the most frequent genitourinary malignancies and has become a pivotal cause of male cancer-related deaths worldwide. Particularly, PCa patients often progress to a castration-resistant disease state after receiving initial hormonal therapy over 2–3 years.[26,27] Advanced metastatic PCa is accompanied with metastasis to bone, lung, and lymph node. Therefore, the morbidity of PCa has exhibited a sharp increase in recent years. However, the development and progression of PCa remains poorly understood. Therefore, it is particularly important to explore the underlying mechanisms associated with prostate malignant transformation, which efforts should hold great promise in the clinical therapy for PCa. It will also greatly benefit PCa patients who may be utilized in the prediction of PCa outcome and therapeutic efficacy.

Hypoxia is one of the most common conditions that drives development and progression of a variety of disease including cancer. Approximately 60% of the solid tumors exhibit less than 1% O_2 concentration in comparison with

Table 2 Stratified analysis of HIF-1α protein expression in PCa and nonmalignant prostate tissue

Categories	Subgroups	n	OR (95% CI)	*P*-value	I^2	P^h
All		17	12.01 (8.22–17.55)	0.000	0.431	0.030
Country	China	11	17.58 (10.12–30.55)	0.000	0.000	0.775
	Other	6	22.97 (4.82–109.39)	0.000	0.680	0.008
Ethnicity	Asian	13	16.89 (10.28–27.75)	0.000	0.024	0.422
	White	4	32.41 (2.76–379.86)	0.006	0.678	0.030
Sample size	≥100	7	9.13 (5.82–14.30)	0.000	0.451	0.091
	<100	10	22.00 (10.31–46.97)	0.000	0.321	0.151
Control source	NP	7	49.10 (15.99–150.83)	0.000	0.000	0.653
	BPH	10	8.98 (5.92–13.61)	0.000	0.370	0.112

Abbreviations: BPH, benign prostatic hyperplasia; HIF-1α, hypoxia-inducible factor-1α; NP, normal prostate tissue; OR, odds ratio; PCa, prostate cancer; P^h, *P*-value of heterogeneity test.

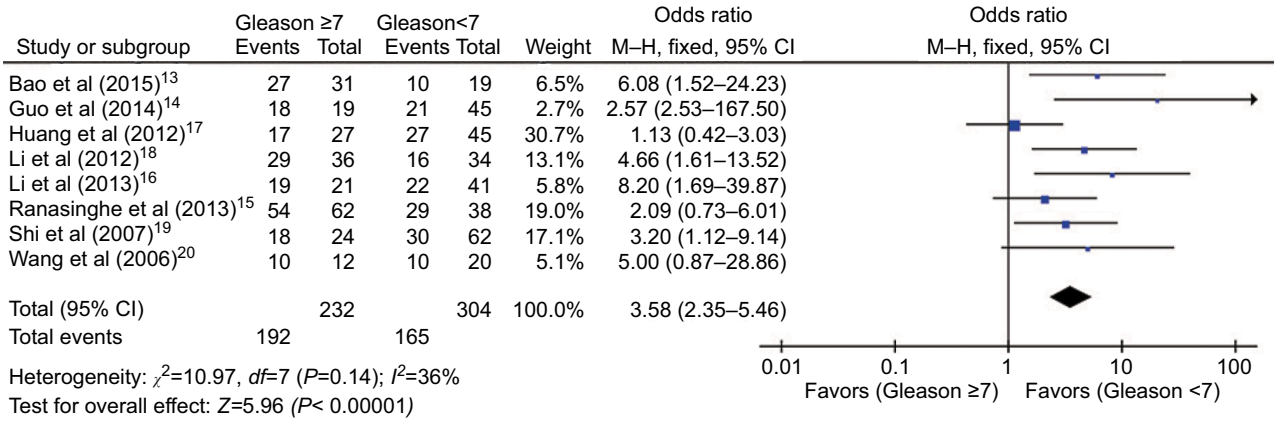

Figure 3 Forest plot for HIF-1α protein expression in different Gleason score of PCa.
Abbreviations: HIF-1α, hypoxia-inducible factor-1α; PCa, prostate cancer.

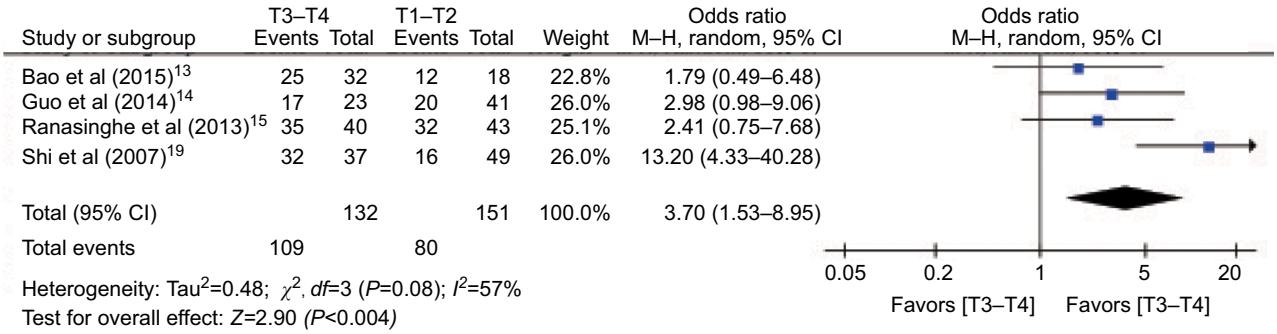

Figure 4 Forest plot for HIF-1α protein expression in different T stage of PCa.
Abbreviations: HIF-1α, hypoxia-inducible factor-1α; PCa, prostate cancer.

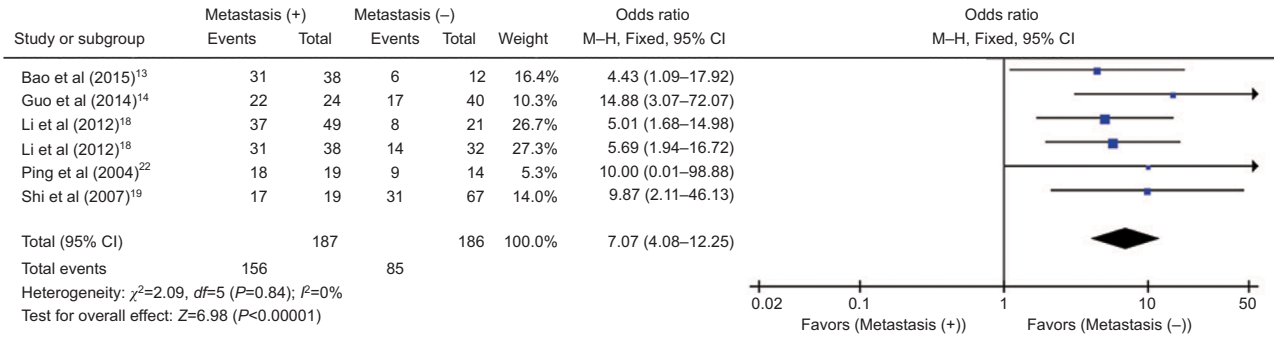

Figure 5 Forest plot for HIF-1α protein expresion in different metastasis status.
Abbreviations: HIF-1α, hypoxia-inducible factor-1α; PCa, prostate cancer.

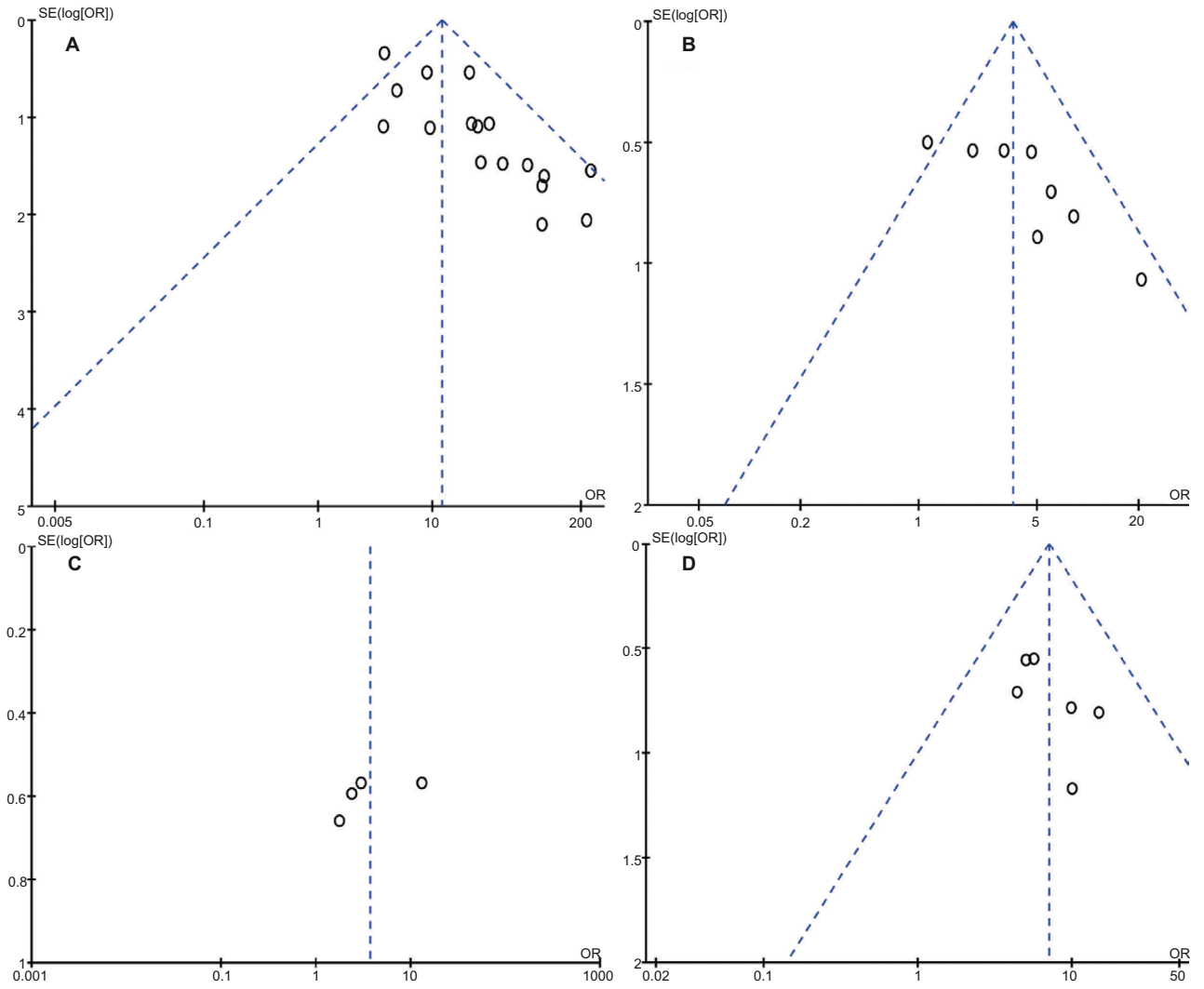

Figure 6 Funnel plots for publication bias.
Notes: (**A**) HIF-1α protein expression in PCa and nonmalignant prostate tissue; (**B**) HIF-1α protein expression in different Gleason score of PCa; (**C**) HIF-1α protein expression in different T stage of PCa; and (**D**) HIF-1α protein expression in different metastasis status.
Abbreviations: HIF-1α, hypoxia-inducible factor-1α; PCa, prostate cancer; OR, odds ratio.

the adjacent normal tissues. Transient or acute hypoxia occurs in tumors with inadequate blood perfusion, while chronic hypoxia occurs in tumors with limitation of oxygen diffusion.[28] The ability of cells to adapt to hypoxia is dependent on a family of HIFs, which induce expression of ~1.0%–1.5% specific target genes.[29] The targets of HIF-1 in the glycolytic pathway consist of glucose transporters 1 and 3 (GLUT1 and GLUT3) and enzymes such as hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA), which are also direct targets of the oncogenic MYC transcription factor.[30,31] In addition, HIF-1α also induces the secretion of interleukin-6, vascular endothelial growth factor (VEGF), and connective tissue growth factor (CTGF) in cancer-associated fibroblasts (CAFs), which are involved in cancer progression by making contributions to invasion, metastasis, and angiogenesis.[32,33] Recently, it has been addressed that HIF-1α could mediate tumor progression through shifting metabolism toward glycolysis, induction of angiogenesis, regulation of apoptosis, induction of migration eventually making cancer cells to escape hostile hypoxic environments, and resist to therapeutics.[34,35] A hallmark of the progression of PCa to advanced disease is the acquisition of androgen-independent growth.[36] It is well established that PCa under hypoxia often possessed aggressive tumor phenotypes, and even chemotherapy or radiotherapy resistance.[37] An effective therapy against PCa under hypoxia is desperately

needed. Recent studies presented the inhibitory effects of tocotrienol and its redox-silent analog which could inhibit the survival of PC3 stem-like cells under hypoxia, primarily through the suppression of HIF-1α signaling, and may subsequently establish the newly effective therapeutic approach for androgen-independent PCa.[38,39]

Recent advances have explored a central role of HIF-1α in PCa development and progression. The investigations that focused on the clinical correlation of HIF-1α with PCa progression were relatively rare and inconclusive, which could be explained by the relatively small sample sizes. Meta-analysis is a useful tool to obtain a relatively precise estimation. As a result, association of HIF-1α expression with PCa clinicopathological significance was explored in current meta-analysis to elucidate the role of HIF-1α in PCa progression. In conclusion, the rate of HIF-1α protein expression in PCa was significantly higher than in nonmalignant prostate tissues. The increased expression of HIF-1α protein was significantly associated with clinicopathological significance for patients suffering from PCa.

Limitations

First, published studies written only in English or Chinese might not provide sufficient evidences which may subsequently result in certain publication bias. Additionally, studies without a consistent HIF-1α cutoff value may influence the ultimate results. Meanwhile, the heterogeneity suggested that potential or undiscovered factors might be ignored. Despite limitations, a certain relationship of HIF-1α expression with PCa clinicopathological significance has been explored in current meta-analysis.

Conclusion

The high expression of HIF-1α protein was significantly associated with clinical diagnostic and clinicopathological significances for patients with PCa. Taken together, our findings have indicated that HIF-1α expression was a potentially diagnostic biomarker of PCa and could potentially be applied for noninvasively monitoring progression of PCa patients in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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