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ORIGINAL ARTICLE

Prognostic value of vascular endothelial growth factor expression in women with ovarian cancer: A meta-analysis

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Summary

Purpose: *Vascular endothelial growth factor (VEGF) is a signal protein which is responsible for angiogenesis through promoting migration and mitosis of endothelial cells. The aim of our study was to investigate the existing evidence about whether VEGF is associated with prognosis of ovarian cancer.*

Methods: *We conducted a meta-analysis of 19 studies (n=1352 patients) that focused on the correlation of VEGF expression with overall survival (OS), disease-free survival (DFS) and progression-free survival (PFS). Data were synthesized with random or fixed effect hazard ratios (HR). The studies were categorized by author/year, number of patients, FIGO stage, histology, cutoff value for VEGF positivity, methods of detection, types of survival analysis, methods of HR estimation, and HR and their 95% confidence interval (CI).*

Results: *Combined HR suggested that VEGF positivity was associated with poor OS, but not with DFS and PFS. The HR and 95% CI were: HR=1.66, 1.22-2.00 in OS; 1.85, 0.56-3.15 in DFS; and 1.23, 0.62-1.84 in PFS. Subgroup analysis showed that VEGF was irrelevant with OS in specimens from tissues (HR=1.32, 95% CI: 0.82-1.82) with 95% CI overlapping 1, but could indicate poor prognosis in specimens from serum (HR=2.07, 95% CI: 1.45-2.70)*

Conclusion: *The OS of the VEGF-positive group with ovarian cancer was significantly poorer than the VEGF-negative group. However, VEGF positivity seems not to be connected with DFS and PFS.*

Key words: *meta-analysis, ovarian cancer, overall survival, vascular endothelial growth factor*

Introduction

Ovarian cancer is the most dominant cause of mortality of the female reproductive system diseases and accounts for about 3% of cancer cases in women according to American Cancer Society [1]. Early stage is difficult to diagnose due to very vague pelvic or abdominal symptoms. The prognosis of ovarian cancer is not optimistic, with OS rates for advanced-stage disease being less than 30% [2]. Prognostic factors such as histological type, FIGO stage and grade of differentiation are associated with survival; these parameters reflect the pathophysiologic features of the tumor, but lack sufficient predictive power for individual prognosis. Recent studies have shown that microvessel density (MVD), cyclooxygenase-2 (COX-2), E-cadherin, P53 autoantibodies and VEGF are prognostic biomarkers in ovarian cancer. Among these biomarkers VEGF has been studied most comprehensively.

VEGF is a signal protein, responsible for angiogenesis by promoting migration and mitosis of endothelial cells. It is synthesized and secreted by various solid tumors, such as lung and colorectal cancer [3,4]. Normal VEGF expression also plays an important role in physiological ovarian function, and insufficient expression of VEGF may lead to disorders including anovulation and miscarriage [4]. Tumor cells are usually hypoxic and nutrient-deprived despite abundant vasculature [5]. Angiogenesis mediated by VEGF provides

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more blood supply to tumors. Angiogenesis, the formation of new vasculature consists of precisely regulated processes that provide more blood supply to the tumor and accelerate metastasis and invasion in ovarian cancer and other malignancies [6]. VEGF-C also plays an important role in lymphangiogenesis which mediates lymphatic metastasis. Beyond that, VEGF probably increases vascular permeability and leakage, which allow ovarian tumor cells seeding to the abdominal or pelvic cavity [7]. The combination of anti-VEGF therapy with conventional chemotherapy has been proved to improve survival compared with chemotherapy alone. Accordingly, it is possible that VEGF could accurately predict patient prognosis. It is therefore necessary to establish whether VEGF has value as prognostic indicator.

Many observational studies have concluded that VEGF overexpression is significantly related with poor survival. However, the results of other studies were inconclusive. To determine whether the angiogenic molecule VEGF is a prognostic indicator for ovarian cancer, we undertook a meta-analysis of all available studies with inconclusive results. The aim of our study was to verify the hypothesis that VEGF positivity in serum or tissue would affect OS, PFS and DFS in patients with ovarian cancer.

Methods

Search strategy

Electronic databases such as Medline, EMBASE and Sciencedirect were searched to identify all related articles about VEGF and ovarian cancer. Studies published between 1995 and March 1st, 2011, were examined. MESH words were designed as 'ovarian neoplasm' and 'vascular endothelial growth factor receptor. At the same time, we screened references from eligible articles as well as reviews and editorials.

Selection criteria

We selected all articles according to the following criteria: (1) VEGF was assessed by immunohistochemistry (IHC), serum (ELISA) or reverse transcription-polymerase chain action (RT-PCR); (2) the endpoint of investigation was OS, PFS or DFS; (3) HR and their 95% CI were reported, or standard error (S.E) and HR were given, or log rank x^2, survival curve and p value (numerical value) were given; (4) univariate but not multivariate analysis was performed; (5) all observed patients ought to be diagnosed as primary ovarian cancer. The following study categories were excluded: (1) in case of the same author or the same medical center with duplicate data, the single most informative study was chosen; (2) follow-up was less than 1 year; (3) non-original articles or borderline ovarian neoplasm; (4) study population was non-human which included SKOV3 or OVCAR3 ovarian cancer cell lines or animals such as rabbit, mouse, pig, and sheep.

Two authors independently evaluated the abstracts of all studies (n=760) to decide whether full-text should be browsed further. Disagreement was resolved by discussing quality assessment and data collection among us. We examined 151 full-texts and pick up information with included and excluded criteria.

Data extraction and analysis

Data were extracted from eligible studies and included author/year, number of patients, FIGO stage, histology, cutoff value for VEGF positivity, methods of detection, types of survival analysis, methods of HR estimation, and HR and their 95% CI.

HR is a definition of both time to event and censoring, and it is recommended for prognostic meta-analyses. For some studies which didn't report HR and 95% CI of univariate analysis directly, we needed to obtain data from survival curves. Survival curve could be read by Engauge Digitizer (version 4.1) which was downloaded from http://sourceforge.net. All the calculation methods were derived from PARMAR [8].

1. For the situation, HR and p value were provided by the original study, but log rank x^2 and 95% CI of HR were missing. The first step was to calculate log rank x^2 with excel using Function "CHIDIST", deg_freedom was "1". The next step was se var((ln(HRi)). And the last step, RevMan 5.1, was used to obtain HR and 95% CI.

2. For the situation, the survival curve and p value were provided by the original study, but HR and 95% CI were missing. HR could be obtained as follows: HR: Ori=observed number of events in the VEGF negative group; Oci= observed number of events in the VEGF positive group; Eri=log rank expected number of events in the VEGF positive group; Eci=log rank expected number of events in the VEGF negative group. Then, HR and its 95% CI could be calculated in accordance with the above method.

3. For the situation, the survival curve and 95% CI of HR were provided by the original study, but HR and log rank x^2 were missing. HR was estimated by se var((ln(HRi)); subsequently, RevMan 5.1 was used to obtain HR and its 95% CI.

For every single study, the survival analysis between VEGF positive and negative groups was considered significant when the p value was <0.05 in two-tailed test (univariate analysis). We marked the results as 'positive' when VEGF positivity predicted poorer OS, DFS, and PFS; otherwise, the results were marked as 'negative'. For the sake of quantitative aggregation of OS, DFS and PFS, we measured the VEGF expression on survival by combining HR and their 95% CI, which was first published by Yusuf et al. [9].

Between-study heterogeneity was assessed by x^2 test and expressed by the I^2 index. When I2>35%, we considered it as heterogeneity, and random effect (I-V heterogeneity) was used. When $I^2 \leq 35\%$, fixed effect was used. We considered a worse survival when HR>1 for VEGF positive group, according to Martin et al. and Barraclough et al. reports [10,11]. This impact of VEGF positive expression on OS, DFS, and PFS was considered statistically significant if the combined HR and its 95% CI didn't overlap 1.

Begg's test, Egger's test and contour-enhanced funnel plot (carried out by STATA 11.0) were used to identify the possibility of publication bias. We considered probable significant publication bias when $p< 0.05$. Egger's test was designed for the Y intercept=0 from a linear regression of normalized effect estimate against precision. Begg's test was focused on testing the interdependence of variance and effect size based on Kendall's method. Furthermore, contour-enhanced funnel plot has the function to indicate regions of statistical significance and contour overlay helped interpret funnel plot and identify whether the cause of asymmetry was due to factors such as variable study quality.

Results

Study characteristics

A total of 760 studies were screened in our systemic analysis. The search strategy yielded 760 titles and abstracts, of which 620 were irrelevant and 9 review articles on VEGF expression of ovarian cancer; following deduplication, two reviewers completed this work independently. Subsequently, 131 full-text studies were read for details, and 25 studies were included in our meta-analysis. Finally, 19 studies (n=1352 patients) [12-30] were included and their main features are summarized and shown in Table 1. Of the 19 ovarian cancer studies, 15 dealt with OS, 7 with DFS, and 5 with PFS. Six studies were excluded, because it was not possible to calculate HR value from known information.

A total of 10 studies dealt with IHC technique alone, while ELISA and other methods were used

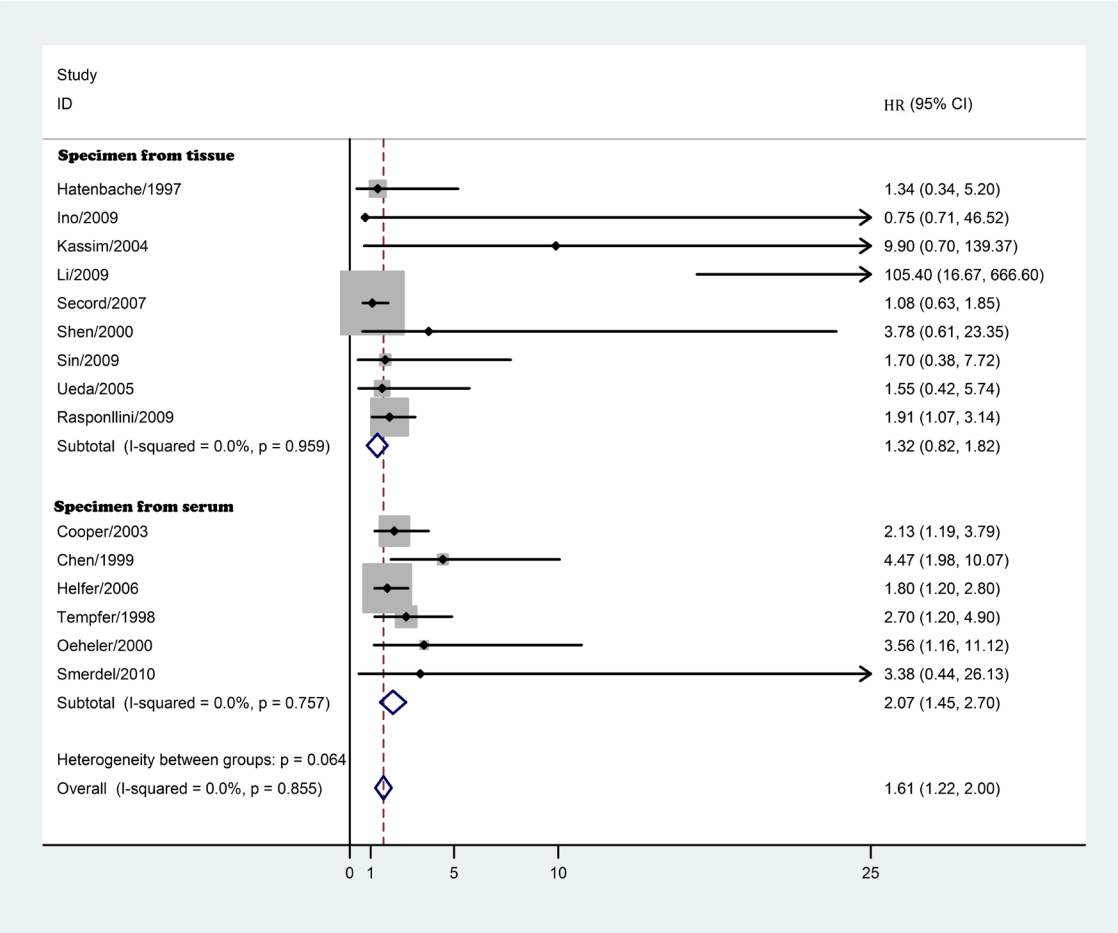

Figure 1. Meta-analysis (Forest plot) of 15 eligible studies assessing vascular endothelial growth factor (VEGF) in OS. HR and its 95% CI for OS is 1.61 (1.22-2.00). Subgroup analysis for specimen from tissue, HR= 1.32 (0.82-1.82), for specimen from serum, HR= 2.07 (1.45-2.70). Each study is shown by the first author/year and the HR with 95% CI.

Table 1. Main characteristics of 19 included studies

First author [Ref] (year-country)	*No.*	*FIGO stage*	*Histology*	*Cutoff value*	*Specimen from tissue or serum*	*Survival analysis*	*Type*	*HR estimation*	*HR(95%CI)*	*Conclusion*
Gadducci [12] (2003-Italy)	45	IV:7, other:38	serous:36, other:9	75%	tissue (IHC)	PFS	VEGF	survival curves	1.07 (0.13,8.44)	Negative
Hartenbach[13] (1997-USA)	18	III:16, IV:2	serous	25 cycles	tissue (RT-PCR)	OS	VEGF	survival curves	1.34 (0.34,5.20)	Negative
Ino [14] (2006-Japan)	67	I+II:39, III+IV:28	serous:22, other:45	10%	tissue (IHC)	OS, PFS	VEGF	given by author	OS:5.75 (0.71,46.52), PFS:4.10 (0.88,1.92)	Positive
Kassim [15] (2004-Egypt)	24	I+II:12, III+IV:12	serous:10, mucinous:7, other:7	120pg/mg	serum	OS	VEGF	survival curves	9.90 (0.70,139.37)	Positive
Li [16] (2009-China)	78	I+II:34, III+IV:44	serous:45, other:33	10%	tissue (IHC)	OS, DFS	VEGF-D	given by author	OS:105.4 (16.67,666.6), DFS:124.6 (16.30,126.05)	Positive
Secord [17] (2007-USA)	67	III:59, IV:8	serous:39, other:24	VEGF/ actin ratio=1.2	tissue (immunoblot)	PFS, OS	VEGF	given by author	OS:1.08 (0.63,1.85), PFS:1.19 (0.72,1.99)	Negative
Shen [18] (2000-Japan)	64	I+II:37, III+IV:27	serous:29, other:35	50%	tissue(IHC)	OS	VEGF	survival curves	3.78 (0.61,23.35)	Positive
Sinn [19] (2009-Germany)	97	I+II:25, III+IV:72	serous:67, other:30	mRNA: 30.52	tissue (RT-PCR)	OS, PFS	VEGF-C	survival curves	OS:1.70 (0.38,7.72), PFS:1.70 (0.42,6.89)	Positive
Ueda [20] (2000-Japan)	73	I+II:23, III+IV:50	serous:47, other:26	50%	tissue (IHC)	OS	VEGF-C	survival curves	1.55 (0.42,5.74)	Positive
Rasponllini [21] (2004-Italy)	83	III	serous	30%	tissue (IHC)	OS, DFS	VEGF	given by author	OS:1.91 (1.07,3.14), DFS:1.63 (0.91,2.91)	Negative
Chen [22] (1999- Taiwan)	56	I+II:20, III+IV:36	serous+mucinous:34, other:22	75% quartile	serum	OS, DFS	VEGF	given by author	OS:4.47 (1.98,10.07), DFS:3.34 (1.58–7.09)	Positive
Cooper [23] (2003-USA)	101	I+II:20, III+IV:81	NC	380 pg/ml	serum	OS	VEGF	given by author	OS:2.13 (1.19,3.79)	Positive
Helfer [24] (2006-Italy)	287	I+II:83, III+IV: 204	serous:166, other:121	380 pg/ml	serum	OS	VEGF	given by author	OS:1.8 (1.2.2.8)	Positive
Tempfer [25] (1998-Austria)	60	I+II:19, III+IV:41	serous+mucinous:51, other:9	826 pg/ mL	serum	OS, DFS	VEGF	given by author	OS:2.7 (1.2,4.9), DFS:1.8 (1.1,3.3)	DFS: positive OS: negative
Oehelер [26] (2000-Germany)	41	I+II:7, III+IV:34	serous:32, other:9	440 pg/ mL	serum	OS	VEGF	given by author	OS:3.56 (1.16,11.12)	Positive

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Brustmann [27] (2004-Austria)	41	I+II:29, III:12	serous	10%	tissue (IHC)	DFS	VEGF	survival curves	2.47 (0.45,13.44)	Positive
Nishida [28] (2004-Japan)	80	I+II:38, III:42	serous+mucinous:47, other:33	10%	tissue (IHC)	DFS	VEGF-A	given by author	6.88 (1.632,27.349)	Positive
Smerdel [29] (2010-Denmark)	38	I+II:6, III+IV:32	serous:35, other:3	540pg/ml	serum	OS, PFS	VEGF	survival curves	OS:3.38 (0.44,26.13), PFS:1.86 (0.35,9.85)	Positive
Gazetti [30] (2000-Italy)	32	I+II:10, III:22	serous	NC	tissue(IHC)	DFS	VEGF	survival curves	1.02(0.83,1.25)	positive

NC: not clear, No: number of patients, OS: overall survival, PFS: progression free survival, DFS: disease free survival, IHC immunohistochemistry, RT-PCR: reverse transcription-polymerase chain action, VEGF: vascular endothelial growth factor

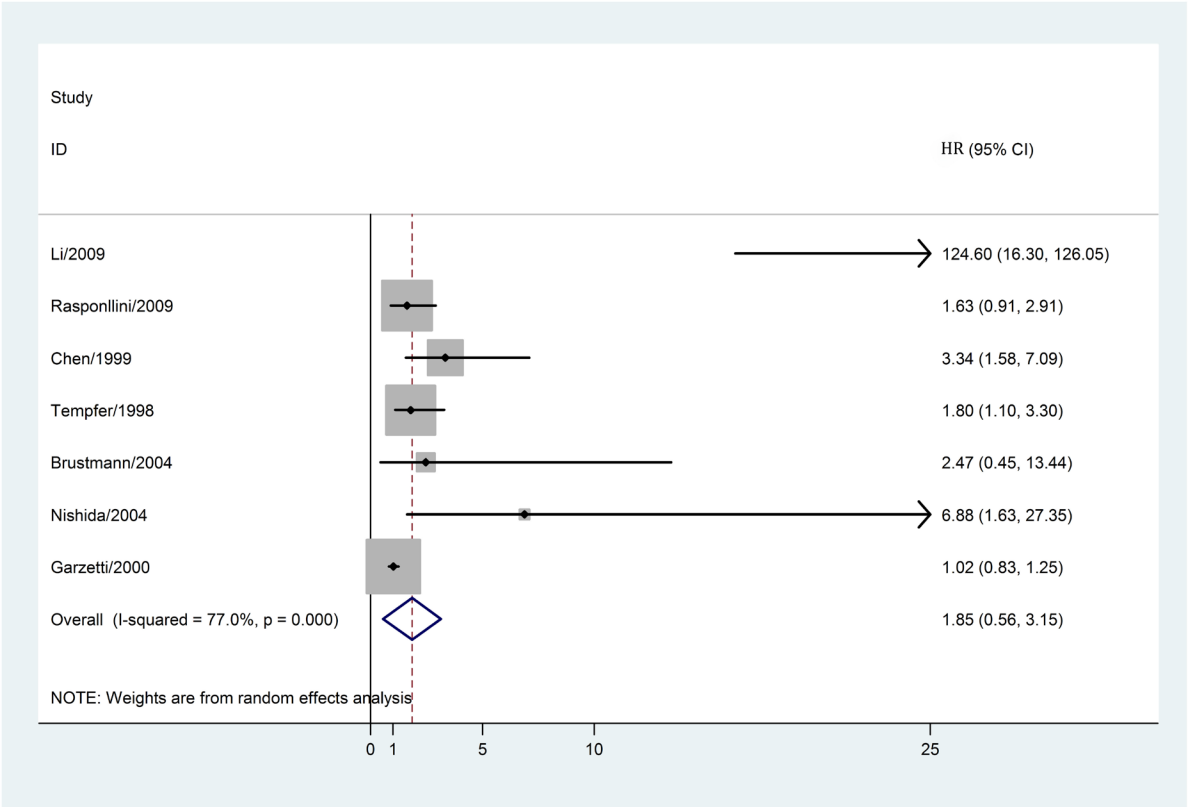

Figure 2. Meta-analysis of 7 eligible studies assessing vascular endothelial growth factor (VEGF) in DFS. HR and its 95% CI for DFS is 1.85 (0.56-3.15). Each study is shown by the first author/year and the HR with 95% CI.

in 6 and 4 studies, respectively. Subgroup analysis was performed according to the origin of the specimen from serum (ELISA) or tissue (IHC, RT-PCR, Western blot, immunoblot). Of 19 studies eligible for meta-analysis, in 10 of them HR estimation was given by the authors, while in 9 HR estimation was calculated from the survival curves (see Methods). FIGO stages III and IV prevailed in the study population (n=894, 66.1%). Eleven of 15 studies using OS were "positive", indicating VEGF expression was a poor prognostic factor in ovarian cancer, while 1 of 7 studies using DFS and 2 of 5 studies using PFS were "negative", indicating no relation of VEGF expression and prognosis.

Meta-analysis

We analyzed HR value of OS between VEGF positive and negative groups. The test of heterogeneity showed x^2=8.16 and I2=0.0%, thus the fixed model was chosen. There was significant

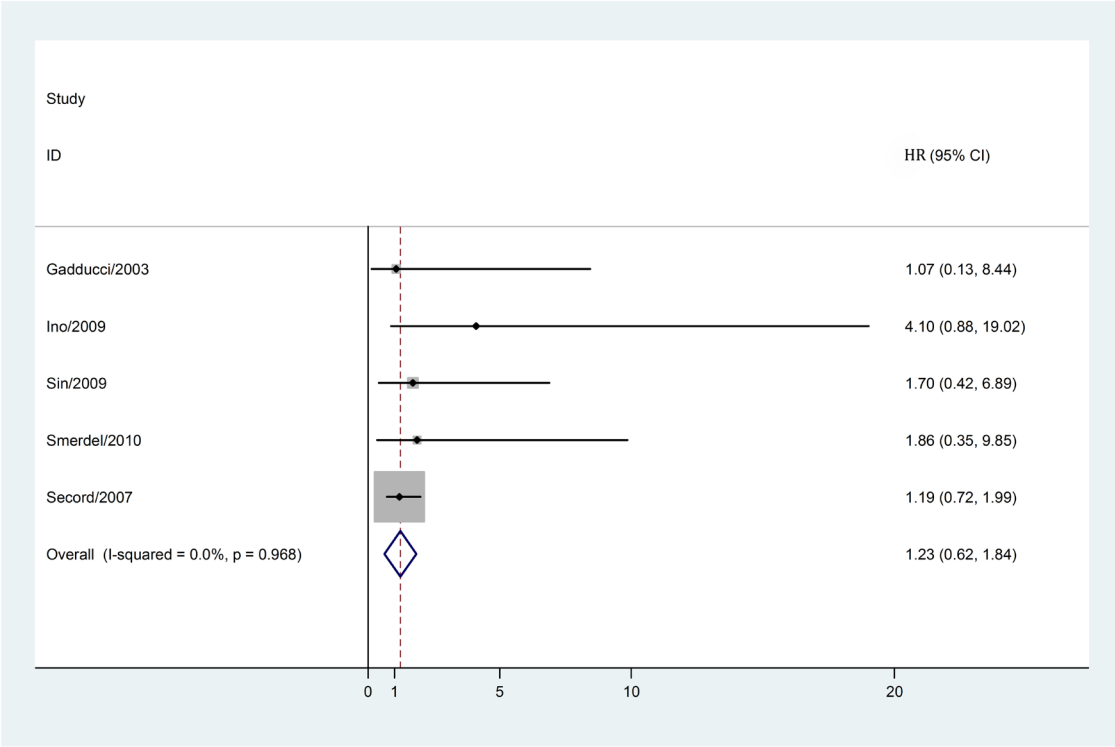

Figure 3. Meta-analysis of 7 eligible studies assessing vascular endothelial growth factor (VEGF) in PFS. HR and its 95% CI for PFS is 1.23 (0.62-1.84). Each study is shown by the first author/year and the HR with 95% CI.

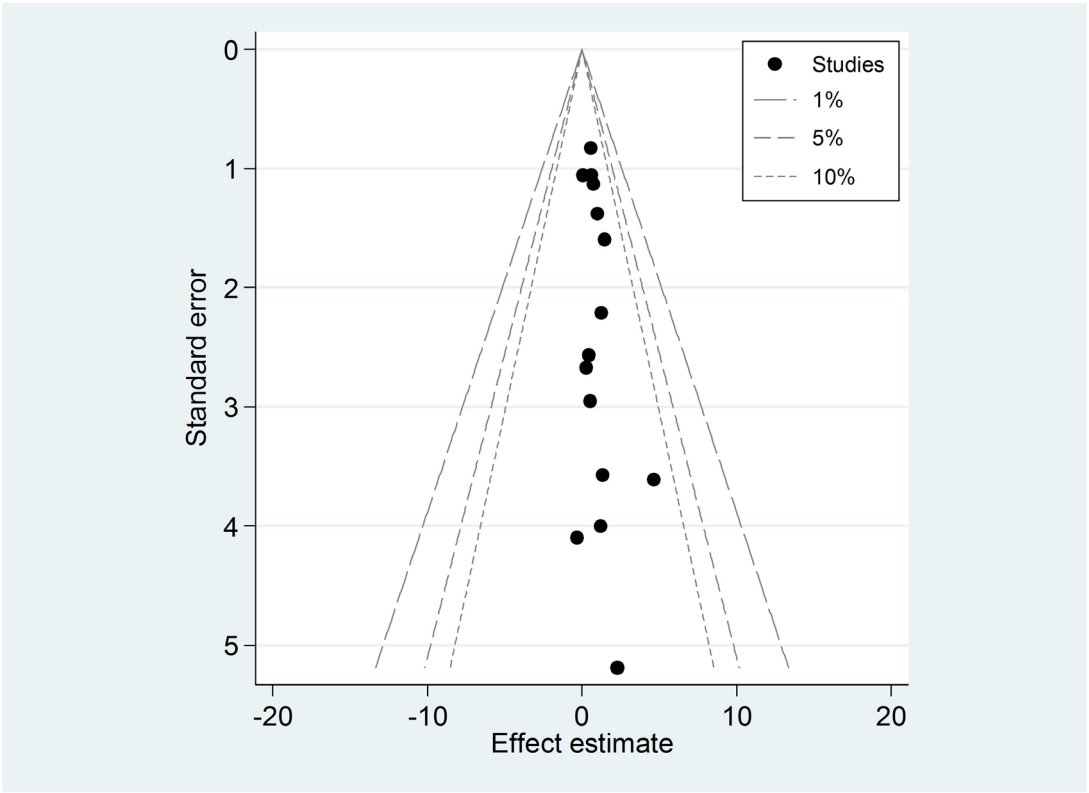

Figure 4. Contour-enhanced funnel plot of 15 eligible studies evaluating the influence of VEGF positivity in OS of ovarian cancer patients.

difference between the 2 groups (HR=1.66, 95% CI:1.22-2.00) and VEGF positivity was associated with poor OS. We then performed subgroup analysis according to the study specimen and the results showed that VEGF was unrelated with OS in tissue specimens (HR=1.32, 95% CI:0.82-1.82) with its 95% CI overlapping with 1. On the contrary, VEGF could indicate poor prognosis in serum specimens (HR=2.07,95% CI:1.45-2.70) (Figure 1).

Among all studies, 7 enabled analysis of DFS between VEGF positive and negative group. Heterogeneity x^2 was 26.12, I^2 77% and Tau^2 1.3978, thus the random model was chosen. VEGF positivity was not associated with DFS (HR=1.85, 95% CI: 0.56, 3.15) (Figure 2). Five studies analyzed the effect of VEGF positivity on PFS. X^2 was 0.55 and I^2 0.0%, so the fixed model was used. The results indicated that VEGF positivity had no effect on PFS (HR=1.23, 95% CI: 0.62-1.84) (Figure 3).

Publication bias

In order to assess the publication bias of meta-analysis, Begg's and Egger's test were performed. Fifteen studies evaluating OS of patients with ovarian cancer yielded a Begg's and Egger's test p=0.235 and p=0.11, respectively. At the same time, confunnel plot (contour-enhanced funnel plot) was undertaken which also indicated absence of publication bias (Figure 4). Similar results were observed for 7 studies for DFS (p=0.368 and p=0.061), respectively and PFS (p=0.806 and p=0.269, respectively). All the above results showed that there was no publication bias in our meta-analysis.

Discussion

The present systematic review and meta-analysis shows that overexpression of VEGF in ovarian cancer is a poor prognostic factor with statistical significance for OS (HR=1.66, 95% CI: 1.22-2.00), but not for DFS and PFS. In all the 19 eligible studies, there were 15, 7 and 5 studies for OS, DFS and PFS respectively, and the main survival analyses were focused on OS. Up until now, OS is the most widely used endpoint in oncology trials, and the clinical significance of PFS remains unclear [31]. Publication bias was absent in our analysis, as confirmed by Begg's test, Egger's test and confunnel plot (Figure 4). As subgroup analysis of OS suggested that serum specimens (HR=2.07, 95% CI: 1.45-2.70) indicated poor prognosis, contrasting the tissue specimens (Figure 1), we think serum VEGF expression could be a strong and important prognostic factor in ovarian cancer. It is remarkable that serum VEGF decreased significantly after therapy, which can explain the conclusion of our study [32]. As FIGO stage III and IV accounted for 894 of 1352 patients, the conclusion may be more suitable for advanced than for early-stage ovarian cancer. We were not able to perform meta-analysis concerning VEGF-A, VEGF-C or VEGF-D alone, because only 4 articles were dealing with these VEGF subtypes.

VEGF impacts the survival of ovarian cancer patients through several aspects. Firstly, VEGF permits plasma proteins such as matrix metalloproteinases (MMPs) and gelatinase A leaking into the pleural and pelvic/abdominal cavity which promotes degradation of the extracellular matrix to enlarge space for ovarian cancer cell growth [33]. With the increased vessels' permeability ascites can be more intense. Secondly, the combination of VEGF and VEGF-R on endothelial cells plays a dominant role in the formation of new vessels. When the vessels integrate with malignant tissue, VEGF is able to inhibit apoptosis and autophagy of fragile new formed vasculature [33,34]. Thus, tumor cells can obtain sufficient oxygen and nutrition from the newly formed vasculature and accelerate their growth. Thirdly, VEGF promotes ovarian cancer metastasis. On the one hand, tumor cells easily penetrate the new formed vessels, and then they survive in the circulation by attaching to the microvasculature of the target tissue. VEGF can also upregulate the expression of MMPs which mediate metastasis [35]. On the other hand, VEGF-C is not only a growth factor for blood vessels but also for genesis of lymphatic vessels. Although ovarian cancer itself lacks effective lymphatic vessels, increased VEGF-C can also promote lymphagiogenesis, thus increasing the risk of lymphatic metastasis. Lastly, VEGF is an autocrine growth factor for tumor cells that express VEGF-R; this maybe one mechanism for tumor growth in ovarian cancer [36].

There are several clinical meanings in our study. Firstly, VEGF expression is an indicator for advanced stage and irradiation resistance for ovarian cancer. Studies showed that VEGF expression was positively correlated with FIGO stage and mitotic activity [4,7]. Ovarian tumor cells' survival after irradiation (2 or 6 Gy single dose) could be enhanced by released VEGF [37]. Secondly, our meta-analysis implies that VEGF can be used as biologic therapeutic target. It is possible to design drugs which target angiogenesis and VEGF itself or the VEGF signaling pathway. In a

randomized phase III clinical trial targeting the VEGF pathway was proven effective in prolonging survival in lung and breast cancer [38]. Animal experiments with ovarian models demonstrated that treatment with VEGF antibody diminished ascites and lowered the permeability of tumor microvessels, as detected by magnetic resonance imaging [4,7]. Wood [39] showed that PTK787/ZK 222584 which is a potent tyrosine kinase inhibitor of VEGF receptor, reached the same conclusion and Hu et al. [40] reported that VEGF plus paclitaxel had the same effect. Taking these aforementioned reports into account, we believe that VEGF-targeted therapeutic approaches could probably improve clinical outcomes in ovarian cancer.

Unfortunately, even using the same detection methods such as IHC or ELISA, the cutoff value varies from 10 to 75% for IHC and from 120 to 826 pg/ml for ELISA. Furthermore, Secord et al. [17] considered VEGF/actin ratio =1.2 as the threshold for obtaining negative results. Brustmann et al. [27] failed to provide any cutoff value although their conclusions were consistent with our results. In order to demonstrate more convincing evidence, we should take adjustment of VEGF positivity into consideration. Our results are not merely influenced by the cutoff value, but some HR values and their 95% CI were calculated from survival curves which, undoubtedly, present errors. Therefore, more raw data are needed to reach more reliable conclusions. Several studies focus on the relationship of VEGF expression and survival, but we often couldn't obtain enough survival information from original studies, resulting in data missing.

In conclusion, our meta-analysis of published studies suggests that OS of the VEGF positive group with ovarian cancer was significantly poorer than the VEGF negative group. However, VEGF positivity seems to be unrelated with DFS and PFS. These results should be confirmed by more comprehensive investigations and randomized controlled trials with large number of patients.

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