

# VEGF is associated with the poor survival of patients with prostate cancer: a meta-analysis

Ping Zhan<sup>1,2</sup>, Ya-Nan Ji<sup>3</sup>, Li-Ke Yu<sup>1</sup>

<sup>1</sup>First Department of Respiratory Medicine, Nanjing Chest Hospital, Nanjing 210029, China; <sup>2</sup>The Collaborative Research (CORE) Group, Sydney, Australia; <sup>3</sup>Jiangsu Province Hospital of Traditional Chinese Medicine, Nanjing 210029, China

Correspondence to: Li-Ke Yu. First Department of Respiratory Medicine, Nanjing Chest Hospital, 215 Guangzhou Road, Nanjing 210029, China. Email: yulike\_nanjing@163.com.

**Background:** Vascular endothelial growth factor (VEGF) is considered as a prime mediator of angiogenesis, and has been implicated in carcinogenesis and metastasis. Various studies examined the relationship between VEGF overexpression with the clinical outcome in patients with prostate cancer, but yielded conflicting results.

**Methods:** Electronic databases updated to July 2013 were searched to find relevant studies. A meta-analysis was conducted with eligible studies which quantitatively evaluated the relationship between VEGF status and survival of patients with prostate cancer. Survival data were aggregated and quantitatively analyzed.

**Results:** We performed a meta-analysis of 9 studies that evaluated the correlation between VEGF overexpression and survival in patients with prostate cancer. Combined hazard ratios suggested VEGF overexpression had an unfavorable impact on overall survival (OS) [hazard ratio (HR) =1.54, 95% CI (confidence interval): 1.25-1.83], but not disease free survival (DFS) (HR=1.23, 95% CI: 0.99-1.47) in patients with prostate cancer. No significant heterogeneity was observed among all studies.

**Conclusions:** VEGF overexpression indicates a poor prognosis for patients with prostate cancer.

**Keywords:** Vascular endothelial growth factor (VEGF); prostate cancer; prognosis; meta-analysis



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## Introduction

Prostate cancer is the most commonly diagnosed internal malignancy among males and is the second leading cause of cancer-related deaths in the US (1). Recently, the number of prostate cancer patients has increased significantly in China. Surgery and radiation therapy are effective for localized disease (2). However, no effective therapeutic strategy is yet available for recurrent or metastatic disease from failed surgery, radiation, chemotherapy, or hormonal therapy. With these limitations, more sensitive and more specific biomarkers are needed to provide valuable information for the diagnosis and identification of prostate cancer development and progression. The main prognostic factors are clinicopathological characteristics of the disease,

including tumor size, stage, and grade. However, the prognostic factors do not fully predict individual clinical outcome. There is the need for better markers to identify patients with poor prognosis at the time of diagnosis. Researches have focused on the potential role of new biological factors involved in the carcinogenic process as prognostic markers in patients with prostate cancer.

Angiogenesis, the formation of new blood vessels from existing vasculature, is an important process in many malignancies including prostate cancer. It is the result of an intricate balance between pro-angiogenic and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) (also referred to as VEGF-A, vascular permeability factor) is a critical pro-angiogenic factor in cancer. The role of VEGF in the regulation of angiogenesis is the object of

intense investigation for more than a decade. The VEGF family is composed of several subtypes, including VEGF-A, -B, -C and -D which exist as numerous splice variant isoforms (3,4). Many anti-angiogenic compounds are being developed, most of which target VEGF and/or its receptors. It is necessary to establish whether VEGF expression is a prognostic marker in prostate cancer.

Many studies have evaluated whether VEGF overexpression may be a prognostic factor for survival in patients with prostate cancer. However, the results of the studies are inconclusive and no consensus has been reached. It is unknown whether differences in these investigations have been mostly due to their limited sample size or genuine heterogeneity. Thus, we conducted a meta-analysis of all available studies relating VEGF overexpression with the clinical outcome in patients with prostate cancer.

## Materials and methods

### Search strategy and study selection

The electronic databases PubMed and CNKI (China National Knowledge Infrastructure) were searched for studies to include in the present meta-analysis. An upper date limit of July 1, 2013 was applied; we used no lower date limit. Searches included the terms “prostate cancer or Pca”, “VEGF”, “vascular endothelial growth factor”, and “prognosis”. We also reviewed the Cochrane Library for relevant articles. The references reported in the identified studies were also used to complete the search.

Studies eligible for inclusion in this meta-analysis met the following criteria: (I) measure VEGF expression in the primary prostate cancer with IHC (immunohistochemistry) or RT-PCR/ELISA (reverse transcription-polymerase chain reaction/enzyme linked immunosorbent assay); (II) provide information on survival [i.e., disease free survival (DFS) and/or overall survival (OS), studies investigating response rates only were excluded] and (III) When the same author reported results obtained from the same patient population in more than one publication, only the most recent report, or the most complete one, was included in the analysis. Two reviewers (P.Z. and Y.J.) independently determined study eligibility. Disagreements were resolved by consensus.

### Data extraction and quality assessment

Data retrieved from the reports included author, publication year, patient source, test method, definition of positivity

(cut-off value), VEGF positive ratio and survival data (Table 1). If data from any of the above categories were not reported in the primary study, items were treated as “not applicable”. We did not contact the author of the primary study to request the information. We did not use prespecified quality-related inclusion or exclusion criteria and did not weigh each study by a quality score, because the quality score has not received general agreement for use in a meta-analysis, especially observational studies (5). The data extraction and quality assessment were reported in previous meta-analysis (6-9).

### Statistical methods

Included studies were divided into two groups for analysis: those with data regarding OS and those regarding DFS. For the quantitative aggregation of the survival results, we measured the impact of VEGF status on survival by HR between the two survival distributions. HRs and 95% confidence intervals (CIs) were used to combine as the effective value. If the HRs and their 95% CIs were given explicitly in the articles, we used crude ones. When these variables were not given explicitly, they were calculated from the available numerical data using methods reported by Parmar *et al.* (10).

Heterogeneity of the individual HRs was calculated with  $\chi^2$  tests according to Peto's method (11). Heterogeneity test with inconsistency index ( $I^2$ ) statistic and  $Q$  statistic was performed. If HRs were found to have fine homogeneity, a fixed effect model was used for secondary analysis; if not, a random-effect model was used. DerSimonian-Laird random effects analysis (12) was used to estimate the effect of serum VEGF overexpression on survival. By convention, an observed HR >1 implies worse survival for the group with serum VEGF overexpression. The impact of VEGF on survival was considered to be statistically significant if the 95% confidence interval (CI) did not overlap with 1. Horizontal lines represent 95% CIs. Each box represents the HR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI represented by its width. The unbroken vertical line is set at the null value (HR=1.0).

Evidence of publication bias was sought using the methods of Egger *et al.* (13) and of Begg *et al.* (14). Intercept significance was determined by the  $t$  test suggested by Egger ( $P < 0.05$  was considered representative of statistically significant publication bias). All of the calculations were

**Table 1** Main characteristics and results of the eligible studies

First author-year	Patients source	N pts	Method	Cut-off	Positive (%)	HR estimation	HR (95% CI)
Weber-2012	Switzerland	103	IHC	Immunoreactive score	23.3	HR	PFS 0.97 (0.39-2.42)
Wang-2011	China	148	IHC	50%	22.9	HR	OS 4.18 (2.17-8.05)
Peyromaure-2007	France	40	IHC	Immunoreactive score	47	HR	PFS 1.38 (0.99-1.94)
Green-2007	UK	50	IHC	Immunoreactive score	56	Surv curve	OS 2.58 (1.47-3.45)
Fukuda-2007	Japan	270	IHC	Immunoreactive score	NA	HR	PFS 1.04 (0.44-2.48)
Shariat-2004	USA	423	ELISA	9.9 pg/mL	NA	HR	PFS 1.21 (1.00-1.61)
West-2001	UK	67	IHC	25%	53	Surv curve	OS 1.32 (1.05-1.72)
George-2001	USA	390	ELISA	260 pg/mL	50	HR	OS 2.42 (1.29-4.54)
Bok-2001	USA	100	ELISA	28 pg/mL	50	HR	OS 1.72 (1.09-2.71)

Abbreviations: VEGF, vascular endothelial growth factor; IHC, immunohistochemistry; ELISA, enzyme linked immunosorbent assay; NA, not applicable; HR, hazard ratio; CI, confidence interval; OS, Overall survival; DFS, Disease-free survival.

**Table 2** Meta-analysis: HR value of OS and DFS in prostate cancer

	Nb	Random effects HR (95% CI)	$\chi^2$ heterogeneity test (P)
Overall for OS	5	1.54 (1.25-1.83)	0.036
Overall for DFS	4	1.23 (0.99-1.47)	0.853

Abbreviations: HR, hazard ratio; Nb, number of studies; OS, Overall survival; DFS, Disease-free survival.

performed by STATA version 11.0 (Stata Corporation, College Station, TX).

## Results

### Study selection and characteristics

Nine studies (15-23) published between 2001 and 2012 were eligible for this meta-analysis. All reported the prognostic value of VEGF status for survival in prostate cancer patients. The total number of patients included was 1,591, ranging from 40 to 423 patients per study (median 177). The major characteristics of the 9 eligible publications are reported in *Table 1*. The studies were conducted in 6 countries (China, Japan, UK, France, Switzerland and USA).

All of the studies reported the prognostic value of VEGF status for survival in patients with prostate cancer. Of the 9 studies, 7 directly reported HRs (multivariate analysis), while the other 2 studies provided survival curves. Among them, the proportion of patients exhibiting serum high VEGF expression in individual studies ranged from 22.9% to 56%. Estimation using survival curves were segregated according to either OS or DFS. A HR on DFS and OS could be extracted for 4 publications and 5 publications of studies, respectively. Six of the 9 studies identified high

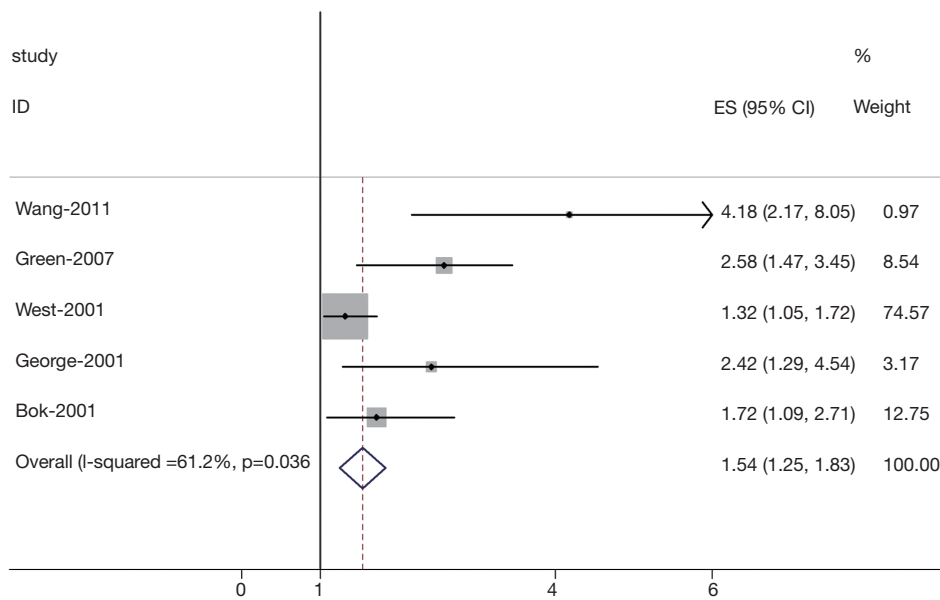
VEGF expression as an indicator of poor prognosis, and the other 3 studies showed no statistically significant impact of high VEGF expression on survival.

### Meta-analysis

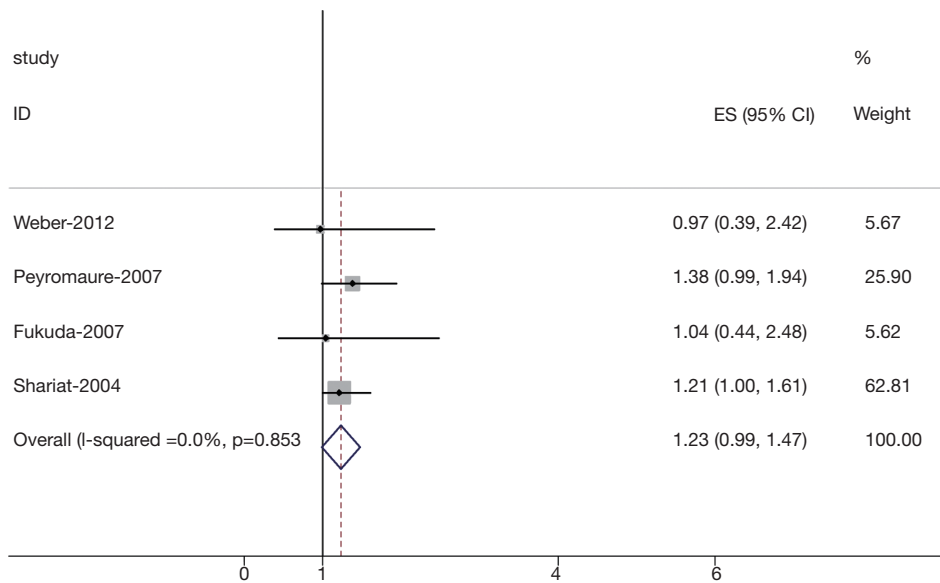
The results of the meta-analysis were shown in *Table 2* and *Figures 1,2*. Overall, the combined HR for all 5 eligible studies evaluating high VEGF status on OS was 1.54 (95% CI: 1.25-1.83), suggesting that high VEGF overexpression was an indicator of poor prognosis for prostate cancer. However, significant heterogeneity was observed among the studies ( $Q=9.39$ ,  $I^2=61.2\%$ ,  $P=0.036$ ). In addition, for DFS analysis, no statistically significant effect of high VEGF level (HR=1.23, 95% CI: 0.99-1.47) in patients with prostate cancer was also observed. ( $Q=4.38$ ,  $I^2=0.0\%$ ,  $P=0.853$ ).

### Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias in the literature. All 5 eligible studies investigating VEGF expression on OS yielded a Begg's test score of  $P=0.142$  and an Egger's test score of  $P=0.054$ , meanwhile according to the funnel plot (*Figure 3*),



**Figure 1** Meta-analysis (Forest plot) of the 5 evaluable studies assessing VEGF in prostate cancer for overall survival.



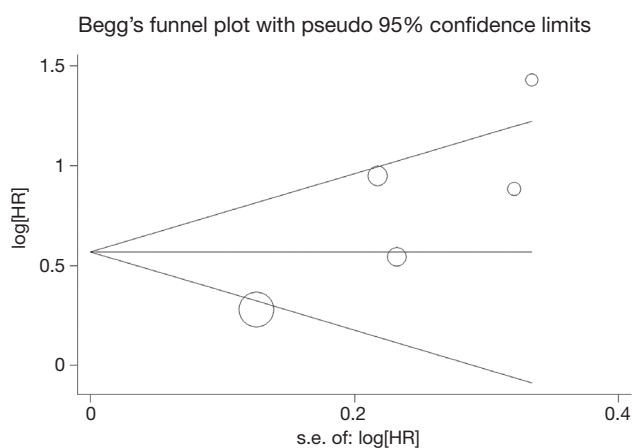
**Figure 2** Meta-analysis (Forest plot) of the 4 evaluable studies assessing VEGF in prostate cancer for disease-free survival.

the absence of publication bias was found. Moreover, the absence of publication biases were found for investigating VEGF expression on DFS (a Begg's test score of  $P=0.174$  and an Egger's test score of  $P=0.452$ ) (Figure 4).

## Discussion

Members of the VEGF family promote two very important

processes *in vivo*, angiogenesis and lymphangiogenesis, which involve growth of new blood and lymphatic vessels from pre-existing vasculature, respectively. VEGF-A exists as a homodimer or can heterodimerize with either VEGF-B or non-VEGF factors such as PlGF (placenta growth factor) (24-26). VEGF-A and VEGF-B promote vascular angiogenesis primarily through activation of vascular endothelial cell associated VEGFR-1 (Flt1) and VEGFR-2

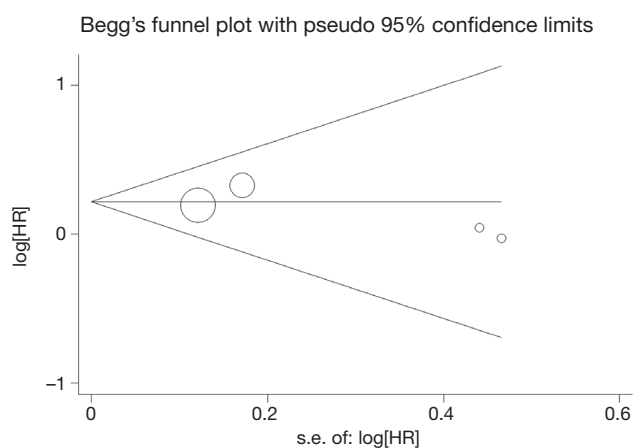


**Figure 3** Funnel plot of the 5 evaluable studies assessing VEGF in prostate cancer for overall survival.

(Flk1/KDR). On the other hand, VEGF-C and VEGF-D which are ligands for VEGFR-2 and VEGFR-3, promote angiogenesis and lymphangiogenesis (27,28).

The present meta-analysis has combined 9 publications including 1,591 patients to yield statistics, indicating a statistically significant role of VEGF on overall survival, but not on disease-free survival in prostate cancer. Our data were consistent with the results of a previous meta-analysis (29) published in 2012 that showed an association between VEGF overexpression and poor survival of patients with prostate cancer. We have improved upon that previous meta-analysis by including more recent related studies and by generally using a more comprehensive search strategy. Screening, study selection and quality assessment were performed independently and reproducibly by two reviewers. We also explored heterogeneity and potential publication bias in accordance with published guidelines.

There were several meta-analyses studying the prognostic value of VEGF in other cancer types, such as head and neck squamous cancer (30), lung cancer (31), colon cancer (32), gastric cancer (33), and hepatocellular carcinoma (34). Association of VEGF overexpression with poor outcomes provides a rationale for anti-angiogenics use in the treatment of cancer. VEGF has become a leading therapeutic target for the treatment of cancer. Potentially therapeutic strategies to inhibit VEGF pathway include monoclonal antibodies directed against VEGF, tyrosine kinase inhibitors (TKIs), and antisense strategies (35). Bevacizumab (Avastin) is a humanized monoclonal antibody directed against VEGF (36). It binds to all isoforms of VEGF-A, thus blocking its binding to VEGFR, but it does



**Figure 4** Funnel plot of the 4 evaluable studies assessing VEGF in prostate cancer for disease-free survival.

not bind to other VEGF molecules, such as VEGF-B or VEGF-C.

The heterogeneity issue was complicated in the systematic review and meta-analysis was. We found no significant heterogeneity among all studies included and subgroup analysis. Another potential source of bias is related to the method of HR and 95% CI extrapolation. If these statistics were not reported by the authors, we calculated them from the data available in the article. If this was not possible, we extrapolated them from the survival curves, necessarily making assumptions about the censoring process. Data for multivariate survival analysis reported in the article were included in the present systematic review and meta-analysis; if these data were not available, data calculated from survival curves by univariate analysis were included. These results should be confirmed by an adequately designed prospective study. Furthermore, the exact value of VEGF overexpression status needs to be determined by appropriate multivariate analysis.

Publication bias (37) is a major concern for all forms of meta-analysis; positive results tend to be accepted by journals, while negative results are often rejected or not even submitted. The present analysis does not support publication bias; the obtained summary statistics likely approximate the actual average. However, it should be noted that our meta-analysis could not completely exclude biases. For example, the study was restricted to papers published in English and Chinese, which probably introduced bias.

In conclusion, our meta-analysis estimated the association between prognostic significance of VEGF overexpression and patients with prostate cancer. As determined in our



meta-analysis, we concluded that VEGF overexpression was associated with poor overall survival, but not disease-free survival, and there is no significant heterogeneity among all studies. To strengthen our findings, well-designed prospective studies with better standardized assessment of prognostic markers should help to explore the relation between VEGF overexpression and the outcome of patients with prostate cancer.

### Acknowledgements

None.

### Footnote

*Conflict of Interest:* The authors have no conflicts of interest to declare.

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