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ASSOCIATION OF VASCULAR ENDOTHELIAL GROWTH FACTORS WITH BREAST CANCER: A REVIEW

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Abstract:

Breast Cancer is the leading cancer diagnosed in women aged 20 - 45 with risk factors including breast density, age and family history. Vascular endothelial growth factors is usually referred as VEGF family, which comprises of VEGFA, VEGFB, VEGFC, VEGFD and placental growth factor. The human VEGF gene is localized in chromosome 6p21.3 and it is organized as eight exons separated by seven introns. The VEGF and VEGFR family system is responsible for regulation of both the vascular and lymphatic endothelium and also plays a key role in tumor formation through promotion of both angiogenesis and lymphangiogenesis. A humble attempt is made to find the association between vascular endothelial growth factors and breast cancer through this review. A literature search was conducted in Pubmed for articles published in the English language using combinations of the following terms: Vascular endothelial growth factors, breast cancer and tumor.

Keywords: Vascular endothelial growth factors, breast cancer, tumor.

Introduction:

Vascular endothelial growth factors (VEGF) is usually referred as VEGF family, which comprises of VEGFA, VEGFB, VEGFC, VEGFD and placental growth factor (PGF). The human VEGF gene is localized in chromosome 6p21.3 and it is organized as eight exons separated by seven introns [1-3]. Alternative exon splicing was initially shown to result in the generation of four different isoforms (VEGFA121, VEGFA165, VEGFA189 and VEGFA206), having 121, 165, 189 and 206 amino acids respectively, after signal sequence cleavage [2, 3] the predominant isoform, lacks the residues encoded by exon 6, whereas VEGFA121 lacks the residues encoded by exons 6 and 7. VEGF121 lacks heparin binding activity because of its acidic property and is free to diffuse into the extracellular space. Due to its bioactivity and biological potency, VEGF165 is the predominant isoform of VEGF [4]. Although VEGF165 is also secreted, a significant fraction remains bound to the cell surface and extracellular matrix (ECM). VEGF189 and VEGF206 are mostly sequestered in the ECM because of their high binding affinity for heparin [5, 6]. Less frequent splice variants also have been reported, such as VEGFA145 and VEGFA183 [7]. The VEGF and VEGFR family system is responsible for regulation of both the vascular and lymphatic endothelium and also plays a key role in tumor formation through promotion of both angiogenesis and lymphangiogenesis.

Role of VEGF in Breast Cancer:

Several lines of evidence implicate the importance of VEGFA in Breast Cancer (BC) [8]. Patients with loco regional ductal cancers have elevated serum VEGFA concentrations in comparison with women with benign breast tumors. The highest concentrations of serum VEGFA were found in metastatic BC, in particular among patients who did not receive cancer therapy for metastatic disease [9]. A significant correlation between VEGFA concentration and microvessel density (MVD) has been reported [10]. A study in 574 node-negative BC patients showed that high VEGFA levels in tumor tissue were associated with larger tumor size, older age and negative progesterone receptor (PR). Tissue microarray of 642 BCs demonstrated that high levels of VEGFA and its receptors- VEGFR-1, VEGFR-2 and NRP-1 were significantly associated with poor survival. This study also demonstrated the correlation between the expression of VEGFA and its receptors within tumor cells, supporting an autocrine and paracrine function of VEGFA [11]. In a study of 50 invasive ductal carcinomas, expressions of VEGFA protein and mRNA were correlated with tumor size, lymph node metastasis and TNM staging. The MVD counts were correlated with the expression of VEGFA and axillary lymph node metastasis [12]. Cox analysis revealed that intratumoral VEGFA was an independent prognostic factor for node-negative BC [13]. High VEGFA and low soluble VEGFR-1 levels (an intrinsic negative counterpart of VEGFA) were significantly associated with poor prognosis [14, 15]. Randomized study of tamoxifen adjuvant treatment in postmenopausal patients revealed that the patients with positive VEGFA had no response to tamoxifen [16]. In advanced BC patients receiving bevacizumab and vinorelbine who had lower baseline plasma VEGFA before treatment had longer time to progress (9.3 months vs. 3.7 months) than those with higher plasma VEGFA [17].

Fibrocystic lesions with the highest vascular density are associated with a greater risk of BC [18]. Histopathologically aggressive ductal carcinoma-in-situ lesions demonstrate higher (MVD) and increased VEGF expression [19, 20]. Numerous studies have indicated that intratumoral VEGF expression is significantly correlated with MVD and poor prognosis in a variety of human solid cancers including BC, brain tumors, head and neck cancer and gastrointestinal cancer [21]. The prognostic value of VEGF has been confirmed not only in immune histochemical studies but also in other studies using enzyme-linked immunosorbent assay (ELISA) and Northern blotting. In most clinical studies that examined the prognostic value of VEGF in primary BC, intratumoral VEGF expression was a significant marker of poor prognosis in both node-negative and node-positive subgroups [22]. Carriers of the C936T allele in the VEGF gene were more frequent among controls (29.4%) than among a cohort of BC patients (17.6%), implying a protective effect for carriers of the variant polymorphism [23]. A recent report also demonstrated that this polymorphism is associated with an improved metastasis-free survival time in patients that have low-grade BC [24]. Increased VEGF expression is associated with impaired response to tamoxifen or chemotherapy in patients with advanced BC [25]. Some studies have shown that VEGF status is a significant predictor of relapse in primary BC patients receiving adjuvant endocrine treatment with tamoxifen [26, 27]. These clinical data appear compatible with the results of

experimental studies in which transfection of hormone-sensitive tumors with the VEGF121 gene rendered them hormone refractory, and antiangiogenesis therapy achieved a combined effect with hormone therapy in animal experiments [28]. A microenvironment rich in VEGF might facilitate up-regulation of growth factor production and intracrine hormone synthesis, although little is known about the mechanism involved. Similarly, VEGF expression level in the tumor tissue was a significant predictor of relapse-free survival and overall survival in node-negative BC patients treated with loco-regional radio therapy [29]. VEGFR-1 antagonists and a tyrosine kinase inhibitor of VEGFR-2 reverted radiation refractory tumor models to a radiation-sensitive phenotype. These findings suggest that the high VEGF expression might define a radio-resistant phenotype [30].

The above review supports the crucial role of VEGF in the transition from benign to malignant breast disease and BC aggressiveness and it should be further investigated in the future prospective studies in different ethnic groups to get more accurate results.

Abbreviations:

VEGF : Vascular endothelial growth factors
PGF : Placental growth factor
ECM : Extracellular matrix
BC : Breast Cancer
PR : Progesterone receptor
MVD : Micro vessel density

References:

1. Vincenti, V.; Cassano, C.; Rocchi, M.; Persico, G. Assignment of the vascular endothelial growth factor gene to human chromosome 6p21.3. Circulation 1996, 93, 1493–1495.
2. Houck, K.A. The vascular endothelial growth factor family: Identification of a fourth molecular species and characterization of alternative splicing of RNA. Mol. Endocrinol. 1991, 5, 1806–1814.
3. Tischer, E. The human gene for vascular endothelial growth factor. Multiple protein forms are encoded through alternative exon splicing. J. Biol. Chem. 1991, 266, 11947–11954.
4. Mura M, dos Santos CC, Stewart D, Liu M: Vascular endothelial growth factor and related molecules in acute lung injury. J Appl Physiol 97:1605-1617, 2004.
5) Ferrara N: VEGF: an update on biological and therapeutic aspects. Cur Opin Biothech 11:517-524, 2000.
6. Ferrara N, Alitalo K: Clinical applications of angiogenic growth factors and their inhibitors. Nat Med 5:1359-1564, 1999.
7. Neufeld, G.; Cohen, T.; Gengrinovitch, S.; Poltorak, Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J. 1999, 13, 9–22.
8. Gasparini, G. Prognostic value of vascular endothelial growth factor in Breast Cancer. Oncologist 2000, 5, 37–44. Int. J. Mol. Sci. 2012, 13 14860.
9. Salven, P.; Perhoniemi, V.; Tykka, H.; Maenpaa, H.; Joensuu, H. Serum VEGF levels in women with a benign breast tumor or Breast Cancer. Breast Cancer Res. Treat. 1999, 53, 161–166.
10. Obermair, A.; Kucera, E.; Mayerhofer, K.; Speiser, P.; Seifert, M.; Czerwenka, K.; Kaider, A.; Leodolter, S.; Kainz, C.; Zeillinger, R. Vascular endothelial growth factor (VEGF) in human Breast Cancer : correlation with disease-free survival. Int. J. Cancer 1997, 74, 455–458.
11. Ghosh, S.; Sullivan, C.A.; Zerkowski, M.P.; Molinaro, A.M.; Rimm, D.L.; Camp, R.L.; Chung, G.G. High levels of vascular endothelial growth factor and its receptors (VEGFR-1, VEGFR-2, neuropilin-1) are associated with worse outcome in Breast Cancer. Human Pathol. 2008, 39, 1835–1843.

12. Xie, X.D.; Qu, S.X.; Liu, Z.Z.; Zhang, F.; Zheng, Z.D. Study on relationship between angiogenesis and micrometastases of peripheral blood in Breast Cancer. J. Cancer Res. Clin. 2009, 135, 413–419.
13. Manders, P.; Beex, L.V.; Tjan-Heijnen, V.C.; Geurts-Moespot, J.; van Tienoven, T.H.; Foekens, J.A.; Sweep, C.G. The prognostic value of vascular endothelial growth factor in 574 node-negative Breast Cancer patients who did not receive adjuvant systemic therapy. Br. J. Cancer 2002, 87, 772–778.
14. Bando, H.; Weich, H.A.; Brokelmann, M.; Horiguchi, S.; Funata, N.; Ogawa, T.; Toi, M. Association between intratumoral free and total VEGF, soluble VEGFR-1, VEGFR-2 and prognosis in Breast Cancer. Br. J. Cancer 2005, 92, 553–561.
15. Toi, M.; Bando, H.; Ogawa, T.; Muta, M.; Hornig, C.; Weich, H.A. Significance of vascular endothelial growth factor (VEGF)/soluble VEGF receptor-1 relationship in BC. Int. J. Cancer 2002, 98, 14–18.
16. Ryden, L.; Stendahl, M.; Jonsson, H.; Emdin, S.; Bengtsson, N.O.; Landberg, G. Tumor-specific VEGF-A and VEGFR2 in postmenopausal Breast Cancer patients with long-term follow-up. Implication of a link between VEGF pathway and tamoxifen response. BC Res. Treat. 2005, 89, 135–143.
17. Burstein, H.J.; Chen, Y.H.; Parker, L.M.; Savoie, J.; Younger, J.; Kuter, I.; Ryan, P.D.; Garber, J.E.; Chen, H.; Campos, S.M.; et al. VEGF as a marker for outcome among advanced Breast Cancer patients receiving anti-VEGF therapy with bevacizumab and vinorelbine chemotherapy. Clin. Cancer Res. 2008, 14, 7871–7877.
18. Guinebretiere JM, Le Monique G, Gavoille A, Bahi J, Contesso G: Angiogenesis and risk of BC in women with fibrocystic disease. J Natl Cancer Inst. 86:635-636, 1994.
19. Guidi AJ, Fischer L, Harris JR, Schnitt SJ: Microvessel density and distribution in ductal carcinoma in situ of the breast. J Natl Cancer Inst 86:614-619, 1994.
20. Guidi AJ, Schnitt SJ, Fischer L, Tognazzi K, Harris JR, Dvorak HF, Brown LF: Vascular permeability factor (vascular endothelial growth factor) expression and angiogenesis in patients with ductal carcinoma in situ of the breast. Cancer 80:1945-1953, 1997.
21. Toi M, Matsumoto T, Bando H: Vascular endothelial growth factor: its prognostic, predictive, and therapeutic implications. Lancet Oncol 2:667-673, 2001.
22. Gasparini G: Prognostic Value of Vascular Endothelial Growth Factor in Breast Cancer. Oncologist 5 Suppl 1:S37-44, 2000.
23. Krippl P, Langsenlehner U, Renner W, Yazdani-Biuki B, Wolf G, Wascher TC, Paulweber B, Haas J, Samonigg H: A common 936 C/T gene polymorphism of vascular endothelial growth factor is associated with decreased BC risk. Int J Cancer 106:468-471, 2003.
24. Langsenlehner U, Samonigg H, Krippl P: Vascular endothelial growth factor gene polymorphism decreases the risk for BC metastasis. Breast Cancer Res Treat 88:S72, 2004.
25. Foekens JA, Peters HA, Grebenchtchikov N, Look MP, Meijer-van Gelder ME, Geurts-Moespot A, vander Kwast TH, Sweep CG, Klijn JG: High tumor levels of vascular endothelial growth factor predict poor response to systemic therapy in advanced Breast Cancer. Cancer Res 61:5407-5414, 2001.
26. Gasparini G, Toi M, Miceli R, Vermeulen PB, Dittadi R, Biganzoli E, Morabito A, Fanelli M, Gatti C, Suzuki H, Tominaga T, Dirix LY, Gion M: Clinical relevance of vascular endothelial growth factor and thymidine phosphorylase in patients with node-positive Breast Cancer treated with either adjuvant chemotherapy or hormone therapy. Cancer J Sci Am 5:101-111, 1999.
27. Linderholm B, Grankvist K, Wilking N, Johansson MTavelin B, Henriksson R: Correlation of vascular endothelial growth factor content with recurrences, survival, and first relapse site in primary node-positive breast carcinoma after adjuvant treatment. J Clin Oncol 18:1423-1431, 2000.
28. Zhang HT, Scott PA, Morbidelli L, Peak S, Moore J,Turley H, Harris AL, Ziche M, Bicknell R: The 121 amino acid isoform of vascular endothelial growth factor is more strongly tumorigenic than other splice variants in vivo. Br J Cancer 83:63-68, 2000.
29. Linderholm B, Tavelin B, Grankvist K, Henriksson R: Does vascular endothelial growth factor (VEGF) predict local relapse and survival in radiotherapy-treated node-negative BC? Br J Cancer 81:727-732 1999.
30. Geng L, Donnelly E, McMahon G, Lin PC, SierraRivera E, Oshinka H, Hallahan DE: Inhibition of vascular endothelial growth factor receptor signalling leads to reversal of tumor resistance to radiotherapy.Cancer Res 61:2413-2419, 2001.