RESEARCH ARTICLE

Prognostic Value of Vascular Endothelial Growth Factor Expression in Patients with Prostate Cancer: a Systematic Review with Meta-analysis

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Abstract

Background: The vascular endothelial growth factor (VEGF) mediates vasculogenesis and angiogenesis through promoting endothelial cell growth, migration and mitosis, and has involvement in cancer pathogenesis, progression and metastasis. However, the prognostic value of VEGF in patients with prostate cancer remains controversial. Objectives: The aim of our study was to evaluate the prognostic value of VEGF in prostate cancer, and summarise the results of related research on VEGF. Methods: In accordance with an established search strategy, 11 studies with 1,529 patients were included in our meta-analysis. The correlation of VEGF-expression with overall survival and progression-free survival was evaluated by hazard ratio, either given or calculated. Results: The studies were categorized by introduction of the author, demographic data in each study, prostate cancer-relatived information, VEGF cut-off value, VEGF subtype, methods of hazard ratio (HR) estimation and its 95% confidence interval (CI). High VEGF-expression in prostate cancer is a poor prognostic factor with statistical significance for OS (HR=2.32, 95%CI: 1.40–3.24). However, high VEGF-expression showed no effect on poor PFS (HR=1.30, 95%CI: 0.88–1.72). Using Begg's, Egger's test and funnel plots, we confirmed lack of publication bias in our analysis. Conclusion: VEGF might be regarded as a prognostic maker for prostate cancer, as supported by our meta-analysis. To achieve a more definitive conclusion enabling the clinical use of VEGF in prostate cancer, we need more high-quality interventional original studies following agreed research approaches or standards.

Keywords: Vascular endothelial growth factor - prognosis - prostate cancer - meta-analysis

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Introduction

Prostate cancer is a remarkable public health issue in the whole world. The incidence of prostate cancer is just second to lung cancer worldwide in men. Data from The American Cancer Society shows that 240,890 men were diagnosed with the disease and 33,730 died of it in 2011 (Brawley, 2012). However, the etiology and pathogenesis of prostate cancer is poorly understood. Treatment strategies for these patients include active surveillance, radiation therapy and surgery (Zilinberg et al., 2012). As often effective, definitive surgery with radical retropubic prostatectomy has raised the 10 years biochemical recurrence rates to 32% (Roehl et al., 2004). Despite the combination of prostate-specific antigen (PSA) molecular forms and other biomarkers have improved prostate cancer detection substantially, the survival rate of patients is still not optimistic. Therefore, many studies dedicated to the exploration of sensitive and specific prognostic factors or models for prostate cancer.

Traditional clinical data such as Tumor-node-metastasis (TNM) system, gleason score and androgen receptor are associated with cancer-related survival(Nassif et al., 2009). However, these non-specific prognostic indicators failed to bring benefit for individual. In recent years, with the gradual deepening research of the tumor pathophysiology, many cancer-related molecules have been studied as prognostic factors for prostate cancer. SHARIAT summarized that vascular endothelial growth factor (VEGF), human glandular kallikrein 2 (hK2), urokinase plasminogen activator (uPA), transforming growth factor-beta 1 (TGF-β1) and interleukin-6 (IL-6) may become helpful prostate cancer diagnostic and prognostic biomarkers for prostate cancer (Shariat et al., 2008). Among them, the VEGF-angiogenesis-tumor pathway gains high-profile attention.

As is demonstrated by plenty of studies, angiogenesis plays a crucial role in cancer pathogenesis, progression and metastasis, while tumor can't grow rapidly or metastasize to distant organs without vessels (Sitohy et al., 2012). The core prosscess was involved in the interaction of vessel oxygenation-perfusion and tumor stimulating (Carmeliet et al., 2011). Although a series of moleculars such as platelet-derived growth factor are involved in angiogenesis, the VEGF family is the predominant proangiogenic factor and has been

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comprehensively studied (Pradeep et al., 2005). VEGF, consisited of VEGF-A,VEGF-B,VEGF-C and VEGF-D, mediates the vasculogenesis and angiogenesis through promoting endothelial cell growth, migration, mitosis (Bates et al., 1999). VEGF is nessary for the establishment of haematopoiesis (Kowanetz et al., 2006), while in pathological state, VEGF promote tumor angiogenesis and vascular permeability. All these evidences mean that VEGF plays a critical role in tumorigenesis and brings a prerequisite value for metastasis.

For prostate cancer, the VEGF targeted molecular therapy and VEGF prognostic value have been studied most comprehensive. VEGF targeted molecular therapy is a novel but hopeful idea for prostate cancer treatment. One recent trial about the typical VEGF targeted drug bevacizumab has shown improvements in prostate-related progression survival but little changes in overall survival (Kelly et al., 2012). Despite this, the biological activity of bevacizumab for prostate cancer is widely convinced. Meanwhile, the association between VEGF singal and prognosis in prostate cancer has been studied for a long time. Several clinical observations have concluded that high VEGF-expression is significantly related with poor overall survival (OS), progression-free survival (PFS) or disease-free survival (DFS), while others deny the relation between VEGF and prostate cancer. The hypothesis regarding VEGF as a predominant candidate of prostate cancer prognostic factor is inspiring, but till now, no consensus has been reached. Our meta-analysis based on the above contention is undertaken to evaluate the prognostic value of VEGF for prostate cancer.

Materials and Methods

Search strategy

We searched PUBMED, MEDLINE, EMBASE, Web of Science databases, Cochrane Library, with the search strategy: (prostate cancer or Pca) and (VEGF or vascular endothelial growth factor). Retrieve documents dating from the time of building the databases to September 2012. 1081 publications were retrieved. Two evaluators (Wong and Peng) screen the retrieved articles independently according to the following inclusion criteria. Any academic disagreement between evaluators was resolved through discussion.

Inclusion criteria

(1) Clinical trials investigating the association between VEGF and the prognosis of primary prostate cancer patients. (2) Tissue, plasma or urine VEGF were assessed by immunohistochemistry (IHC), ELISA or reverse transcription-polymerase chain action (RT-PCR). (3) The endpoint index was OS, PFS or DFS. (4) Log-Hazard ratio (HR) and its 95%CI were reported, or standard error and HR were given, or HR could be calculated by logrank X2, survival curve and P value. (5) The Statistical methods were performed by univariate or multivariate Kaplan-Meier analysis.

Exclusion criteria

(1) Duplicate data or repeat analysis (When studies were published by the same auther, journal with higher influence factor or the larger sample size would be included). (2) literature with the total number of cases less than 20. (3) Non-human research. We sought the full text of all available literatures that may agree with the inclusion criteria, and the final selection decision was made according to the full text reading.

Data extraction and analysis

The required data and extracted from eligible studies included: (1) introduction of the author. (2) demographic data in each study. (2) prostate cancer-relatived information including histology, clinical stage, gleason score, and the periexperimental treatment. (3) VEGF cut-off value, VEGF subtype, quantitative methods for VEGF. (4) methods of HR estimation, HR and its 95% confidence interval (CI).

In data analysis of every eligible study, we marked the results as '(+)' when VEGF predicted a poorer survival period (OS/PFS/DFS). Otherwise, results were marked as '(-)' when VEGF didn't predicted a poorer survival period. Survival analysis between VEGF positive group and VEGF negative group was considered significant when the P-value was <0.05 in two-tailed test (univariate analysis). For quantitative aggregation and simultaneous analysis of OS, DFS and PFS, we measured the VEGF effect using combining HR and its 95%CI which was first proposed by Peto (Yusuf et al., 1985). As a result, HR and its 95%CI extraction was our concentration. HR and its 95%CI was either directly extracted from original articles or calculated by survival information according to the method proposed by Parmar. Refering to Barraclough and Martin's articles(Martin et al., 2004; Barraclough et al., 2011), We regarded poorer survival for high VEGF-expression when reported HR>1. What's more, the impact of high VEGF expressin on prostate cancer related OS, PFS, and DFS was considered with statistical significance if the combined HR and its 95%CI didn't overlap 1. The heterogeneity analysis between studies was evaluated by Chi-square test and expressed by inconsistency index I^2. If the Chi-square test showed $I^2>35\%$, we regarded Statistical heterogeneity significant, and random effect (I-V heterogeneity) would be chosen. Otherwise fixed model woule be used when $I^2\leq35\%$. We also explored potential causes of heterogeneity with meta-regression analysis. Publication bias of this meta-analysis was evaluated. Begg's, Egger's Test and funnel plot was made. If studies appear to be missing in areas of low statistical significance, then the asymmetry is possibly due to publication bias. On the other hand, if missing in areas of high statistical significance, then publication bias is a less likely source of the funnel asymmetry. The analyses were all carried out by Stata version 12.0.

Results

Characteristics of selected studies

Our search strategy yielded 1081 titles and abstracts. After preliminary filter, 660 of them were irrelevant and 132 review articles on VEGF induction in prostate cancer. 289 of 1081 articles were reviewed in detail, and 12 of

Table 1. Main Characteristic of 11 Included Studies

Author (year)	Country	No	Specimen source	VEGF subtype	VEGF assay	Cutoff vaule	Survival analysis	HR estimation	HR and (95%CI) P	Prognostic value
Weber DC (2012)	Switzerland	4-13	Tissue	VEGF-A	IHC	Immunoreactive score	PFS	Given	0.97(0.39-2.42)	(-)
Wang Q (2011)	China	5-28	Tissue	VEGF	IHC	50%	OS	Given	4.18(2.17-8.05)	(+)
Mori R (2010)	USA	5-18	Tissue	VEGF-A VEGF-C	PCR	VEGF-A:4.25 VEGF-C:0.44	OS and DFS	Given	OS: 0.49 (0.27–0.86) PFS:0.73 (0.40–1.31)	(-) (-)
Svatek RS (2009)	USA	2-27	Plasma	VEGF	IHC	Not Clear	DFS	Given	1.00;p=0.86	(-)
Peyromaure M (2007)	France	2-10	Tissue	VEGF-A	IHC	Immunoreactive score	PFS	Given	1.38(0.99-1.94)	(+)
Green MM (2007)	UK	2-20	Tissue	VEGF	IHC	Immunoreactive score	OS	Survival	2.58(1.47-3.45)	(+)
Fukuda H (2007)	Japan	2-28	Tissue	VEGF	IHC	Immunoreactive score	PFS	Given	1.04(0.44-2.48)	(-)
Shariat SF (2004)	USA	8-3	Plasma	VEGF	ELISA	9.9pg/ml	PFS	Given	1.01(1.00-1.01)	(+)
West AF (2001)	UK	2-27	Tissue	VEGF	IHC	25%	OS	Survival	1.32(1.05-1.72)	(+)
George DJ (2001)	USA	7-16	Plasma	VEGF	ELISA	260pg/ml	OS	Given	2.42(1.29-4.54)	(+)
Bok RA (2001)	USA	4-10	Urine	VEGF	ELISA	28pg/ml	OS	Given	1.72(1.09-2.71)	(+)

*No, number of patients; OS, overall survival; PFS, progression free survival; IHC, immunohistochemistry; HR, hazard ratio; (+): positive; (-): negative

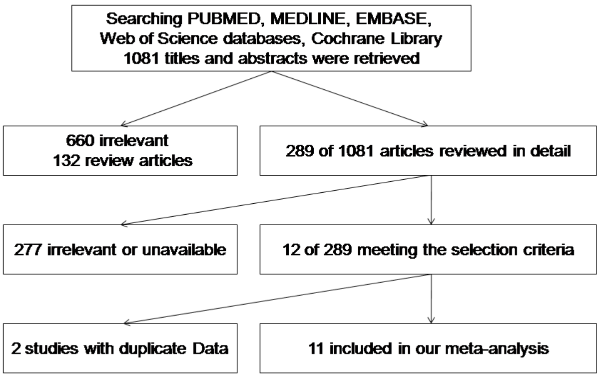

Figure 1. The Xow Diagram of Search Strategy

them meeting the selection criteria. Exluding the duplicate of two articals, at last, 11 (Bok et al., 2001; George et al., 2001; West et al., 2001; Shariat et al., 2004; Fukuda et al., 2007; Green et al., 2007; Peyromaure et al., 2007; Svatek et al., 2009; Mori et al., 2010; Wang et al., 2011; Weber et al., 2012) were included in our meta-analysis. The articles collection process is diagramed as (Figure 1).

A total of 1529 patients were included in this meta-analysis, ranging from 40 to 423 patients per study. The main characteristics of the 11 eligible articals were shown in (Table 1). Specimens of 7 studies were taken from cancer tissue, while 3 studies used plasma specimens. Specially in Bok's publication, urine VEGF level was detected as the major research target. A total of 7 studies dealt with immunohistochemistry (IHC) technique alone, while ELISA and PCR methods were in 3 and 1 studies respectively. The HR estimation of the 9 eligible studies for the meta-analysis was given by authors, while 2 were calculated using survival curves in accordance with the method proposed by Parmar. For each single study, 5 of 6 studies using OS identified high VEGF-expression as an indicator of poor prognosis (defined as '(+)' in Methods), while 2 of 6 studies using PFS identified (+). And the rest studies showed no statistically significant effect of high VEGF-expression on survival period (Table 1).

Meta-analysis

We first analyzed HR value of OS between VEGF positive and VEGF negative groups. 6 studies used OS as prognostic endpoint index, and were included in VEGF-OS analysis. Homogeneity could be accepted (Test of heterogeneity shown that I^2=94.6%), thus random model was chosen to clculate the summary HR. The HRs ranged

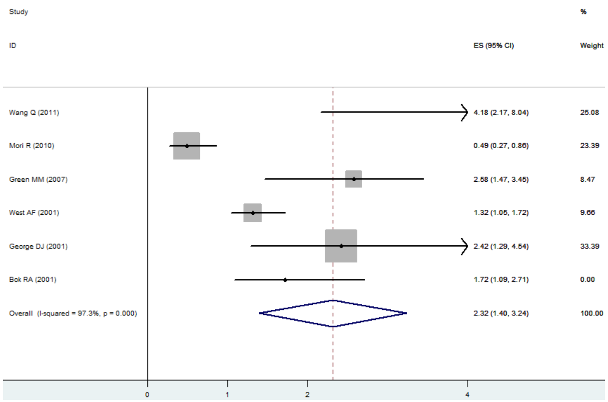

Figure 2. The Association Between Vascular Endothelial Growth Factor (VEGF) and Overall Survival of Prostate Cancer Stratified by HR Estimation. Meta-analysis of 6 eligible studies evaluating VEGF in overall survival. HR and its 95% CI is 2.32 (1.40–3.24)

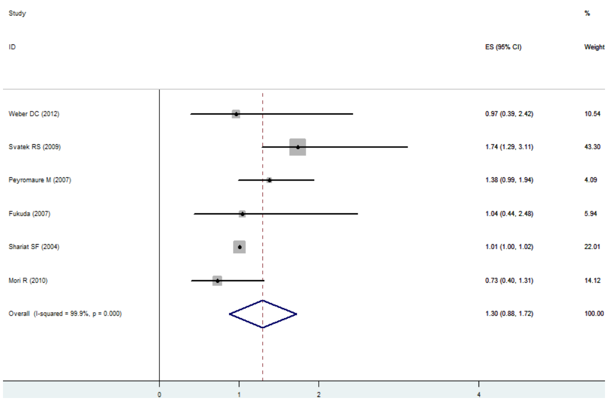

Figure 3. The Association Between Vascular Endothelial Growth Factor (VEGF) and Progression-Free Survival of Prostate Cancer Stratified by HR Estimation. Meta-analysis of 6 eligible studies evaluating VEGF in Progression-Free Survival. HR and its 95% CI is 1.30 (0.88-1.72)

from 0.49 to 4.18 among these 6 studies. In the pooled analysis, the summary HR associated with VEGF positive conditions in comparison with VEGF negative conditions was 2.32 (95%CI: 1.40–3.24, P=0.000), suggesting that high VEGF-expression was associated with poor OS (Figure 2).

Similarly, the VEGF-PFS analysis was undertaken. Among all studies, 6 enabled analysis of PFS between VEGF positive and VEGF negative groups. Test of heterogeneity shown that I^2=94.6%, thus we chosen random model to clculate the summary HR. The HRs of these 6 studies ranged from 0.73 to 1.74. In the pooled analysis, the summary HR was 1.30 (95%CI: 0.88–1.72, P = 0.000), with a 95%CI overlap 1, suggesting that high VEGF-expression has no effect on poor PFS (Figure 3).

Publication bias

At last, Begg's and Egger's test were performed in order to assess the publication bias of our meta-analysis. 6 studies evaluating OS of patients with prostate cancer yielded a Begg's and Egger's test which p=0.260 and p=0.243 respectively. Similarly, Begg's and Egger's test for 6 studies about PFS was calculated which p=1.000 and p=0.371. Meanwhile, funnel plot was undertaken which also indicated absence of publication bias. Considering all the above results, we regarded that there was no publication bias for the observed effect of our meta-analysis.

Discussion

As far as we know, this is the first study performed by meta-analysis to elucidate the prognostic value of VEGF for OS and PFS in patients with prostate cancer. The results of our meta-analysis show that the high VEGF-expression in prostate cancer is a poor prognostic factor with statistical significance for OS (HR=2.32, 95%CI: 1.40–3.24), which suggests a 2.32-fold higher OS for prostate patients with the positive detection of VEGF. This final result about OS is consistent with 5 of 6 included studies which are (+). However, High VEGF-oxpression shows no effect on poor PFS (HR=1.30, 95%CI: 0.88–1.72). Using Begg's, Egger's test and funnel plot, we regard an absent publication bias in our analysis. These results are somewhat encouraging, which may provide further basis for the development of new marker for prostate cancer prognosis and for the development of anti-angiogenic drugs for prostate cancer therapy.

But on the other hand, there are several limitations of our meta-analysis that might present a potential source of variability of the meta-analysis: (1) Different specimen from Tissue, plasma or urine for VEGF quantitation were merged in analysis. (2) We failed to perform meta-analysis concerning VEGF subtypes (VEGF-A, VEGF-B, VEGF-C and VEGF-D) alone. (3) Different authors used different methods (IHC, ELISA or PCR) identifying VEGF-expression. (4) No standard of cutoff value brings variability for VEGF positive and negative. (5) Methodology for extrapolating unreported HR might be a potential bias in HR estimates. If allowed, we should conduct subgroup analysis to eliminate the above heterogeneity. However, the limited number of eligible studies make it difficult overcoming all these troubles. Although our results suggested that High VEGF-oxpression is an available prognostic factor for OS in patients with prostate cancer, we could not identify the independent prognostic role of VEGF due to these limitations. As a result, it is nessary to regard these results smartly.

Considering hypothesis of tumor angiogenesis, tumor cells are thought to be able to recruit their own blood supply (Kaban et al., 2002). This process, which has been termed as 'angiogenic switch', is the basis of further expanding and metastasizing (Banerjee et al., 2007). We now recognize several molecules involved in the regulation of 'angiogenic switch' such as VEGF, basic fibroblast growth factor, platelet-derived endothelial cell growth factor and angiopoietin (Shijubo et al., 2003). As the advent of specific methods to detect VEGF, quantitative observation of tumor angiogenesis intensified, and plenty of different-designed studies tried to clarify the VEGF effect on malignancy. It is now widely accepted that VEGF is the most prominent cytokine in angiogenesis which is responsible for endothelial cell differentiation, migration, proliferation, tube formation, and vessel assembly (Fong et al., 1995). Once the VEGF effects, possibly including diagnosis, prognosis, prevention and treatment effects, would be explicitly understood, a series of tumor-related clinical problems might be acrossed.

With the deepening study of prostate cancer pathophysiology, the VEGF value in prostate cancer has attracted our eye-sight. Since 2000, a few previous preliminary studies have showed Plasma VEGF levels were higher in prostate cancer patients than those with negligible risk of prostate cancer (Duque et al., 1999; Caine et al., 2004). Additionally, the VEGF-expression and prostate cancer Gleason sum were closely linked in Kuniyasu's study using immunohistochemical staining and rapid colorimetric in situ hybridization (Kuniyasu et al., 2000). The prognostic significance of plasma VEGF Levels in patients with hormone-refractory prostate cancer was first proved by George in 2001 (George et al., 2001). Similarly, elevated levels of VEGF level either in plasma or urine were proved correlating with advanced stage, progression and poor patient outcomes in prostate cancer. The latest view indicates that VEGF single nucleotide polymorphisms (SNPs) predict the cancer susceptibility, and relate to interindividual variation in anti-VEGF therapeutic response of prostate cancers (Jain et al., 2009). However, all these exciting reports on this topic provide conflicting evidence, and so far none of these reports have brought great change in clinical practice. But new therapeutic drugs against VEGF target have shown the potential to be brought into clinical treatment for prostate cancer. Recently, several randomized Phase 2 studies assessing docetaxel in patients with metastatic hormone-refractory prostate carcinoma provided some very encouraging benefit for prostate cancer patients, although either failing or being too immature to show some benefit in the primary time-to-event endpoints (Pili et al., 2010). The concept of vascular targeting effect for prostate cancer is further supported by another Phase 2 study suggesting efficacy of bevacizumab when added to docetaxel (Ross et al., 2012). Further studies of Phase 3 trials or newer agents targeting the VEGF pathway, either alone or in combination, are underway.

In conclusion, VEGF might be regarded as a prognostic maker for prostate cancer, especially for OS, which was supported by our meta-analysis. To achieve a more definitive conclusion enabling the clinical use of VEGF in prostate cancer, we need more high-quailty interventional original studies following agreed research approach or standard.

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