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Cancer and Vascular endothelial growth factor Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.
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Key words: cancer; life; research; literature; cell

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

The following introduces recent reports as references in the related studies.

Abdel-Rahman, O. (2015). "Targeting vascular endothelial growth factor (VEGF) pathway in gastric cancer: preclinical and clinical aspects." Crit Rev Oncol Hematol **93**(1): 18-27.

The prognosis of advanced gastric cancer has been dreadful with the majority of patients dying of their disease within 1 year of the diagnosis. In the advanced stage several therapeutic options can be discussed, including molecular targeted agents, but biological predicting factors are lacking. A number of molecular targets have been studied over the last decade bringing to several phase II studies; however very few agents moved into phase III clinical trials. The VEGFR-2 inhibitor monoclonal antibody ramucirumab has been recently approved in advanced progressing gastric cancer. This article reviews the basic science as well as clinical data of VEGF signaling in advanced gastric cancer with special emphasis on the different VEGF targeting agents tested previously in this disease.

Adams, J., et al. (2000). "Vascular endothelial growth factor (VEGF) in breast cancer: comparison of plasma, serum, and tissue VEGF and microvessel density and effects of tamoxifen." Cancer Res **60**(11): 2898-2905.

The assessment of angiogenesis in breast cancer is of importance as a key indicator of survival and response to therapy. Circulating vascular endothelial growth factor (VEGF) measurements may provide a less subjective analysis than microvessel density (MVD) or immunohistochemical analysis of VEGF expression; however, most studies have used serum, which is now known to largely reflect platelet-derived VEGF concentrations. This study examined for the first time both plasma (VEGFp) and serum (VEGFs) VEGF concentrations in 201 blood samples from pre- and postmenopausal healthy controls and from patients with benign breast disease, localized breast cancer, breast cancer in remission, or metastatic breast cancer and related these to other clinicopathological markers. VEGFp but not VEGFs concentrations of patients with localized disease were significantly elevated compared with normal controls ($P = 0.016$). Patients with metastatic disease had higher VEGFp and VEGFs levels than normal controls ($P < 0.001$, $P = 0.044$ respectively), and higher VEGFp, but not VEGFs, than patients with benign disease ($P = 0.009$) and patients with localized disease ($P = 0.004$). However, the highest VEGFp and VEGFs concentrations were seen in patients in remission compared with normal controls ($P < 0.001$ and $P = 0.008$, respectively). VEGFp concentrations in patients in remission were also higher than in patients with

benign disease (P = 0.01) or patients with localized disease (P = 0.005). Tamoxifen treatment was significantly associated with higher circulating and platelet-derived VEGF levels. Circulating VEGF did not correlate with any clinicopathological factor, including MVD or VEGF expression. VEGF expression was significantly correlated with estrogen receptor status and inversely correlated with tumor grade. MVD correlated with tumor size. Tamoxifen-induced increases in VEGF may be important in clinical prognosis or associated pathologies.

Akagi, K., et al. (2000). "Vascular endothelial growth factor-C (VEGF-C) expression in human colorectal cancer tissues." Br J Cancer **83**(7): 887-891.

Vascular endothelial growth factor-C (VEGF-C) functions specifically to induce lymphangiogenesis. We examined the relationship between expression of VEGF-C and clinicopathological features in patients with colorectal cancer. The expression of VEGF-C in the 99 primary tumours and 18 metastatic lymph nodes from colorectal cancer patients was examined immunohistochemically. To verify VEGF-C mRNA expression, reverse transcriptase-polymerase chain reaction (RT-PCR) was carried out. The expression of VEGF-C correlated with lymphatic involvement, lymph nodes metastasis, and depth of invasion. On the other hand, correlations were nil with regard to gender of the patients, histologic type, venous involvement, and liver metastasis. The expression of VEGF-C in metastatic lymph nodes was fairly consistent with this expression in the primary tumour. Survival time was shorter for VEGF-C positive groups than for VEGF-C negative ones, but with no statistically significant difference. RT-PCR findings revealed that the expression of VEGF-C mRNA correlated mostly with that of VEGF-C protein expression. VEGF-C may play an important role in lymphatic spread of colorectal cancer.

Albalawi, I. A., et al. (2020). "Genetic Effects of Vascular Endothelial Growth Factor A (VEGF-A) and Its Association with Disease Progression in Breast Cancer Population of Saudi Arabia." Asian Pac J Cancer Prev **21**(1): 139-145.

AIM: Previous studies have shown that vascular endothelial growth factor (VEGFA) gene variants were associated with breast cancer risk. The goal of the current study was to evaluate the genetic effects of the vascular endothelial growth factor (VEGF) on the risk of breast cancer and its association with disease progression. METHODOLOGY: This case control study was conducted on 110 Breast cancer cases and 110 gender matched healthy controls. Vascular endothelial growth factor A (VEGF-A) 1 (-460T>C) genotyping was performed using Amplification refractory mutation system PCR method. The vascular endothelial growth factor A (VEGF-A) (-460T>C) genotypes were collated with different clinicopathological features of breast cancer patients. RESULTS: A significant difference was observed between the genotype distribution of VEGF-A (-460T>C) among breast cancer cases and gender matched healthy controls (p=0.006). The frequencies of all three genotypes CC,CT,TT reported in the breast cancer patients and sex matched healthy controls were 4.54%, 46.36% ,49.20% and 7.27%, 64.54%, 28.18% respectively. The increased susceptibility to breast cancer disease was found to be associated with VEGF (-460T>C) CC vs TT variant in codominant inheritance model OR 2.78 (0.83-9.26) RR 1.68(1.01 to 2.81) P=0.04. A significant association was reported with VEGF (-460T>C) (CC+CT vs. TT) variant in recessive inheritance model, (OR=2.45 (95% CI= (1.40-4.29), P=0.003. Our findings indicated that VEGF (-460T>C) TT genotype is associated with an increased susceptibility to breast cancer disease. Our result indicates a potential dominant effect of VEGF (-460T>C) TT genotype on susceptibility to the breast cancer disease. CONCLUSION: VEGF (-460T>C) TT genotype significantly increased the risk of breast cancer. VEGF-A (-460T>C) genetic ariability was significantly associated with distant metastasis of the disease. It may be a useful as predisposing genetic marker for breast cancer .Further studies with larger sample sizes are necessary to confirm our findings.
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Al-Moundhri, M. S., et al. (2009). "Gastric cancer risk predisposition and prognostic significance of vascular endothelial growth factor (VEGF) gene polymorphisms--a case-control study in an Omani population." Mol Carcinog **48**(12): 1170-1176.

Vascular endothelial growth factor (VEGF) plays a central role in angiogenesis, tumor growth, and metastasis. We investigated the associations between VEGF gene polymorphisms and gastric cancer (GC) risk predisposition and prognostic characteristics in an Omani population, an ethnic group which has not been studied previously. We analyzed three VEGF polymorphisms (+405 G/C, -460 T/C, and +936 C/T) by the extraction of genomic DNA from peripheral blood of 130 GC patients and 130 control subjects followed by VEGF genotyping using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis. There were no significant associations between the VEGF polymorphisms and GC risk. There were significant correlations between the +405 C/C genotype and both poor tumor differentiation (P = 0.007) and lymph node metastasis (P = 0.03) and between the -460 T/T genotype and poor tumor differentiation (P = 0.03) with a statistical trend

toward lymph node involvement (P = 0.05). VEGF gene polymorphisms had no significant effects on survival, but the VEGF +405 G/G genotype had a statistical trend toward lower survival rate with a hazard ratio of 1.6 [95% CI, 0.9-2.9] compared with the VEGF +405 CC/GC combined genotype (P = 0.049). Multivariate analysis showed that disease stage at diagnosis and the +405 G/G genotype were independent variables of adverse prognostic significance. There were no associations between the six common haplotypes identified and both GC risk predisposition and survival. The current study suggests that VEGF polymorphisms have no role in GC risk predisposition, but may have prognostic significance in GC patients.

Anannamcharoen, S. and T. Nimmanon (2012). "Study of the vascular endothelial growth factor (VEGF) expression and microvascular density (MVD) in primary colorectal cancer specimens." J Med Assoc Thai **95**(8): 1041-1047.

OBJECTIVE: Determine the relationship between vascular endothelial growth factor (VEGF) expression and microvascular density (MVD) in primary colorectal cancer specimens including the prognostic value by evaluating the correlation between various common reported prognostic histopathologic indictors and these two angiogenic parameters. The Inter-observer reliability on VEGF and MVD measurement was also determined. MATERIAL AND METHOD: Anti-VEGF and anti-factor CD34 monoclonal antibodies immunohistochemical staining was performed in 40 randomly selected formalin-fixed paraffin-embedded colorectal cancer specimens of non-stage-IV patients who underwent curative resection using. Immunoreactive in 25% or more carcinoma cells was categorized as positive. The intensity of VEGF expression was graded in a semiquantitative fashion, ranging from 0 to 2 Tumor MVD was determined by counting any endothelial cells stained with CD34 per two randomly selected fields at x200 magnification in each slide. The correlation between VEGF expression and MVD was evaluated. Inter-observer agreement was assessed by comparing the results of VEGF and MVD measurements made by two pathologists. RESULTS: A moderate correlation was found between the percentage of positive immunoreactive cells and the intensity of VEGF immunoreactive staining (correlation value of 0.436, $p < 0.05$). MVD was found having no correlation with both the percentage of positive immunoreactive cells and intensity of VEGF immunoreactive staining (the correlation value of -0.056, $p = 0.732$ and 0.108, $p = 0.506$, respectively). Neither MVD nor VEGF expression in primary colorectal cancer tissue was found having a significant correlation with any common reported prognostic histopathologic indictors. In counting CD34-stained endothelial cells, this study revealed a high intra-observer correlation coefficient of 0.886 (95% CI: 0.715-0.955) for the first pathologist and 0.913 (95% CI: 0.782-0.965) for the second. High inter-observer reliability was found in both MVD and VEGF measurement with a substantial agreement (agreement: 95%, kappa = 0.643) between the two pathologists. CONCLUSION: In primary colorectal cancer tissues, there was no significant relationship between MVD and VEGF expression. This study revealed a high intra and inter-observer reliability on VEGF and MVD measurement. Neither MVD nor VEGF expression provided predictive value of advanced or aggressiveness of disease. Further studies on larger sample size would help validate these results.

Appelmann, I., et al. (2010). "Angiogenesis inhibition in cancer therapy: platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) and their receptors: biological functions and role in malignancy." Recent Results Cancer Res **180**: 51-81.

Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogen in vitro and an angiogenic inducer in a variety of in vivo models. VEGF gene transcription is induced in particular in hypoxic cells. In developmental angiogenesis, the role of VEGF is demonstrated by the finding that the loss of a single VEGF allele results in defective vascularization and early embryonic lethality. Substantial evidence also implicates VEGF as a mediator of pathological angiogenesis. In situ hybridization studies demonstrate expression of VEGF mRNA in the majority of human tumors. Platelet-derived growth factor (PDGF) is mainly believed to be an important mitogen for connective tissue, and also has important roles during embryonal development. Its overexpression has been linked to different types of malignancies. Thus, it is important to understand the physiology of VEGF and PDGF and their receptors as well as their roles in malignancies in order to develop antiangiogenic strategies for the treatment of malignant disease.

Bae, S. J., et al. (2008). "Gender-specific association between polymorphism of vascular endothelial growth factor (VEGF 936C>T) gene and patients with stomach cancer." Yonsei Med J **49**(5): 783-791.

PURPOSE: Angiogenesis plays an important role in the growth, progression, and metastasis of tumors. Vascular endothelial growth factor (VEGF) overexpression has been associated with advanced stage and poor survival in several cancers. We investigated the present case-control study to determine whether there is an association between the VEGF

936C>T polymorphism and stomach cancer. PATIENTS AND METHODS: The association of functional single nucleotide polymorphisms (SNPs) of the VEGF gene with stomach cancer development was evaluated in a case-control study of 154 Korean stomach cancer patients. Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. RESULTS: Our results revealed significant association of T allele-bearing genotypes with increased risk for stomach cancer development. Genotype frequencies of the VEGF 936C>T polymorphisms were significantly different between patient and control groups (CT, AOR: 2.007, 95% CI: 1.277-3.156, TT, AOR: 4.790, 95% CI: 1.174-19.539, CT+TT, AOR: 2.147, 95% CI: 1.382-3.337). When stratified by gender and age, genotype frequencies were significantly different for stomach cancer in women and in patients younger than 55 years (in women, CT, OR: 3.049, 95% CI: 1.568-5.930, CT+TT, OR: 3.132, 95% CI: 1.638-5.990; in < 55 years, CT, OR: 3.306, 95% CI: 1.413-7.732, CT+TT, OR: 3.967, 95% CI: 1.729-9.104). In addition, this association partially remained in cases with intestinal and diffuse-type stomach cancer. CONCLUSION: Our present study suggests that the VEGF 936C>T polymorphism is a susceptibility factor for stomach cancer, at least in Korean. These observations, however, require further confirmation by a larger multi-ethnic study.

Bae, S. J., et al. (2008). "Gender-specific association between polymorphism of vascular endothelial growth factor (VEGF 936 C>T) gene and colon cancer in Korea." Anticancer Res **28**(2B): 1271-1276.

BACKGROUND: Angiogenesis is an essential process in the development, growth and metastasis of malignant tumors such as colon cancer. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor. A case control study was carried out to determine whether there is an association between the VEGF 936C>T polymorphism and colon cancer. PATIENTS AND METHODS: DNA samples taken from 262 colon cancer patients and 229 healthy controls were amplified by polymerase chain reaction for the VEGF 936C>T polymorphism. RESULTS: Genotype frequencies of the VEGF 936C>T polymorphism were significantly different between patient and control groups (CT+TT, odds ratio(OR): 1.524, 95% confidence interval (CI): 1.033-2.249). When stratified by gender and age, the frequencies of the T allele-bearing genotypes significantly increased risk for colon cancer in women and patients younger than 55 years (in women, OR: 1.996, 95% CI: 1.151-3.464 and in <55 years, OR: 4.156, 95% CI: 1.885-9.163). In addition, this association remained in most cases with distal and proximal colon cancer. CONCLUSION: Our study suggests that the VEGF 936C>T polymorphism might be a genetic determinant for colon cancer, at least in Koreans.

Balbi, G., et al. (2006). "Vascular endothelial growth factor (VEGF): can we use it as prognostic factor in endometrial cancer?" Minerva Ginecol **58**(5): 411-415.

AIM: The aim of the study was to investigate if VEGF levels reflect the severity of endometrial cancer and the clinic relationship between microvasal density (MVD) and concentration of VEGF in tumor. METHODS: The study was conducted on 22 patients affected by endometrial cancer who were submitted to total abdominal radical hysterectomy plus bilateral salpingo-ophorectomy. VEGF (pg/mL) and MVD values were measured on histologic specimens of endometrial cancer obtained during the surgical treatment. The means and standard deviations of estimated values were calculated and a statistical comparison was effected by student t test for not coupled data. Pearson correlation test was used to analyze the eventual correlation among VEGF and MVD values in overall patients. RESULTS: We have documented that VEGF expression and MVD change according to FIGO stage, lympho-vascular infiltration and lymph node involvement. Pearson correlation test shows a good linear positive correlation in overall patients between VEGF and MVD values. CONCLUSIONS: Results obtained show a possible use of VEGF as prognostic factor in endometrial cancer. Confirmation of these data may permit both to identify high-risk patients, who must be treated with a more aggressive treatment, and to use an angiogenic therapy in endometrial cancer.

Banys-Paluchowski, M., et al. (2018). "The clinical relevance of serum vascular endothelial growth factor (VEGF) in correlation to circulating tumor cells and other serum biomarkers in patients with metastatic breast cancer." Breast Cancer Res Treat **172**(1): 93-104.

PURPOSE: VEGF is one of the most important angiogenesis-stimulating cytokines and has been previously shown to be overexpressed in several solid cancers. The aim of the present study was to assess the clinical relevance of serum VEGF (sVEGF) in a large cohort of metastatic breast cancer patients and to explore the relationship between sVEGF and other blood-based biomarkers. METHODS: Two hundred fifty-three patients with metastatic breast cancer were enrolled in this prospective, multicentre study. Blood samples were collected before start of first-line or later-line treatment. sVEGF was quantified by a commercially available ELISA. Circulating tumor cells (CTCs) were detected using CellSearch and other biomarkers (EGFR, HER2, RAS p21, TIMP1, CAIX)

by ELISA. RESULTS: Levels of sVEGF were determined in all patients, with a median concentration of 231 pg/ml. After a median follow-up of 19 months, median overall survival (OS) was 10.2 months in patients with sVEGF levels above the upper quartile (i.e. 367 pg/ml), while median OS has not been reached in patients with sVEGF < 367 pg/ml (p < 0.001). Median progression-free survival (PFS) was 4.8 months for patients with sVEGF >/= 367 pg/ml versus 9.1 months with sVEGF levels < 367 pg/ml (p < 0.001). Patients with sVEGF levels >/= 367 pg/ml and >/= 5 CTCs had the shortest OS, while those with sVEGF < 367 pg/ml and non-elevated CTCs had the longest OS. CTCs, grading, line of therapy and RAS p21 were independent predictors of OS. sVEGF, line of therapy and CTCs were independent predictors of PFS in the multivariate analysis. CONCLUSIONS: Metastatic breast cancer patients with elevated levels of sVEGF have significantly worse clinical outcome. This finding supports the biological role of VEGF in breast cancer. TRIAL REGISTRATION: Current Controlled Trials ISRCTN59722891 (DETECT).

Belgore, F. M., et al. (2001). "Plasma levels of vascular endothelial growth factor (VEGF) and its receptor, Flt-1, in haematological cancers: a comparison with breast cancer." Am J Hematol **66**(1): 59-61.

Raised plasma VEGF is found in some cancers but levels of its receptor soluble Flt-1 (sFlt-1) are unreported. Hypothesising increased levels to be present in haematological cancers, we measured both by ELISA in 22 patients with haematological cancer, 22 with breast cancer, and in age- and sex-matched controls. VEGF was raised in both patients groups compared to controls (P < 0.01) but was higher in haematological cancer compared to breast cancer (P = 0.0238). There was no difference in levels of sFlt-1. Our data point to changes in levels of plasma VEGF, but not sFlt-1, in haematological cancer that may have pathophysiological consequences.

Benlahfid, M., et al. (2018). "Endocrine gland-derived vascular endothelial growth factor (EG-VEGF) and its receptor PROKR2 are associated to human colorectal cancer progression and peritoneal carcinomatosis." Cancer Biomark **21**(2): 345-354.

BACKGROUND: The highest risk factor for mortality among malignant tumors is metastasis. Endocrine gland-derived vascular endothelial growth factor (EG-VEGF) is an angiogenic factor which biological activity is mediated via two G protein-coupled receptors, prokineticin receptor1 (PROKR1) and PROKR2. Recent studies suggested that EG-VEGF expression is deregulated in multiple cancers including colorectal cancer (CRC). METHODS: Using distinctive CRC and peritoneal carcinomatosis (PC) cohorts and a corresponding control cohort, we determined the circulating levels of EG-VEGF and its in situ expression, and that of its related receptors. RESULTS: Circulating EG-VEGF levels were significantly increased in patients with metastatic PC compared to CRC and control patients (p< 0.05). Furthermore, according to clinicopathologic examinations, local EG-VEGF expression correlated with higher tumor and nodal stages (p< 0.001) of CRC. EG-VEGF and PROKR2 were highly expressed in colorectal primary lesions compared to positive controls. PROKR1 expression was lower and did not change in tumor specimens. Also, EG-VEGF and its receptor PROKR2 were differentially expressed in the colorectal primary lesions and in the control groups. CONCLUSION: Altogether these findings suggest that EG-VEGF/receptors system might be an important actor in the CRC progression into PC and might be involved in the ability of tumor cells to invade other organs. Circulating EG-VEGF could be proposed as a prognostic marker in human CRC and its progression into PC.

Borre, M., et al. (2000). "Association between immunohistochemical expression of vascular endothelial growth factor (VEGF), VEGF-expressing neuroendocrine-differentiated tumor cells, and outcome in prostate cancer patients subjected to watchful waiting." Clin Cancer Res **6**(5): 1882-1890.

Tumor growth is dependent on angiogenesis, which is thought to be controlled by angiogenic factors. Therefore, the immunoreactivity of the angiogenic cytokine vascular endothelial growth factor (VEGF) was semiquantitatively scored in archival prostate tumors obtained at diagnosis in 221 patients followed expectantly. At diagnosis, 125 patients suffered from clinically localized disease. Median length of follow-up was 15 years, and 57% of the patients eventually died of prostate cancer. All of the tumors exhibited cytoplasmic staining for VEGF. The staining intensity was weak in 47 tumors and moderate and strong in 107 and 67, respectively. VEGF expression was significantly correlated with microvessel density (MVD; median, 43; range, 16-151; P = 0.014), increasing T-classification (P = 0.001), dedifferentiation (P < 0.001), and disease-specific survival (P = 0.013). Strongly VEGF-immunoreactive, neuroendocrine-differentiated (NE) tumor cells were observed in 125 tumors. NE expression was significantly correlated with increasing MVD, increasing T-classification, dedifferentiation, and survival (all, P < 0.001). MVD and NE tumor cell expressions were significant variables in a multivariate analysis that included patients with clinically localized prostate cancer only. VEGF and NE expression were significantly correlated with MVD, clinical

characteristics, and disease-specific survival. NE expression was a significant prognostic marker in localized prostate cancer patients, whereas the applied semiquantitatively scoring of VEGF expression was inadequate to make this growth factor provide any additional prognostic information. Moreover, the significant VEGF expression of NE tumor cells suggests an additional important character of these cells in the involvement in disease progression.

Bouzoubaa, S. M., et al. (2020). "Vascular endothelial growth factor (VEGF) and Endocrine gland-VEGF (EG-VEGF) are down regulated in head and neck cancer." Clin Otolaryngol **45**(5): 788-795.

OBJECTIVE: To characterise the role of VEGF, EG-VEGF and its receptors in the development and progression of HNC. DESIGN: Human serum and tissues samples were collected from healthy, epulis and HNC patients and used for ELISA assays and immunohistochemistry studies, respectively. SETTING: Ibn Rochd Hospital of Casablanca (Morocco), INSERM and University of Grenoble Alpes (France). PARTICIPANTS: We used serum from 64 patients with head and neck cancers and from 71 controls without general pathology. Tissues samples were collected from seven patients with OSCC and from seven patients with Epulis. MAIN OUTCOME MEASURES: We compared circulating VEGF and EG-VEGF in normal and HNC patients and determined the expression, localisation and quantification of VEGF, EG-VEGF and its receptors; PROKR1 and PROKR2 as well as Ki67, CD31 and CD34 in OSCC and Epulis patients. RESULTS: Both EG-VEGF and VEGF circulating levels were significantly decreased in the HNC ($P < .01$). OSCC patients expressed less EG-VEGF and VEGF proteins, higher PROKR1 and PROKR2 with no change in CD31 and CD34 levels. A significant increase in Ki67 was observed in OSCC. CONCLUSIONS: We demonstrated that circulating VEGF and EG-VEGF are downregulated in HNC patients and in OSCC tissue. EG-VEGF receptors were increased in OSCC, along with a stabilisation of two key markers of angiogenesis. These findings strongly suggest that downregulation of angiogenesis in HNC might explain its moderate metastatic feature.

Broll, R., et al. (2001). "Vascular endothelial growth factor (VEGF)--a valuable serum tumour marker in patients with colorectal cancer?" Eur J Surg Oncol **27**(1): 37-42.

INTRODUCTION: Neo-angiogenesis, of great importance for tumour growth and nutrition, is preferentially mediated by the cytokine vascular endothelial growth factor (VEGF), which has a direct effect on vascular endothelial cell proliferation and migration. This study was designed to clarify whether VEGF is a suitable tumour marker in sera of patients with a colorectal cancer, and whether VEGF concentrations in sera and tumour tissues are correlated with tumour extension (pTNM) and especially with tumour volume or size. Furthermore, the influence of VEGF levels on patients >> prognosis was examined. METHODS: VEGF serum concentrations of 122 patients with colorectal cancer and 65 controls were determined with an ELISA kit. Additionally, VEGF concentrations of tumour and normal tissue were measured in 38 patients using the same ELISA. RESULTS: Our results demonstrate that VEGF is not a suitable diagnostic tumour marker in patients with colorectal cancer due to its low sensitivity (36%). However, a combination of the serum tumour markers CEA and VEGF can significantly increase the pre-operative diagnostic sensitivity to 62%. VEGF serum levels differed significantly between patients (mean 438 pg/ml) and controls (mean 203 pg/ml), and also between tumour and normal tissue (984 vs 89 pg/mg protein). Serum concentration showed a significant correlation to tumour volume and size. Patients with VEGF serum levels greater than cut-off had a poorer prognosis than those less than or equal to cut-off. For this reason VEGF could be used as a predictor of patients >> outcome.

Brueckl, W. M., et al. (2008). "Increased vascular-endothelial growth factor (VEGF) tumor expression and response to epidermal growth factor receptor (EGF-R) inhibitor erlotinib in non-small cell lung cancer (NSCLC)." J Thorac Oncol **3**(3): 314-316.

A 37-year-old female never smoker with metastatic large cell carcinoma of the lung had a partial response to a second line palliative therapy with the EGF-R tyrosine kinase inhibitor erlotinib after platinum based first line therapy failed. Molecular analysis of the primary and a liver metastasis did neither find any EGF-R mutation nor an EGF-R amplification. However, both the primary and the metastasis showed an increased gene expression of vascular-endothelial growth factor-A in contrast to normal tissue, which was confirmed by immunohistochemistry. To our knowledge, this is the first report about a high vascular-endothelial growth factor-A expression in the tumor of a patient responding to an EGF-R inhibitor postulating that there might be a link between both tyrosine kinase pathways.

Cacev, T., et al. (2008). "Vascular endothelial growth factor polymorphisms -1154 G/A and -460 C/T are not associated with VEGF mRNA expression and susceptibility to sporadic colon cancer." DNA Cell Biol **27**(10): 569-574.

Vascular endothelial growth factor (VEGF) is important mediator of angiogenesis, and its expression

in colorectal tumors is related to tumor progression. VEGF expression has been detected in normal mucosa, primary colon cancers, and metastatic tumors, and patients with low VEGF expression have a better survival rate. In addition, anti-VEGF monoclonal antibody improves overall survival when used in combination with existing metastatic colorectal cancer therapy. Therefore, prediction of VEGF production based on individual genetic background might be important for predicting the course of the disease and the efficacy of anticancer treatment. The number of studies evaluating the influence of VEGF polymorphisms on cancer susceptibility is growing; however, their results are often conflicting. In addition, these studies are rarely accompanied with the expression analysis examining the influence of these polymorphisms on mRNA expression in tumor tissue. In this study, we have examined the influence of VEGF polymorphisms -1154 G/A and -460 C/T on VEGF mRNA expression and susceptibility to sporadic colon cancer by real-time PCR-SNP and mRNA expression analysis. The study included population control group consisting of 160 unrelated volunteers and a group of 160 patients with sporadic colon cancer. According to our results, -1154 G/A and -460 C/T do not influence VEGF mRNA expression in colorectal tumors and susceptibility to sporadic colon cancer, although the role of other polymorphisms cannot be excluded.

Carrillo-de Santa Pau, E., et al. (2010). "Vascular endothelial growth factor (VEGF) serum levels are associated with survival in early stages of lung cancer patients." Cancer Invest **28**(4): 393-398.

AIM: Evaluate the serum vascular endothelial growth factor (VEGF) levels in the prognosis of lung cancer patients. METHODS: Fifty-four serum samples were analyzed for VEGF concentrations (79.3% nonsmall cell lung cancer (NSCLC) and 20.7% small cell lung cancer). RESULTS: Patients with serum VEGF-A levels higher than the mean of the patients studied (434.93 pg/mL) presented a shorter median survival time than those with lower levels (p =.04), as in patients with NSCLC tumors (p =.04) and in those with stages I-II (p <.05), and high serum VEGF-A levels. CONCLUSION: Elevated VEGF serum levels have a negative prognostic impact on survival in NSCLC and early stages of lung cancer patients.

Cascinu, S., et al. (2000). "Differences of vascular endothelial growth factor (VEGF) expression between liver and abdominal metastases from colon cancer. Implications for the treatment with VEGF inhibitors." Clin Exp Metastasis **18**(8): 651-655.

The vascular endothelial growth factor (VEGF) plays a central role in promoting angiogenesis, and it is the target of innovative anti-cancer therapies. In colorectal carcinomas, differences in the VEGF expression have been found between the primary tumor and its metastases. We postulated that differences in the VEGF expression may also exist between liver and abdominal metastases from colon cancer. Consecutive colon cancer patients with liver or abdominal metastases were considered eligible for the study. Biopsies had to be performed before chemotherapy and the VEGF analysis were conducted through immunohistochemistry. The staining results were correlated to the metastatic pattern. The study population consisted of 41 patients with a metastatic site in the liver in 19 patients and the abdomen in 22 patients. A positive VEGF staining was found in 19 of the 41 metastatic samples (46%). Cases with positive VEGF expression were found more frequently in abdominal (15 out of 22 patients; 68%) than in liver metastases (4 out of 19 patients; 21%). Also, the degree of VEGF immunoreactivity was significantly higher in abdominal than in liver metastases. Evidence is supported that the VEGF expression may be different between colon cancer metastatic sites. The efficacy of anti-VEGF treatments may depend on the VEGF expression status, and this finding deserves further investigation.

Celen, O., et al. (2004). "Correlation of vascular endothelial growth factor (VEGF) and CEA with clinicopathological variables in colorectal cancer patients." Neoplasma **51**(4): 293-299.

The aim of the presented study is to analyze VEGF levels and its correlation with the clinicopathological characteristics of patients with colorectal carcinoma. Thirty-three patients with colorectal adenocarcinoma and 10 healthy controls were evaluated by estimation of VEGF and CEA levels and correlation with clinicopathological features. The serum VEGF and CEA concentrations of colorectal patients were higher than the healthy controls ($p<0.05$). Patients in advanced stage had high levels of both markers but these differences were not statistically significant. There was a positive correlation between both markers and, tumor size and peritumoral vascular invasion (PVI) but when compared VEGF with CEA, VEGF had a stronger correlation. Diagnostic sensitivity of VEGF for colorectal carcinoma was higher than the sensitivity of CEA and combining both markers the sensitivity to predict colorectal carcinoma was higher than of each marker alone. Our study indicated that VEGF compared to CEA had a higher diagnostic sensitivity for colorectal carcinoma and might provide even additional information about tumor features.

Cesario, J. M., et al. (2017). "A simple method to induce hypoxia-induced vascular endothelial growth factor-A (VEGF-A) expression in T24 human bladder

cancer cells." In Vitro Cell Dev Biol Anim **53**(3): 272-276.

Angiogenesis is an essential process for the establishment, development, and dissemination of several malignant tumors including bladder cancer. The hypoxic condition promotes the stabilization of hypoxia-inducible factor 1 alpha (HIF-1alpha), which translocates to the nucleus to mediate angiogenic factors including the vascular endothelial growth factor A (VEGF-A). AnaeroGen system was developed for microbiology area to create a low oxygen tension required to the growth of anaerobic bacteria. Here, we hypothesized the use of AnaeroGen system to induce hypoxia in T24 human bladder carcinoma cells, in order to promote the overexpression of VEGF-A. T24 cells were cultured in six-well plates containing McCoy medium. Exposures of T24 cells to hypoxia for 1, 8, 24, and 48 h were performed using the Oxoid AnaeroGen system, while T24 cells under normoxia were used as control. The expression of VEGF-A and HIF-1alpha was analyzed by real-time PCR. ELISA for HIF-1alpha was carried out. The VEGF-A expression increased significantly by Oxoid AnaeroGen-induced hypoxia in a time-depending manner, reaching the peak in 48 h of hypoxia. Although HIF-1alpha mRNA was not changed, HIF-1alpha protein was increased in the presence of hypoxia, reaching a peak at 8 h. These results demonstrated that the Oxoid AnaeroGen system is a simple method to expose T24 cells to hypoxia and efficiently to upregulate VEGF expression in T24 cells.

Chen, Y. N. and Y. Gu (2009). "[Vascular endothelial growth factor (VEGF)-D in association with VEGF receptor-3 in lymphatic metastasis of breast cancer]." Ai Zheng **28**(12): 1337-1343.

Breast carcinoma is the most common malignant tumor in women. For these patients, lymph node metastasis is one of the most important prognostic factors. Recent studies suggest that lymphangiogenesis can contribute to the lymphatic metastasis in tumors. Several members of vascular endothelial growth factor (VEGF) family, such as VEGF-C, VEGF-D, and VEGF receptor-3 (VEGFR-3), have been found to promote lymphangiogenesis in breast cancer. However, there are still some controversy about the prognostic value of VEGF-D and the relation between VEGFR-3 and lymphangiogenesis. This article tried to provide an overview of the research progress of lymphangiogenic factor VEGF-D and its receptor VEGFR-3 in lymphatic metastasis of breast cancer.

Cheng, D., et al. (2013). "Serum vascular endothelial growth factor (VEGF-C) as a diagnostic and prognostic marker in patients with ovarian cancer." PLoS One **8**(2): e55309.

VEGF-C is regarded as one of the most efficient factors in regulating lymphangiogenesis. The aim of this study was to better understand the role of VEGF-C in the progression of ovarian cancer and to assess its diagnostic and prognostic significance. A total of 109 patients with ovarian cancer, 76 patients with benign ovarian diseases, and 50 healthy controls were recruited in this study. Serum levels of VEGF-C were determined by ELISA method. The results showed that serum levels of VEGF-C were significantly higher in the patients with ovarian cancer than those with benign ovarian diseases and healthy controls ($P<0.01$). Serum level of VEGF-C was correlated with FIGO stage, lymph node metastasis, tumor resectability, and survival of the patients ($P<0.05$). The areas of receiver operating curves of VEGF-C were higher than those of CA125 in different screening groups. Analysis using the Kaplan-meier method indicated that patients with high VEGF-C had significantly shorter overall survival time than those with low VEGF-C ($P<0.0001$). In a multivariate analysis along with clinical prognostic parameters, serum VEGF-C was identified as an independent adverse prognostic variable for overall survival. These results indicated that serum VEGF-C may be a clinically useful indicator for diagnostic and prognostic evaluation in ovarian cancer patients.

Chiarotto, J. A. and R. P. Hill (1999). "A quantitative analysis of the reduction in oxygen levels required to induce up-regulation of vascular endothelial growth factor (VEGF) mRNA in cervical cancer cell lines." Br J Cancer **80**(10): 1518-1524.

The presence of hypoxia (low oxygen concentrations) in solid tumours correlates with poor prognosis, increased metastasis, and resistance to radiotherapy and some forms of chemotherapy. Malignant cells produce an angiogenesis factor, vascular endothelial growth factor (VEGF), which may increase metastatic ability and is up-regulated in the presence of hypoxia. Clinical data for cancers of the cervix and head and neck relate oxygen levels in the tumour to treatment outcome. This suggests the possibility that the presence of VEGF mRNA might be used as a marker for relevant levels of hypoxia. Suspension cultures of three human cervical cancer cell lines, SiHa, ME-180 and HeLa, were used to investigate up-regulation of VEGF mRNA levels following exposure to precisely defined oxygen concentrations for 2 or 4 h. An oxygen sensor was used to confirm the actual levels of dissolved oxygen present. The oxygen concentrations which caused half-maximal upregulation (the Km value) of VEGF mRNA level in the three cell lines were similar except for one instance (Km at 4 h: SiHa 27.0 +/- 5.7 microM, ME-180 16.8 +/- 3.3 microM, HeLa 13.0 +/- 1.8 microM,

SiHa and HeLa P = 0.01). The Km values for the HeLa cell line as measured at 2 h (24.9 +/- 0.8 microM) and 4 h (13.0 +/- 1.8 microM) were significantly different (P < 0.0001). VEGF mRNA half-lives measured in air were consistent with values in the literature (SiHa 59.8 +/- 5.8 min, ME-180 44.4 +/- 7.2 min, HeLa 44.5 +/- 6.3 min). Differences in oxygen consumption at low oxygen concentrations were noted between the different cell lines. Stirring in suspension culture was found to induce VEGF mRNA in SiHa cells. The presence of VEGF mRNA may be a marker for radiobiologic hypoxia.

Cho, J. H., et al. (2007). "Maspin expression in early oral tongue cancer and its relation to expression of mutant-type p53 and vascular endothelial growth factor (VEGF)." Oral Oncol **43**(3): 272-277.

Even though oral tongue cancer is generally diagnosed at an early stage, the prognosis is poor due to frequent recurrence. Therefore, it is important to identify factors predictive of recurrence and to treat aggressively those patients with a high probability of recurrence. The relationship between angiogenesis and recurrence in tongue cancer has been widely investigated but no consensus has been reached. Mutant-type p53 and VEGF are known to be related to angiogenesis, and maspin is a potent angiogenic inhibitor but its role in tongue cancer has scarcely been examined. We observed the expression of maspin, mutant-type p53 and VEGF by immunohistochemistry in 33 patients with stages I and II oral tongue cancer. And the relationships between maspin, mutant-type p53, VEGF expression and recurrence were analyzed. Maspin and VEGF displayed a cytoplasmic staining pattern and mutant-type p53 a nuclear pattern. None of expression of maspin, mutant-type p53, and VEGF was significantly correlated with tumor recurrence (p=0.34, 0.56, and 0.33, respectively) and survival. Maspin expression was negatively correlated with both mutant-type p53 expression (p=0.02), and VEGF expression (p=0.01). There was no correlation between age, sex, clinical staging, and recurrence. In conclusion, the expression of maspin is not related to recurrence of early stage oral tongue cancer. It is inversely correlated with that of mutant-type p53 and of VEGF, suggesting that the maspin gene is a mutant-type p53 target in vivo and may contribute to regulate VEGF expression.

Chuai, Y., et al. (2021). "Vascular endothelial growth factor (VEGF) targeting therapy for persistent, recurrent, or metastatic cervical cancer." Cochrane Database Syst Rev **3**: CD013348.

BACKGROUND: Cervical cancer ranks as the fourth leading cause of death from cancer in women. Historically, women with metastatic or recurrent cervical cancer have had limited treatment options. New anti-angiogenesis therapies, such as vascular endothelial growth factor (VEGF) targeting agents, offer an alternative strategy to conventional chemotherapy; they act by inhibiting the growth of new blood vessels, thereby restricting tumour growth by blocking the blood supply. OBJECTIVES: To assess the benefits and harms of VEGF targeting agents in the management of persistent, recurrent, or metastatic cervical cancer. SEARCH METHODS: We performed searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, online registers of clinical trials, and abstracts of scientific meetings up until 27 May 2020. SELECTION CRITERIA: We examined randomised controlled trials (RCTs) that evaluated the use of VEGF targeting agents alone or in combination with conventional chemotherapy or other VEGF targeting agents. DATA COLLECTION AND ANALYSIS: Three review authors independently screened the results of search strategies, extracted data, assessed risk of bias, and analysed data according to the standard methods expected by Cochrane. The certainty of evidence was assessed via the GRADE approach. MAIN RESULTS: A total of 1634 records were identified. From these, we identified four studies with a total of 808 participants for inclusion. We also identified two studies that were awaiting classification and nine ongoing studies. Bevacizumab plus chemotherapy versus chemotherapy Treatment with bevacizumab plus chemotherapy may result in lower risk of death compared to chemotherapy alone (hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.62 to 0.95; 1 study, 452 participants; low-certainty evidence). However, there are probably more specific adverse events when compared to chemotherapy alone, including gastrointestinal perforations or fistulae (risk ratio (RR) 18.00, 95% CI 2.42 to 133.67; 1 study, 440 participants; moderate-certainty evidence); serious thromboembolic events (RR 4.5, 95% CI 1.55 to 13.08; 1 study, 440 participants; moderate-certainty evidence); and hypertension (RR 13.75, 95% CI 5.07 to 37.29; 1 study, 440 participants; moderate-certainty evidence). There may also be a higher incidence of serious haemorrhage (RR 5.00, 95% CI 1.11 to 22.56; 1 study, 440 participants; low-certainty evidence). In addition, the incidence of serious adverse events is probably higher (RR 1.44, 95% CI 1.16 to 1.79; 1 study, 439 participants; moderate-certainty evidence). The incremental cost-effectiveness ratio was USD 295,164 per quality-adjusted life-year (1 study, 452 participants; low-certainty evidence). Cediranib plus chemotherapy versus chemotherapy Treatment with cediranib plus chemotherapy may or may not result in similar risk of death when compared to chemotherapy alone (HR 0.94, 95% CI 0.53 to 1.65; 1 study, 69 participants; low-certainty evidence). We found very uncertain

results for the incidences of specific adverse events, including gastrointestinal perforations or fistulae (RR 3.27, 95% CI 0.14 to 77.57; 1 study, 67 participants; very low-certainty evidence); serious haemorrhage (RR 5.45, 95% CI 0.27 to 109.49; 1 study, 67 participants; very low-certainty evidence); serious thromboembolic events (RR 3.41, 95% CI 0.14 to 80.59; 1 study, 60 participants; very low-certainty evidence); and serious hypertension (RR 0.36, 95% CI 0.02 to 8.62; 1 study, 67 participants; very low-certainty evidence). In addition, there may or may not be a similar incidence of serious adverse events compared to chemotherapy alone (RR 1.15, 95% CI 0.75 to 1.78; 1 study, 67 participants; low-certainty evidence). Apatinib plus chemotherapy or chemotherapy/brachytherapy versus chemotherapy or chemotherapy/brachytherapy Treatment with apatinib plus chemotherapy or chemotherapy/brachytherapy may or may not result in similar risk of death compared to chemotherapy alone or chemotherapy/brachytherapy alone (HR 0.90, 95% CI 0.51 to 1.60; 1 study, 52 participants; low-certainty evidence). However, hypertension events may occur at a higher incidence as compared to chemotherapy alone or chemotherapy/brachytherapy alone (RR 5.14, 95% CI 1.28 to 20.73; 1 study, 52 participants; low-certainty evidence). Pazopanib plus lapatinib versus lapatinib Treatment with pazopanib plus lapatinib may result in higher risk of death compared to lapatinib alone (HR 2.71, 95% CI 1.16 to 6.31; 1 study, 117 participants; low-certainty evidence). We found very uncertain results for the incidences of specific adverse events, including gastrointestinal perforations or fistulae (RR 2.00, 95% CI 0.19 to 21.59; 1 study, 152 participants; very low-certainty evidence); haemorrhage (RR 2.00, 95% CI 0.72 to 5.58; 1 study, 152 participants; very low-certainty evidence); and thromboembolic events (RR 3.00, 95% CI 0.12 to 72.50; 1 study, 152 participants; very low-certainty evidence). In addition, the incidence of hypertension events is probably higher (RR 12.00, 95% CI 2.94 to 49.01; 1 study, 152 participants; moderate-certainty evidence). There may or may not be a similar incidence of serious adverse events as compared to lapatinib alone (RR 1.45, 95% CI 0.94 to 2.26; 1 study, 152 participants; low-certainty evidence). Pazopanib versus lapatinib Treatment with pazopanib may or may not result in similar risk of death as compared to lapatinib (HR 0.96, 95% CI 0.67 to 1.38; 1 study, 152 participants; low-certainty evidence). We found very uncertain results for the incidences of specific adverse events, including gastrointestinal perforations or fistulae (RR 1.03, 95% CI 0.07 to 16.12; 1 study, 150 participants; very low-certainty evidence); haemorrhage (RR 1.03, 95% CI 0.31 to 3.40; 1 study, 150 participants; very low-certainty evidence); and thromboembolic events (RR 3.08, 95% CI 0.13 to 74.42; 1 study, 150 participants; very low-certainty evidence). In addition, the incidence of hypertension events is probably higher (RR 11.81, 95% CI 2.89 to 48.33; 1 study, 150 participants; moderate-certainty evidence). The risk of serious adverse events may or may not be similar as compared to lapatinib (RR 1.31, 95% CI 0.83 to 2.07; 1 study, 150 participants; low-certainty evidence). AUTHORS' CONCLUSIONS: We found low-certainty evidence in favour of the use of bevacizumab plus chemotherapy. However, bevacizumab probably increases specific adverse events (gastrointestinal perforations or fistulae, thromboembolic events, hypertension) and serious adverse events. We found low-certainty evidence that does not support the use of cediranib plus chemotherapy, apatinib plus chemotherapy, apatinib plus chemotherapy/brachytherapy, or pazopanib monotherapy. We found low-certainty evidence suggesting that pazopanib plus lapatinib worsens outcomes. The VEGF inhibitors apatinib and pazopanib may increase the probability of hypertension events.

Coskun, U., et al. (2003). "Serum leptin, prolactin and vascular endothelial growth factor (VEGF) levels in patients with breast cancer." Neoplasma **50**(1): 41-46.

Angiogenesis plays an important role in tumor growth and metastasis in solid tumors. VEGF is an important regulator of tumor angiogenesis. Both leptin and prolactin have also been suggested to have roles in the regulation of angiogenic process. In our study, we measured serum leptin, prolactin and VEGF levels in 30 metastatic, 55 non-metastatic breast cancer patients and 25 control subjects. Serum leptin levels were found to be similar in non-metastatic (38.1+/-19.5 ng/ml), metastatic patients (39.6+/-16.3 ng/ml) and control subjects (35.6+/-13.9 ng/ml) ($p>0.05$). There was no statistically significant difference between patients with visceral metastasis (44.0+/-16.8 ng/ml) and patients with bone metastasis (35.2+/-15.0 ng/ml) ($p>0.05$). Serum prolactin levels were found to be similar in non-metastatic (12.2+/-10.7 ng/ml), metastatic patients (11.6+/-8.2 ng/ml) and control subjects (12.3+/-8.1 ng/ml), ($p>0.05$). Moreover, serum prolactin levels were not different in patients with visceral (11.4+/-8.8 ng/ml) and bone metastasis (11.8+/-8.0 ng/ml), ($p>0.05$). Metastatic patients had higher serum VEGF levels (249.8+/-154.9 pg/ml), when compared to the non-metastatic patients (138.7+/-59.3 pg/ml) and control subjects (108.4+/-47.7 pg/ml), ($p<0.05$). There was no difference in serum VEGF levels in non-metastatic patients and control subjects ($p>0.05$). Patients with visceral metastasis (337.0+/-168.0 pg/ml) had higher serum VEGF levels, when compared to patients with bone metastasis (162.6+71.8 pg/ml), ($p<0.05$). Serum VEGF activity may be used to evaluate angiogenic and metastatic activity in breast

cancer patients. However, serum leptin and prolactin levels does not seem to be related with angiogenic activity and metastasis in breast cancer patients.

Curigliano, G., et al. (2005). "Systemic effects of surgery: quantitative analysis of circulating basic fibroblast growth factor (bFGF), Vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta) in patients with breast cancer who underwent limited or extended surgery." Breast Cancer Res Treat **93**(1): 35-40.

BACKGROUND: To assess if feature, extent and duration of surgery could influence levels of systemic proangiogenic cytokines vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-beta). PATIENTS AND METHODS: We collected blood samples from 82 consecutive breast cancer patients who underwent various types of surgery, classified according to the magnitude of tissue injury in: minimal (quadrantectomy), moderate (mastectomy without reconstruction), and heavy [mastectomy followed by reconstruction with transversus recto-abdominal muscle cutaneous flap (TRAM)]. Samples were collected one day before surgery (D(-1)), at the end of surgical tumor removal (D0), and on 1st (D(+1)), 2nd (D(+2)) and 5th (D(+5)) day after surgery. Serum VEGF, bFGF and TGF-beta levels were measured by the enzyme immunoassay method. RESULTS: On average a continuous decrease was observed for all growth factors from the day before operation to the 5th day after operation. On day (D(+5)) an increase was observed for patients who underwent extended respect to moderate surgery. These differences were found statistically significant for bFGF and VEGF ($p = 0.05$ and $p = 0.025$ respectively). A statistically different trend for type of operation was observed also for TGF-beta at 24-48 h: a minor reduction, compared to time of operation, was observed for minimal surgery, an intermediate reduction for moderate surgery and a higher decrease for extended surgery. CONCLUSIONS: Angiogenic cytokines perioperative levels could be increased on 5th day (D(+5)) by extent of surgery and should induce perioperative stimulation of residual cancer cells. A better understanding of the time interval during which the sequelae of events in wound healing occur may be the basis for defining new therapeutic strategies that can interfere with tumor outgrowth sparing wound healing processes.

Dan, L. A., et al. (2016). "No associations of a set of SNPs in the Vascular Endothelial Growth Factor (VEGF) and Matrix Metalloproteinase (MMP) genes with survival of colorectal cancer patients." Cancer Med **5**(9): 2221-2231.

In this study, we aimed to investigate the associations of genetic variations within select genes functioning in angiogenesis, lymph-angiogenesis, and metastasis pathways and the risk of outcome in colorectal cancer patients. We followed a two-stage analysis: First, 381 polymorphisms from 30 genes (eight Vascular Endothelial Growth Factor (VEGF) and 22 Matrix Metalloproteinase [MMP] genes) were investigated in the discovery cohort ($n = 505$). Then, 16 polymorphisms with the lowest P-value in this analysis were investigated in a separate replication cohort ($n = 247$). Genotypes were obtained using the Illumina((R)) HumanOmni-1-Quad (discovery cohort) and Sequenom MassArray((R)) (replication cohort) platforms. The primary outcome measure was overall survival (OS). Kaplan-Meier, univariate and multivariable Cox regression methods were used to test the associations between genotypes and OS. Four SNPs (rs12365082, rs11225389, rs11225388, and rs2846707) had the univariate analysis $P < 0.05$ in both the discovery and replication cohorts. These SNPs are in linkage disequilibrium with each other to varying extent and are located in the MMP8 and MMP27 genes. In the multivariable analysis adjusting for age, stage, and microsatellite instability status, three of these SNPs (rs12365082, rs11225389, rs11225388) were independent predictors of OS ($P < 0.05$) in the discovery cohort. However, the same analysis in the replication cohort did not yield statistically significant results. Overall, while the genetic variations in the VEGF and MMP genes are attractive candidates as prognostic markers, our study showed no evidence of associations of a large set of SNPs in these genes and overall survival of colorectal cancer patients in our study.

Deacon, K., et al. (2012). "Elevated SP-1 transcription factor expression and activity drives basal and hypoxia-induced vascular endothelial growth factor (VEGF) expression in non-small cell lung cancer." J Biol Chem **287**(47): 39967-39981.

VEGF plays a central role in angiogenesis in cancer. Non-small cell lung cancer (NSCLC) tumors have increased microvascular density, localized hypoxia, and high VEGF expression levels; however, there is a lack of understanding of how oncogenic and tumor microenvironment changes such as hypoxia lead to greater VEGF expression in lung and other cancers. We show that NSCLC cells secreted higher levels of VEGF than normal airway epithelial cells. Actinomycin D inhibited all NSCLC VEGF secretion, and VEGF minimal promoter-luciferase reporter constructs were constitutively active until the last 85 base pairs before the transcription start site containing three SP-1 transcription factor-binding sites; mutation of these VEGF promoter SP-1-binding sites eliminated

VEGF promoter activity. Furthermore, dominant negative SP-1, mithramycin A, and SP-1 shRNA decreased VEGF promoter activity, whereas overexpression of SP-1 increased VEGF promoter activity. Chromatin immunoprecipitation assays demonstrated SP-1, p300, and PCA/F histone acetyltransferase binding and histone H4 hyperacetylation at the VEGF promoter in NSCLC cells. Cultured NSCLC cells expressed higher levels of SP-1 protein than normal airway epithelial cells, and double-fluorescence immunohistochemistry showed a strong correlation between SP-1 and VEGF in human NSCLC tumors. In addition, hypoxia-driven VEGF expression in NSCLC cells was SP-1-dependent, with hypoxia increasing SP-1 activity and binding to the VEGF promoter. These studies are the first to demonstrate that overexpression of SP-1 plays a central role in hypoxia-induced VEGF secretion.

Dong, X., et al. (2003). "[Expression of vascular endothelial growth factor (VEGF) C and VEGF receptor 3 in non-small cell lung cancer]." Zhonghua Bing Li Xue Za Zhi **32**(2): 128-132.

OBJECTIVE: To study the relationship between angiogenesis and lymphangiogenesis with the expression of vascular endothelial growth factor C (VEGF-C) and VEGFR-3 in human non-small cell lung cancer (NSCLC). METHODS: Samples of 76 NSCLC cases with the neighboring noncancerous tissue were studied using anti- VEGF-C, VEGFR-3 and CD34 antibodies. Assessment of lymphatic vessel density and microvessel density (MVD) were performed. RESULTS: VEGF-C expression in NSCLC was associating with the differentiation of tumor cells (P = 0.009). Expression of VEGF-C and VEGFR-3 was significantly associated with lymph node metastasis (P = 0.008 and P = 0.013 respectively) and lymphatic invasion (P = 0.027 and P = 0.020 respectively). A significant positive correlation was found between VEGF-C in cancer cells and VEGFR-3 in lymphatic endothelial cells (P = 0.009). The number of lymphatic vessels (P = 0.006) and microvascular (P = 0.046) in VEGF-C positive tumors was significantly larger than in VEGF-C-negative tumors. Lymphatic vessel density was closely related to lymph node metastasis (P = 0.010), lymphatic invasion (P = 0.019) and clinical stages (P = 0.015). MVD was closely related to blood metastasis (P < 0.001) and clinical stages (P < 0.001). Patients with positive VEGF-C expression had a worse prognosis than those with a negative VEGF-C expression (P < 0.001). CONCLUSIONS: VEGF-C/VEGF-D in NSCLCs, are related to lymphangiogenesis and angiogenesis, as well as to the occurrence and the development of lung cancers. VEGF-C promotes intratumoral lymphangiogenesis via VEGFR-3, resulting facilitated invasion of cancer cells into the lymphatic vessels. VEGF-C expression can be a useful predictor of poor prognosis in NSCLC.

Donnem, T., et al. (2010). "Combination of low vascular endothelial growth factor A (VEGF-A)/VEGF receptor 2 expression and high lymphocyte infiltration is a strong and independent favorable prognostic factor in patients with nonsmall cell lung cancer." Cancer **116**(18): 4318-4325.

BACKGROUND: There seems to be a close interplay between angiogenesis and the immune system. The authors of this report investigated the prognostic role of angiogenic markers in coexpression with immune system markers in patients with nonsmall cell lung cancer (NSCLC). METHODS: Tumor resection samples from 335 patients with stage I to IIIA NSCLC were obtained, and tissue microarrays were constructed. Immunohistochemistry was used to evaluate the expression of vascular endothelial growth factor (VEGF) A (VEGF-A), VEGF receptor 2 (VEGFR-2), and lymphocytes that were positive for the cluster of differentiation 4 (CD4) and CD8 coreceptors. RESULTS: In univariate analysis, 5-year survival rates were 87% for the combination of low tumor cell expression of VEGF-A and VEGFR-2 (downward arrowVEGF-A/ downward arrowVEGFR-2) and high tumor cell expression of CD4 and CD8 (upward arrowCD4/ upward arrowCD8) (n = 19), 58% for mixed combinations (n = 290), and 27% for the upward arrowVEGF-A/ upward arrowVEGFR-2 and downward arrowCD4/ downward arrowCD8 combination (n = 26). In multivariate analysis, the coexpression of upward arrowVEGF-A/ upward arrowVEGFR-2 and downward arrowCD4/ downward arrowCD8 was an independent negative prognostic factor (hazard ratio, 9.16; 95% confidence interval, 2.11-39.8; P = .003). CONCLUSIONS: Low tumor cell VEGF-A and VEGFR-2 expression in combination with high adaptive immune cell expression in the tumor-related stroma had a strong and independent favorable prognostic impact in patients with NSCLC.

Dunst, J., et al. (1999). "Low hemoglobin is associated with increased serum levels of vascular endothelial growth factor (VEGF) in cancer patients. Does anemia stimulate angiogenesis?" Strahlenther Onkol **175**(3): 93-96.

BACKGROUND: Vascular endothelial growth factor (VEGF) is an endothelial cell specific mitogen with strong angiogenic activity. Expression of VEGF may therefore be an indicator for the angiogenic potential and biological aggressiveness of a tumor. Recently, measurement of the VEGF-protein in sera has become available. We report results of serum-VEGF in an unselected group of patients with cancer with special emphasis on a possible role of anemia.

PATIENTS AND METHODS: Between August 1997 and January 1998, serum-levels of VEGF were determined in a total number of 54 consecutive patients with previously untreated, non-metastatic carcinomas at the Department of Radiotherapy at the Martin-Luther University Halle-Wittenberg. The age ranged from 35 through 89 years with a median age of 67 years. All patients had locoregional confined disease without evidence of hematogenous metastases. Tumor sites were gynecological cancers in 22, head and neck in 14, gastrointestinal in 13, lung in 4 and prostate in 1 case. Forty-four patients had squamous carcinomas and 10 adenocarcinomas. Prior to treatment, routine laboratory work-up was done including measurement of serum-vascular endothelial growth factor (VEGF). The pretreatment hemoglobin ranged from 8.9 through 15.6 g/dl with a median of 13 g/dl. VEGF was measured with a quantitative sandwich enzyme immunoassay technique. RESULTS: The serum levels of VEGF in 40 patients with benign diseases ranged from 57 through 891 pg/ml with a mean of 267 +/- 170 pg/ml. In the investigated 54 cancer patients, VEGF ranged from 62 through 2,609 pg/ml with a mean of 614 +/- 551 pg/ml. Age, UICC/FIGO-stage, T- or N-category, primary tumor site, grade and histologic type had no significant impact on VEGF-serum levels. There was, however, an association between hemoglobin level and serum-VEGF with an increased mean serum-VEGF in 26 patients with a low hemoglobin (< 13 g/dl) as compared to 28 patients with a hemoglobin > 13 g/dl (805 +/- 656 vs 438 +/- 360, p = 0.016, 2-sided t-test). CONCLUSIONS: With regard to the recently established correlation between anemia and intratumoral hypoxia, the increased serum-VEGF levels in patients with low hemoglobin may be explained via hypoxia-induced VEGF secretion. This would suggest that anemia may stimulate angiogenesis via hypoxia. The hypothesis, however, requires further investigation and might have important therapeutical impact.

Dziadziuszko, R., et al. (2001). "Expression of vascular endothelial growth factor (VEGF) and its receptor FLK-1 in non-small cell lung cancer (NSCLC)--a preliminary report." Folia Histochem Cytobiol **39 Suppl 2**: 100-101.

The assessment of tumour angiogenesis in NSCLC is presently a subject of intensive research with potential clinical applications. In this study, the expression of VEGF and FLK-1 was examined by immunohistochemistry in 67 archival tumour samples obtained from NSCLC patients treated by radical resection. Distribution of age, sex, tumour stage and histology was typical for patient population in Poland. VEGF expression (more than 25% of positive cells) was noted in 65% of tumour cells. FLK-1 expression was observed in 91% of tumour cells. Neither the number of positive cells nor the staining intensity correlated with the clinical variables (all p values >0.05, chi-square test). No correlation was noted between the expression of VEGF and FLK-1 (p=0.35, chi-square test). In survival analysis, neither the number of positive cells nor the staining intensity of both molecules was of prognostic significance. The expression of VEGF and FLK-1 in NSCLC cells was confirmed in this study. The relation to clinical variables and survival will be further assessed in a larger group of patients.

Eroglu, A., et al. (2017). "Vascular endothelial growth factor (VEGF)-C, VEGF-D, VEGFR-3 and D2-40 expressions in primary breast cancer: Association with lymph node metastasis." Adv Clin Exp Med **26**(2): 245-249.

BACKGROUND: Two members of the vascular endothelial growth factor (VEGF) family, VEGF-C and -D, are known as lymphangiogenic growth factors and play an important role in tumor lymphangiogenesis via activation of the VEGF receptor (VEGFR)-3, which is expressed in lymphatic endothelial cells. D2-40 is a specific antibody for lymphatic vessel density (LVD). OBJECTIVES: In the present study, we have aimed to evaluate whether intraand peri-tumoral D2-40-positive lymphatic vessels affect lymph node metastasis and to investigate the relationship between LVD and lymph node metastasis in breast cancer. MATERIAL AND METHODS: We have evaluated the relationships between lymph node metastasis and VEGF-C, VEGF-D, VEGFR-3 and D2-40 expressions in breast cancer cells using immunohistochemistry. VEGF-C, VEGF-D and VEGFR-3 expression were found in tumor cells in the majority of the cases (83.75, 97.5 and 95%, respectively). RESULTS: There was a significant positive relationship between VEGF-D expression and lymph node metastasis ($p < 0.05$) however no significant association was found in VEGF-C and VEGFR-3 expressions. It was found that patients with high-expression of VEGF-D have a high level of both periand intra-tumoral LVD compared to those with low expression of VEGF-D ($p < 0.05$). CONCLUSIONS: Our results support that examination of VEGF-D expression in breast cancer cells may be beneficial in the identification of lymph node metastasis.

Faviana, P., et al. (2002). "Neoangiogenesis in colon cancer: correlation between vascular density, vascular endothelial growth factor (VEGF) and p53 protein expression." Oncol Rep **9**(3): 617-620.

Angiogenesis is an essential requirement for the development, progression and metastasis of malignant tumors. Vascular endothelial growth factor

(VEGF) plays an essential role in the development of angiogenesis of numerous solid malignancies, including colon cancer. The tumor suppressor gene p53 is a potent transcriptional regulator of genes which are involved in many cellular activities, including cell-cycle arrest, apoptosis and angiogenesis. In order to better understand the relation among p53 status, VEGF expression and microvessels count (MVC) in colon cancer, we evaluated immunoreactivity for CD34 endothelium-associated antigen, VEGF and p53 proteins in 43 cases of colon adenocarcinoma. Our results demonstrated an association between VEGF expression, p53 status and angiogenesis, suggesting that mutant p53 plays a central role in promoting angiogenesis in colon cancer progression.

Ferrer, F. A., et al. (1997). "Vascular endothelial growth factor (VEGF) expression in human prostate cancer: in situ and in vitro expression of VEGF by human prostate cancer cells." J Urol **157**(6): 2329-2333.

PURPOSE: A growing body of literature supports the role of angiogenesis in the development and spread of a variety of human cancers including prostate cancer (Pca). Angiogenesis is controlled by chemical signals known as angiogenic factors (AF) however, little is known about angiogenesis factors in prostate cancer. We evaluated the in situ and in vitro expression of vascular endothelial growth factor (VEGF), a potent angiogenic factor, in archival prostate cancer specimens and prostate cancer cell cultures during unstimulated and cytokine stimulated conditions. METHODS: Ex-vivo studies involved immunohistochemical analysis for VEGF expression and distribution in 25 archival specimens including, prostate cancer, benign prostatic hyperplasia (BPH) and normal prostate tissue. In-vitro studies utilized prostate cancer cells (DU-145) grown in culture and stimulated with cytokines thought to induce VEGF (i.e. IL-1 alpha, IL-1 beta, TNF-alpha and TNF-beta). Cell culture supernatants were analyzed by ELISA for VEGF levels. RESULTS: Immunohistochemical studies demonstrated that in 20 of 25 specimens prostate cancers cells stained positively for VEGF. BPH and normal prostate cells displayed little staining for VEGF. DU-145 prostate cancer cells produced low levels of VEGF in unstimulated conditions. Induction of DU-145 cells with cytokines resulted in differential stimulation whereby TNF was a potent inducer of VEGF, and IL-1 produced lesser but statistically significant increases in VEGF expression. CONCLUSIONS: Our immunohistochemical results indicate that significant levels of VEGF are present in prostate cancer, but not in BPH or normal prostate cells in-vivo. In-vitro studies suggest that differential regulation of angiogenesis factor expression by IL-1 and TNF occurs in prostate cancer. Identifying the angiogenesis factors involved in prostate cancer growth and understanding their regulation will lead to the development of anti-angiogenic strategies useful for diagnostic studies and therapeutic interventions.

Fersis, N., et al. (2004). "Changes in vascular endothelial growth factor (VEGF) after chemoendocrine therapy in breast cancer." Eur J Gynaecol Oncol **25**(1): 45-50.

PURPOSE: Angiogenesis has been proposed as a possible target for anticancer treatment, either by inhibition of the production of angiogenic factors or by inhibition of endothelial cell proliferation. The impact of preoperative chemoendocrine therapy is unknown in the regulation of angiogenic factors, but recent reports suggest that anticancer drugs have antiangiogenic activity. METHODS: The expression of two angiogenic factors VEGF and Angiopoetin-1 were quantified at different concentrations of doxorubicin, docetaxel, tamoxifen, exemestane and letrozol on MCF-7 and T47D cells. RESULTS: Low-drug concentrations led to increased VEGF-A gene transcription whereas high (10-fold increased) drug concentrations suppressed gene expression. A similar cell reaction was observed for VEGF protein with a smaller variety in the extent of modulation. Incubation of MCF-7 cells to different drugs showed a similar dose-dependent modulation of Angiopoietin-1 gene expression with enhancement at low-drug concentrations. CONCLUSION: Treatment of breast cancer cells following a preoperative protocol showed a dose-dependent expression of VEGF and Angiopoetin-1. Only high-drug concentrations were followed by a decreased secretion of both factors whereas low concentrations induced up-regulation of VEGF and Angiopoietin 1.

Findeisen, R., et al. (2000). "Chemiluminometric determination of tissue polypeptide antigen (TPA), cancer antigen 15-3 (CA 15-3), carcinoembryonic antigen (CEA) in comparison with vascular endothelial growth factor (VEGF) in follow-up of breast cancer." Luminescence **15**(5): 283-289.

Vascular endothelial growth factor (VEGF), tissue polypeptide antigen (TPA), cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) were measured in 314 sera of breast cancer patients and in 58 sera of women without breast cancer. VEGF was determined using a sandwich enzyme immunoassay technique (ELISA) and the tumour markers TPA, CA 15-3 and CEA with an immunoluminometric assay (ILMA). The breast cancer patients were staged according to the TNM classification stages 0-IV (by UICC) in patient groups with a compatible prognosis. Median and range of each stage were investigated. The

cut-off values (95th and 97.5th percentile of control group) of VEGF, TPA, CA15-3 and CEA were determined; sensitivities for each parameter and for all combinations of two parameters were investigated for these cut-offs and the receiver operating characteristic (ROC) curves were calculated. The differences between the control group and stages 0-3 were shown to be non-significant for CA 15-3 and CEA but significant for VEGF and TPA. Significant differences were found in stage 4 for VEGF and all three markers. The increase in sensitivity of VEGF from stage 0 to stage 3 and the decrease from stage 3 to stage 4 can be interpreted based on the role of VEGF in the angiogenesis. The quantification of VEGF could give additional information for selecting patients for systemic adjuvant therapy.

Fontanini, G., et al. (1997). "Neoangiogenesis and p53 protein in lung cancer: their prognostic role and their relation with vascular endothelial growth factor (VEGF) expression." Br J Cancer **75**(9): 1295-1301.

Following up-regulation of an angiogenesis inhibitor by the wild-type p53 protein proven recently, we have analysed on the one hand the prognostic impact of microvessel count (MC) and p53 protein overexpression in non-small-cell lung carcinoma (NSCLC) progression and, on the other hand, the inter-relation between the microvascular pattern and the p53 protein expression. Moreover, we assessed the expression of vascular endothelial growth factor (VEGF), one of the pivotal mediators of tumour angiogenesis, in order to investigate its relation to p53 protein expression and MC. Tumours from 73 patients resected for NSCLC between March 1991 and April 1992 (median follow-up 47 months, range 32-51 months) were analysed using an immunohistochemical method. In univariate analysis, MC and p53 accumulation were shown to affect metastatic nodal involvement, recurrence and death significantly. Multiple logistic regression analysis showed an important prognostic influence of MC and nodal status on overall (P = 0.0009; P = 0.01) and disease-free survival (P = 0.0001; P = 0.03). Interestingly, a strong statistical association was observed between p53 nuclear accumulation and MC (P = 0.0003). The same inter-relationship was found in non-squamous histotype (P = 0.002). When we analysed the concomitant influence of MC and p53 expression on overall survival, we were able to confirm a real predominant role of MC in comparison with p53. With regard to VEGF expression, p53-negative and lowly vascularized tumours showed a mean VEGF expression significantly lower than p53-positive and highly vascularized cancers (P = 0.02). These results underline the prognostic impact of MC and p53 protein accumulation in NSCLC and their reciprocal inter-relationship, supporting the hypothesis of a wild-type p53 regulation on the angiogenetic process through a VEGF up-regulation.

Fujimoto, J., et al. (1999). "Progestins suppress estrogen-induced expression of vascular endothelial growth factor (VEGF) subtypes in uterine endometrial cancer cells." Cancer Lett **141**(1-2): 63-71.

Vascular endothelial growth factor (VEGF) contributes to the early advancement of uterine endometrial cancers that conserve hormone dependency via angiogenic activity. This process prompted us to study sex steroidal suppression of VEGF expression in Ishikawa cells (a line of well-differentiated uterine endometrial cancer cells). Estrogen transiently induced VEGF subtype (VEGF165 and VEGF121) secretion from Ishikawa cells. Progestins (progesterone, medroxyprogesterone acetate (MPA) and 17 alpha-hydroxyprogesterone) suppressed the estrogen-induced events. In conclusion, progestins could suppress VEGF-related angiogenic potential, which contributes to tumor growth in the early stage of uterine endometrial cancers that conserve estrogen dependency.

Gadducci, A., et al. (1999). "Serum preoperative vascular endothelial growth factor (VEGF) in epithelial ovarian cancer: relationship with prognostic variables and clinical outcome." Anticancer Res **19**(2B): 1401-1405.

Substantial experimental and clinical evidence links tumor growth, progression and metastatic potential with neoangiogenesis. This process is modulated by several angiogenic growth factors, such as vascular endothelial growth factor (VEGF). Little data are currently available on serum VEGF levels in cancer patients. In the present retrospective investigation preoperative serum VEGF was higher in 53 patients with epithelial ovarian cancer than in 25 patients with benign ovarian disease as controls (median, range: 229.7, 23.5-1807.5 pg/ml versus 140.3, 14.7-1038.7 pg/ml, p = 0.034). With regard to FIGO stage, antigen values were significantly elevated in stage III-IV (p = 0.027) but not in stage I-II ovarian cancer patients when compared to controls. In patients with advanced disease preoperative serum VEGE was significantly related to the presence of ascites (p = 0.013), but not to common prognostic variables, response to chemotherapy and survival. In conclusion, preoperative serum VEGF assay reflects tumor progression and ascites generation in epithelial ovarian cancer, but it seems to have a limited predictive and prognostic value in patients with advanced disease.

Ghosh, S. and P. Maity (2004). "Isolation and purification of vascular endothelial growth factor

(VEGF) from ascitic fluid of ovarian cancer patients." Pathol Oncol Res **10**(2): 104-108.

Vascular Endothelial Growth Factor (VEGF) or Vascular Permeability Factor (VPF) is an angiogenic cytokine expressed by many human and animal tumors. Because of the importance of VEGF in animal tumors, we purified VEGF/VPF from ascitic fluid of ovarian cancer patients with heparin sepharose column. The purified protein gave protein bands of 37 and 26 kD, respectively in 12% SDS PAGE. The specificity of the purified protein was determined with dot blot, trans-immunoblot and ELISA using polyclonal goat anti-VEGF antibody (Santa Cruz Biotechnology). The vasodilatatory effect of the purified protein was confirmed by a vascular permeability assay on mouse. A polyclonal mouse antibody was raised against the purified protein, which recognized the same protein by ELISA, transimmunoblot and dot-blot analysis. It has been also found that the raised polyclonal antibody in mouse- and the commercial VEGF polyclonal antibody (Santa Cruz Biotechnology) both inhibited in vitrocell proliferation of human MCF-7 cell line. This study shows for the first time an effort to purify VEGF from human source.

Giannice, R., et al. (2013). "Chemokines mRNA expression in relation to the Macrophage Migration Inhibitory Factor (MIF) mRNA and Vascular Endothelial Growth Factor (VEGF) mRNA expression in the microenvironment of endometrial cancer tissue and normal endometrium: a pilot study." Cytokine **64**(2): 509-515.

Tumor microenvironment inflammatory cells play a major role in cancer progression. Among these, the Tumor Associated Macrophages (TAMs) infiltration depends on the kind of chemokine, cytokines and growth factors secreted by the tumor cells and by the stroma in response to the cancer invasion. TAMs have been found to promote anti-tumor response in early stages and to stimulate neovascularization and metastases in advanced disease. In the microenvironment chemo-attractants of many human cancers, MIF and VEGF correlate with an increased TAMs recruitment. In addition, MIF enhances tumor cells metastases by modulating the immune responses and by promoting the angiogenesis related to VEGF. On the contrary the inhibition of MIF can lead to cell cycle arrest and apoptosis. Some chemokines (e.g. CXCL12, CXCL11, CXCL8) and their receptors, thanks to their ability to modulate migration and proliferation, are involved in the angiogenetic process. In this study we compared the expression of MIF mRNA with VEGF mRNA expression and with mRNA expression of other chemokines related to neo-angiogenesis, such as CXCL12, CXCL11, CXCL8 and CXCR4, in human endometrial cancer tissue (EC) and normal endometrium (NE). Fresh samples of EC tissue and NE were extracted from 15 patients with FIGO stage I-III undergoing primary surgery. Some of the tissue was sent for histology and part of it was treated with RNA later and stored at -80 degrees C. Four patients dropped out. A significant up-regulation of MIF mRNA in EC tissue versus NE samples (P=0.01) was observed in all 11 patients. The MIF mRNA over-expression was coincident with a VEGF mRNA overexpression in 54% of patients (P=NS). MIF mRNA was inversely related to CXCL12 mRNA expression (P=0.01). MIF over-expression was significantly related to low grading G1-2 (P=0.01), endometrial type I (P=0.05), no lymphovascular spaces invasion (P=0.01) and 3years DFS (P=0.01). As reported in previous studies on patients with breast cancer, our data suggest that the up-regulation of MIF in patients with endometrial cancer might be related to the inhibition of distant and lymphatic spread.

Gonzalez-Palomares, B., et al. (2017). "Vascular Endothelial Growth Factor (VEGF) Polymorphisms and Serum VEGF Levels in Women With Epithelial Ovarian Cancer, Benign Tumors, and Healthy Ovaries." Int J Gynecol Cancer **27**(6): 1088-1095.

OBJECTIVE: This study analyzed the relation of 5 single-nucleotide polymorphisms (SNPs) in the VEGF (vascular endothelial growth factor) gene in patients with epithelial ovarian cancer (EOC), compared with patients carrying benign tumors or healthy ovaries. We studied serum VEGF levels and the relation with SNPs and association between VEGF SNPs and haplotypes with progression-free survival (PFS) in patients with cancer. METHODS: The genotyping of VEGF gene polymorphisms (-2578 C/A, -1154 G/A, -460 T/C, +405 G/C, +936 C/T) was performed in DNA isolated from blood samples of 100 women. The different genotypes were evaluated by quantitative real-time polymerase chain reaction. Vascular endothelial growth factor protein concentration was assessed in serum using solid-phase sandwich enzyme-linked immunosorbent assay. RESULTS: We found statistically significant differences in the distribution of VEGF genotypes among the 3 groups of patients: -2578 C/A between those with EOC and healthy ovary (P = 0.04), -460 T/C between those with EOC and healthy ovary (P = 0.03), and -460 T/C between those with benign tumors and healthy ovary (P = 0.02). Vascular endothelial growth factor serum levels were analyzed in patients with EOC. Higher levels were found in patients with clear cell carcinoma compared with those with serous, mucinous, or endometrioid tumors (P < 0.05). No clear association was observed between VEGF SNPs and serum VEGF levels. There was no significant

correlation between VEGF SNPs and PFS. In haplotype analysis, CGTCT and CGTGT showed worse prognosis without reaching the statistical significance. CGCGC and AGTGC haplotypes had statistically significant differences among patients with EOC, benign tumors, and healthy ovaries (Ps = 0.046 and 0.041, respectively). CONCLUSIONS: The distribution of VEGF genotypes was different in patients with EOC, compared with those with benign tumors or women with healthy ovaries. Vascular endothelial growth factor serum levels were higher in patients with clear cell carcinoma. No correlation was found with improved PFS, but CGTCT and CGTGT haplotypes showed worse prognosis.

Goulart, A., et al. (2019). "The correlation between serum vascular endothelial growth factor (VEGF) and tumor VEGF receptor 3 in colorectal cancer." Ann Surg Treat Res **97**(1): 15-20.

PURPOSE: Despite plasma biomarkers offering a number of advantages over tissue-based markers, the relationship between serum vascular endothelial growth factor (VEGF) and VEGF receptor (VEGF-R) tumor expression in colorectal cancer (CRC) is still unclear. This study was designed to establish the relationship between the concentration of serum VEGF and tumor VEGF-R expression in patients with CRC. METHODS: A prospective study of consecutive patients undergoing elective colorectal surgery during 1 year. Preoperative VEGF was determined by enzyme-linked immunosorbent assay and VEGF-R3 by immunochemistry. RESULTS: The initial sample included 134 patients with CRC diagnosis. Results showed significant association of serum values of VEGF with VEGF-R3 expression ($P < 0.001$), even in the presence of confounders (sex, age, body mass index, tumor location, and surgical approach). The estimated effect size was high (eta(2) = 0.35). CONCLUSION: Serum VEGF has a significant correlation with tumoral VEGF-R3 expression in CRC.

Gray, R. T., et al. (2013). "Long-term follow-up of immunocytochemical analysis of vascular endothelial growth factor (VEGF), and its two receptors, VEGF-R1 (Flt-1) and VEGF-R2 (Flk-1/KDR), in oesophagogastric cancer." Int J Biol Markers **28**(1): 63-70.

BACKGROUND: The prognostic significance of immunocytochemical analysis of tumour vascular endothelial growth factor (VEGF) and its 2 receptors, VEGF-R1 and VEGF-R2, remains incompletely investigated in patients with oesophagogastric cancer. METHODS: Patients undergoing surgical resection were prospectively recruited between February 1999 and August 2000. Immunocytochemical analysis of VEGF, VEGF-R1 (Flt-1) and VEGF-R2 (Flk-1/KDR) was undertaken using validated techniques. Patients were followed up over a 10-year period using the Northern Ireland Cancer Registry. RESULTS: Sixty-one patients were recruited (male=45, 73.8%) with a median age of 66.0 years (range 39-83). Forty-seven (77.0%) adenocarcinomas and 14 (23.0%) squamous cell carcinomas were resected. UICC tumour staging was: stage I=14.7%, II=24.6%, III=54.1% and IV=6.6%. VEGF, VEGF-R1 and VEGF-R2 were over-expressed in tumour epithelial cells. VEGF-R2 expression was decreased in the presence of lymphovascular invasion and higher tumour grade. The 10-year survival rate was 19.7% (n=12) with a median follow-up of 808 (IQR 356-2313) days. On univariate analysis only lymphovascular invasion significantly predicted poor prognosis in this cohort (p=0.05). CONCLUSION: VEGF, VEGF-R1 and VEGF-R2 were over-expressed in tumour epithelial cells. VEGF-R2 expression was decreased in the presence of more aggressive pathological variables. Larger studies are required to assess the prognostic significance of these biomarkers in oesophagogastric cancer.

Gray, R. T., et al. (2012). "Quantification of tumour and circulating vascular endothelial growth factor (VEGF) in patients with oesophagogastric cancer: a long-term follow-up study." Br J Biomed Sci **69**(2): 71-75.

Vascular endothelial growth factor (VEGF) is an angiogenic cytokine that regulates tumour angiogenesis. The prognostic significance of VEGF expression remains incompletely investigated for patients with oesophagogastric cancer. This study assesses the significance of tumour VEGF (T-VEGF) and circulating VEGF (C-VEGF) expression in a 10-year follow-up of patients with oesophagogastric cancer. Patients undergoing surgical resection were prospectively recruited between February 1999 and August 2000. Circulating VEGF, derived both from plasma (P-VEGF) and serum (S-VEGF), and T-VEGF were assessed using a commercial enzyme-linked immunosorbent assay (ELISA). As platelet count may contribute to C-VEGF, pre-operative platelet levels were also recorded to exclude a confounding effect. Patients were followed up over a 10-year period using the Northern Ireland Cancer Registry. Sixty-one patients were recruited (men=45) with a mean age of 65.7 years. The 10-year survival was 19.7% (n=12) with a median follow-up of 808 days (inter-quartile range [IQR]: 349.5-2358.5). Union for International Cancer Control (UICC) tumour staging was Stage I=9 (14.8%), Stage II=15 (24.6%), Stage III=33 (54.1%) and Stage IV=4 (6.6%). The only significant relationship between clinicopathological features and the study variables was for S-VEGF, which was elevated in patients with advanced T-stage ($P = 0.05$).

Circulating VEGF did not correlate with platelet count. Although a trend towards decreased survival was observed for patients who had positive lymph nodes (P = 0.08) and advanced UICC stage (P = 0.09) on univariate analysis, only lymphovascular invasion significantly predicted poor prognosis in this cohort (P = 0.05). Therefore, ELISA quantification of circulatory or tumour VEGF does not appear to be a significant predictor of mortality in patients with oesophagogastric cancer.

Greb, R. R., et al. (1999). "Vascular endothelial growth factor A (VEGF-A) mRNA expression levels decrease after menopause in normal breast tissue but not in breast cancer lesions." Br J Cancer **81**(2): 225-231.

We hypothesized that the regulation of microvascular functions and angiogenesis in breast tissue, a well known target of ovarian steroid action, is dependent on the hormonal exposure of the breast. Relative expression levels of VEGF-A (vascular endothelial growth factor A), a putative key regulator of angiogenesis in breast cancer, were analysed in the tumour and the adjacent non-neoplastic breast tissue of 19 breast cancer patients by quantitative reverse transcriptase polymerase chain reaction. In non-neoplastic breast specimens the expression levels of all detected VEGF-A-isoforms (189, 165, 121) were significantly higher in premenopausal compared to post-menopausal women (P = 0.02) and were inversely correlated with the patient's age (P = 0.006). In contrast, in cancerous tissues menopausal status had no influence on VEGF-A-expression levels. Benign and malignant tissues exhibited a similar expression pattern of VEGF-A-isoforms relative to each other. Thus, the regulation of the vasculature in normal breast tissue, as opposed to breast cancer tissue, appears to be hormonally dependent. Endogenous and therapeutically used hormonal steroids might, therefore, cause clinically relevant changes of the angiogenic phenotype of the human breast.

Green, M. M., et al. (2007). "Expression of vascular endothelial growth factor (VEGF) in locally invasive prostate cancer is prognostic for radiotherapy outcome." Int J Radiat Oncol Biol Phys **67**(1): 84-90.

PURPOSE: Vascular endothelial growth factor (VEGF) is an important hypoxia-inducible pro-angiogenic protein that has been linked with an adverse survival outcome after radiotherapy in other cancer types: we hypothesized that this may also occur in prostate cancer. A retrospective study was, therefore, carried out to evaluate the potential of tumor VEGF expression to predict radiotherapy outcome in patients with high-risk prostate cancer. METHODS AND MATERIALS: Fifty patients with locally advanced (T3 N0 M0) tumors of Gleason score > or =6, and who received radiotherapy alone as primary treatment for their disease, were studied. Vascular endothelial growth factor expression was assessed on pretreatment diagnostic tumor biopsies using a semiquantitative immunohistochemical scoring system. The results were analyzed in relation to clinicopathologic factors and patient outcome including biochemical failure and disease-specific mortality. RESULTS: High VEGF expression was associated with a poor prognosis: in univariate log rank analysis, VEGF was the only significant prognostic factor for disease-specific survival (p = 0.035). High VEGF expression also associated with increased Gleason score (p = 0.02), but not posttreatment biochemical failure. CONCLUSION: High tumor expression of VEGF identified patients at high risk of failure of treatment with radiotherapy. These patients might benefit from additional treatment approaches incorporating anti-angiogenic or hypoxia-specific agents.

Groves, M. D., et al. (2009). "Biomarkers of disease: cerebrospinal fluid vascular endothelial growth factor (VEGF) and stromal cell derived factor (SDF)-1 levels in patients with neoplastic meningitis (NM) due to breast cancer, lung cancer and melanoma." J Neurooncol **94**(2): 229-234.

BACKGROUND: Breast cancer, lung cancer and melanoma metastasize to the meninges in 5-15% of patients. The identification of specific biomarkers of disease may allow for earlier diagnosis and treatment. Preclinical evidence suggests the possible relevance of SDF-1 and VEGF in the homing and neoangiogenesis of metastases. We chose to measure these molecules in the cerebrospinal fluid (CSF) of melanoma, breast, and lung cancer patients being evaluated for neoplastic meningitis (NM). MATERIALS AND METHODS: We collected CSF from patients with these cancers who were being evaluated for possible NM. CSF was assayed for SDF-1 and VEGF levels using Enzyme-linked Immunosorbent Assay (ELISA) assays. RESULTS: CSF samples from 89 patients met criteria for analysis, including 41 with breast cancer, 35 with lung cancer and 13 with melanoma. Twenty-five percent (22/89) of all samples were positive for malignant cells; 8/41 (20%) from breast cancer, 10/35 (29%) from lung cancer and 4/13 (31%) from melanoma. CSF VEGF levels were available from 83 patients, and were elevated (>20 pg/ml) in 15/22 (68%) of patients with positive CSF cytology and normal (<20 pg/ml) in 59/61 (97%) of patients with negative CSF cytology. The two patients with negative CSF cytology who also had elevated CSF VEGF levels had MRI evidence of NM. CSF SDF-1 levels were available from 81 patients, and were elevated (>950 pg/ml) in 11/18 (61%) of patients with positive CSF cytology and normal (<950 pg/ml) in 57/63 (90%) of

patients with negative CSF cytology. CONCLUSIONS: Elevated CSF levels of VEGF are sensitive and highly specific for the diagnosis of NM from breast cancer, lung cancer and melanoma, and may serve as a useful biomarker of NM in high risk patients. CSF SDF-1 levels add little to the diagnostic information provided by CSF VEGF. Evaluation of CSF VEGF levels as a trigger for early treatment in high risk breast cancer, lung cancer and melanoma patients at risk for NM, is warranted.

Halmaciu, I., et al. (2012). "[Preliminary results regarding vascular endothelial growth factor (VEGF-A) levels in the serum of gastric cancer patients]." Rev Med Chir Soc Med Nat Iasi **116**(2): 446-451.

UNLABELLED: The most studied VEGF molecule is VEGF-A (Vascular Endothelial Growth Factor). Its involvement in various neoplastic processes represents an intensely controversial hypothesis. MATERIAL AND METHODS: This is a prospective study extending over a period of 7 months, and including 38 hospitalized patients who underwent surgery for gastric cancer between 01/01/2011-07/01/2011, at the Surgery Departments of the Emergency Clinical County Hospital Mures. Survival rate was determined based on age and gender of the patients, the macroscopic and microscopic appearance of the tumor, and pT, N, M parameters of the resected specimens. All these tumor parameters were correlated with preoperative VEGF-A levels, measured at the Central Laboratory of the Emergency Clinical County Hospital Mures, using plasma samples and a human VEGF ELISA kit with cross-reactivity with VEGF 165 (BioLife Group), according to the instructions provided by the manufacturer. No enrolled patient had any preoperative treatment. In order to establish the reference value for VEGF-A in serum, we tested a group of 14 apparently healthy persons, and we calculated a mean value. RESULTS: The reference value for VEGF-A in serum was 157.3 pg/ml. In gastric cancer patients the preoperative VEGF-A levels were 376, 188 +/- 247.11, showing significant elevation vs. the control group ($p < 0.001$), but it did not correlate with any of the tested tumor parameters. Survival rate displayed statistical correlation with histological type of the tumor, and VEGF-A serum levels, so that patients with intestinal type gastric cancer showed a superior survival vs. those with diffuse type ($p = 0.0043$). A better survival was noted in patients with VEGF-A serum levels over the threshold value of 173 pg/ml. DISCUSSION AND CONCLUSIONS: The VEGF-A levels in serum are significantly increased preoperatively in gastric cancer patients, compared to apparently healthy persons, but they do not show correlation with tumor parameters. As a result it cannot be used as prognostic factor, but it may be an evolution marker. Survival rate is significantly higher in intestinal type gastric cancers, ads compared to the diffuse type, as well as in patients with serum VEGF-A values over the threshold value.

Hanrahan, V., et al. (2003). "The angiogenic switch for vascular endothelial growth factor (VEGF)-A, VEGF-B, VEGF-C, and VEGF-D in the adenoma-carcinoma sequence during colorectal cancer progression." J Pathol **200**(2): 183-194.

Angiogenesis is essential for tumour growth and metastasis. It is controlled by angiogenic factors, one of the most important being vascular endothelial growth factor (VEGF)-A. Although its role has been demonstrated in many tumour types including colorectal carcinoma (CRC), the importance of the newer family members in adenoma, invasive tumour growth, and progression to a metastatic phenotype has been poorly characterized in CRC. The aim of this study was to determine the role and timing of the VEGF angiogenic switch during CRC progression. We measured the gene expression of VEGF ligands (VEGF-A, VEGF-B, VEGF-C, and VEGF-D) and their receptors (VEGFR-1, VEGFR-2, and VEGFR-3), in normal colorectal tissues ($n = 20$), adenomas ($n = 10$), and in CRC ($n = 71$) representing different Duke's stages using ribonuclease protection assay, semi-quantitative relative reverse transcriptase polymerase chain reaction, together with the pattern of their expression by immunohistochemistry. VEGF-A mRNA was the most abundant in colorectal tissue, followed by VEGF-B, VEGF-C, and VEGF-D. VEGF-A and VEGF-B mRNAs were significantly more abundant in adenomas ($p = 0.0003$ and $p = 0.04$ respectively) compared with normal tissues, while VEGF-A and VEGF-C were significantly increased in carcinomas compared with normal tissues ($p = 0.0006$ and $p = 0.0009$ respectively). A significantly greater amount of VEGF-C mRNA was present in carcinomas compared with adenomas ($p = 0.03$), whereas there was a significant reduction of VEGF-B in carcinomas compared with adenomas ($p = 0.0002$). VEGF-D mRNA was significantly more abundant in normal tissues than in adenomas ($p = 0.0001$) and carcinomas ($p < 0.0001$). In normal tissues distant from the primary tumour, there was a significantly greater amount of VEGF-A and VEGF-D mRNA in patients with Duke's B and Duke's C respectively, compared with Duke's A stage tumours ($p = 0.04$ and $p = 0.01$ respectively). Immunohistochemistry showed low basal levels of all ligands in histologically normal tissues and their expression in the epithelium of tumours reflected the levels of mRNA expression identified. VEGF-A and VEGF-C mRNA levels correlated significantly with tumour grade ($p = 0.01$ and $p = 0.01$ respectively) and tumour size ($p = 0.001$ and $p = 0.01$ respectively), but

not with patient age, sex, presence of infiltrative margin, lymphocytic response, vascular invasion, Duke's stage, or lymph node involvement ($p > 0.05$). VEGF-B mRNA correlated with an infiltrative margin ($p = 0.04$) but no other clinicopathological variable, and expression of VEGF-D demonstrated no association with any parameter examined. VEGFR-1 was significantly correlated with tumour grade ($p = 0.02$), Duke's stage ($p < 0.001$), and lymph node involvement ($p = 0.004$), VEGFR-2 with lymph node involvement ($p = 0.02$), and VEGFR-3 did not correlate with any of the clinicopathological variables tested. These results suggest that VEGF-A and VEGF-B play a role early in tumour development at the stage of adenoma formation and that VEGF-C plays a role in advanced disease when there is more likelihood of metastatic spread. The finding of increased levels of VEGF-A and VEGF-D expression in normal tissues collected from a site distant from the primary tumour indicates changes in the surrounding tumour environment that may enhance the subsequent spread of tumour cells.

Hashim, A. F., et al. (2010). "Vascular endothelial growth factor (VEGF) receptor expression correlates with histologic grade and stage of colorectal cancer." Libyan J Med **5**.

BACKGROUND: Colorectal carcinoma (CRC) is the seventh-most common malignancy and is the main cause of death in Iraq. The incidence of this cancer has increased sharply after the invasion of Iraq in 2003. AIM: To estimate immunohistochemical expression of vascular endothelial growth factor (VEGF) in CRC in relation to other parameters, such as grade and stage of tumour. METHODS: Formalin fixed, paraffin-embedded blocks from 52 patients (27 male and 25 female) with CRC were included in this study. A group of 22 patients with non-cancerous colonic tissues were included as a control group. Avidin-biotin complex method was employed for immunohistochemical detection of VEGF. RESULTS: VEGF immuno-expression was positive in 51.9% of CRC, while it was 18.2% in the normal colonic tissue ($p <0.05$). VEGF immunostaining was positively correlated with grade of colonic malignancy ($p <0.05$). CONCLUSION: These findings provide further evidence for the role of VEGF in the carcinogenesis of CRC. However, VEGF could not be well correlated with stage of tumour and hence may be a poor prognostic parameter of state of malignancy of colonic carcinoma.

Hata, K., et al. (2011). "Expression of the vascular endothelial growth factor (VEGF) gene in epithelial ovarian cancer: an approach to anti-VEGF therapy." Anticancer Res **31**(2): 731-737.

AIM: A monoclonal antibody that targeted vascular endothelial growth factor (VEGF) resulted in a dramatic suppression of tumor growth in vivo, which led to the development of bevacizumab, a humanized variant of anti-VEGF antibody, as an anticancer agent. The aims of this study were to clarify the significance of VEGF gene expression in relation to clinicopathological parameters and to identify potential candidates for anti-VEGF therapy with bevacizumab. PATIENTS AND METHODS: VEGF gene expression was analyzed by real-time quantitative reverse transcription-polymerase chain reaction in 178 surgical epithelial ovarian cancer specimens. This gene expression was correlated with clinicopathological parameters and patient survival. RESULTS: The median VEGF gene expression level and range relative to GAPDH were 0.147 and 0.016-2.44, respectively. Patients were dichotomized into two groups with low and high expression levels by using the median value as the cutoff. VEGF gene expression did not affect prognosis of patients overall ($p = 0.541$). Although statistical significance was not noted, we found the prognosis of patients with high VEGF gene expression tended to be worse than that of those with low VEGF gene expression by univariate Cox regression analysis ($p = 0.085$) in patients with stage III-IV cancer. Macroscopic residual disease (positive; $p = 0.012$) was significantly associated with poor prognosis in univariate Cox regression analysis in patients with stage III-IV cancer. Moreover, presence of macroscopic residual disease was positively associated with VEGF gene expression ($p = 0.030$) in patients with stage III-IV cancer. CONCLUSION: Patients with epithelial ovarian cancer with tumors with positive macroscopic residual disease and high VEGF gene expression could be potential candidates for anti-VEGF therapy with bevacizumab.

Hodorowicz-Zaniewska, D., et al. (2012). "Evaluation of serum concentrations of vascular endothelial growth factor (VEGF) in breast cancer patients." Pol J Pathol **63**(4): 255-260.

The aim of the study was to assess the value of vascular endothelial growth factor (VEGF) measurements in breast cancer patients with respect to recognized clinicopathological prognostic factors. The study was conducted in 87 women with histologically confirmed breast cancer who underwent surgical treatment and 37 healthy women. Vascular endothelial growth factor concentration levels in the blood samples of patients were correlated with the size of the primary tumor, lymph nodes in the armpit, cancer stage, histological type, grading, multifocality, status of estrogen and progesterone receptors and HER-2 protein expression. Statistical analysis did not show any correlation between concentrations of VEGF and any

of the selected parameters. The comparison of VEGF concentrations showed a slightly raised level of VEGF in women with the disease as opposed to the healthy subjects but the differences were not statistically significant ($p = 0.472$). Similar results were obtained for marker CEA ($p = 0.09$), while the level of Ca 15-3 in both groups differed significantly ($p < 0.001$) reaching higher values in the patients with diagnosed breast cancer. Vascular endothelial growth factor concentrations in breast cancer patients do not correlate with recognized clinicopathological prognostic factors and CEA and Ca 15-3 markers, which does not preclude the potential role of VEGF as an independent prognostic factor.

Hoffmann, S., et al. (2007). "Differential effects of cetuximab and AEE 788 on epidermal growth factor receptor (EGF-R) and vascular endothelial growth factor receptor (VEGF-R) in thyroid cancer cell lines." Endocrine **31**(2): 105-113.

This study evaluated the role of EGF and the effects of EGF-targeting drugs (Cetuximab, AEE 788) on growth, apoptosis, and autocrine VEGF-secretion of thyroid cancer (TC) cells. Autocrine activation of the epidermal growth factor receptor (EGF-R) is commonly regarded to contribute to the malignant phenotype of TC cells and may therefore represent a rational therapeutic target. Out of a number of TC cell lines two anaplastic (Hth74, C643), one follicular (FTC133), and one papillary thyroid cancer cell line (TPC1) were analyzed in depth for VEGF-R-and EGF-R-expression, basal and EGF-stimulated (1-100 ng/ml) VEGF protein secretion and proliferation. Subsequently the antiprolifereative and antiangiogenic effect of cetuximab (Erbitux), a monoclonal antibody that blocks the EGF-R and AEE 788, a novel dual-kinase inhibitor of EGF-R and VEGF-R were assessed, and the downstream EGF-R signal transduction was analyzed by means of detecting phosphorylated pEGF-R, pVEGF-R, pAkt, and p-MAPK. EGF stimulated VEGF-mRNA expression and protein secretion in all TC cell lines. The EGF-R antagonist Cetuximab consistently decreased VEGF secretion in all TC cell lines (min. 15%, n.s. in C643 cells and max. 90% in Hth74 cells, $P < 0.05$), but did not affect tumor cell proliferation in vitro. In contrast, the EGF-R- and VEGF-R-kinase inhibitor AEE 788 not only reduced VEGF secretion (min. 55%, $P < 0.05$ in C643 and max. 75%, $P < 0.05$, in FTC133), but also exhibited a dose-dependent inhibition of tumor cell proliferation (min. 75%, $P < 0.05$ in C643 and max. 95%, $P < 0.05$ in Hth74) and was a potent inductor of apoptosis in two of four TC cell lines. These effects were always accompanied by reduced levels of pEGF-R, pVEGF-R, pAkt, and pMAPK. Although inhibition of the EGF-receptor by Cetuximab potently disrupts autocrine secretion of VEGF, only the concurrent inhibition of the VEGF- and EGF receptor, e.g., by AEE 788 induces reduced proliferation and apoptosis in vitro. This suggests a particular rationale for the use of tyrosine kinase inhibitors with dual modes of action such as AEE 788 in thyroid cancer.

Hogendorf, P., et al. (2014). "Pancreatic head carcinoma and vascular endothelial growth factor (VEGF-A) concentration in portal blood: its association with cancer grade, tumor size and probably poor prognosis." Arch Med Sci **10**(2): 288-293.

INTRODUCTION: Vascular endothelial growth factor (VEGF) is overexpressed in pancreatic cancer. Although VEGF has been shown to be a probable marker for poor prognosis, the VEGF concentration in portal blood has not yet been clinically reported in pancreatic ductal adenocarcinoma (PDAC). The aim of the study was to measure VEGF-A portal blood concentration in patients with PDAC and to evaluate its performance as a prognostic marker. MATERIAL AND METHODS: Thirty-six consecutive patients out of 57 operated on for pancreatic head lesion with pathologically verified diagnosis of PDAC were enrolled in this study. We evaluated the VEGF concentration in portal blood samples obtained intraoperatively and associated their values with tumor size, stage, grade and survival. RESULTS: The portal VEGF-A concentration was associated with tumor grade (G1: 80.52 +/-43.05 vs. G2: 185.39 +/-134.98, $p = 0.006$, G2: 185.39 +/-134.98 vs. G3: 356.46 +/-229.12, $p = 0.08$), and there was a positive correlation with tumor size ($r = 0.42$, $p < 0.05$). In the multivariate regression analysis high levels of VEGF-A were not correlated with poor survival (HR = 5.22, 95% CI = -0.6457 to 3.9513, $p = 0.19$). CONCLUSIONS: The portal VEGF-A concentration is associated with tumor grade and size. The correlation of portal VEGF-A with poor survival is not clear and needs further investigation.

Homer, J. J., et al. (2001). "The expression of vascular endothelial growth factor (VEGF) and VEGF-C in early laryngeal cancer: relationship with radioresistance." Clin Otolaryngol Allied Sci **26**(6): 498-504.

Angiogenesis is essential for tumour growth and invasion. Vascular endothelial growth factor (VEGF) is a prime mediator of tumour angiogenesis. VEGF-C is a closely related protein that effects lymphatic endothelial cells and may be important in the process of lymphatic metastasis. The purpose of this study was to evaluate the expression of these cytokines in patients with T1 and T2a glottic, squamous cell carcinoma, in comparison with normal epithelial control tissue, to ascertain any association with

radioresistance. Twenty-two tumours treated by radiotherapy (13 radiosensitive, nine radioresistant) and seven normal control tissues were studied. The minimum follow-up was 2 years after radiotherapy. Expression of VEGF and VEGF-C was evaluated by immunohistochemistry of formalin-fixed, paraffin-embedded biopsy specimens. Analysis was carried out using a quantitative computer image analyser. Both VEGF and VEGF-C were detectable in tumour and normal control specimens. There was increased expression in tumour specimens of both VEGF ($P = 0.03$) and VEGF-C ($P < 0.001$). In addition, the expression of VEGF-C was associated with tumours of higher histological grade ($P = 0.021$). There was, however, no difference in VEGF and VEGF-C expression between radioresistant and radiosensitive tumours. The expression of VEGF and VEGF-C is increased in early laryngeal squamous cell carcinoma (SCC). However, measuring the expression of these proteins cannot predict radioresistance in this tumour group.

Hormbrey, E., et al. (2003). "The relationship of human wound vascular endothelial growth factor (VEGF) after breast cancer surgery to circulating VEGF and angiogenesis." Clin Cancer Res **9**(12): 4332-4339.

PURPOSE: The assessment of locally produced proangiogenic cytokines may be an indicator of the stromal response of an individual to wounding or cancer. This study describes the profile of VEGF production in human surgical wounds in both breast cancer patients and reduction mammoplasty controls, and assesses the changes in systemic VEGF levels and platelet profiles perioperatively. EXPERIMENTAL DESIGN: Perioperative surgical wound fluid samples and blood were collected daily up to 13 days from 52 patients undergoing breast cancer surgery (local tumor burden), delayed breast reconstruction (previous tumor burden but none present at the time of surgery), or breast reduction surgery (noncancer control). Samples were analyzed for VEGF by ELISA RESULTS: VEGF levels in surgical wound fluid were lowest on day 1 followed by an early peak on day 2 of >900% the corresponding serum value. There was a trend in the VEGF response at the day-2 time point: reduction > reconstruction > cancer subgroups, with a significant difference between the reduction and cancer subgroups ($P < 0.05$). There was a 20-30-fold variation in the response between days 1 and 2, and within subgroups. CONCLUSIONS: Much higher local concentrations of angiogenic factors may need to be antagonized for effective antiangiogenic therapy, and there is great heterogeneity between patients. The small peripheral blood changes compared with large tumor fluid changes show that there is a tissue barrier. This has relevance for design of antiangiogenic therapy trials, highlighting the need for individually tailored treatment with biologically targeted interventions.

Howard, E. M., et al. (2004). "Correlation and expression of p53, HER-2, vascular endothelial growth factor (VEGF), and e-cadherin in a high-risk breast-cancer population." Int J Clin Oncol **9**(3): 154-160.

BACKGROUND: Many genetic traits common to aggressive breast carcinoma have been identified; yet little is known about the interrelationships of such traits during tumor development, especially in women prone to aggressive cancer. This study examined the expression of four biological markers associated with poor prognosis at each stage of breast cancer progression in primary tumors from women of lower economic status and assessed the relationship between these markers. METHODS: Archived primary breast tumors from 77 patients were assessed by immunohistochemical analysis for expression of human epidermal growth receptor 2 (HER-2), p53, vascular endothelial growth factor (VEGF), and e-cadherin, and the relationships between the expressions of these molecules were studied. RESULTS: Twenty-two (29%) patients had advanced (stage III or IV) disease. HER-2, VEGF, e-cadherin, and p53 signal were positive for 31 (40%), 58 (75%), 63 (82%), and 37 (48%) of patients, respectively. Among the markers tested, only p53 exhibited a significant association between expression and stage of the disease ($P = 0.012$). Expression of e-cadherin was positively associated with HER-2 overexpression ($P = 0.004$), and high levels of HER-2 occurred with strongly positive e-cadherin tumors. Marginally significant positive associations were observed between HER-2 and p53 signal ($P = 0.06$), and between disease stage and e-cadherin expression ($P = 0.08$). CONCLUSION: The significant tendency toward expression of e-cadherin in conjunction with HER-2 overexpression in breast cancer is a novel finding. The association of p53 with more advanced stages of cancer emphasizes it as a key participant in metastatic processes in breast cancer. Many genetic traits common to aggressive breast carcinoma have been identified; yet little is known about the interrelationships of such traits during tumor development, especially in women prone to aggressive cancer. This study examined the expression of four biological markers associated with poor prognosis at each stage of breast cancer progression in primary tumors from women of lower economic status and assessed the relationship between these markers.

Huang, Q., et al. (2019). "[The poor prognosis is correlated with the high expression of vascular endothelial growth factor (VEGF) and low expression of thrombospondin 1 (TSP-1) in patients with breast

cancer]." Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi **35**(9): 828-831.

Objective To investigate the correlations between the expression of vascular endothelial growth factor (VEGF) and thrombospondin 1 (TSP-1) in breast cancer and the prognosis. Methods Immunohistochemical staining was used to detect the expression of VEGF and TSP-1 in 160 cases of breast cancer tissues and adjacent tissues, and the relationships between them were analyzed. Results The expression of TSP-1 significantly decreased and the expression of VEGF significantly increased in breast cancer tissues. Low expression of TSP-1 and high expression of VEGF were significantly associated with high clinical stage, poor differentiation, and lymph node metastasis. After 3 years of follow-up, the recurrence rate was 15.6%. Spearman rank correlation analysis showed that there was a positive correlation between the prognosis recurrence rate and the positive expression rate of VEGF (r=0.459), but negatively correlated with the positive expression rate of TSP-1 (r=-0.543). Logistic regression analysis showed that TSP-1 positive expression rate, VEGF positive expression rate, lymph node metastasis and clinical stage were the main independent risk factors for prognosis and recurrence. Conclusion The high expression of VEGF and the low expression of TSP-1 in breast cancer tissues are significantly correlated with the main clinical features. The recurrence rate of patients with high expression of VEGF and low expression of TSP is high.

Huang, T. H., et al. (2015). "Prophylactic administration of fucoidan represses cancer metastasis by inhibiting vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) in Lewis tumor-bearing mice." Mar Drugs **13**(4): 1882-1900.

Fucoidan, a heparin-like sulfated polysaccharide, is rich in brown algae. It has a wide assortment of protective activities against cancer, for example, induction of hepatocellular carcinoma senescence, induction of human breast and colon carcinoma apoptosis, and impediment of lung cancer cells migration and invasion. However, the anti-metastatic mechanism that fucoidan exploits remains elusive. In this report, we explored the effects of fucoidan on cachectic symptoms, tumor development, lung carcinoma cell spreading and proliferation, as well as expression of metastasis-associated proteins in the Lewis lung carcinoma (LLC) cells-inoculated mice model. We discovered that administration of fucoidan has prophylactic effects on mitigation of cachectic body weight loss and improvement of lung masses in tumor-inoculated mice. These desired effects are attributed to inhibition of LLC spreading and proliferation in lung tissues. Fucoidan also down-regulates expression of matrix metalloproteinases (MMPs), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) and vascular endothelial growth factor (VEGF). Moreover, the tumor-bearing mice supplemented with fucoidan indeed benefit from an ensemble of the chemo-phylacticity. The fact is that fucoidan significantly decreases viability, migration, invasion, and MMPs activities of LLC cells. In summary, fucoidan is suitable to act as a chemo-preventative agent for minimizing cachectic symptoms as well as inhibiting lung carcinoma metastasis through down-regulating metastatic factors VEGF and MMPs.

Inai, T., et al. (2004). "Inhibition of vascular endothelial growth factor (VEGF) signaling in cancer causes loss of endothelial fenestrations, regression of tumor vessels, and appearance of basement membrane ghosts." Am J Pathol **165**(1): 35-52.

Angiogenesis inhibitors are receiving increased attention as cancer therapeutics, but little is known of the cellular effects of these inhibitors on tumor vessels. We sought to determine whether two agents, AG013736 and VEGF-Trap, that inhibit vascular endothelial growth factor (VEGF) signaling, merely stop angiogenesis or cause regression of existing tumor vessels. Here, we report that treatment with these inhibitors caused robust and early changes in endothelial cells, pericytes, and basement membrane of vessels in spontaneous islet-cell tumors of RIP-Tag2 transgenic mice and in subcutaneously implanted Lewis lung carcinomas. Strikingly, within 24 hours, endothelial fenestrations in RIP-Tag2 tumors disappeared, vascular sprouting was suppressed, and patency and blood flow ceased in some vessels. By 7 days, vascular density decreased more than 70%, and VEGFR-2 and VEGFR-3 expression was reduced in surviving endothelial cells. Vessels in Lewis lung tumors, which lacked endothelial fenestrations, showed less regression. In both tumors, pericytes did not degenerate to the same extent as endothelial cells, and those on surviving tumor vessels acquired a more normal phenotype. Vascular basement membrane persisted after endothelial cells degenerated, providing a ghost-like record of pretreatment vessel number and location and a potential scaffold for vessel regrowth. The potent anti-vascular action observed is evidence that VEGF signaling inhibitors do more than stop angiogenesis. Early loss of endothelial fenestrations in RIP-Tag2 tumors is a clue that vessel phenotype may be predictive of exceptional sensitivity to these inhibitors.

Iovino, F., et al. (2008). "Serum vascular endothelial growth factor (VEGF) levels correlate with tumor

VEGF and p53 overexpression in endocrine positive primary breast cancer." Cancer Invest **26**(3): 250-255.

Vascular endothelial growth factor (VEGF) is a potent stimulator of angiogenesis, associated with unfavorable clinical characteristics in breast cancer. The aim of this study was to evaluate different angiogenic markers in endocrine-positive breast cancer patients. The authors analyzed serum and tumor samples from 71 patients with endocrine-positive operable primary breast cancer to determine the expression and the possible relationship between circulating serum VEGF levels, tumor VEGF expression, microvessel density (MVD), and other immunohistochemical parameters. Basal VEGF serum levels were significantly higher in breast cancer patients than in healthy controls. A significant correlation was observed between basal VEGF serum concentrations, microvessel density ($p = 0.01$) and p53 status ($p = 0.004$). Intratumoral VEGF expression was significantly associated with neoplastic embolization ($p = 0.041$) and circulating VEGF levels ($p = 0.047$). The results confirm that in primary endocrine-positive breast cancer serum VEGF levels are elevated and show a positive relationship with tumor VEGF and p53 overexpression.

Ishigami, S. I., et al. (1998). "Predictive value of vascular endothelial growth factor (VEGF) in metastasis and prognosis of human colorectal cancer." Br J Cancer **78**(10): 1379-1384.

Vascular endothelial growth factor (VEGF) may affect the phenotype of cancer cells, such as growth velocity and metastatic potential, due to its probable multifunctional property including a mitogenic activity for vascular endothelial cells. The present study was designed to investigate the association of VEGF mRNA expression with progression and metastasis of human colorectal cancer. The level of VEGF mRNA expression was quantified by Northern blot hybridization in tumorous and non-tumorous tissues obtained from 60 primary colorectal cancer patients. The ratio of the former to the latter was defined as the VEGF T/N ratio, and the prognostic significance of this ratio, following surgery, in addition to the relationship to progression and metastatic potential, was evaluated. The value of the VEGF T/N ratio was significantly correlated with the depth of tumour infiltration ($P=0.046$), the incidence of liver metastasis ($P < 0.0001$) and lymph node metastasis ($P=0.036$). Patient prognosis was estimated by the Kaplan-Meier method and the log-rank test. When the VEGF T/N ratio was higher than 4.8 for which the chi2 value of the log-rank test was maximal, the tumour was defined as showing overexpression of VEGF mRNA. Patients with overexpression of VEGF mRNA demonstrated poorer survival than patients without overexpression of VEGF mRNA ($P < 0.001$). The overall estimated hazard ratio for death in patients with overexpression of VEGF mRNA was 1.94 according to a multivariate analysis ($P=0.005$). Thus, VEGF is associated with the progression, invasion and metastasis of colorectal cancer, and overexpression of VEGF mRNA in the primary tumour is assumed to be closely correlated with poor prognosis in colorectal cancer patients. Moreover, the VEGF T/N ratio may be used as an independent prognostic marker in colorectal cancer patients.

Jackson, M. W., et al. (1997). "Vascular endothelial growth factor (VEGF) expression in prostate cancer and benign prostatic hyperplasia." J Urol **157**(6): 2323-2328.

PURPOSE: Vascular endothelial growth factor (VEGF) is a potent inducer of endothelial cell growth and is expressed at elevated levels in several tumor types. In this study immunohistochemical localization and distribution of isoforms of VEGF were examined in malignant and non-malignant human prostatic tissues. MATERIALS AND METHODS: Immunohistochemical localization of VEGF was performed on thirty well, moderately and poorly differentiated stage D2 prostate cancer specimens and twenty benign prostatic hyperplasia (BPH) specimens. VEGF mRNA was determined by polymerase chain reaction and VEGF protein isoforms were detected by Western blotting of prostate cancer and BPH specimens. RESULTS: Cytoplasmic immunoreactivity for VEGF was detected in tumor cells and peritumoral stromal cells of prostate cancer specimens and in non-malignant glandular epithelial cells and interglandular stromal cells in BPH specimens. Staining was focal with areas of strongly to weakly stained cells adjacent to negatively staining areas. mRNA's for VEGF121, VEGF165 and VEGF189 were present in all benign and malignant prostate specimens. VEGF protein isoforms of molecular sizes corresponding to VEGF165 and VEGF189 were detected in cytosolic extracts of prostate cancers and BPH specimens by Western blotting. In addition, two novel higher molecular weight immunoreactive bands were detected in the prostate specimens. CONCLUSIONS: Widespread distribution of VEGF in prostate cancers and BPH specimens suggest that the VEGF165, VEGF189 isoforms and novel 90 and 110 kD forms detected may contribute to the establishment or progression of these conditions.

Jennbacken, K., et al. (2005). "Expression of vascular endothelial growth factor C (VEGF-C) and VEGF receptor-3 in human prostate cancer is associated with regional lymph node metastasis." Prostate **65**(2): 110-116.

BACKGROUND: Vascular endothelial growth factor C (VEGF-C) and its receptor, VEGFR-3, have been implicated as important factors in the formation of lymphatic vessels and recent evidence suggests that tumor lymphangiogenesis promotes lymphatic metastasis. METHODS: The expression of VEGF-C and VEGFR-3 was examined in 22 human prostate cancer specimens with immunohistochemistry. A semi-quantitative scoring system was used for evaluation of staining. RESULTS: Expression of VEGF-C was stronger in prostate cancer areas in comparison to adjacent benign glands. In addition, patients with lymph node metastases had a significantly higher expression of VEGF-C than patients without lymph node metastases. Interestingly, VEGFR-3 was expressed in malignant prostate epithelial cells and its expression was significantly higher in the lymph node positive group compared to the lymph node negative group. CONCLUSIONS: The results of the present study indicate that increased expression of VEGF-C and VEGFR-3 play a role in prostate cancer progression and in metastasis to regional lymph nodes.

Jeon, Y. J., et al. (2014). "Interplay between 3'-UTR polymorphisms in the vascular endothelial growth factor (VEGF) gene and metabolic syndrome in determining the risk of colorectal cancer in Koreans." BMC Cancer **14**: 881.

BACKGROUND: Polymorphisms in angiogenesis-related genes and metabolic syndrome (MetS) risk factors play important roles in cancer development. Moreover, recent studies have reported associations between a number of 3'-UTR polymorphisms and a variety of cancers. The aim of this study was to investigate the associations of three VEGF 3'-UTR polymorphisms (1451C > T [rs3025040], 1612G > A [rs10434], and 1725G > A [rs3025053]) and MetS with colorectal cancer (CRC) susceptibility in Koreans. METHODS: A total of 850 participants (450 CRC patients and 400 controls) were enrolled in the study. The genotyping of VEGF polymorphisms was performed by TaqMan allelic discrimination assays. Cancer risks of genetic variations and gene-environment interactions were assessed by adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of multivariate logistic regression analyses. RESULTS: VEGF 1451C > T was significantly associated with rectal cancer risk (Dominant model; AOR =1.58; 95% CI = 1.09 - 2.28; p = 0.015) whereas VEGF 1725G > A correlated with MetS risk (Dominant model; AOR =1.61; 95% CI =1.06 - 2.46; p = 0.026). Of the gene-environment combined effects, the interaction of VEGF 1451C > T and MetS contributed to increased rectal cancer risk (AOR = 3.15; 95% CI = 1.74 - 5.70; p < .001) whereas the combination of VEGF 1725G > A and MetS was involved with elevated colon cancer risk (AOR = 2.68; 95% CI = 1.30 - 1.55; p =0.008). CONCLUSIONS: Our results implicate that VEGF 1451C > T and 1725G > A may predispose to CRC susceptibility and the genetic contributions may be varied with the presence of MetS.

Joo, Y. E., et al. (2002). "The role of vascular endothelial growth factor (VEGF) and p53 status for angiogenesis in gastric cancer." Korean J Intern Med **17**(4): 211-219.

BACKGROUND: Angiogenesis is of crucial importance for tumor growth and development of metastases. Vascular endothelial growth factor (VEGF) has a potent angiogenic activity and mutations of the p53 gene has been thought to upregulate VEGF. The purpose of our study was to evaluate the prognostic significance of these tumor biomarkers for angiogenesis relative to the information derived from established clinicopathological parameters in gastric cancer. METHODS: In this study, we conducted an immunohistochemical investigation of VEGF and p53 expression in 145 tissue samples obtained from gastric cancer patients undergoing curative surgical treatment. To evaluate angiogenesis, microvessel density (MVD) was counted by staining endothelial cells immunohistochemically using anti-CD34 monoclonal antibody. RESULTS: High MVD was significantly associated with depth of tumor invasion and distant metastasis (p = 0.004, 0.021, respectively). Moreover, overall survival for patients with high MVD were significantly lower than that of low MVD (p = 0.048). Positive expression of VEGF correlated significantly with lymph node and distant metastasis (p = 0.040, 0.048, respectively). However, no significant correlation was found between p53 expression and various clinicopathological parameters. VEGF positive tumors showed a higher MVD than VEGF negative tumors (p = 0.028). The expression of p53 did not correlate with VEGF expression. Also, the relationship between the status of p53 expression and MVD had not statistically significant differences. In the multivariate analysis, status of VEGF, p53 expression and MVD were not an independent prognostic factor. CONCLUSION: VEGF seems to be an important, clinically relevant inducer of angiogenesis and angiogenesis assessed by the MVD may be a useful marker for predicting metastasis in gastric cancer. However, further studies are warranted to clarify the impact of p53 on the angiogenesis and the prognostic significance of angiogenesis in gastric cancer.

Kakeya, H. and H. Osada (2004). "[Development of novel angiogenesis inhibitors targeting VEGF (vascular endothelial growth factor) for cancer chemotherapy]." Nihon Rinsho **62**(7): 1264-1270.

Recent progress in cancer biology has revealed that angiogenesis is a promising target for new anticancer drugs. Angiogenesis is tightly regulated by the balance between stimulatory and inhibitory angiogenic factors, and the imbalance of these regulators causes dysfunction of angiogenesis. Vascular endothelial growth factor (VEGF) is one of the best characterized pro-angiogenic factors, and multiple strategies have been studied to inhibit the pathway; i. e. production and secretion of VEGF receptor, VEGF binding to its receptor, tyrosine kinase activity of VEGF, and signaling pathway downstream induced by VEGF. In this article, the summary of function of VEGF family as well as recent promising drugs under clinical trials including bevacizumab (Avastin), a humanized monoclonal antibody developed against VEGF, and several small molecule inhibitors targeting VEGF function are described.

Kapahi, R., et al. (2014). "Vascular endothelial growth factor (VEGF) gene polymorphisms and breast cancer risk in Punjabi population from North West India." Tumour Biol **35**(11): 11171-11181.

The purpose of this study was to evaluate the association of seven VEGF promoter polymorphisms with breast cancer risk in Punjabi population from North West India. We screened DNA samples of 102 sporadic breast cancer patients and 102 unrelated healthy, gender, and age-matched individuals for seven VEGF promoter polymorphisms [-417 C/T (rs833062), -172 C/A (rs59260042), -165 C/T (rs79469752), -160 C/T, -152 G/A (rs13207351), -141 A/C (rs28357093) and -116 G/A (rs1570360)] by direct sequencing. The frequency of GG, GA, and AA genotype of -152 G/A polymorphism was 26.47 vs 38.34%, 46.08 vs 51.96%, and 27.45 vs 9.80%, in patients and controls, respectively. VEGF -152 AA genotype was significantly associated with increased risk for breast cancer (OR = 4.04, 95%CI, 1.69-9.68, p = 0.001; recessive model OR = 3.48, 95%CI, 1.59-7.63, p = 0.001). For VEGF -116 G/A polymorphism, G and A allele frequencies were 65.2 vs 76.47% and 34.8 vs 23.53% in patients and controls, respectively. Individuals having -116 AA genotype (OR = 3.40; 95%CI, 1.24-9.37; p = 0.014) and A allele (OR = 1.73; 95%CI, 1.12-2.67; p = 0.012) were associated with increased risk for breast cancer. VEGF -165 C/T and -141 A/C polymorphisms were associated with reduced risk for breast cancer. There was significantly decreased frequency of CT genotype (4.90 vs 18.63%; p = 0.002) and T allele (2.45 vs 9.31%; p = 0.003) of -165 C/T polymorphism among breast cancer patients as compared to controls. VEGF -141 A and C allele frequency were 96.57 vs 91.18% and 3.43 vs 8.82% in patients and controls, respectively. Significant reduced risk for breast cancer was observed with AC genotype (OR = 0.34, 95%CI, 0.14-0.86; p = 0.019) and C allele (OR = 0.37; 95%CI, 0.15-0.89; p = 0.023) of -141 A/C polymorphism. We did not observe association of VEGF -417 T/C, -172 C/A, -160 C/T polymorphisms with breast cancer risk in the studied subjects (p > 0.05). The VEGF -152 G/A and -116 G/A polymorphisms were found to be significantly associated with increased risk for breast cancer while -165 C/T and -141 A/C polymorphisms were found to be associated with decreased risk for breast cancer in Punjabi population from North West India.

Kawai, H., et al. (2002). "Direct interaction between BRCA1 and the estrogen receptor regulates vascular endothelial growth factor (VEGF) transcription and secretion in breast cancer cells." Oncogene **21**(50): 7730-7739.

Mutational inactivation of BRCA1 confers increased risk for breast cancer. However, the underlying basis for the breast tissue-restricted, tumor-suppressive properties of BRCA1 remains poorly defined. Here, we show that BRCA1 and the estrogen receptor alpha (ER-alpha) modulated vascular endothelial growth factor (VEGF) gene transcription and secretion in breast cancer cells. ER-alpha interacted in vitro and in vivo with BRCA1, and this interaction was mediated by the AF-2 domain of ER-alpha and two domains of BRCA1, the amino-acid residues 1-306 and 428-683. Endogenous interaction of ER-alpha with BRCA1 was observed in normal MCF-10A breast epithelial cells and in breast cancer cells (MCF-7 and T47D), and this interaction was significantly reduced in the presence of estrogen. Furthermore, ER-alpha induced activation of VEGF gene transcription, using human VEGF promoter-luciferase reporter constructs. The AF-2 domain of ER-alpha was also shown to induce VEGF gene transcription activation similar to that obtained with the full-length ER-alpha. However, in the presence of BRCA1, VEGF gene transcription activation and VEGF protein secretion were significantly inhibited in a dose-dependent manner. The BRCA1 domain of 1-683 amino acid residues was required for this inhibition of VEGF gene transcription activation. Three mutated forms of BRCA1 (A1708E, M1775R and Y1853X), that have been identified in familial breast cancers, failed to associate with ER-alpha and to suppress VEGF promoter activity and VEGF protein secretion. Overexpression of wild-type BRCA1 in HCC-1937 breast cancer cells that lack endogenous functional BRCA1 significantly reduced VEGF secretion in these cells. These results demonstrate a novel pathogenic mechanism whereby mutations in BRCA1, via their interaction with ER-alpha, could promote tumorigenesis through the hormonal regulation of mammary epithelial cell proliferation and impaired

VEGF function, which may lead to cancer growth and angiogenesis.

Kawczyk-Krupka, A., et al. (2016). "ALA-induced photodynamic effect on vitality, apoptosis, and secretion of vascular endothelial growth factor (VEGF) by colon cancer cells in normoxic environment in vitro." Photodiagnosis Photodyn Ther **13**: 308-315.

BACKGROUND: Cancer therapy is often based on combination of conventional methods of cancer treatment with immunotherapy. Photodynamic therapy (PDT) is one of the immunomodulating methods used in oncology. We examined how PDT influences the secretory activity of colon cancer cells in vitro, especially the secretion of vascular endothelial growth factor (VEGF) in aerobic conditions. METHODS: We used two cancer cell lines with different malignancy potentials: a metastatic SW620 line and a non-metastatic SW480 line. In the first stage of the experiment, we exposed each cell line to three different concentrations of photosensitizer's precursor: 5-aminolevulinic acid (ALA) and varying levels of light radiation, after which we assessed cell viability and apoptosis induction in these lines, using the MTT and LDH assays. Then, we determined the secretion of VEGF by these cells in aerobic conditions and under the ALA-PDT parameters at which cells presented the highest viability. RESULTS: Photodynamic treatment with ALA did not influence on VEGF secretion by the non-metastatic SW480 cells, but caused a decrease in VEGF secretion by the metastatic SW 620 cell line by 29% ($p<0.05$). SW 620 cell line secreted more actively VEGF than the SW480 cells, both before and after photo dynamic therapy ($p<0.05$). CONCLUSION: The outcome of this in vitro study presented a beneficial effect of ALA-PDT, resulting in a decrease of VEGF secretion in the more malignant SW620 cell lines. Further studies should be considered to confirm the clinical relevance of this finding.

Kazama, S., et al. (2007). "Vascular endothelial growth factor-C (VEGF-C) is a more specific risk factor for lymph node metastasis than VEGF-D in submucosal colorectal cancer." Hepatogastroenterology **54**(73): 71-76.

BACKGROUND/AIMS: It is useful to decide whether lymphatic involvement or lymph node metastasis exists before polypectomy or operation in submucosal colorectal cancer. Whether vascular endothelial growth factor-C (VEGF-C) or VEGF-D could predict lymph node metastasis and lymphatic involvement is uncertain. METHODOLOGY: Expression of the VEGF-C and VEGF-D in human submucosal colorectal cancers was investigated in paraffin-embedded stepwise sections by means of immunohistochemistry, and the correlation between immunohistochemical expression pattern and clinicopathological features was also evaluated. RESULTS: The results showed that VEGF-C overexpression correlated with lymphatic involvement ($P = 0.01$) and lymph node metastasis ($P = 0.02$), but VEGF-D overexpression did not correlate significantly. In multivariate analysis lymphatic invasion was the predictive factor ($P = 0.0129$), but VEGF-C positivity was not predictive ($P = 0.3437$). CONCLUSIONS: These results may suggest that VEGF-C is a more specific risk factor for lymph node metastasis than VEGF-D in submucosal colorectal cancer.

Kido, Y. (2001). "Vascular endothelial growth factor (VEGF) serum concentration changes during chemotherapy in patients with lung cancer." Kurume Med J **48**(1): 43-47.

Vascular endothelial growth factor (VEGF) is one of the most important angiogenic factors. This study aimed at clarifying the clinical significance of the changes in the serum VEGF (S-VEGF) concentrations in patients with lung cancer during anticancer chemotherapy. Subjects comprised 29 patients with lung cancer (13 adenocarcinomas, 7 squamous cell carcinomas, and 9 small cell carcinomas) who were treated with cisplatin-based chemotherapy. S-VEGF was measured by ELISA. We compared the S-VEGF concentrations between the responders and nonresponders to anticancer chemotherapy. S-VEGF concentrations before treatment of the chemotherapy (pretreatment S-VEGF concentrations) were correlated with the number of WBC, neutrophil count, monocyte count and platelet count but not the lymphocyte count. The mean pretreatment S-VEGF concentrations in responders and those in nonresponders were not significantly different, 509.7 pg/ml in the former and 382.8 pg/ml in the latter, respectively., The S-VEGF concentrations in the responders decreased to a mean of 356.0 pg/ml and 304.1 pg/ml during and at the end of therapy, respectively while those in the nonresponders increased to a mean of 474.2 pg/ml and 598.4 pg/ml during and at the end of therapy. The S-VEGF concentration changes in the responders were significantly different from those in the nonresponders ($p = .006$). The S-VEGF concentration may relate to tumor burden, however it may not be a good marker for tumor burden, because it can be influenced by various factors such as neutrophil which increases during infection. A decrease in S-VEGF concentrations may improve neoangiogenesis and the immune response, and may correlate with improvements in the quality of life and survival of patients.

Kim, J. S., et al. (2009). "Single-nucleotide polymorphisms (SNPs) and haplotype analysis in vascular endothelial growth factor (VEGF) gene in the

patients with Parkinson disease and lung cancer." Arch Gerontol Geriatr **48**(3): 287-290.

The epidemiologic data on smoking in association with Parkinson disease (PD) is puzzling. A lower incidence of smoking-related malignancies, especially lung cancer, has been reported by several studies in the patients with PD. In this study, we investigated polymorphic variations in the vascular endothelial growth factor (VEGF) gene, which has been proposed having a pivotal role in progressive damage of nigral dopaminergic neurons, between Korean patients with 188 PD and 321 lung cancer patients. There were no significant differences in the tested single-nucleotide polymorphisms (SNPs) between patients with PD and lung cancer; however, one haplotype was significantly different in comparisons between the two diseases. These results suggest that VEGF genetic polymorphisms might help understand the low incidence of lung cancer in the patients with PD.

Kim, S. H., et al. (2006). "Correlations of oral tongue cancer invasion with matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) expression." J Surg Oncol **93**(4): 330-337.

BACKGROUND AND OBJECTIVES: In oral tongue cancer, the degree of tumor invasion has a significant effect on the prognosis. We hypothesized that the destruction of extracellular matrix and neovascularization are related to tumor infiltration mechanism. By studying the tissues of early stage oral tongue cancer patients, we are intending to clarify the invasion-related factors. MATERIALS AND METHODS: To demonstrate the invasion process in early T-stage oral tongue cancer, the expressions of extracellular matrix destruction-related molecules (MMP-2, MMP-9) and neovascularization-related molecule (VEGF) were observed by immunohistochemical study. Also, staining of CD31 was done for quantification of neovascularization. We analyzed relationship between expression of each substances and tumor invasion depth, tumor free survival rates, and cervical lymph node metastasis rate. RESULTS: The expression rates of MMP-2, MMP-9, VEGF in 38 early oral cancer patients were 52.6%, 78.9%, and 52.6%, respectively. Significant correlation was found between the VEGF expression and microvessel density showed by CD31 immunohistochemical staining ($P < 0.001$). VEGF expressions were significantly related with tumor invasion depth ($P = 0.002$). The tumor-free survival rate of those patients with VEGF-positive tumors was significantly poorer than in those with VEGF-negative tumors ($P = 0.019$). CONCLUSIONS: These results indicate that VEGF is a useful marker for predicting the tumor invasion in patients with early tongue cancer.

Kim, Y. J., et al. (2019). "Genetic polymorphisms of vascular endothelial growth factor (VEGF) associated with gastric cancer recurrence after curative resection with adjuvant chemotherapy." BMC Cancer **19**(1): 483.

BACKGROUND: The relationship between polymorphisms in vascular endothelial growth factor (VEGF) and gastric cancer is still inconclusive. We investigated whether there is an association between VEGF genetic polymorphisms and risk of gastric cancer, and evaluated the recurrence of advanced gastric cancer after curative resection with adjuvant chemotherapy according to VEGF genetic polymorphisms. METHODS: The association of functional single nucleotide polymorphisms (SNPs) of the VEGF gene (+936C > T, - 634G > C, - 2578C > A, + 1612G > A) were evaluated. Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. A total of 151 patients with gastric cancer were enrolled, and the control group consisted of 413 individuals with esophago-gastroduodenoscopy who were randomly selected through health screening. All of the enrolled patients had curative resections with completion of adjuvant capecitabine and oxaliplatin combination chemotherapy and the initial metastatic cases were excluded. During the regular follow-up protocol, the episodes of the recurrence were documented and the specific genotype and allelic frequencies were evaluated. RESULTS: As for the cancer risk, there were no significant differences in specific genotypes and allelic frequencies. The mean follow-up period was 28.82 +/- 30.92 (12 ~ 72) months and the recurrence rate was 28.3%. In the patients carrying the 936-C allele, the recurrence rate of gastric cancer was high ($P = 0.02$). Disease-free interval was significantly different between the patients carrying the 936-CC and 936-CT/TT genotype ($P = 0.02$). CONCLUSIONS: VEGF 936-C allele is associated with poor prognosis, but not risk of gastric cancer. In the patients carrying the 936-C allele, more potent adjuvant treatment would be considered.

Kimura, H., et al. (2008). "Preoperative serum vascular endothelial growth factor-C (VEGF-C) levels predict recurrence in patients with esophageal cancer." Anticancer Res **28**(1A): 165-169.

BACKGROUND: Circulating vascular endothelial growth factor-C (VEGF-C) levels were measured in patients with esophageal cancer to assess the value of VEGF-C as a biomarker for predicting tumor recurrence. PATIENTS AND METHODS: Preoperative serum samples were acquired from 80 patients and healthy volunteers who served as normal controls. VEGF-C levels were assessed using enzyme-linked immunosorbent assay (ELISA). RESULTS: The

preoperative serum VEGF-C level in patients with esophageal cancer was significantly higher than in healthy volunteers. Furthermore, patients with recurrence had significantly higher preoperative serum VEGF-C levels than patients without recurrence, and a high preoperative serum VEGF-C level was found to be an independent risk factor for recurrence, in addition to lymph node metastasis. CONCLUSION: Preoperative VEGF-C levels may reflect malignancy, such as lymph node metastasis, and predict recurrence in patients with esophageal cancer. Therefore, the preoperative VEGF-C level may be a useful biomarker for choice of multimodality therapy.

Kinoshita, J., et al. (2001). "Clinical significance of vascular endothelial growth factor-C (VEGF-C) in breast cancer." Breast Cancer Res Treat **66**(2): 159-164.

Vascular endothelial growth factor-C (VEGF-C) is a specific ligand which induces lymphangiogenesis. We examined the expression of VEGF-C protein to determine its role in the progression of breast cancer. Immunohistochemical analysis revealed that VEGF-C was overexpressed in 39 of 98 breast cancer specimens (39.8%) but not in adjacent normal mammary glands. The expression of VEGF-C showed a significant correlation with lymphatic vessel invasion (p = 0.0004). It is noteworthy that the 5-year disease free survival rate of the VEGF-C positive group was significantly poorer than that of negative group (p = 0.0356). We suggest that as expression of VEGF-C is not implicated in lymphatic spread, it may prove to be a promising marker to predict the recurrence of breast cancer.

Kirkpatrick, K., et al. (2002). "The mRNA expression of cyclo-oxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) in human breast cancer." Curr Med Res Opin **18**(4): 237-241.

AIMS: There is a growing body of evidence that cyclo-oxygenase 2 (COX-2) plays an important role in carcinogenesis and angiogenesis of human tumours. The present study aims to compare COX-2 expression in human breast cancer and adjacent non-cancerous tissue (ANCT), and to identify any correlation between COX-2 and VEGF expression. METHODS: Total cellular RNA was extracted from frozen breast tissue samples according to standard methodology. The mRNA copy numbers for COX-2 and vascular endothelial growth factor 189 (VEGF-189) were determined 40 infiltrating carcinomas and 40 matched ANCT specimens using quantitative RT-PCR and TaqMan methodology. RESULTS: The COX-2 mRNA copy number per microg of RNA was two-fold higher in ANCT compared with the cancerous tissue (p = 0.01). Median mRNA copy number was 5.44 x 10(6) for ANCT and 2.30 x 10(6) for tumour, (ANCT range: 1 x 10(6) to 4.12x 10(7)) (tumour range: 1.29 x 10(5) to 1.07 x 10(7)). There was a significant correlation between COX-2 and VEGF-189 mRNA copy numbers in the cancer specimens (correlation coefficient = 0.5528, p = 0.0076). CONCLUSIONS: COX-2 mRNA is overexpressed in both human breast cancer and ANCT. We found higher levels in the matched ANCT which suggests that paracrine effects may be important in the role of COX-2 in mammary carcinogenesis. Furthermore, our results indicate that in human breast cancers COX-2 overexpression is linked to VEGF-189 overexpression and therefore tumour angiogenesis.

Kirwan, C. C., et al. (2009). "Platelet release of Vascular Endothelial Growth Factor (VEGF) in patients undergoing chemotherapy for breast cancer." J Angiogenes Res **1**: 7.

BACKGROUND: Venous thromboembolism (VTE) following breast cancer chemotherapy is common. Chemotherapy-induced alterations in markers of haemostasis occur during chemotherapy. In this study we investigated the changes in serum and plasma VEGF, together with platelet release of VEGF and related these to the development of VTE at 3 months. METHODS: Serum and plasma VEGF, together with platelet release of VEGF were measured prior to chemotherapy and at 24 hours; four-, eight days and three months following commencement of chemotherapy in early and advanced breast cancer patients and in age and sex matched controls. Duplex ultrasound imaging was performed after one month or if symptomatic. RESULTS: Of 123 patients 9.8% developed VTE within three months. Serum and plasma VEGF were increased in advanced breast cancer as was platelet release of VEGF. Prior to chemotherapy a 100 microg/ml increase in serum VEGF was associated with a 40% increased risk of VTE, while a 10 microg/ml increase in plasma VEGF was associated with a 20% increased risk of VTE. Serum VEGF showed a different response to chemotherapy in those who developed VTE. CONCLUSION: A group of patients at risk of VTE could be identified, allowing targeted thromboprophylaxis. Whether or not the response in VEGF during chemotherapy has any angiogenic significance remains to be elucidated.

Kozlowski, M., et al. (2013). "Serum tissue inhibitor of metalloproteinase 1 (TIMP-1) and vascular endothelial growth factor A (VEGF-A) are associated with prognosis in esophageal cancer patients." Adv Med Sci **58**(2): 227-234.

PURPOSE: The matrix metalloproteinases, tissue inhibitors of metalloproteinases and angiogenesis contribute to growth and spread of cancer. We

investigated the correlation between pretreatment serum levels of tissue inhibitor of metalloproteinase 1 (TIMP-1) and vascular endothelial growth factor A (VEGF-A), and clinicopathologic features and survival in patients with esophageal cancer (EC). MATERIAL/METHODS: Serum TIMP-1 and VEGF-A were measured by enzyme-linked immunosorbent assay (ELISA) in 89 patients with EC, and 30 healthy controls. RESULTS: Serum TIMP-1 and VEGF-A levels were significantly higher in patients with esophageal carcinoma than in the control group ($p=0.001$ and $p<0.001$, respectively). High levels of TIMP-1 were associated with histological type ($p<0.001$), tumor depth ($p<0.001$), stage ($p<0.001$) and lymph node metastases ($p=0.001$). Subgroup analysis showed that tumor size ($p<0.001$), tumor depth ($p<0.001$), stage ($p<0.001$), lymph node metastases ($p=0.002$), distant metastases ($p=0.009$) and resectability ($p=0.003$), were correlated with an elevated level of VEGF-A. Patients with elevated levels of TIMP-1 and VEGF-A had a significantly lower overall survival ($p=0.02$ and $p=0.048$, respectively), and disease-free survival (TIMP-1, $p<0.001$). CONCLUSION: High serum levels of TIMP-1 and VEGF-A were found to be associated with tumor progression and unfavorable prognosis in patients with EC.

Kumar, H., et al. (2002). "Kinetics of postoperative serum vascular endothelial growth factor (VEGF)--can it be used to predict curative resections in colorectal cancer?" Anticancer Res **22**(6B): 3717-3722.

BACKGROUND: Vascular endothelial growth factor (VEGF) is considered to be probably the most important and final mediator of neovascularisation. We have shown that VEGF can predict stage in colorectal cancer (Clin Cancer Res 1998, 17). This study was conducted to study the kinetics of serum VEGF after colorectal resections over ten postoperative days. PATIENTS AND METHODS: The study comprised 154 healthy controls and 108 colorectal resections (79 curative, 15 palliative and 14 benign). Samples were collected at 4-6 hours, days 1,3,5,7 and 10 post surgery. RESULTS: Six-hour levels were significantly lower in the curative group ($p < 0.0005$) but not in the benign and palliative groups ($p = 0.27$ and 0.3, respectively). Sensitivity and specificity at 20% cut-off fall in VEGF gives 83.5% sensitivity with 80% specificity in predicting curative resection. CONCLUSION: Early postoperative serum VEGF levels show significant fall and may help to identify the oncological status of colorectal cancer resections.

Kurebayashi, J., et al. (1999). "Expression of vascular endothelial growth factor (VEGF) family members in breast cancer." Jpn J Cancer Res **90**(9): 977-981.

Vascular endothelial growth factor (VEGF)-A is known to play an important role in tumor angiogenesis. Three additional members of the VEGF family, VEGF-B, -C and -D, have recently been discovered. VEGF-C and VEGF-D are ligands for VEGF receptor-3, which is expressed in the endothelium of lymphatic vessels. The expression of VEGF-C is known to be associated with the development of lymphatic vessels. Therefore, it is conceivable that VEGF-C and VEGF-D might play a role in the development of lymphatic vessels in solid tumors. To obtain some clue as to this role, we developed a semi-quantitative reverse transcription-polymerase chain reaction method to investigate the mRNA expression levels of each VEGF family member in breast cancer. All the VEGF family members were expressed at different levels in seven human breast cancer cell lines explored. Although VEGF-A and VEGF-B expressions were detected in both node-positive and node-negative breast tumors, VEGF-C expression was detected only in node-positive tumors. VEGF-D expression was detected only in an inflammatory breast cancer and a tumor which developed an inflammatory skin metastasis. These findings suggest a possible relationship between the expression level of VEGF-C and/or VEGF-D and the development of lymphatic tumor spread.

Kushlinskii, N. E., et al. (2014). "Insulin-like growth factors (IGF), IGF-binding proteins (IGFBP), and vascular endothelial growth factor (VEGF) in blood serum of patients with colorectal cancer." Bull Exp Biol Med **156**(5): 684-688.

Serum levels of insulin-like growth factors (IGF-1 and IGF-2), IGF-binding proteins (IGFBP-1, IGFBP-2, and IGFBP-3) and vascular endothelial growth factor (VEGF) were measured by standard ELISA technique in 95 primary colorectal cancer patients and 48 healthy individuals. Significant increase in serum levels of IGF-1, IGFBP-2, and VEGF and decrease in IGFBP-3 level were demonstrated in patients in comparison with the control group; in male patients, serum level of IGF-2 was also increased. Sensitivity of IGF-1 as the prospective diagnostic marker of colorectal cancer was 80% and specificity was 75% at the threshold level of 140 ng/ml. Serum levels of IGF-1 significantly decreased with age in both patients and healthy donors, but in patients, this correlation was much weaker. These parameters did not correlate with the main clinical and morphological indices, such as dissemination, localization, and histological structure of colorectal cancer.

Kusumanto, Y. H., et al. (2007). "Circulating vascular endothelial growth factor (VEGF) levels in advanced stage cancer patients compared to normal controls and

diabetes mellitus patients with critical ischemia." Drug Target Insights **2**: 105-109.

Anti-angiogenic therapy is emerging as a valuable tool in the treatment of patients with cancer. As VEGF is a central target in anti-angiogenic therapy, its levels in the circulation might be relevant in selecting tumor types or patients likely to respond to this treatment. Additional VEGF has been recognized as a key factor in the pathogenesis of diabetic retinopathy. Recently anti-angiogenic therapy has been advocated in this situation.We measured VEGF levels in whole blood in 42 patients with high grade (n = 26) and low grade (n = 16) end stage cancer, and in 28 healthy controls and 37 patients with diabetes related vascular disease. Only 2/26 patients in the group of high grade cancer had significantly elevated VEGF levels, 1/16 in the low grade group and 1/28 in the healthy control group. In contrast, in 10/37 diabetic patients the mean VEGF levels were significantly elevated compared to the other groups. The mean level in these diabetic patients was significantly elevated compared to the other groups.These data indicate the limitation of the use of circulating VEGF levels as a potential selection criterion for anti-angiogenic therapy in cancer patients and suggest further studies into its application in the management of diabetic complications.

Laack, E., et al. (2005). "Pretreatment vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) serum levels in patients with metastatic non-small cell lung cancer (NSCLC)." Lung Cancer **50**(1): 51-58.

PURPOSE: In the present study, we investigated the prognostic value of vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP)-9 serum levels in patients with metastatic non-small cell lung cancer (NSCLC). PATIENTS AND METHODS: From September 1999 to June 2001, pretreatment serum levels of VEGF and MMP-9 were analysed in 194 patients of a randomized phase III trial with enzyme-linked immunoassays. RESULTS: Patients with a VEGF serum level higher than the median serum level (10,995 pg/ml) had a significantly shorter overall survival than those with a lower serum level (P=0.04). The MMP-9 serum level did not correlate with survival. In a multivariate Cox regression analysis, only the pretreatment serum level of VEGF, the Karnofsky performance status, and the presence of bone metastases were identified as independent prognostic factors. CONCLUSIONS: The pretreatment VEGF serum level was identified as independent prognostic factor in this study and may help to assess individual risk and treatment profiles in patients with metastatic NSCLC.

Lee, L., et al. (2006). "Biomarkers for assessment of pharmacologic activity for a vascular endothelial growth factor (VEGF) receptor inhibitor, PTK787/ZK 222584 (PTK/ZK): translation of biological activity in a mouse melanoma metastasis model to phase I studies in patients with advanced colorectal cancer with liver metastases." Cancer Chemother Pharmacol **57**(6): 761-771.

PTK/ZK is a novel, oral angiogenesis inhibitor that specifically targets all 3 vascular endothelial growth factor (VEGF) receptor tyrosine kinases and is currently in phase III clinical trials. In early clinical trials, PTK/ZK demonstrated a dose-dependent reduction in tumor vascular parameters as measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and an acute increase in plasma VEGF levels. The reduction in tumor vascularity was significantly correlated with improved clinical outcome in patients with advanced colorectal cancer and liver metastases. To assess the predictive value of a mouse model of tumor metastases, comparisons were performed for the biological activity of PTK/ZK in the mouse model and in patients with liver metastases in the clinical phase I trials. An orthotopic, syngeneic mouse model was used: C57BL/6 mice injected in the ear with murine B16/BL6 melanoma cells which metastases to the cervical lymph-nodes. The primary tumor and spontaneous metastases express VEGF and VEGF receptors and respond to treatment with VEGFR tyrosine kinase inhibitors. PTK/ZK was administered orally, with assessments by DCE-MRI of the metastases and plasma VEGF taken predose and at 3 days posttreatment and efficacy determined at 7 days posttreatment. Dose-ranging studies in naive mice provided preclinical pharmacokinetic data, while two dose-escalation phase I studies provided clinical pharmacokinetic data. An exposure-response relationship was observed both for mouse metastases (measured as % tumor weight treated/control) and for human liver metastases (measured as % regression). In the B16/BL6 model, the active dose of 50 mg/kg PTK/ZK yielded 62.4 (+/- 16.0) h microM plasma exposure, which is comparable to the plasma area under the concentration time curve (AUC) achieved by the 1000 mg dose of PTK/ZK used in clinical trials. At this exposure level in clinical trials, DCE-MRI showed a reduction in the area under the enhancement curve (IAUC) to 47% of baseline. At a similar exposure in the PTK/ZK-treated mice, a reduction in IAUC to 75% of baseline was observed. Furthermore, at doses of 50 mg/kg PTK/ZK and above, an increase in plasma VEGF level 10 h after drug administration was observed in mice which was consistent with findings from the clinical trials. In conclusion, the preclinical pharmacodynamics of PTK/ZK correlate well with

clinical activity in phase I trials over comparable exposures to the drug. Thus, data from this preclinical model proved to be consistent with and thus predictive of the biologic effects of PTK/ZK in phase I/II clinical trials.

Lee, S. J., et al. (2009). "No association of vascular endothelial growth factor-A (VEGF-A) and VEGF-C expression with survival in patients with gastric cancer." Cancer Res Treat **41**(4): 218-223.

PURPOSE: Although the vascular endothelial growth factor (VEGF) superfamily has been identified to critically influence tumor-related angiogenesis, the prognostic significance of a VEGF expression in gastric cancer is still controversial. Accordingly, the present study analyzed the VEGF-A and VEGF-C expressions and their impact on the prognosis of patients with gastric cancer. MATERIALS AND METHODS: Three hundred seventy-five consecutive patients who underwent surgical resection for gastric adenocarcinoma with a curative intent were enrolled in the present study. Immunohistochemical staining for VEGF-A and VEGF-C was performed using the formalin fixed, paraffin embedded tumor tissues. RESULTS: Positive VEGF-A and VEGF-C expressions were observed in 337 (90.1%) and 278 (74.9%) cases, respectively. The survival analysis showed that the expression of VEGF-A and VEGF-C had no effect on the OS and DFS. On the multivariate analysis that included age, gender and the TNM stage, no significant association between the grade of the VEGF-A or VEGF-C expression and survival was observed. CONCLUSION: The current study suggests that the tissue expression of VEGF-A or VEGF-C alone is not an independent prognostic marker for patients with surgically resected gastric adenocarcinoma.

Leis-Filho, A. F., et al. (2021). "Expression and prognostic significance of vascular endothelial growth factor-A (VEGF-A) and its receptor in canine prostate cancer." Prostate **81**(14): 1021-1031.

BACKGROUND: Vascular endothelial growth factor-A (VEGF-A) and its receptor, VEGF receptor-2 (VEGFR-2), represent a complex family of angiogenic molecules consisting of different ligands and receptors. Due to the importance of VEGF-A/VEGFR-2 signaling in tumor proliferation and angiogenesis, this study aimed to evaluate the protein and gene expression levels of VEGF-A and VEGFR-2 in canine prostate cancer (PC). METHODS: We analyzed VEGF-A and VEGFR-2 expression in 87 PC samples by immunohistochemistry and quantitative-polymerase chain reaction. PC samples were graded according to the Gleason score and the immunohistochemical staining for VEGF-A and VEGFR-2 was quantified using a selected threshold from the ImageJ Software. Microvascular density was assessed by cluster of differentiation 31 staining and counting the number of positive vessels. Additionally, the homology of VEGF-A and VEGFR-2 between humans and dogs was assessed, followed by the construction of a protein structure homology model to compare the tertiary structures of these proteins in both species. RESULTS: Negative to weakly positive expression levels of VEGF-A and VEGFR-2 were observed in the epithelial cells of the normal prostate (NP) and prostatic hyperplasia samples. In contrast, the canine proliferative atrophy and PC samples exhibited higher VEGF-A ($p < .0001$) and VEGFR-2 ($p < .0001$) compared to NP. Moreover, positive correlations between the expression levels of VEGF-A and VEGFR-2 (Spearman's coefficient (r) = .68, $p = .013$) and the expression levels of VEGF-A and VEGFR-2 proteins ($r = .8$, $p < .0001$) were also observed in the NP samples. Additionally, the patients with PC exhibiting higher VEGFR-2 expression levels experienced a shorter survival period ($p = .0372$). Furthermore, we found an association between the microvascular density and overall survival. Dogs with a higher number of vessels showed a shorter survival time. We further demonstrated that the VEGF-A and VEGFR-2 exhibited high homology between humans and dogs, and identified their protein structures in both species. CONCLUSIONS: In conclusion, VEGFR-2 appears to be an independent prognostic factor in animals with PC. VEGF-A and VEGFR-2 are highly conserved between humans and dogs, which can be investigated further in future cross-species studies to explore their therapeutic applications.

Leng, W. D., et al. (2013). "Vascular endothelial growth factor (VEGF) gene polymorphisms and risk of head and neck cancer: a meta-analysis involving 2,444 individuals." Mol Biol Rep **40**(10): 5987-5992.

The association between vascular endothelial growth factor (VEGF) gene polymorphisms and risk of head and neck cancer (HNC) were investigated in many published studies; however, the currently available results are inconclusive. Therefore, we conducted this meta-analysis for deriving a more precise estimation of association between VEGF polymorphisms and the risk of HNC. Finally, we yield eight case-control studies involving six polymorphisms contain 2,444 individuals from PubMed, Embase, and CNKI up to January 30, 2013 (last updated on May 4, 2013). The results of meta-analysis showed that all the six polymorphisms of VEGF were not associated with risk of HNC [OR 1.25, 95 % CI (0.60-1.58) for TT vs. CC for 936 C/T; OR 1.41, 95 % CI (0.79-2.52) for GG vs. AA for -1,154 A/G; OR 0.97, 95 % CI (0.38-2.50) for CC vs. GG for 405 G/C; OR 1.44, 95 % CI (0.80-

2.61) for AA vs. CC for 2,578 C/A; OR 1.27, 95 % CI (0.77-3.72) for TT vs. CC for -460 C/T; and OR 0.87, 95 % CI (0.37-2.06) for GG vs. CC for -634 G/C]. When performed subgroup analysis according to ethnicity for VEGF 936 C/T, the results suggested that it was not associated with the risk of HNC for either Asians [OR 0.84, 95 % CI (0.27-2.56) for TT vs. CC] or Caucasians [OR 2.10, 95 % CI (0.82-5.37) for TT vs. CC]. However, due to the limitations of this meta-analysis, more well designed, larger sample size, and adjusted risk factors studies are suggested to further assess the findings.

Lewy-Trenda, I., et al. (2005). "Expression of vascular endothelial growth factor (VEGF) in vulvar squamous cancer and VIN." Pol J Pathol **56**(1): 5-8.

Angiogenesis plays an important role both in progression of solid tumors and in metastasizing. An invasive growth of a neoplasm is mainly connected with appearing of blood vessels within a tumor. Inhibition of angiogenesis in solid neoplasms may deter both tumor growth and metastases. New treatment strategies based on suppressing of angiogenesis and selective damaging of neoplastic blood vessels may prove to be as efficient as those based on direct destruction of neoplastic cells. One of important angiogenic factors is vascular endothelial growth factor (VEGF), which is produced by neoplastic cells and shows high promitotic activity almost entirely for endothelial cells (paracrine activity). We decided to investigate VEGF expression in precancerous lesions as well as in squamous cancers of vulva. Our material included 31 cases of vulvar squamous cancer, 28 cases of VIN (vulvar intraepithelial neoplasia) III, 10 VIN II cases and 12 VIN I cases. A diagnosis was established according to WHO criteria on the ground of post-operative histopathological examination complemented with proliferation index estimated by the use of MIB-1 antibody. Immunohistochemical examinations were performed on paraffin-embedded material, using MIB-1 antibody (Immunotech), VEGF antibody (Santa Cruz), Goat serum Normal (DAKO), DAKO StreptAB-Complex/HRP Duet, Mouse/Rabbit DAKO DAB Chromogen Tablets, TBS (Sigma). Positive cytoplasmic expression of anti-VEGF polyclonal antibody (diffuse and/or focal and of various intensity) was observed in almost all samples from precancerous and cancerous lesions. The expression was especially strong and diffuse in all cancer cases; in cases of VIN it was mainly focal and weak.

Lieto, E., et al. (2008). "Expression of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) is an independent prognostic indicator of worse outcome in gastric cancer patients." Ann Surg Oncol **15**(1): 69-79.

BACKGROUND: Unlike other human tumors, gastric cancer remains a great therapeutic challenge since no standardized postoperative treatment exists. Knowledge of molecular pathways determining the behavior of individual gastric tumors seems to be crucial for therapeutic decisions, and evaluation of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) expression might be critical for prognosis, assessment, and identification of patients that could be treated with tailored therapies. METHODS: VEGF and EGFR determination was performed in 88 gastric cancer samples as well as 25 normal gastric mucosa specimens from non-cancer patients using a commercially available immunohistochemistry kit. In all samples, the correlation of VEGF and EGFR expression was investigated with each other, and with other prognostic indicators in all samples, and, finally, with survival rates in 69 patients undergoing potentially curative surgery. RESULTS: Forty-eight per cent (42 cases) of gastric cancers expressed VEGF, and 44% (39 cases) stained for EGFR. In curatively treated patients, VEGF and EGFR expression was demonstrated to correlate with worse survival in both univariate and multivariate analyses. Molecular profiling was shown to more accurately estimate the risk of cancer-related death than TNM stage, and, of most interest, to allow sorting out high-risk patients within the same stage. CONCLUSIONS: These findings provide evidence that contemporary evaluation of VEGF and EGFR expression may be crucial to select gastric cancer patients with poor prognosis who may benefit of tailored treatments.

Lim, M. S. (2006). "Re: Correlational of oral tongue cancer inversion with matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) expression, by Kim S-H, Cho NH, Kim K, et al." J Surg Oncol **93**(4): 253-254.

Lin, S. S., et al. (2009). "Curcumin inhibits the migration and invasion of human A549 lung cancer cells through the inhibition of matrix metalloproteinase-2 and -9 and Vascular Endothelial Growth Factor (VEGF)." Cancer Lett **285**(2): 127-133.

It is well known that matrix metalloproteinases (MMPs) act an important role in the invasion, metastasis and angiogenesis of cancer cells. Agents suppressed the MMPs could inhibited the cancer cells migration and invasion. Numerous evidences had shown that curcumin (the active constituent of the dietary spice turmeric) has potential for the prevention and therapy of cancer. Curcumin can inhibit the formation of tumors in animal models of carcinogenesis and act on a variety of molecular targets involved in cancer development. There is however, no

available information to address the effects of curcumin on migration and invasion of human lung cancer cells. The anti-tumor invasion and migration effects of lung cancer cells induced by curcumin were examined. Here, we report that curcumin suppressed the migration and invasion of human non-small cell lung cancer cells (A549) in vitro. Our findings suggest that curcumin has anti-metastatic potential by decreasing invasiveness of cancer cells. Moreover, this action was involved in the MEKK3, p-ERK signaling pathways resulting in inhibition of MMP-2 and -9 in human lung cancer A549 cells. Overall, the above data shows that the anticancer effect of curcumin is also exist for the inhibition of migration and invasion in lung cancer cells.

Linderholm, B., et al. (2004). "Overexpression of c-erbB-2 is related to a higher expression of vascular endothelial growth factor (VEGF) and constitutes an independent prognostic factor in primary node-positive breast cancer after adjuvant systemic treatment." Eur J Cancer **40**(1): 33-42.

The aim of this study was to investigate possible associations between the expression of c-erbB-2 and the angiogenic factors vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), p53 status, routine breast cancer prognostic factors and survival. Expression of c-erbB-2, VEGF, bFGF, and p53 protein was determined with an enzyme-linked immunosorbent assay (ELISA) in 656 patients with primary breast cancer (median follow-up time of 83 months). In 60 cases, we also used immunohistochemistry (IHC) for c-erbB-2 evaluation, to be used as a reference for the ELISA. Overexpression of c-erbB-2 was significantly related to a higher expression of VEGF, lower bFGF content, negative steroid receptor status, and a high S-phase fraction. In multivariate analysis, c-erbB-2 was an independent prognostic factor for relapse-free survival (RFS) and overall survival (OS) in all patients, and in node-positive patients, irrespective of the adjuvant systemic therapy. Combined survival analyses regarding c-erbB-2 and VEGF yielded additional prognostic information.

Linderholm, B., et al. (1999). "Does vascular endothelial growth factor (VEGF) predict local relapse and survival in radiotherapy-treated node-negative breast cancer?" Br J Cancer **81**(4): 727-732.

The aim of this study was to determine the association of vascular endothelial growth factor (VEGF) content in 302 consecutive node-negative breast cancer (NNBC) patients treated with only locoregional radiotherapy to relapse free- (RFS) and overall survival (OS). VEGF content in tumour cytosols was measured by an enzymatic immunoassay for the major isoform VEGF165. The median age was 56 years, the median follow-up time 56 months. A wide range (0.01-144.79 pg microg(-1) DNA) of VEGF content was found (median 1.92). Significant associations were found between VEGF and oestrogen receptor (ER) content, progesterone receptor (PR) and tumour size (P = 0.005). Univariate analysis displayed significant reduced RFS and OS for patients with higher VEGF content (P = 0.0113 and P = 0.0075 respectively). A total of 43 recurrences have been found (ten local relapses within the breast, five in the axillary or supraclavicular lymph nodes and 28 distant metastasis). There was no significant correlation between the localization of the relapse and the VEGF content. Multivariate analysis suggested VEGF as the only predictor of OS (relative risk (RR) = 3.6, 95% confidence interval (CI) = 0.97-13.37), and in patients with T1 tumours (n = 236) the multivariate analysis clearly displayed VEGF as the only independent predictor of both RFS and OS (RR = 5.1, CI = 1.07-24.59). In the subgroup with ER-positive tumours (n = 229), multivariate analysis showed VEGF as the only significant predictor of RFS and OS (RR = 10.44, CI = 1.26-86.38). The results suggest VEGF165 as a predictor of RFS and OS in NNBC patients treated with locoregional radiotherapy, comprising especially patients with favourable prognosis of T1 tumours, or ER-positive tumours. The high VEGF expression might define a radioresistant phenotype, or indicate an early distant spread which might require adjuvant systemic treatment.

Linderholm, B. K., et al. (2009). "Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer." Ann Oncol **20**(10): 1639-1646.

BACKGROUND: Triple-negative breast cancer (TNBC) lacking expression of steroid receptors and human epidermal growth factor receptor 2, having chemotherapy as the only therapeutic option, is characterised by early relapses and poor outcome. We investigated intratumoural (i.t.) levels of the pro-angiogenic cytokine vascular endothelial growth factor (VEGF) and survival in patients with TNBC compared with non-TNBC. PATIENTS AND METHODS: VEGF levels were determined by an enzyme immunosorbent assay in a retrospective series consisting of 679 consecutive primary breast cancer patients. RESULTS: Eighty-seven patients (13%) were classified as TNBC and had significantly higher VEGF levels; median value in TNBC was 8.2 pg/microg DNA compared with 2.7 pg/microg DNA in non-TNBC (P < 0.001). Patients with TNBC had statistically significant shorter recurrence-free survival [hazard ratio (HR) = 1.8; P = 0.0023], breast cancer-corrected survival (HR

= 2.2; P = 0.004) and overall survival (HR = 1.8; P = 0.005) compared with non-TNBC. Patients with TNBC relapsed earlier than non-TNBC; mean time from diagnosis to first relapse was 18.8 and 30.7 months, respectively. The time between first relapse and death was also shorter in TNBC: 7.5 months versus 17.5 months in non-TNBC (P = 0.087). CONCLUSIONS: Our results show that TNBC have higher i.t. VEGF levels compared with non-TNBC. Ongoing clinical trials will answer if therapy directed towards angiogenesis may be an alternative way to improve outcome in this poor prognosis group.

Ling, M. T., et al. (2005). "Overexpression of Id-1 in prostate cancer cells promotes angiogenesis through the activation of vascular endothelial growth factor (VEGF)." Carcinogenesis **26**(10): 1668-1676.

Androgen-independent metastatic prostate cancer is the main cause of cancer related death in men. One of the reasons for this is the lack of understanding of the molecular mechanisms leading to the metastatic progression of prostate cancer. In this study, we have demonstrated that overexpression of Id-1 (inhibitor of differentiation/DNA synthesis), a member of the helix-loop-helix family proteins, is a key factor in promoting angiogenesis through activation of the vascular endothelial growth factor (VEGF) in prostate cancer cells. Using prostate cancer cells ectopically transfected with the Id-1 gene, we found that upregulation of Id-1 induced VEGF secretion through activation of the VEGF gene transcription. Downregulation of Id-1, however, led to the suppression of VEGF secretion and its gene promoter activity. The association between Id-1 and VEGF was also confirmed on human xenografts by immunohistochemical staining. In addition, the growth medium generated by the Id-1 expressing cells was able to promote morphological changes as well as capillary tube formation in human umbilical vein endothelial cells (HUVECs) at similar degrees to the recombinant human VEGF. Furthermore, inhibition of VEGF function by the treatment with an Flk-1 inhibitor, SU1498, or with the VEGF neutralizing antibody resulted in the reverse of the angiogenic effect on HUVECs. Our results suggest that overexpression of Id-1 in prostate cancer cells may provide an autocrine signal to promote angiogenesis through the activation of VEGF. Since increased Id-1 has been reported in many types of advanced human cancers, our results indicate that downregulation of Id-1 may be a novel target to inhibit the growth of metastatic cancers through the suppression of angiogenesis.

Lissoni, P., et al. (2000). "Chemotherapy and angiogenesis in advanced cancer: vascular endothelial growth factor (VEGF) decline as predictor of disease control during taxol therapy in metastatic breast cancer." Int J Biol Markers **15**(4): 308-311.

Angiogenesis is essential for tumor growth. Since vascular endothelial growth factor (VEGF) represents the main angiogenic factor, the control of VEGF secretion could constitute the most important mechanism to achieve the inhibition of angiogenesis-related processes. High blood concentrations have been proven to correlate with poor prognosis in advanced cancer. In experimental conditions, chemotherapeutic agents such as taxol appeared to inhibit VEGF-induced angiogenesis, while at present there are no data about the influence of chemotherapy on VEGF secretion in cancer patients. This preliminary study was performed to evaluate the effect of taxol therapy on VEGF secretion in advanced cancer patients in relation to the clinical response. The study included 14 patients with metastatic breast cancer who were treated with taxol monochemotherapy (175 mg/m2 i.v. every 21 days for three cycles). Serum levels of VEGF were measured by ELISA in blood samples collected before therapy and at 21-day intervals. The clinical response consisted of partial response (PR) in three and stable disease (SD) in six patients, whereas the other five patients had progressive disease (PD). Abnormally high pre-treatment levels of VEGF were seen in 8/14 patients. VEGF mean values significantly decreased during taxol therapy in patients with PR or SD, whereas no decline was observed in patients with PD. Moreover, the percent of normalization or decline greater than 50% in VEGF levels was significantly higher in patients with PR or SD than in those with PD (5/9 vs. 0/5). This preliminary study would suggest that the efficacy of taxol therapy in metastatic breast cancer - at least in terms of disease stabilization - may be associated with a decrease in VEGF blood levels followed by potential inhibition of cancer-related neovascularization.

Lissoni, P., et al. (1998). "Vascular endothelial growth factor (VEGF) serum levels during cancer immunotherapy with IL-2: preliminary considerations." Int J Biol Markers **13**(2): 98-101.

Neoangiogenesis has been proven to play a fundamental role in promoting cancer spread, and vascular endothelial growth factor (VEGF) is known to represent one of the most important angiogenic factors. The present study was planned to investigate changes in VEGF secretion in cancer patients undergoing immunotherapy with IL-2, with the aim of establishing whether VEGF variations play a role in mediating the IL-2-induced control of neoplastic diseases. The study involved 14 metastatic renal cell cancer patients treated with IL-2 immunotherapy (6 million IU/day subcutaneously for 6 days/week for 4 weeks). The clinical response consisted of partial response (PR) in

3, stable disease (SD) in 6 and progressive disease (PD) in the remaining 5 patients. VEGF serum levels were measured by an enzyme immunoassay designed to determine both bound and unbound VEGF. No significant changes in VEGF mean levels occurred during IL-2 therapy. Moreover, neither in patients with PR or SD nor in those with PD did the mean serum levels of VEGF change significantly in response to IL-2. This preliminary study seems to exclude that changes in the angiogenic factor VEGF may play a role in mediating the therapeutic efficacy of IL-2 cancer immunotherapy. However, since the method of measurement used in our study was designed to detect the total amount of VEGF, it cannot be excluded that changes in the free fraction of the molecule may occur during IL-2 cancer immunotherapy.

Lissoni, P., et al. (2001). "Abnormally enhanced blood concentrations of vascular endothelial growth factor (VEGF) in metastatic cancer patients and their relation to circulating dendritic cells, IL-12 and endothelin-1." J Biol Regul Homeost Agents **15**(2): 140-144.

Elevated VEGF blood concentrations have been proven to be associated with poor prognosis in human neoplasms. This finding is generally explained as a consequence of the potential angiogenic properties of VEGF itself. However, preliminary experimental studies suggest that VEGF, in addition to its angiogenic activity, may also play an immunosuppressant role by inhibiting dendritic cell (DC) maturation. The present study was performed to analyze blood levels of VEGF in cancer patients in relation to those of another potentially angiogenic tumor growth factor, endothelin-1 (ET-1), and to the absolute number of circulating immature and mature DC, and serum levels of the best known antitumor cytokine, IL-12. The study was performed in 100 healthy controls and in 80 solid tumor patients (colorectal cancer: 24; gastric cancer: 17; cancer of pancreas: 4; lung cancer: 13; breast cancer: 11; renal cell cancer: 6; gynecologic tumors: 5), 48 of whom showed distant organ metastases. In each patient, we have evaluated serum concentrations of VEGF-165, total VEGF, ET-1, IL-12 and the circulating number of immature (CD123+) and mature (CD11c+) DC. Mean serum levels of VEGF-165 were significantly higher in metastatic patients than in controls or in non-metastatic patients, whereas the total amounts of VEGF were not significantly higher. Moreover, it has been observed that patients with abnormally elevated blood concentrations of VEGF-165 showed significantly lower mean values of immature DC, mature DC and IL-12 and significantly higher mean levels of ET-1 than those with normal concentrations. This study, by confirming that advanced neoplastic disease may be associated with increased endogenous secretion of VEGF, seems to suggest that the association between high blood levels of VEGF and poor prognosis in cancer does not depend only on VEGF-induced stimulation of the neovascularization, but also on VEGF-related immunosuppression.

Liu, S. and W. Qian (2012). "Need for clarification of data in a recent meta-analysis on vascular endothelial growth factor (VEGF) and risk of breast cancer." Cytokine **60**(3): 596.

Liu, W., et al. (2018). "Association of Vascular Endothelial Growth Factor (VEGF) Gene Polymorphisms With Gastric Cancer and Its Development, Prognosis, and Survival." Technol Cancer Res Treat **17**: 1533034617753810.

The relationship between vascular endothelial growth factor gene polymorphism and gastric cancer risk and its development, prognosis, and survival are still being debated. This meta-analysis was performed to assess these relationships. The association reports were identified from PubMed, Embase, Cochrane Library, and CBM-disc (China Biological Medicine Database), and eligible studies were included and calculated using the meta-analysis method. VEGF+936C/T, VEGF+405 G>C, VEGF-460 T>C, VEGF-1498 T>C, and VEGF-2578 C>A gene polymorphisms were found to be unassociated with gastric cancer risk for the overall population in this meta-analysis, whereas the VEGF-634 G>C GG genotype was associated with gastric cancer risk in the overall population. Furthermore, VEGF-634 G>C C allele and the GG genotype were associated with gastric cancer risk in Caucasians, and VEGF+1612G/A gene polymorphism was associated with gastric cancer risk for the Asian population. VEGF+936C/T gene polymorphism was not associated with the stage of cancer, lymph node metastasis, Lauren classification, or survival of gastric cancer. However, VEGF+936C/T T allele and TT genotype were associated with the tumor size of gastric cancer. In conclusion, the VEGF-634 G>C GG genotype was associated with gastric cancer risk in the overall population with the VEGF-634 G>C C allele and GG genotype being associated with risk in Caucasians and VEGF+1612G/A in the Asian population.

Luo, T., et al. (2013). "Vascular endothelial growth factor (VEGF) gene polymorphisms and breast cancer risk in a Chinese population." Asian Pac J Cancer Prev **14**(4): 2433-2437.

Vascular endothelial growth factor (VEGF) is a potent regulator of angiogenesis and thereby involved in the development and progression of solid tumours. Associations between three VEGF gene polymorphisms (-634 G/C, +936 C/T, and +1612 G/A)

and breast cancer risk have been extensively studied, but the currently available results are inconclusive. Our aim was to investigate associations between three VEGF gene polymorphisms and breast cancer risk in Chinese Han patients. We performed a hospital-based case-control study including 680 female incident breast cancer patients and 680 female age-matched healthy control subjects. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis was performed to detect the three VEGF gene polymorphisms. We observed that women carriers of +936 TT genotypes [odds ratio (OR) =0.46, 95% confidence interval (CI) = 0.28, 0.76; P=0.002] or 936 T-allele (OR=0.81, 95% CI= 0.68, 0.98; P=0.03) had a protective effect concerning the disease. Our study suggested that the +1612G/A polymorphism was unlikely to be associated with breast cancer risk. The -634CC genotype was significantly associated with high tumor aggressiveness [large tumor size (OR=2.63, 95% CI=1.15, 6.02; P=0.02) and high histologic grade (OR=1.47, 95% CI= 1.06, 2.03; P=0.02)]. The genotypes were not related with other tumor characteristics such as regional or distant metastasis, stage at diagnosis, or estrogen or progesterone receptor status. Our study revealed that the VEGF -634 G/C and +936 C/T gene polymorphisms may be associated with breast cancer in Chinese Han patients.

Machado, D. E., et al. (2010). "Higher expression of vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 (Flk-1) and metalloproteinase-9 (MMP-9) in a rat model of peritoneal endometriosis is similar to cancer diseases." J Exp Clin Cancer Res **29**: 4.

BACKGROUND: Endometriosis is a common disease characterized by the presence of a functional endometrium outside the uterine cavity, causing pelvic pain, dysmenorrheal, and infertility. This disease has been associated to development of different types of malignancies; therefore new blood vessels are essential for the survival of the endometrial implant. Our previous observations on humans showed that angiogenesis is predominantly found in rectosigmoid endometriosis, a deeply infiltrating disease. In this study, we have established the experimental model of rat peritoneal endometriosis to evaluate the process of angiogenesis and to compare with eutopic endometrium. METHODS: We have investigated the morphological characteristics of these lesions and the vascular density, VEGF and its receptor Flk-1 and MMP-9 expression, and activated macrophage distribution, using immunohistochemistry and RT-PCR. RESULTS: As expected, the auto-transplantation of endometrium pieces into the peritoneal cavity is a well-established method for endometriosis induction in rats. The lesions were cystic and vascularized, and demonstrated histological hallmarks of human pathology, such as endometrial glands and stroma. The vascular density and the presence of VEGF and Flk-1 and MMP-9 were significantly higher in endometriotic lesions than in eutopic endometrium, and confirmed the angiogenic potential of these lesions. We also observed an increase in the number of activated macrophages (ED-1 positive cells) in the endometriotic lesions, showing a positive correlation with VEGF. CONCLUSION: The present endometriosis model would be useful for investigation of the mechanisms of angiogenesis process involved in the peritoneal attachment of endometrial cells, as well as of the effects of therapeutic drugs, particularly with antiangiogenic activity.

Mao, K., et al. (2008). "The prognostic value of vascular endothelial growth factor (VEGF)-A and its receptor in clinically localized prostate cancer: a prospective evaluation in 100 patients undergoing radical prostatectomy." Can J Urol **15**(5): 4257-4262.

OBJECTIVES: To study the prognostic value of vascular endothelial growth factor (VEGF)-A and its receptor VEGFR-1 in localized prostate cancer. METHODS: One hundred patients undergoing radical prostatectomy (RP) for clinically localized prostate cancer were prospectively included. Plasma levels of VEGF-A were measured preoperatively. After intervention, tissue microarrays were built from the RP specimens. VEGF-A and VEGFR-1 expressions in prostate cancer tissue were determined using immunochemistry. Then the associations between plasma levels of VEGF-A, VEGF-A and VEGFR-1 expressions in prostate cancer tissue, and the outcome of patients were analyzed. RESULTS: After a median follow-up of 22 months, 14 patients experienced biological recurrence of prostate cancer. There was no correlation between plasma VEGF-A and the risk of recurrence following RP. Moreover, there was no correlation between VEGF-A expression or VEGFR-1 expression in prostate cancer tissue and the risk of recurrence after RP. CONCLUSIONS: Plasma levels of VEGF-A, the expression of VEGF-A and that of VEGFR-1 in prostate cancer tissue did not affect patients outcome following RP. VEGF-A and its receptor VEGFR-1 may have no prognostic value in localized prostate cancer. Further studies with longer follow-up are mandatory to confirm these findings.

Mao, Z., et al. (2019). "PVT1 Promotes Angiogenesis by Regulating miR-29c/Vascular Endothelial Growth Factor (VEGF) Signaling Pathway in Non-Small-Cell Lung Cancer (NSCLC)." Med Sci Monit **25**: 5418-5425.

BACKGROUND Lung cancer is a common tumor. Non-small-cell lung cancer (NSCLC) accounts

for over 85% of lung cancer and has a high degree of malignancy. Angiogenesis plays an important role in NSCLC progression. Some studies have found that PVT1 can promote angiogenesis in tumor tissues, but the role of PVT1 in angiogenesis in NSCLC, as well as the underlying mechanism, is unclear. MATERIAL AND METHODS To explore the role of PVT1 in NSCLC, qRT-PCR, Western blot, luciferase reporter assay, and ELISA were carried out for detecting the relationship among PVT1, miR-29c, and VEGF. Tube formation assay was used to assess the role of PVT1 in angiogenesis in NSCLC. RESULTS Our results showed that higher PVT1 was expressed in NSCLC and the elevated PVT1 was closely related to angiogenesis and poor prognosis in NSCLC. Further functional analysis showed that higher PVT1 expression could promote angiogenesis by regulating VEGF in NSCLC. Mechanistically, the luciferase reporter assay confirmed that VEGF was the targeted gene of miR-29c. In addition, we found that miR-29c is an inhibitory target of PVT1. CONCLUSIONS We found that PVT1 promotes angiogenesis through targeting the miR-29c/VEGF signaling pathway in NSCLC.

Martinez-Fierro, M. L., et al. (2013). "Positive association between vascular endothelial growth factor (VEGF) -2578 C/A variant and prostate cancer." Cancer Biomark **13**(4): 235-241.

BACKGROUND: Vascular endothelial growth factor (VEGF) gene is an important angiogenesis regulator related to cancer development and progression. We evaluated the association between -2578 C/A (rs699947) VEGF polymorphism and PCa in Mexican subjects, to contribute to knowledge of VEGF role in genetic epidemiology of prostate cancer (PCa). OBJECTIVE: The aim of this study was to evaluate the association between -2578 C/A VEGF variant and PCa in Mexican population. METHODS: A total of 249 men (77 PCa cases and 172 controls) from the Northwestern region of Mexico were screened for the -2578 C/A VEGF variant. The polymorphism was determined by polymerase chain reaction-based restriction analysis. RESULTS: Genotype frequencies for C/C, C/A, and A/A, were 0.48, 0.49, 0.03 for cases and 0.41, 0.45, 0.14 for controls respectively. Genotype A/A of -2578 VEGF variant reduces the risk of PCa in an 84% among studied population (Odds Ratio 0.16; 95% CI: 0.04-0.71, P=0.007). C/C carriers showed an increased PCa risk of 6.1 times among the study population. CONCLUSIONS: Inheritance of -2578 A/A genotype of VEGF gene may modify PCa susceptibility risk in Mexican population.

Mathur, R. S. and S. P. Mathur (2005). "Vascular endothelial growth factor (VEGF) up-regulates epidermal growth factor receptor (EGF-R) in cervical cancer in vitro: this action is mediated through HPV-E6 in HPV-positive cancers." Gynecol Oncol **97**(1): 206-213.

OBJECTIVES: Epidermal Growth Factor Receptor (EGF-R) up-regulation in cervical cancer cells leads to an increase in cell proliferative Insulin-like Growth Factor II (IGF-II) and Vascular Endothelial Growth Factor (VEGF) and a decrease of the anti-proliferative IGF-binding protein-3 (IGF-BP3). The objectives for this study are: (a) to find if VEGF, in turn, up-regulates EGF-R and down-regulates IGF-BP3; (b) to determine if human papilloma virus (HPV-E6) mediates this action of VEGF in HPV-positive cells; and (c) to verify if these effects are reflected in changes in cell proliferation METHODS: We used HPV-positive HeLa (Black), ME-180 and CaSki (Caucasian) and HPV-negative HT-3 (Caucasian) cell lines. (a) Levels of HPV-E6 in the HPV-positive cells were enumerated after treating the cells for 24 h with 20 ng/ml of VEGF using our semi-quantitative immunofluorescent antibody assay. (b) Cellular levels of EGF-R, HPV-E6, IGF-II and IGF-BP3 were enumerated in ME-180 and CaSki cells incubated for 24 h with 5, 10 and 20 ng/ml of VEGF. (c) HPV-negative HT-3 and HPV-positive ME-180 and CaSki cells were incubated with 20 ng/ml VEGF alone or in combination with antibodies to HPV-E6 and EGF-R. HPV-E6 (measured only in HPV-positive cells), EGF-R, IGF-II and IGF-BP3 levels were measured. (d) Cell proliferation was determined using cell proliferation Bradykinine-U colorimetric assay, in HT-3, HeLa and ME-180 cell lines in the presence of VEGF alone and with HPV-E6 antibodies. RESULTS: (a) In all the HPV-positive cell lines, 20 ng/ml VEGF significantly increased (30-50%; $P < 0.0001$) the HPV-E6. (b) In the ME-180 and CaSki cells, VEGF treatment up-regulated EGF-R, IGF-II and HPV-E6 and down-regulated IGF-BP3 in a dose-dependent manner ($P < 0.001$). (c) These effects of VEGF were eliminated when the HPV-positive cells were co-incubated with antibodies to HPV-E6 or EGF-R. In the HPV-negative HT-3 cells, VEGF decreased IGF-BP3 while increasing EGF-R and IGF-II levels. Antibodies to EGF-R eliminated these effects ($P < 0.0001$). (d) Treatment with VEGF resulted in increased cell proliferation in HT-3, HeLa and ME-180 cells; co-incubation with HPV-E6 antibodies abrogated this effect only in the HPV-positive cells. CONCLUSIONS: In cervical cancer, VEGF up-regulates EGF-R and down-regulates IGF-BP3, thus amplifying the cell proliferative activity of EGF-R. This action of VEGF seems to be mediated, directly through EGF-R or indirectly through HPV-E6 in the HPV-positive cancers, while EGF-R up-regulation appears to play a major role in the HPV-negative cervical cancers.

Mathur, S. P., et al. (2005). "Serum vascular endothelial growth factor C (VEGF-C) as a specific biomarker for advanced cervical cancer: Relationship to insulin-like growth factor II (IGF-II), IGF binding protein 3 (IGF-BP3) and VEGF-A [corrected]." Gynecol Oncol **98**(3): 467-483.

OBJECTIVES: An early non-invasive diagnosis of cervical cancer and its metastasis can save lives. We have shown that serum IGF-II levels can be effectively used for a specific early diagnosis of cervical cancer. Here, we shall determine if serum levels of vascular endothelial growth factors B and C (VEGF-A [corrected] VEGF-C) associated with vasculogenic and lymphogenic metastasis may be used for an early diagnosis of advanced metastatic cervical cancer and compare these levels with those of the serum IGF-II and IGF-binding protein 3 (IGF-BP3). MATERIAL AND METHODS: (a) Serum levels of IGF-II, IGF-BP3, VEGF-A [corrected] (VEGF(165)) and VEGF-C (ELISA kits) were determined in: 82 controls with normal Pap smears; 29 women with atypical squamous cells of undetermined significance (ASCUS) and normal cervical biopsy; 46 ASCUS and cervical intraepithelial neoplasia (CIN) on biopsy; 8 pre-therapy CIN-I; 23 successfully treated CIN-I; 75 persistent CIN-I; 14 CIN-II/III pre-therapy; 14 successfully treated CIN-II/III; 70 persistent CIN-II/III; 86 pre-therapy cervical cancer; 26 in early grades of cervical cancer; 21 in late grades of cervical cancer; 22 cervical cancer patients in remission; 50 persistent cervical cancer; 18 with ovarian cancer; and 57 with endometrial cancer. (b) Serial serum samples collected over 5 years in 5 women with progressing cervical cancer were also tested. (c) Serum and tissue VEGF-C were enumerated in 20 matched serum (ELISA) and tissue (semi-quantitative immunofluorescent antibody assay) samples from controls, early cervical cancer, late cervical cancer, ovarian cancer and endometrial cancer patients. Student's t test, chi-square analysis and linear regression analysis were used. RESULTS: (a) As anticipated, serum IGF-II levels were elevated as early as ASCUS with CIN on biopsy and continued to be elevated in CIN (all grades; pre-therapy and persistent) and cervical cancer (pre-therapy, early, late and persistent). Serum IGF-II levels were normal in ASCUS with normal biopsy, successfully treated CIN-I, II/III, cervical cancer as well as pre-therapy ovarian and endometrial cancers (therapy efficacy: $P < 0.0001$ by chi-square analysis). Serum IGF-BP3 showed a significant decrease with advancing disease. Serum VEGF-A [corrected] levels were the highest in pre-therapy, early, advanced and persistent cervical cancer, as well as in ovarian and endometrial cancers. Serum VEGF-C levels, on the other hand, were the highest in late and persistent cervical cancers, but not in ovarian or endometrial cancers. (b) In the 5 women with serial samples, the serum levels of the growth factors showed similar trends. (c) VEGF-C levels in serum and tissue were elevated in cervical cancers especially in advanced grades, while they were normal in serum and tissue from the controls and women with ovarian and endometrial cancers. There was a highly significant positive correlation between VEGF-C and IGF-II and a negative correlation between IGF-BP3 and VEGF-C ($P < 0.0001$). CONCLUSION: Serum IGF-II up-regulation is specific to cervical cancer and helps in the early diagnosis of malignant proliferation, while serum VEGF-C up-regulation appears to be a unique marker for an early diagnosis of cervical cancer metastasis. VEGF-C and IGF-II systems appear to be interrelated in cervical cancer, contributing to the early malignant cell proliferation and lympho-vascular metastasis. Serum IGF-BP3 and VEGF-A [corrected] appear to be common markers for all gynecological cancers.

Matsui, T., et al. (2015). "Vascular endothelial growth factor C (VEGF-C) expression predicts metastasis in tongue cancer." Oral Surg Oral Med Oral Pathol Oral Radiol **120**(4): 436-442.

OBJECTIVE: We evaluated predictive factors for cervical lymph node metastasis of tongue squamous cell carcinoma (SCC). STUDY DESIGN: We present a retrospective analysis of 90 patients with T1-2 N0 SCC who underwent primary excision as initial treatment without preoperative radiotherapy or chemotherapy. We examined the clinicopathologic factors (gender, age, clinical stage, surgical margin, grade of differentiation, lymphatic invasion, tumor depth of invasion, pattern of invasion [POI]) and immunohistochemical factors (vascular endothelial growth factor [VEGF]-A and VEGF-C expression) to predict the probability of lymph node metastasis. RESULTS: The local progression-free 5-year survival rate was 100%. Tumor depth of invasion (>/=4 mm, $P = .022$), POI (score >4, $P = .000$), and VEGF-C expression ($P = .008$) were associated with the lymph node metastasis of tongue SCC in a multiple logistic regression analysis (odds ratios [ORs]: 5.075, 17.383, and 9.533, respectively). CONCLUSIONS: The local control rate of tongue SCC in the early stages has significantly improved as a result of development of surgical techniques. On the other hand, we believe that tumor depth of invasion (>/=4 mm), POI, and VEGF-C expression all need to be considered in the preoperative and postoperative planning stages for tongue cancer treatment.

Matsuura, M., et al. (2009). "Autocrine loop between vascular endothelial growth factor (VEGF)-C and VEGF receptor-3 positively regulates tumor-associated

lymphangiogenesis in oral squamoid cancer cells." Am J Pathol **175**(4): 1709-1721.

Numerous past studies have suggested a critical role of the paracrine effect between tumor vascular endothelial growth factor (VEGF)-C and lymphatic FLT-4 in solid tumor-associated lymphangiogenesis. In contrast, the pathophysiological role of tumor cell-associated FLT-4 in tumor progression remains to be elucidated. Here, we investigated this role using a tumor implantation model. SAS cells, an oral squamous carcinoma cell line expressing both VEGF-C and FLT-4 but neither FLK-1/KDR nor VEGF-D were adopted for experiments. Stable transformants of dominant-negative (dn) SAS cells were established in which the cytoplasmic domain-deleted FLT-4 was exogenously overexpressed, which can lead to inactivation of endogenous FLT-4 through competitive antagonism and is associated with down-activation of endogenous FLT-4-related intracellular signals. In vitro and in vivo proliferation assays showed lower proliferative activity of dn-SAS cells. An immunohistochemical study revealed that the tumor lymphangiogenesis was significantly suppressed, and the level of human VEGF-C mRNA was significantly lower in dn-SAS cell-derived tumor tissues. Moreover, in vitro studies demonstrated that the significant suppression of VEGF-C and VEGF-A expression was evident in dn-SAS cells or wild-type SAS cells treated with either the FLT-4 kinase inhibitor MAZ51 or the inhibitor of FLT-4-related signals. These findings together suggested that the VEGF-C/FLT-4 autocrine loop in tumor cells was a potential enhancer system to promote cancer progression, and FLT-4 in tumor tissue might become an effective target for cancer therapy.

Menendez, J. A., et al. (2005). "Does endogenous fatty acid metabolism allow cancer cells to sense hypoxia and mediate hypoxic vasodilatation? Characterization of a novel molecular connection between fatty acid synthase (FAS) and hypoxia-inducible factor-1alpha (HIF-1alpha)-related expression of vascular endothelial growth factor (VEGF) in cancer cells overexpressing her-2/neu oncogene." J Cell Biochem **94**(5): 857-863.

Her-2/neu (erbB-2) oncogene overexpression is associated with increased tumor progression and metastasis. Fatty acid synthase (FAS), the key lipogenic enzyme responsible for the endogenous synthesis of fatty acids, has been shown to be one of the genes regulated by Her-2/neu at the level of transcription, translation, and biosynthetic activity. Interestingly, we recently established that both pharmacological inhibition of FAS activity and silencing of FAS gene expression specifically suppress Her-2/neu oncoprotein expression and tyrosine-kinase activity in breast and ovarian Her-2/neu overexpressors. Unraveling the functional organization of this novel bi-directional molecular connection between Her-2/neu and FAS-dependent neoplastic lipogenesis is a major challenge that the field is only beginning to take on. Considering that Her-2/neu overexpression correlates with increased expression of the hypoxia inducible factor-1alpha (HIF-1alpha), which, in a mitogen-activated protein kinase (MAPK)-dependent manner, plays a key role in the expression of several genes including cytokines such as vascular endothelial growth factor (VEGF), we hypothesized that FAS blockade should result in a concomitant down-regulation of VEGF. Unexpectedly, the specific inhibition of the de novo fatty acid synthesis with the small-molecule inhibitor of FAS activity C75 resulted in a dramatic dose-dependent enhancement (up to 500% increase) of VEGF secretion in Her-2/neu-overexpressing SK-Br3, BT-474, and SKOV3 cancer cells. Concurrently, FAS blockade drastically activated MAPK and promoted further a prominent accumulation of HIF-1alpha in Her-2/neu overexpressors. Moreover, U0126-induced inhibition of MAPK activity completely abolished C75-induced up-regulation of HIF-1alpha expression and VEGF secretion, whereas it did not modulate C75-induced down-regulation of Her-2/neu oncogene. Importantly, RNA interference (RNAi)-mediated silencing of the FAS gene recapitulated C75's effects by up-regulating VEGF secretion, MAPK activation and HIF-1alpha expression. Therefore, it appears that perturbation of cancer-associated endogenous fatty metabolism triggers a "hypoxia-like" (oxygen-independent) condition that actively rescues Her-2/neu-dependent MAPK --> HIP-1alpha --> VEGF cascade. It is tempting to suggest that an intact FAS-catalyzed endogenous fatty acid metabolism is a necessary metabolic adaptation to support the enhanced ability of Her-2/neu-overexpressing cancer cells to survive cellular hypoxia in a HIF-alpha-dependent manner.

Moon, H. S., et al. (2000). "Concentration of vascular endothelial growth factor (VEGF) and transforming growth factor-beta1 (TGF-beta1) in the serum of patients with cervical cancer: prediction of response." Int J Gynecol Cancer **10**(2): 151-156.

The aim of this study was to determine the value of the measurement of serum VEGF and TGF-beta1 levels in the diagnosis of cervical cancer and to see whether these levels decrease after treatment for cervical cancer. We measured serum VEGF and TGF-beta1 levels through EIA in patients with CIN (n = 35), and cervical squamous cell cancer (n = 48). We also measured serum VEGF, TGF-beta1, and SCC antigen levels before and after radiotherapy in 13 cervical squamous cell cancer patients. The sizes of the tumors in those patients were measured by a computer

tomography scan or magnetic resonance imaging. The serum VEGF levels were different between CIN and cervical cancer groups ($P < 0.1$), and the serum TGF-beta 1 levels in the cervical cancer group were lower than those in the other groups ($P < 0.05$). The serum VEGF levels were significantly related to the serum TGF-beta 1 levels in the cervical cancer patients ($P < 0.01$). In the cervical cancer patients, the decrease in the circulating VEGF levels after receiving radiotherapy was related to the decrease in tumor size ($P < 0.01$). While the measurement of serum VEGF level is adjuvant in diagnosing cervical cancers, serial serum VEGF level measurements may find a clinical use in the follow-up of women treated for cervical cancer.

Morita, S., et al. (2013). "Association between bevacizumab-related hypertension and vascular endothelial growth factor (VEGF) gene polymorphisms in Japanese patients with metastatic colorectal cancer." Cancer Chemother Pharmacol **71**(2): 405-411.

PURPOSE: Bevacizumab, a monoclonal antibody that binds to VEGF, has a well-known toxic effect of hypertension. We studied possible associations between bevacizumab-related hypertension and gene polymorphisms to assure safer cancer therapy. METHODS: We retrospectively studied 60 Japanese patients with metastatic colorectal cancer who had received bevacizumab-based chemotherapy. Genotypes were determined for five well-known functional single-nucleotide polymorphism of the VEGF gene at positions C-2578A, T-1498C, G-1154A, G-634C, and C936T. Hypertension was graded according to CTCAE v4.0 on the basis of home blood pressure. RESULTS: The VEGF-2578 C/C and -1498 T/T genotypes were associated with significantly less hypertension during the first 2 months of bevacizumab-based chemotherapy ($p = 0.004$, $p = 0.025$, respectively). During the treatment period as a whole, the VEGF-2578 C/C and 936 C/C genotypes were associated with less hypertension ($p = 0.031$, $p = 0.043$, respectively). Preexisting hypertension was not associated with bevacizumab-related hypertension. CONCLUSIONS: This study demonstrated a significant relation between a lower incidence of grade 2 or higher bevacizumab-related hypertension and the VEGF-2578 C/C genotype for the entire treatment period in Japanese patients with metastatic colorectal cancer. This genotype might be useful for ensuring safer treatment of patients who receive bevacizumab-based chemotherapy.

Nagano, H., et al. (2007). "Endocrine gland-derived vascular endothelial growth factor (EG-VEGF) expression in colorectal cancer." J Surg Oncol **96**(7): 605-610.

BACKGROUND AND OBJECTIVES: Vascular endothelial growth factor (VEGF) is known as an important factor in the growth and metastasis of cancer cells. In 2001, a novel angiogenesis factor, endocrine gland-derived vascular endothelial growth factor (EG-VEGF), was cloned. In this study, we investigated the expression of EG-VEGF in colorectal cancer, the relationship between its expression and clinicopathological factors, and the in vitro activity of EG-VEGF transfectants. METHODS: We determined expression levels of EG-VEGF in 113 advanced colorectal cancers resected in our hospital by quantitative PCR, and compared the expression levels and clinicopathological findings by multivariate analyses. RESULTS: The expression of EG-VEGF mRNA was positive in 31 cancers and negative in 82 cancers. We found that compared with the negative expression of the EG-VEGF gene, its positive expression was more frequently associated with hematogenous metastasis, and was associated with a poorer survival rate. In addition, EG-VEGF transfectants showed a higher degree of in vitro tubular formation than control cells. CONCLUSIONS: We speculate that, in colorectal cancers, the EG-VEGF gene functions as an important factor in angiogenesis in primary and metastatic lesions, and consider that it is useful as a novel prognostic factor. EG-VEGF molecule-targeted therapy has the potential for improving survival rates.

Nagao, M., et al. (2020). "[A Case of Advanced Rectal Cancer with Metastasis Successfully Treated with an Anti-Vascular Endothelial Growth Factor (VEGF) Drug]." Gan To Kagaku Ryoho **47**(12): 1719-1721.

A 63-year-old asymptomatic woman was diagnosed with multiple liver tumors and a left pulmonary tumor by CT. Colonoscopy(CS)showed a Type 2, quarter circular tumor on Rb. The diagnosis was cT3N1aM1b(H3, PUL1), cStage b rectal cancer. She was administered 8 courses of induction-adjuvant chemotherapy with CAPOX and bevacizumab(BEV). After the chemotherapy, CT and CS revealed shrinkage(up to 50%)of the metastatic liver tumor and primary tumor, and decreasing tumor marker levels. Laparoscopic abdominoperineal resection and partial hepatectomy(S5/6, S8)were performed. After the operation, she was administered 2 courses of chemotherapy with UFT and LV, after which thoracoscopy-assisted upper lobectomy of the left lung was performed. Currently, at 1 and a half years after treatment, no recurrence has been observed, and she is being followed up as an outpatient.

Naikoo, N. A., et al. (2017). "SNP and Haplotype Analysis of Vascular Endothelial Growth Factor

(VEGF) Gene in Lung Cancer Patients of Kashmir." Asian Pac J Cancer Prev **18**(7): 1799-1804.

Vascular endothelial growth factor (VEGF) is a major mediator of angiogenesis involving tumor growth and metastasis. In this large case-control study, we investigated whether functional polymorphisms (+405C>G, +936C>T) in the VEGF gene are associated with the risk of lung cancer. The study investigates the association between variants of VEGF gene and lung cancer. We performed single nucleotide polymorphism (SNP), haplotype and linkage disequilibrium studies on 100 patients and 128 healthy controls with 2 SNPs in the VEGF gene. The results were analyzed using logistic regression models, adjusted for age and sex. No Significant association was detected between individual SNPs and lung cancer using all the models of inheritance (codominant, dominant, recessive, over dominant and additive) for finding an association between genotypes and the cancer risk. The P values obtained for two markers were nonsignificant (P>0.05). Haplotype analysis produced additional support for the non-association of individual haplotypes/ all haplotypes with the cancer risk (Global association P=0.56). Our findings suggest the non-involvement of genetic variants (+405C>G, +936C>T) of the VEGF gene in the etiology of lung cancer.

Nash, G. F. (2007). "Tissue factor (TF) and vascular endothelial growth factor (VEGF) expression in colorectal cancer: relation with cancer recurrence." Colorectal Dis **9**(9): 858-859.

Nguyen, Q. D., et al. (2006). "Inhibition of vascular endothelial growth factor (VEGF)-165 and semaphorin 3A-mediated cellular invasion and tumor growth by the VEGF signaling inhibitor ZD4190 in human colon cancer cells and xenografts." Mol Cancer Ther **5**(8): 2070-2077.

We recently showed by DNA microarray analysis that vascular endothelial growth factor (VEGF) receptor (VEGFR) is expressed in HCT8/S11 human colon cancer cells, suggesting that several angiogenic factors may target colon cancer cells themselves. In this study, transcripts encoding the VEGF-165 and semaphorin 3A (Sema3A) receptors and coreceptors Flt-1, KDR/Flk-1, plexin A1, and neuropilins NP-1 and NP-2 were identified by reverse transcription-PCR in the human colon cancer cell lines HCT8/S11, HT29, HCT116, and PCmsrc. Collagen invasion induced by VEGF-165 and Sema3A in HCT8/S11 cells (EC(50), 0.4-1 nmol/L) required p42/44 mitogen-activated protein kinase and signaling through RhoA/Rho-kinase-dependent and -independent pathways, respectively. As expected, the VEGFR signaling inhibitor ZD4190 selectively abrogated the proinvasive activity of VEGF in collagen gels (IC(50), 10 nmol/L) and chick heart fragments. We identify a novel function for VEGF-165 and Sema3A as proinvasive factors for human colorectal cancer cells. Interestingly, oral administration of the single drug ZD4190 to athymic mice (50 mg/kg/d, once daily) inhibited by 70% the growth of HCT8/S11 tumor cell xenografts. Combinations between the src tyrosine kinase inhibitor M475271 and ZD4190 or cisplatin resulted in additive therapeutic activity against LNM35 human lung tumor xenografts. Our data have significant implications for new therapeutic approaches and individualized treatment targeting VEGFR and src signaling pathways in combination with established clinical drugs at primary tumors and distant metastases in colon and lung cancer patients.

Nicolini, A., et al. (2004). "Vascular endothelial growth factor (VEGF) and other common tissue prognostic indicators in breast cancer: a case-control study." Int J Biol Markers **19**(4): 275-281.

VEGF is a specific mitogen and survival factor for endothelial cells and a key promoter of angiogenesis in physiological and pathological conditions. Nevertheless, VEGF tissue evaluation in cancer patients as a prognostic factor compared to the conventional histological and biological parameters is still controversial. In this case-control study, tissue VEGF was retrospectively determined by immunohistochemistry and related to T, N, ER, PgR, c-erbB-2, p53, MIB-1 and cyclin D1 in 129 breast cancer patients. Seventy-four of these patients had developed distant metastases postoperatively. The remaining 55 patients had remained disease-free >10 years after surgery. In 17 (13%) of the 129 patients (six with distant metastases and eleven disease-free) tissue and plasma VEGF were concomitantly evaluated. In univariate analysis no significant differences in VEGF and tumor size were found between metastatic and disease-free patients, whereas there were significant differences in N, ER, PgR, c-erbB-2, p53, MIB-1 and cyclin D1 (p ranging from 0.001 to 0.0001). In multivariate analysis VEGF showed less significance than N, ER, c-erbB-2, MIB-1 and cyclin D1 ($p = 0.012$, $p = 0.007$, $p = 0.005$, $p = 0.005$, $p = 0.002$ and $p = 0.001$, respectively). VEGF was a significant unfavorable prognostic indicator only in the N+ subset ($p = 0.015$), while ER ($p = 0.05$ and $p = 0.021$) and MIB-1 ($p = 0.031$ and $p = 0.022$) were significant in both the N+ and N- subgroups. In multivariate analysis in the 74 metastatic cases VEGF did not show any significance in relation to disease-free interval and overall survival from the time of mastectomy and from the time of relapse, whereas N and PgR did (p ranging from 0.018 to 0.001). In conclusion, tissue VEGF does not seem a suitable candidate to replace conventional

histological and other common biological prognostic factors in breast cancer.

Niklinska, W., et al. (2001). "Expression of vascular endothelial growth factor (VEGF) in non-small cell lung cancer (NSCLC): association with p53 gene mutation and prognosis." Lung Cancer **34 Suppl 2**: S59-64.

Vascular endothelial growth factor (VEGF) is a multifunctional cytokine that increases microvascular permeability and directly stimulates endothelial cell growth and angiogenesis. Recent evidence suggests that the genetic regulation of angiogenesis is also of crucial importance and that oncogenes and tumor suppressor genes can regulate it. The aim of this study was to determine the prognostic value of VEGF and its possible association with p53-gene mutation in 89 stage I-IIIa surgically treated NSCLC patients. DNA sequencing of the p53 gene (exons 5-8) showed 40 mutations (45%). Among the 89 NSCLC patients, immunoreactivity for VEGF was weakly, moderately and strongly positive in 35 (39%),36 (40%) and 18 (20%) cases, respectively. A strong, statistically significant association was found between the presence of a p53 gene mutation and expression of VEGF (P<0.001). The positive result of the p53 mutation increased the odds of observing a higher level of VEGF expression approximately 9.5 times (95% confidence interval: [3.44,25.89]). In the univariate analysis of survival, increasing levels of VEGF expression were associated with poor prognosis (P<0.001 for trend). In the multivariate analysis, after adjusting for the presence of a p53-gene mutation, gender, TNM stage and histological type, the prognostic effect of VEGF expression level was marginally non-significant (P=0.077). When the two-category quantification of the VEGF level was considered (low vs. intermediate/high), a marginally significant (P=0.024), unfavorable effect of intermediate/high levels of VEGF expression, independent of the effect of the presence of a p53-gene mutation, was found. In conclusion, we found that the p53 mutation was closely related to VEGF expression. Additionally, we observed that an intermediate/high expression of VEGF might be a useful indicator of prognosis in NSCLC. This latter conjecture, suggested by an analysis of the data, ought however, to be independently verified in further studies.

Obermair, A., et al. (1999). "Correlation of the serum concentration of vascular endothelial growth factor (VEGF) and hemoglobin levels in patients with epithelial ovarian cancer." Ann Oncol **10**(8): 998.

Obermair, A., et al. (1997). "Vascular endothelial growth factor (VEGF) in human breast cancer: correlation with disease-free survival." Int J Cancer **74**(4): 455-458.

Studies have shown that microvessel density influences breast-cancer prognosis. Since tumor angiogenesis is considered to be substantially affected by the excretion of vascular endothelial growth factor (VEGF) from tumor cells, we examined whether VEGF concentration is different in malignant and in non-malignant breast tissue. It was also of interest to discover whether intratumoral VEGF concentration influences disease-free survival (DFS) of breast-cancer patients. Analysis is based on 120 tissue specimens taken from breast fibromas (n = 23), normal epithelial breast tissue adjacent to fibromas (n = 8) and invasive breast cancer (n = 89). VEGF concentration was quantified by using an immunoassay. Microvessel density was determined by immunostaining for factor-VIII-related antigen. Median VEGF concentration is given in pg/mg protein (25%-quantile-75%-quantile) and it was 0 (0-1.8) in normal breast tissue, 9.8 (0.52-43.0) in fibromas and 130.4 (50.8-362.2) in invasive carcinomas. A univariate Cox model revealed that node status, tumor size, estrogen-receptor concentration, histological grading and microvessel density were prognostic factors for disease-free survival in breast cancer. We found a significant correlation between VEGF concentration and microvessel count, but VEGF concentration did not significantly influence disease-free survival. Although VEGF protein was found at a significantly higher concentration in malignant than in non-malignant tissue, determination of intratumoral VEGF protein by an enzyme immunoassay was not prognostically relevant in our patient population.

Obermair, A., et al. (1998). "Concentration of vascular endothelial growth factor (VEGF) in the serum of patients with suspected ovarian cancer." Br J Cancer **77**(11): 1870-1874.

As a promoter of angiogenesis, vascular endothelial growth factor (VEGF) is believed to play a pivotal role in tumour growth and metastasis. The aim of this study was to determine the value of preoperative serum VEGF levels in the early diagnosis of ovarian cancer and in the differential diagnosis of adnexal masses. We examined preoperative serum VEGF levels in healthy women (n = 131), patients with benign ovarian cysts (n = 81) and in ovarian cancer patients (n = 44) by using an ELISA (R&D Systems, Minneapolis, MN, USA). A logistic regression model was carried out to determine the influence of VEGF and CA 125 on the probability of malignancy. VEGF revealed a significant influence on the odds of presenting with malignancy vs healthy women (P = 0.001). At 363.7 pg ml(-1), VEGF achieved a sensitivity of 54% and a specificity of 77%. With respect to the differentiation between benign cysts and ovarian cancer, CA 125 (P < 0.0001) but not

VEGF (P = 0.229) predicts the presence of malignancy in a multivariate model. In conclusion, VEGF does not appear to be a useful tool in the early diagnosis of ovarian cancer or for indicating the absence or presence of malignancy in patients with an adnexal mass.

Oh, S. Y., et al. (2013). "The relationship of vascular endothelial growth factor gene polymorphisms and clinical outcome in advanced gastric cancer patients treated with FOLFOX: VEGF polymorphism in gastric cancer." BMC Cancer **13**: 43.

BACKGROUND: The aim of this study is to evaluate the associations between vascular endothelial growth factor (VEGF) Single-nucleotide polymorphisms (SNPs) and clinical outcome in advanced gastric cancer patients treated with oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX). METHODS: Genomic DNA was isolated from whole blood, and six VEGF (-2578C/A, -2489C/T, -1498 T/C, -634 G/C, +936C/T, and +1612 G/A) gene polymorphisms were analyzed by PCR. Levels of serum VEGF were measured using enzyme-linked immunoassays. RESULTS: Patients with G/G genotype for VEGF -634 G/C gene polymorphism showed a lower response rate (22.2%) than those with G/C or C/C genotype (32.3%, 51.1%; P = 0.034). Patients with the VEGF -634 G/C polymorphism G/C + C/C genotype had a longer progression free survival (PFS) of 4.9 months, compared with the PFS of 3.5 months for those with the G/G (P = 0.043, log-rank test). By multivariate analysis, this G/G genotype of VEGF -634 G/C polymorphism was identified as an independent prognostic factor (Hazard ratio 1.497, P = 0.017). CONCLUSION: Our data suggest that G/G genotype of VEGF -634 G/C polymorphism is related to the higher serum levels of VEGF, and poor clinical outcome in advanced gastric cancer patients.

Ohta, M., et al. (2003). "The significance of circulating vascular endothelial growth factor (VEGF) protein in gastric cancer." Cancer Lett **192**(2): 215-225.

We examined the vascular endothelial growth factor (VEGF) levels in peripheral blood and drainage vein (plasma and serum), and then these were compared with local VEGF expression from gastric cancer. Peripheral blood plasma VEGF levels was increased in the patients with venous invasion, and moderately correlated with the number and ratio of lymph nodes with metastasis. Local VEGF expression was correlated significantly with tumor size, advanced stage and lymph node metastasis, but not correlated with peripheral VEGF levels. The level of plasma VEGF in peripheral veins is one of the sensitive markers of the status of gastric cancer.

Oommen, S., et al. (2011). "Vascular endothelial growth factor A (VEGF-A) induces endothelial and cancer cell migration through direct binding to integrin {alpha}9{beta}1: identification of a specific {alpha}9{beta}1 binding site." J Biol Chem **286**(2): 1083-1092.

Integrin alpha9beta1 mediates accelerated cell adhesion and migration through interactions with a number of diverse extracellular ligands. We have shown previously that it directly binds the vascular endothelial growth factors (VEGF) A, C, and D and contributes to VEGF-induced angiogenesis and lymphangiogenesis. Until now, the alpha9beta1 binding site in VEGF has not been identified. Here, we report that the three-amino acid sequence, EYP, encoded by exon 3 of VEGF-A is essential for binding of VEGF to integrin alpha9beta1 and induces adhesion and migration of endothelial and cancer cells. EYP is specific for alpha9beta1 binding and neither requires nor activates VEGFR-2, the cognate receptor for VEGF-A. Following binding to EYP, integrin alpha9beta1 transduces cell migration through direct activation of the integrin signaling intermediates Src and focal adhesion kinase. This interaction is biologically important because it mediates in vitro endothelial cell tube formation, wound healing, and cancer cell invasion. These novel findings identify EYP as a potential site for directed pharmacotherapy.

Oshika, Y., et al. (2000). "Ribozyme approach to downregulate vascular endothelial growth factor (VEGF) 189 expression in non-small cell lung cancer (NSCLC)." Eur J Cancer **36**(18): 2390-2396.

The aim of this study was to further clarify the role of the cell-associated isoform of vascular endothelial growth factor (VEGF189) on tumour growth and vascularity. Five isoforms of VEGF have been identified with different biological activities. VEGF121, VEGF145, VEGF165, VEGF189, VEGF206 are generated by alternative splicing. We used a hammerhead-type ribozyme (V189Rz) to suppress VEGF189 mRNA. The V189Rz specifically cleaved exon 6 of VEGF189 mRNA, but showed no activity against the VEGF121 or VEGF165 isoforms. The V189Rz was introduced into the human non-small cell lung cancer (NSCLC) cell line (OZ-6/VR). The expression level of VEGF189 mRNA was decreased in the OZ-6/VR cells, while VEGF121 and 165 expression was unaltered. The OZ-6/VR cells xenotransplanted into nude mice showed markedly reduced vascularisation and growth, whereas the cell line did not show any decreased growth under tissue culture conditions. The OZ-6/VR cells (1 x 10(5) cells/mouse) formed no tumours, whereas the parental OZ-6 cells formed large tumours within 8 weeks. The specific suppression of VEGF189 by the ribozyme

decreased vascularity and xenotransplantability of the lung cancer cell line. Thus, the cell-associated isoform of VEGF, VEGF189, might have a key role in stromal vascularisation and the growth of NSCLC xenografts in vivo.

Pan, L., et al. (2013). "Vascular endothelial growth factor (VEGF) expression in locally advanced prostate cancer: secondary analysis of radiation therapy oncology group (RTOG) 8610." Radiat Oncol **8**: 100.

BACKGROUND: Angiogenesis is a key element in solid-tumor growth, invasion, and metastasis. VEGF is among the most potent angiogenic factor thus far detected. The aim of the present study is to explore the potential of VEGF (also known as VEGF-A) as a prognostic and predictive biomarker among men with locally advanced prostate cancer. METHODS: The analysis was performed using patients enrolled on RTOG 8610, a phase III randomized control trial of radiation therapy alone (Arm 1) versus short-term neoadjuvant and concurrent androgen deprivation and radiation therapy (Arm 2) in men with locally advanced prostate carcinoma. Tissue samples were obtained from the RTOG tissue repository. Hematoxylin and eosin slides were reviewed, and paraffin blocks were immunohistochemically stained for VEGF expression and graded by Intensity score (0-3). Cox or Fine and Gray's proportional hazards models were used. RESULTS: Sufficient pathologic material was available from 103 (23%) of the 456 analyzable patients enrolled in the RTOG 8610 study. There were no statistically significant differences in the pre-treatment characteristics between the patient groups with and without VEGF intensity data. Median follow-up for all surviving patients with VEGF intensity data is 12.2 years. Univariate and multivariate analyses demonstrated no statistically significant correlation between the intensity of VEGF expression and overall survival, distant metastasis, local progression, disease-free survival, or biochemical failure. VEGF expression was also not statistically significantly associated with any of the endpoints when analyzed by treatment arm. CONCLUSIONS: This study revealed no statistically significant prognostic or predictive value of VEGF expression for locally advanced prostate cancer. This analysis is among one of the largest sample bases with long-term follow-up in a well-characterized patient population. There is an urgent need to establish multidisciplinary initiatives for coordinating further research in the area of human prostate cancer biomarkers.

Pedersen, M. W., et al. (2001). "Coregulation of glucose uptake and vascular endothelial growth factor (VEGF) in two small-cell lung cancer (SCLC) sublines in vivo and in vitro." Neoplasia **3**(1): 80-87.

We examined the relationship between (18)F-labeled 2-fluro-2-deoxy-d-glucose (FDG) uptake, and expression of glucose transporters (GLUTs) in two human small-cell lung cancer (SCLC) lines CPH 54A and CPH 54B. Changes in the expression of GLUTs and vascular endothelial growth factor (VEGF) during 12-, 18-, and 24 hours of severe hypoxia in vivo (xenografts) and in vitro (cell cultures) were recorded for both tumor lines. The two SCLC lines are subpopulations of the same patient tumor. In spite of their common genomic origin they represent consistently different metabolic and microenvironmental phenotypes as well as treatment sensitivities. There were higher levels of Glut-1 protein in 54B and a correspondingly higher FDG uptake in this tumor line (P<.001). During hypoxia a significant upregulation of in VEGF mRNA, GLUT-1 mRNA, and Glut-1 and -3 protein occurred with a distinctly different time course in the two cell lines. A similar co-upregulation of GLUT and VEGF was seen in hypoxic tumors of both lines. There were no significant changes of HIF-1alpha mRNA during hypoxia in either of the cell lines. A more detailed understanding of such correlations between glucose metabolism, angiogenesis, and microenvironmental phenotype of tumors, by positron emission tomography (PET) and molecular techniques might further sophisticate our interpretation of glycolytic predominance in tumors as seen by 18FFDG PET.

Perrone, G., et al. (2004). "Correlation of p53 and bcl-2 expression with vascular endothelial growth factor (VEGF), microvessel density (MVD) and clinico-pathological features in colon cancer." Cancer Lett **208**(2): 227-234.

This study was designed to elucidate the possible relationship between tumour related genes and angiogenesis in colon cancer. The protein expression of p53, bcl-2, Von Willebrand factor and vascular endothelial growth factor (VEGF) were analysed by immunohistochemistry in 57 paraffin-embedded colon cancer. The results showed that microvessel density (MVD) was lower in VEGF negative tumours than in VEGF positive ones (P<0.0001). MVD and VEGF in p53 negative tumours were significantly lower than in p53 positive tumours (respectively, P=0.003 and P<0.0001). Moreover, positive correlations were recorded between VEGF expression and MVD, and bcl-2 expression (respectively, P<0.0001 and P=0.009). Our data confirm the central role of VEGF in angiogenesis and suggest direct correlations among p53, bcl-2 and VEGF expression in colon cancer.

Ray, A., et al. (2013). "Loss of epigenetic Kruppel-like factor 4 histone deacetylase (KLF-4-HDAC)-mediated transcriptional suppression is crucial in increasing vascular endothelial growth factor (VEGF) expression in breast cancer." J Biol Chem **288**(38): 27232-27242.

Vascular endothelial growth factor (VEGF) is recognized as an important angiogenic factor that promotes angiogenesis in a series of pathological conditions, including cancer, inflammation, and ischemic disorders. We have recently shown that the inflammatory transcription factor SAF-1 is, at least in part, responsible for the marked increase of VEGF levels in breast cancer. Here, we show that SAF-1-mediated induction of VEGF is repressed by KLF-4 transcription factor. KLF-4 is abundantly present in normal breast epithelial cells, but its level is considerably reduced in breast cancer cells and clinical cancer tissues. In the human VEGF promoter, SAF-1- and KLF-4-binding elements are overlapping, whereas SAF-1 induces and KLF-4 suppresses VEGF expression. Ectopic overexpression of KLF-4 and RNAi-mediated inhibition of endogenous KLF-4 supported the role of KLF-4 as a transcriptional repressor of VEGF and an inhibitor of angiogenesis in breast cancer cells. We show that KLF-4 recruits histone deacetylases (HDACs) -2 and -3 at the VEGF promoter. Chronological ChIP assays demonstrated the occupancy of KLF-4, HDAC2, and HDAC3 in the VEGF promoter in normal MCF-10A cells but not in MDA-MB-231 cancer cells. Co-transfection of KLF-4 and HDAC expression plasmids in breast cancer cells results in synergistic repression of VEGF expression and inhibition of angiogenic potential of these carcinoma cells. Together these results identify a new mechanism of VEGF up-regulation in cancer that involves concomitant loss of KLF-4-HDAC-mediated transcriptional repression and active recruitment of SAF-1-mediated transcriptional activation.

Rinaldo, F., et al. (2007). "RalA regulates vascular endothelial growth factor-C (VEGF-C) synthesis in prostate cancer cells during androgen ablation." Oncogene **26**(12): 1731-1738.

Prostate cancer mortality is primarily due to failure to cure patients with metastatic disease. In its early stages, prostate cancer growth is enhanced by androgens. As such, the primary therapy for advanced (locally extensive or metastatic) prostate cancer consists of androgen deprivation therapy by pharmacotherapeutic or surgical means. Eventually, the tumor recurs owing to a transition from androgen-dependence to a highly metastatic and androgen refractory (androgen depletion-independent) phenotype. As the detailed molecular mechanism underlying this transition to a more aggressive phenotype is poorly understood, it has been difficult to develop effective treatments for this advanced stage of the disease. We have previously reported an increase in vascular endothelial growth factor-C (VEGF-C) expression in human prostate cancer cells after androgen withdrawal. We have also shown increased expression of the androgen receptor co-activator BAG-1L by VEGF-C, suggesting the involvement of this growth factor in transactivation of the androgen receptor, even at low concentrations of androgen. In our present study, we show that androgen deprivation of human prostate carcinoma cells activates the small GTPase, RalA, a molecule important for human oncogenesis. RalA activation leads to VEGF-C upregulation. We also show that elevated levels of intracellular reactive oxygen species in prostate cancer cells under androgen-ablated conditions is the major inducer of RalA activation and VEGF-C synthesis.

Rinck-Junior, J. A., et al. (2015). "Vascular endothelial growth factor (VEGF) polymorphism and increased risk of epithelial ovarian cancer." J Cancer Res Clin Oncol **141**(1): 69-73.

INTRODUCTION: Angiogenesis (AG) is essential for epithelial ovarian cancer (EOC) development. Vascular endothelial growth factor (VEGF), encoded by the VEGF gene, and endostatin, the product of the COL18A1 gene, act as a potent promoter and an inhibitor of AG, respectively. In the present study, we tested whether VEGF C936T and COL18A1 D104N polymorphisms alter the risk of EOC. METHODS: Genomic DNA from 131 EOC patients and 137 controls were analyzed by polymerase chain reaction and restriction fragment length polymorphism methods. The differences between groups were analyzed by chi (2) or Fisher's exact test and logistic regression analysis. RESULTS: The frequency of the VEGF 936CC genotype was higher in patients than in controls (84.8% vs. 75.3%, P = 0.03). Individuals with respective genotypes had a 1.98 (95% CI 1.04-3.78)-fold increased risk of EOC than those with the remaining genotypes. An excess of VEGF 936CC plus COL18A1 DN genotype was seen in patients when compared to controls (48.6% vs. 30.5%); however, only a tendency toward a statistically significant difference in genotype frequencies was found in the study (P = 0.06), reflecting a trend toward an increased risk of 2.44 for EOC in carriers of the combined genotype. CONCLUSION: Our data present, for the first time, preliminary evidence that VEGF C936T alone or combined with the COL18A1 D104N polymorphism of AG constitutes an important inherited EOC determinant.

Roselli, M., et al. (2003). "Vascular endothelial growth factor (VEGF-A) plasma levels in non-small cell lung

cancer: relationship with coagulation and platelet activation markers." Thromb Haemost **89**(1): 177-184.

Platelet activation, commonly found in lung cancer patients, may cause the release of angiogenic factors, such as vascular endothelial growth factor (VEGF-A). The present study was designed to investigate whether plasma VEGF-A levels were associated to different stages of non-small cell lung cancer (NSCLC). Moreover, sP-selectin, prothrombin fragment 1+2 (F1+2), thrombin-antithrombin III complex (TATc) and D-dimer levels were measured to test the hypothesis of an involvement of platelet and coagulation activation in tumor angiogenesis. VEGF-A, sP-selectin, F1+2, TATc and D-dimer levels were elevated in 65 patients with NSCLC, particularly in metastatic patients. sP-selectin ($p < 0.003$) and F1+2 ($p < 0.005$) levels were independently associated to VEGF-A. In addition, patients with positive levels of both sP-selectin and F1+2 had the highest levels of VEGF-A. In conclusion, our findings support the hypothesis that thrombin generation might induce platelet activation and VEGF-A release in NSCLC.

Saglam, D. A., et al. (2008). "[The evaluation to relationship between serum vascular endothelial growth factor (VEGF) level, metastases and other tumor markers in patients with lung cancer]." Tuberk Toraks **56**(1): 50-55.

Vascular endothelial growth factor (VEGF) is a potent mediator of angiogenesis. Increased expression of VEGF may be associated with advanced stage and poor prognosis in patients with lung cancer. We investigated the relationship between serum VEGF level and lung cancer stage. We also studied the correlation between serum VEGF level and some other tumor markers. Forty newly diagnosed lung cancer (31 non-small cell, 9 small cell) patients and 25 age-matched controls were enrolled in this study. Serum VEGF levels of lung cancer group (345.16 +/- 159.36 pg/mL) were significantly higher than that of the control group (230.36 +/- 47.87 pg/mL) ($p< 0.001$). The area under the ROC curve was 0.727 ($p< 0.05$) for serum VEGF threshold of 249.8 pg/mL predictive sensitivity and specificity, for lung cancer were respectively 70.0% and 76.0%. There were no significant relationship between serum VEGF level and age, gender, histologic type, lung cancer stage, distant metastases and site of metastases. In addition, there were no correlation between serum VEGF level and other tumor markers (NSE, CYFRA 21-1, CEA, CA125, LDH).

Salven, P., et al. (1998). "High pre-treatment serum level of vascular endothelial growth factor (VEGF) is associated with poor outcome in small-cell lung cancer." Int J Cancer **79**(2): 144-146.

Vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis and vascular permeability. Increased serum VEGF concentrations (S-VEGF) have been found in patients with various types of human cancer, including cancer of the lung. However, the clinical and prognostic significance of S-VEGF in cancer is unknown. We measured S-VEGF, using enzyme-linked immunosorbent assay, in sera taken from 68 untreated patients with small-cell lung cancer (SCLC) at the time of diagnosis. The patients were treated with 6 cycles of cisplatin and etoposide, and were randomly assigned to receive recombinant interferon, leukocyte interferon or neither. S-VEGF ranged from 70 to 1738 pg/ml (mean, 527 pg/ml). The patients who achieved partial or complete response to treatment had lower pre-treatment S-VEGF than the non-responding patients ($p = 0.0083$, Mann-Whitney test). High (>527 pg/ml) S-VEGF was associated with poor survival ($p = 0.012$, Log Rank Test), and all 3-year survivors had lower than mean pre-treatment S-VEGF. In a multivariate analysis, S-VEGF and stage were the only independent prognostic factors, and the estimated 3-year survival of the patients with limited stage disease and low pretreatment S-VEGF ($n = 17$, 25% of all patients) was 41% ($p = 0.0055$, log rank test). These data show that high pretreatment S-VEGF is associated with poor response to treatment and unfavourable survival in patients with SCLC treated with combination chemotherapy with or without interferon.

Sartippour, M. R., et al. (2002). "Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells." J Nutr **132**(8): 2307-2311.

Investigators have shown that green tea and its main catechin epigallocatechin-3 gallate (EGCG) may decrease the risk of cancer. Our previous study showed that green tea extract (GTE) as well as its individual catechin components inhibited MDA-MB231 breast cancer cell and human umbilical vein endothelial cell (HUVEC) proliferation. Further, GTE suppressed breast cancer xenograft size and decreased the tumor vessel density in vivo. In the current study, we investigated the effect of GTE on the major angiogenic factor vascular endothelial growth factor (VEGF) in an in vitro experiment. GTE or EGCG (40 mg/L) significantly decreased the levels of the VEGF peptide secreted into conditioned media. This occurred in both HUVEC and human breast cancer cells and the effect was dose dependent. Furthermore, GTE and EGCG decreased the RNA levels of VEGF in MDA-MB231 cells. This inhibition occurred at the transcriptional regulation level and was accompanied by a significant decrease in VEGF promoter activity. We also showed that GTE decreased c-fos and c-jun RNA transcripts, suggesting that activator protein (AP)-1-responsive

regions present in the human VEGF promoter may be involved in the inhibitory effect of GTE. Furthermore, GTE suppressed the expression of protein kinase C, another VEGF transcription modulator, in breast cancer cells. Inhibition of VEGF transcription appeared to be one of the molecular mechanism(s) involved in the antiangiogenic effects of green tea, which may contribute to its potential use for breast cancer treatment and/or prevention.

Scartozzi, M., et al. (2012). "Role of vascular endothelial growth factor (VEGF) and VEGF-R genotyping in guiding the metastatic process in pT4a resected gastric cancer patients." PLoS One **7**(7): e38192.

In radically resected gastric cancer the possibility to predict the site of relapse could be clinically relevant for the selection of post-surgical management. We previously showed that specific tumour integrins genotypes are independently associated with either peritoneal or hematogenous metastases (ITGA and ITGV). Recently VEGF and VEGF-R polymorphisms have been demonstrated to potentially affect tumour angiogenesis and the metastatic process in gastric cancer. We then investigated the role of VEGFs and VEGF-R genotyping in determining either peritoneal carcinosis or hematogenous metastases in radically resected gastric cancer patients. Tumour genotyping for integrins (ITGA and ITGV) was also performed according to our previous findings. Genotyping for VEGF-A, VEGF-C, VEGFR-1,2,3 and ITGA and ITGV was carried out on pT4a radically resected gastric tumours recurring with either peritoneal-only carcinosis or hematogenous metastases. 101 patients fulfilled the inclusion criteria: 57 with peritoneal carcinomatosis only and 44 with hematogenous spread only. At multivariate analysis, intestinal histology and the AC genotype of rs699947 (VEGFA) showed to independently correlate with hematogenous metastases ($p = 0.0008$ and 0.008 respectively), whereas diffuse histology and the AA genotype of rs2269772 (ITGA) independently correlated with peritoneal-only diffusion ($p = <0.0001$ and 0.03 respectively). Our results seem to indicate that combining information from genotyping of rs699947 (VEGFA, AC), rs2269772 (ITGA, AA) and tumour histology could allow clinicians to individuate gastric cancer at high risk for recurrence either with peritoneal or hematogenous metastases. The selection tool deriving from this analysis may allow an optimal use of the available treatment strategies in these patients.

Sezginturk, M. K. (2011). "A new impedimetric biosensor utilizing VEGF receptor-1 (Flt-1): early diagnosis of vascular endothelial growth factor in breast cancer." Biosens Bioelectron **26**(10): 4032-4039.

A new impedimetric biosensor, based on the use of vascular endothelial growth factor receptor-1 (VEGF-R1), was developed for the determination of vascular endothelial growth factor (VEGF). VEGF-R1 was immobilized through covalent coupling with 3-mercaptopropionic acid which formed a self-assembled monolayer on gold electrodes. Cyclic voltammetry (CV) and electrochemical impedance spectroscopy techniques were employed to characterize the immobilization process and to detect VEGF. To successfully construct the biosensor current, experimental parameters were optimized. Kramers-Kronig Transform was performed on the experimental impedance data. The obtained results provided a linear response range from 10 to 70 pg/mL human VEGF. The applicability of the developed biosensor in the determination of VEGF in a spiked artificial human serum sample was experienced, yielding average recovery of 101%, in that order, with an average relative deviation value less than 5%.

Shinkaruk, S., et al. (2003). "Vascular endothelial cell growth factor (VEGF), an emerging target for cancer chemotherapy." Curr Med Chem Anticancer Agents **3**(2): 95-117.

Angiogenesis is a process of development and of growth of new capillary blood vessels from pre-existing vessels. When pathological, it contributes to the development of numerous types of tumors, and the formation of metastases. In order to grow, carcinoma need new blood vessels to form so that they can feed themselves. Therefore, nowadays the concept according to which the development of cancer is angiogenesis dependent is generally recognized. This concept makes the control of tumoral angiogenesis one of the promising therapeutic ways in cancerology. The transition from the latent phase to the invasive and metastatic phase of a cancer is linked to what is called the angiogenic switch. It implies complex cellular and molecular interactions between cancerous cells, endothelial cells and the components of the extra-cellular matrix and namely the existence of specific proteins secreted by the tumoral cells able to stimulate the proliferation of capillary endothelial cells. Among them, VEGF, Vascular Endothelial Growth Factor was found in several types of tumors. It has shown a tumoral angiogenic activity in vitro and in vivo, and thus is a privileged target for the control of angiogenesis in an anti-tumoral goal. The role of VEGF in tumoral angiogenesis has been extensively studied. It has been proved to undergo as well autocrine as paracrine stimulation of tumoral angiogenesis. During the last few years, several members of the VEGF family have been described namely the VEGF-

A, B, C, D, E and placenta growth factor (PlGF) among which VEGF-A (121 aminoacids) plays a role of prime importance in angiogenesis. VEGF is a 45 kDA glycoprotein, homodimeric, basic, and able to bind heparin. The three-dimensional structure of VEGF has been recently determined, by X-rays diffraction, and NMR spectroscopy. The different forms of the VEGF bind to receptors that exhibit a tyrosine-kinase activity (RTK). The specific action of the VEGF on the endothelial cells is mainly regulated by two types of RTK of the VEGF family, VEGFR1, or Flt-1, and VEGFR2, or KDR/Flk-1. Mutagenesis studies have shown that only a small number of VEGF residues are important and essential for the binding with RTK. Data described to date from the studies of VEGF/RTK interactions agree to the hypothesis that KDR receptor is the main human receptor responsible for the VEGF activity in both physiological and pathological vascular development, and VEGF-KDR signalling pathway has been validated as a priority target for the development of anti- and pro- angiogenic agents. Therefore angiogenesis mediated by VEGF constitutes a new target for anti-cancer therapy which has explored through different ways of intervention aiming at the blocking of the tumoral angiogenesis. The main ones are: -Struggle against the stroma degradation and invasion by the neo-vessels -Inhibition of activated endothelial cells. -Inhibition of angiogenic factors production and of their receptors. -Inhibition of the VEGF signal pathway, by peptides blocking the bond between VEGF and its receptors through the inhibition of intracellular transduction of VEGF signal. In conclusion, this bibliographic study allows to situate works of medicinal chemistry in the context of present knowledge concerning the vascular endothelial growth factor (VEGF) and its role in angiogenesis.

Siejka, A., et al. (2012). "GHRH antagonist inhibits focal adhesion kinase (FAK) and decreases expression of vascular endothelial growth factor (VEGF) in human lung cancer cells in vitro." Peptides **37**(1): 63-68.

Lung cancers which show increased vascularization and high microvessel density are considered highly metastatic and with poor prognosis. Growth hormone releasing hormone (GHRH) antagonists are anticancer agents without adverse events in lung cancer tumor models. In the present study we investigated the in vitro effect of GHRH antagonist, MZ-5-156, on focal adhesion kinase (FAK) activity, on the expression of MMP-2 and MMP-9 metalloproteinases, as well as on vascular endothelial growth factor (VEGF) levels in A549 non-small cell lung (NSCLC) cancer cells and H727 bronchial carcinoid cells. We demonstrate for the first time that GHRH antagonist, MZ-5-156, inhibits FAK signaling in lung cancer cells and decreases the expression of additional factors involved in angiogenesis and invasion. In contrast, GHRH itself counteracted these effects. Our study contributes to the further understanding of the processes which govern the mechanism of action of GHRH and its antagonists in cancers.

Song, N., et al. (2014). "Vascular endothelial growth factor (VEGF) -2578C/A and -460C/T gene polymorphisms and lung cancer risk: a meta-analysis involving 11 case-control studies." Tumour Biol **35**(1): 859-870.

The aim of this meta-analysis is to generate large-scale evidence on whether common vascular endothelial growth factor (VEGF) gene polymorphisms (-2578C/A [dbSNP: rs699947] and -460C/T [dbSNP: rs833061]) are associated with lung cancer. A literature search of PubMed, Embase, Web of Science, Cochrane Library, and CBM databases was conducted to identify all eligible studies published before May 3, 2013. Crude odds ratios (ORs) with their corresponding confidence intervals (95% CIs) were used to evaluate the strength of the association. Eleven case-control studies were included with a total of 3,861 lung cancer cases and 3,676 controls in this meta-analysis. For the VEGF -2578C/A polymorphism, the combined results showed that there exist highly significant risk factors for individuals carrying the A allele resulting in lung cancer, and the magnitude of this effect was similar in smoker patients and squamous cell carcinoma (SCC) patients. Unlike the situation with the -2578C/A polymorphism, the VEGF -460C/T polymorphism is not associated with the risk of lung cancer in neither Asians nor Caucasians. However, when stratified according to smoking status and histological types of lung cancer, we found that the T allele (-460C/T) was associated with decreased lung cancer risk among nonsmoker patients and SCC patients. Our findings showed that the -2578C/A polymorphism may increase lung cancer risk, especially in smoker patients and SCC patients, whereas the -460C/T polymorphism may decrease lung cancer risk, especially in nonsmoker patients and SCC patients.

Stefanou, D., et al. (2004). "Expression of vascular endothelial growth factor (VEGF) and association with microvessel density in benign prostatic hyperplasia and prostate cancer." In Vivo **18**(2): 155-160.

BACKGROUND: Tumor angiogenesis is an absolute requirement for tumor growth and a prognostic factor for various malignant neoplasms. Recent reports in the literature have addressed the importance of the VEGF system in benign prostatic hyperplasia (BPH) and adenocarcinoma, however the results are controversial. The aim of the present study was to determine and compare the levels of VEGF

expression and vascularity in BPH and prostate carcinoma. MATERIALS AND METHODS: We examined 60 prostate adenocarcinomas and 64 benign prostatic hyperplasias. Angiogenesis was estimated by determining microvessel counts (MVC), with the use of anti-CD31 and anti-CD34 antibodies. Expression of VEGF was also evaluated immunohistochemically. RESULTS AND CONCLUSION: Our data showed that angiogenesis was more prominent in carcinomas than in BPH. Furthermore, increased MVC was significantly associated with high-grade carcinomas. Angiogenesis was correlated with VEGF expression and it was, at least in part, mediated by the latter. Thus, prostate adenocarcinoma may represent a suitable neoplasm for antiangiogenic treatment in combination with conventional therapies.

Su, J., et al. (2019). "Ultrasound-mediated destruction of vascular endothelial growth factor (VEGF) targeted and paclitaxel loaded microbubbles for inhibition of human breast cancer cell MCF-7 proliferation." Mol Cell Probes **46**: 101415.

AIMS: Vascular endothelial growth factor (VEGF) can promote cell division, proliferation and migration. In this study, we aimed to investigate roles of ultrasound-mediated destruction of VEGF-targeted and paclitaxel (PTX)-loaded lipid microbubbles (VTPLLM + US) in human breast cancer cells. METHODS: The activity of MCF-7cells was determined by cell counting Kit-8. Flow cytometry was performed to detect the cells apoptosis and cell cycle. The expression of cell cycle-associated proteins, matrix metalloprotein-9 (MMP-9), VEGF and apoptosis-associated proteins were detected by qRT-PCR and Western blot. RESULTS: The obtained data suggested that VTPLLM + US promoted the G1 phase cell cycle arrest and suppressed the viability of MCF-7 cells. We also found that VTPLLM + US accelerated cells apoptosis. Cell cycle-associated proteins and VEGF expression were modulated by VTPLLM + US. Moreover, VTPLLM + US was found to regulate the expression levels of apoptosis-associated proteins in MCF-7 cells. Our findings suggested that VTPLLM + US suppressed the proliferation and accelerated the apoptosis of MCF-7 cells through regulating VEGF expression. CONCLUSIONS: The potential effects of VTPLLM + US on apoptosis of MCF-7 cells suggest that applying VTPLLM + US might be an effective strategy in breast cancer therapies.

Sun, P., et al. (2008). "RNA interference (RNAi)-mediated vascular endothelial growth factor-C (VEGF-C) reduction interferes with lymphangiogenesis and enhances epirubicin sensitivity of breast cancer cells." Mol Cell Biochem **308**(1-2): 161-168.

It has been reported that over-expression of vascular endothelial growth factor-C (VEGF-C) in tumors leads to increased lymphangiogenesis and resistance to chemotherapy. Therefore, we hypothesized that VEGF-C would be a good molecular target for cancer gene therapy. In this study, we silenced the expression of VEGF-C with the highly specific post-transcriptional suppression of RNA interference (RNAi) in human breast cancer MCF-7 cell line. The expression of VEGF-C was examined by reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA), and the effect of plasmid on human lymphatic endothelial cells (HLECs) in vitro was analyzed by migration and 3-(4, 5-dimethylt-hiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. The sensitivity to anticancer agents was evaluated by MTT and apoptosis assay, and apoptosis-related genes bcl-2/bax ratio was determined by Western Blotting. Results showed that of three siRNA-expressing vectors, P-1/siRNA most significantly suppressed the expression of VEGF-C mRNA and protein (38.1% of control and 117.8 +/- 24.2 pg/ml, respectively) and interfered with proliferation and migration of HLECs in vitro. Moreover, transfection of VEGF-C/siRNA combined with Epirubicin markedly decreased breast cancer cells viability, reaching up to 38.5%, and increased apoptosis rate from 13.1% to 38.9%, as determined by decrease of bcl-2/bax ratio. In summary, VEGF-C would be a good molecular target, and a combination of Epirubicin and RNAi targeting VEGF-C could be an effective means for suppressing lymphatic metastasis and enhancing chemosensitivity of human breast cancer cells.

Tammali, R., et al. (2011). "Aldose reductase inhibition prevents hypoxia-induced increase in hypoxia-inducible factor-1alpha (HIF-1alpha) and vascular endothelial growth factor (VEGF) by regulating 26 S proteasome-mediated protein degradation in human colon cancer cells." J Biol Chem **286**(27): 24089-24100.

The development of intratumoral hypoxia, a hallmark of rapidly progressing solid tumors, renders tumor cells resistant to chemotherapy and radiation therapy. We have recently shown that inhibition of aldose reductase (AR), an enzyme that catalyzes the reduction of lipid aldehydes and their glutathione conjugates, prevents human colon cancer cell growth in culture as well as in nude mouse xenografts by inhibiting the NF-kappaB-dependent activation of oxidative stress-mediated inflammatory and carcinogenic markers. However, the role of AR in mediating hypoxic stress signals is not known. We therefore investigated the molecular mechanisms by which AR inhibition prevents the hypoxia-induced

human colon cancer cells growth and invasion. Our results indicate that AR inhibition by the pharmacological inhibitor fidarestat or ablation by AR-specific siRNA prevents hypoxia-induced proliferation of HT29, SW480, and Caco-2 colon cancer cells. Furthermore, hypoxia-induced increase in the level of HIF-1alpha in colon cancer cells was significantly decreased by AR inhibition. During hypoxic conditions, treatment of HT29 cells with the AR inhibitor fidarestat significantly decreased the expression of vascular endothelial growth factor, a down target of HIF-1alpha, at both mRNA and protein levels and also prevented the activation of PI3K/AKT, GSK3beta, Snail, and lysyl oxidase. Furthermore, inhibition of hypoxia-induced HIF-1alpha protein accumulation by AR inhibition was abolished in the presence of MG132, a potent inhibitor of the 26 S proteasome. In addition, AR inhibition also prevented the hypoxia-induced inflammatory molecules such as Cox-2 and PGE2 and expression of extracellular matrix proteins such as MMP2, vimentin, uPAR, and lysyl oxidase 2. In conclusion, our results indicate that AR mediates hypoxic signals, leading to tumor progression and invasion.

Tammali, R., et al. (2019). "Expression of Concern: Aldose reductase inhibition prevents hypoxia-induced increase in hypoxia-inducible factor-1 alpha (HIF-1alpha) and vascular endothelial growth factor (VEGF) by regulating 26 S proteasome-mediated protein degradation in human colon cancer cells." J Biol Chem **294**(5): 1634.

Tamura, M., et al. (2004). "The combination assay with circulating vascular endothelial growth factor (VEGF)-C, matrix metalloproteinase-9, and VEGF for diagnosing lymph node metastasis in patients with non-small cell lung cancer." Ann Surg Oncol **11**(10): 928-933.

BACKGROUND: The aim of the present study was to evaluate the diagnostic utility of levels of circulating vascular endothelial growth factor (VEGF)-C, matrix metalloproteinase-9 (MMP-9), and VEGF and to verify that the combination assay of these circulating factors is a clinically useful indicator to predict the presence of lymph node metastasis in non-small cell lung cancer (NSCLC). METHODS: A series of 78 patients who underwent surgery for NSCLC was used in this study. Serum VEGF-C and VEGF and plasma MMP-9 levels were analyzed with enzyme-linked immunosorbent assay (ELISA) kits. Logistic regression models were used to analyze the influence of VEGF-C, MMP, and VEGF levels on the probability of presence or absence of lymph node metastasis. RESULTS: Patients with lymph node metastasis had higher serum VEGF- C, VEGF, and plasma MMP-9 concentrations than did those without metastasis (VEGF-C, P = .0004; VEGF, P = .001). Serum VEGF-C reached a sensitivity of 85% and specificity of 68% when a cutoff value of 1762.0 pg/mL was applied, while VEGF reached 80% sensitivity and 59% specificity at 316.8 pg/mL. MMP-9 reached a sensitivity of 63% and specificity of 75% when a cutoff value of 51.4 ng/mL was applied. In the ROC curve analysis, VEGF-C (0.761) had the biggest areas under the ROC curve, followed by MMP-9 (0.723) and VEGF (0.694). Combination assay of three markers had higher sensitivity and specificity for prediction than single-marker assays (AUC = 0.837). CONCLUSIONS: This study has confirmed that combination assay of three markers to determine VEGF-C, MMP-9, and VEGF expression in circulation detects lymph node metastasis in NSCLC with higher accuracy than single-marker assays.

Tanaka, T., et al. (2010). "Vascular endothelial growth factor C (VEGF-C) in esophageal cancer correlates with lymph node metastasis and poor patient prognosis." J Exp Clin Cancer Res **29**: 83.

BACKGROUND: The diagnosis of lymph node metastasis in esophageal cancer by the presence and number of metastatic lymph nodes is an extremely important prognostic factor. In addition, the indication of non-surgical therapy is gaining more attention. Vascular endothelial growth factor C (VEGF-C) is potentially lymphangiogenic and selectively induces hyperplasia of the lymphatic vasculature. In this study, we investigated the expression of VEGF-C and whether it correlated with various clinico-pathologic findings. METHODS: KYSE series of esophageal cancer cell lines and 106 patients with primary esophageal squamous cell carcinomas who had undergone radical esophagectomy were analyzed. VEGF-C mRNA expression was determined by quantitative RT-PCR. RESULTS: High expression of VEGF-C was detected in most of the KYSE cell lines, especially KYSE410, yet, in an esophageal normal epithelium cell line, Het-1A, VEGF-C was not detected. In the clinical specimen, the expression of VEGF-C in the cancerous tissue was higher than in the corresponding noncancerous esophageal mucosa (p = 0.026). The expression of VEGF-C was found to be higher in Stage2B-4A tumors than in Stage0-2A tumors (p = 0.049). When the patients were divided into two groups according to their expression levels of VEGF-C (a group of 53 cases with high expression and a group of 53 cases with low expression), the patients with high VEGF-C expression had significantly shorter survival after surgery than the patients with low expression (p = 0.0065). Although univariate analysis showed that high expression of VEGF-C was a statistically significant prognostic factor, this was not

shown in multivariate analysis. In the subgroup of patients with Tis and T1 tumors, the expression of VEGF-C was higher in N1 tumors than in N0 tumors ($p = 0.029$). The survival rate of patients from the high expression group ($n = 10$) was lower than that in the low expression group ($n = 11$), and all the patients in the low VEGF-C expression group survived. CONCLUSIONS: The expression of VEGF-C correlates with lymph node metastasis and poor prognosis. In patients with Tis and T1 esophageal tumors, the expression of VEGF-C may be a good diagnostic factor for determining metastasis of the lymph node.

Tarnowski, B., et al. (2004). "Vascular endothelial growth factor (VEGF) levels and mutation of the BRCA1 gene in breast cancer patients." Breast Cancer Res Treat **88**(3): 287-288.

The aim of the study was to compare VEGF serum levels in breast cancer patients with and without BRCA1 gene mutation. We enrolled 80 patients, 22 premenopausal and 58 postmenopausal. We found statistically significant lower levels of VEGF in patients with BRCA1 gene mutation as compared with breast cancer patients without this mutation.

Tas, F., et al. (2006). "Serum vascular endothelial growth factor (VEGF) and bcl-2 levels in advanced stage non-small cell lung cancer." Cancer Invest **24**(6): 576-580.

The characteristic changes in cancer process are assumed to be genetic alterations about the imbalance of cell proliferation and apoptotic cell death. This study was conducted to determine the value of the circulating vascular endothelial growth factor (VEGF) and Bcl-2 in patients with advanced stage non-small cell lung cancer (NSCLC). These serum factors were measured of 52 NSCLC patients pathologically verified on before and after chemotherapy in comparison with 16 healthy controls by using ELISA method. Both of the serum levels of VEGF ($p = 0.015$) and Bcl-2 ($p < 0.001$) were increased significantly in NSCLC patients compared with the healthy controls. No statistically significant relationships between investigated elevated serum parameters and various characteristics of patients and disease such as stage and tumor burden were determined. Likewise, we also found no correlation between serum VEGF and Bcl-2. Cytotoxic therapy of patients was accompanied by unchanged serum levels of serum factors. The median survival of all patients was 27 weeks and one-year survival rate was 22.4 percent. With the median serum levels as the cut-off value, patients were divided into high- and low-serum parameter groups. While we found that patients' performance status ($p < 0.0001$), serum LDH level ($p = 0.0002$), response to chemotherapy ($p = 0.0023$), and stage of the disease ($p = 0.0085$) were prognostic factors for survival, serum VEGF ($p = 0.48$) and Bcl-2 ($p = 0.91$) levels were determined as ineffective on survival in patients with advanced NSCLC. In conclusion, our data suggest that these serum factors, VEGF and Bcl-2, are useful diagnostic factors, not predictive and prognostic markers for overall survival in advanced NSCLC patients.

Tas, F., et al. (2006). "Serum vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) levels in small cell lung cancer." Cancer Invest **24**(5): 492-496.

This study was conducted to determine the value of the angiogenic serum factors, vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8), in patients with small cell lung cancer (SCLC). These serum angiogenic factors were measured of 34 SCLC patients on the before and after chemotherapy in comparison with 20 healthy controls using ELISA method. Serum levels of VEGF and IL-8 were significantly increased in SCLC patients compared with healthy controls ($p < 0.001$). No statistically significant relationships was found between investigated elevated serum angiogenic parameters and various characteristics of patients and disease such as disease stage and tumor burden. Likewise, we also found no correlation between serum angiogenic factors. Cytotoxic therapy of patients was accompanied by unchanged serum levels of angiogenic factors. Contrary to serum IL-8, elevated serum levels of VEGF was determined as a prognostic factor for survival by univariate analysis ($p = 0.05$). Multivariate analysis revealed that independent prognostic factors of overall survival included only response to chemotherapy and weight loss ($p < 0.001$ for both). In conclusion, our data suggest that the angiogenic serum factors, VEGF and IL-8, are useful diagnostic factors, but not predictive and prognostic markers for overall survival in SCLC patients.

Toi, M., et al. (2002). "Significance of vascular endothelial growth factor (VEGF)/soluble VEGF receptor-1 relationship in breast cancer." Int J Cancer **98**(1): 14-18.

Angiogenesis, the formation of new blood vessels, is controlled by a balance between positive and negative endothelial regulatory factors. Soluble vascular endothelial growth factor receptor-1 (sVEGFR1), a naturally occurring soluble form of VEGFR1, is a negative counterpart of the vascular endothelial growth factor (VEGF) signaling pathway, which has been characterized as one of the most important endothelial regulators in human tumor angiogenesis. In our study, we examined the expression of sVEGFR1 in 110 primary breast carcinomas, and

assessed its clinical significance. Ninety-four of 110 tumors showed > or = 0.1 ng/mg protein of sVEGFR1 (range:0. 1-6.9 ng/mg protein; median: 1.03 ng/mg protein) as determined by a specific enzyme-linked immunosorbent assay (ELISA). Immunoblot analysis confirmed the presence of sVEGFR1 in breast tumor tissues. The levels of sVEGFR1 were correlated significantly with the levels of VEGF. There was no significant correlation between the levels of sVEGFR1 and any clinico-pathological factors including age, menopause, nodal involvement and hormone receptor status. A univariate prognosis analysis showed that the intratumoral VEGF status, as determined by ELISA, was a significant prognostic indicator, but sVEGFR1 status was not. In the combined analysis, however, the ratio of sVEGFR1 and VEGF levels provided more statistically significant prognostic value than VEGF status alone. Tumors in which the sVEGFR1 levels exceeded VEGF levels 10-fold had a markedly favorable prognosis. Multivariate analysis also demonstrated that the ratio of sVEGFR1 and VEGF was an independent prognostic indicator after nodal status. In conclusion, sVEGFR1, an intrinsic inhibitor of VEGF, frequently co-expressed with VEGF in primary breast cancer tissues. The intratumoral balance between sVEGFR1 and VEGF levels might be crucial for the progression of breast cancer.

Tokunaga, T., et al. (1998). "Vascular endothelial growth factor (VEGF) mRNA isoform expression pattern is correlated with liver metastasis and poor prognosis in colon cancer." Br J Cancer **77**(6): 998-1002.

Vascular endothelial growth factor (VEGF) is a well known factor that induces angiogenesis. Four isoforms, i.e. VEGF206, 189, 165, and 121, have been identified. We examined the isoform patterns of VEGF mRNA using reverse transcription polymerase chain reaction (RT-PCR) analysis in 61 colon cancers. All the colon cancers examined expressed VEGF121. The isoform patterns were classified into three groups: type 1, VEGF121; type 2, VEGF121 + VEGF165; type 3, VEGF121 + VEGF165 + VEGF189. Three of the 61 colon cancers examined showed type 1 expression, 26 showed type 2 expression and 32 showed the type 3 pattern. The patients with liver metastases showed the type 3 isoform expression pattern at a significantly higher incidence (12 of 16, 75%) than those without liver metastasis (20 of 45, 44%) (P=0.036). The type 3 isoform pattern was significantly associated with M1 stage (P=0.019). The patients with colon cancer and the type 3 isoform pattern showed significantly poor prognosis (P < 0.01, Cox-Mantel). The colon cancers with the type 3 pattern showed a significantly higher involvement of veins (P=0.006). These observations suggest that the aberrant type 3 expression pattern of VEGF189 mRNA isoforms is correlated with liver metastasis, M stage, and poor prognosis in colon cancer.

Tseng, F. J., et al. (2010). "A fusion protein with the receptor-binding domain of vascular endothelial growth factor-A (VEGF-A) is an antagonist of angiogenesis in cancer treatment: Simultaneous blocking of VEGF receptor-1 and 2." Cancer Biol Ther **10**(9): 865-873.

Vascular endothelial growth factor (VEGF) is an angiogenic factor that signals through VEGFR-1 and VEGFR-2, which are expressed preferentially in proliferating endothelial cells. Thus, simultaneous blockage of both VEGF receptors may provide a more efficient therapeutic response in cancer treatment. We created a recombinant fusion protein (RBDV-IgG1 Fc), which is composed of the receptor binding domain of human VEGF-A (residues 8-109) and the Fc region of human IgG1 immunoglobulin. The recombinant protein can bind to both mouse VEGFR-1 and VEGFR-2 to decrease VEGF-induced proliferation and tube formation of endothelial cells in vitro. In this study, the RBDV-IgG1 Fc fusion protein reduced the effects of proliferation, migration and tube formation induced by VEGF in murine endothelial cells in vitro. In vivo tumor therapy with RBDV-IgG1 Fc resulted in tumor inhibition by reducing angiogenesis. Pathological evidence also shows that RBDV-IgG1 Fc can seriously damage vessels, causing the death of tumor cells. These findings suggest that this chimeric protein has potential as an angiogenesis antagonist in tumor therapy.

Tsutsumi, S., et al. (2005). "Vascular endothelial growth factor C (VEGF-C) expression in pT2 gastric cancer." Hepatogastroenterology **52**(62): 629-632.

BACKGROUND/AIMS: The purpose of this study was to determine whether the vascular endothelial growth factor C (VEGF-C) protein expression was related to the clinicopathologic features of patients with pT2 (primary tumor invasion of muscularis propria or subserosa) gastric cancer. METHODOLOGY: The expression of VEGF-C protein was investigated retrospectively in 102 patients with pT2 gastric cancer. Immunohistochemical staining of the paraffin sections was performed using a polyclonal antibody to VEGF-C. RESULTS: Normal gastric mucosa was not immunoreactive with an anti-VEGF-C antibody. Among the 102 tumors examined, 27 (26.5%) showed high expression of VEGF-C protein. No staining was observed in the normal tissue surrounding the tumor. There were no significant differences in age, gender, or histological types. With regard to the clinicopathological characteristics, significant differences were observed in depth of tumor invasion (muscularis propria vs. subserosa; p<0.05), lymph node metastasis (p<0.001), and stage grouping

(p<0.001). The prognosis for VEGF-C-positive patients was worse than that for VEGF-C-negative patients in terms of overall survival, and VEGF-C expression was an independent prognostic indicator (p=0.023) by multivariable analysis. CONCLUSIONS: Determination of VEGF-C expression is important in predicting nodal metastasis and poor clinical outcome in pT2 gastric cancer patients.

Tu, J., et al. (2014). "rs833061 and rs699947 on promoter gene of vascular endothelial growth factor (VEGF) and associated lung cancer susceptibility and survival: a meta-analysis." Med Sci Monit **20**: 2520-2526.

BACKGROUND: As 2 important SNPs located in the promoter region of VEGF gene, the roles of rs833061 (-460C>T) and rs699947 (-2578C>A) in lung cancer susceptibility and survival remain inconclusive and controversial. MATERIAL/METHODS: For better understanding of these 2 SNPs in lung cancer risk and survival, a meta-analysis was performed to pool findings of previous studies and to generate large-scale evidence. RESULTS: Based on the 10 eligible studies included, this study observed that the -460C>T polymorphism generally had no significant effect on lung cancer risk. However, subgroup analysis found that -460TT homozygote variant might confer significantly increased cancer risk for Asians (TT vs. CC: OR=1.69, 95% CI 1.08-2.63, p=0.02), but not in Caucasians. Similar results were observed in -2578C>A in Asians (AA vs. CC: OR=3.00, 95% CI 1.51-5.95, p=0.002; AA vs. AC: OR=3.15, 95% CI 1.00-9.91, p=0.05; AA vs. (AC+CC): OR=2.92, 95% CI 1.51-5.65, p=0.001). In lung cancer survival, 4 trials included had conflicting results. One found -460C>T polymorphism had no effect on survival, 1 observed risk increasing, while the remaining 2 observed risk decreasing. This inconsistency was closely related to the different therapeutic practices applied in different studies, the effects of which were significantly affected by VEGF expression. CONCLUSIONS: -460TT and -2578AA homozygote might lead to significantly increased cancer risk for Asians, but the effects on survival remain to be explored. These 2 SNPs might be potential indicators of lung cancer risk for Asians and should be considered when planning chemotherapy and radiotherapy for lung cancer patients.

Ueno, Y. (2006). "[Implication of vascular endothelial growth factor (VEGF) in human head and neck cancer]." Nihon Jibiinkoka Gakkai Kaiho **109**(3): 163-170.

PURPOSE: Metastatic activity is one parameter indicating the malignancy of tumor cells. Angiogenesis has now been extensively studied to clarify the mechanisms of tumor growth and metastasis. Vascular endothelial growth factor (VEGF) is an angiogenic cytokine expressed by many human and animal tumors. We studied the role of VEGF in tumor growth by transfecting the VEGF gene into tumor cells and analyzing the survival period of nude mice implanted with these transfected tumor cells. MATERIALS AND METHODS: Cell line: The tumor cell line, OKK-LN, was established from human maxillary squamous cell carcinoma and used in this study. The tumor cells did not produce VEGF in the culture supernatant. Transfection: OKK-LN cells were stably transfected with sense VEGF165 cDNA or with the vector alone. The full-length VEGF165 cDNA was cloned into an expression vector (pCIneo). The DNA transfection was performed by the lipofection method, and the limiting dilution method was used for cloning. ELISA was used to measure VEGF in the culture supernatant. As a control, OKK-LN cells were transfected with the vector alone without VEGF (OKK-LN/pCIneo). The tumor cells were subcutaneously injected into nude mice (Balb/c nu/nu, 6W), and the survival period and tumor volume were analyzed. Effects of angio-suppressive agent, TNP-470, and anti-VEGF antibody on tumor growth and angiogenesis: TNP-470 (supplied by Takeda Pharmaceutical Co., Ltd.) and monoclonal anti-human VEGF antibodies were intraperitoneally administered to mice implanted with tumor cells once a week and twice a week for 5 weeks, respectively. The effects of TNP-470 and anti-VEGF antibodies were analyzed by examining tumor size and survival rate and immunohistologically using CD31 monoclonal antibody. RESULTS: Tumor cells transfected with sense VEGF 165 cDNA (referred to as OKK-LN/pCIneo VEGF) produced VEGF in the supernatant permanently, confirming the establishment of a VEGF-producing human cancer cell line. We observed marked tumor growth and a shortened survival period by nine days in the OKK-LN/pCIneo-VEGF group, compared to the control group. The administration of TNP-470 and anti-VEGF antibody significantly suppressed tumor growth. The immunohistological study showed the significant suppression of a number of tumor vessels in anti-VEGF antibody-administered mice. CONCLUSION: Our data strongly suggests that VEGF plays an important role in tumor growth and that treatment by anti-VEGF antibody may be a promising strategy against head and neck cancers.

Valdehita, A., et al. (2007). "Vasoactive intestinal peptide (VIP) increases vascular endothelial growth factor (VEGF) expression and secretion in human breast cancer cells." Regul Pept **144**(1-3): 101-108.

Previous studies have shown that vasoactive intestinal peptide (VIP) and its receptors (VPAC(1) and VPAC(2) receptors) are involved in promotion and growth of many human tumours including breast

cancer. Here we investigated whether VIP regulates the expression of the main angiogenic factor, vascular endothelial cell growth factor (VEGF) in human oestrogen-dependent (T47D) and oestrogen-independent (MDA-MB-4687) breast cancer cells. Semiquantitative and quantitative real-time RT-PCRs were used at mRNA level whereas enzyme immunoanalysis was performed at protein level. Both cancer cell lines expressed VIP and VPAC(1) (but not VPAC(2)) receptors that were functional as shown by VIP stimulation of adenylate cyclase activity. VIP induced VEGF expression at both mRNA and protein levels following a time-dependent pattern. The responses were faster in T47D than in MDA-MB-468 cells. The observed VIP regulation of VEGF expression appears to be modulated at least by the cAMP/protein kinase A (PKA) and the phosphoinositide 3-kinase (PI3-K) signalling systems as shown by studies of adenylate cyclase stimulation and using specific kinase inhibitors such as H89 and wortmannin. These actions suggest a proangiogenic potential of VIP in breast cancer.

VanCleave, T. T., et al. (2010). "Interaction among variant vascular endothelial growth factor (VEGF) and its receptor in relation to prostate cancer risk." Prostate **70**(4): 341-352.

BACKGROUND: Prostate cancer (PCa) incidence and mortality are disproportionately high among African-American (AA) men. Its detection and perhaps its disparities could be improved through the identification of genetic susceptibility biomarkers within essential biological pathways. Interactions among highly variant genes, central to angiogenesis, may modulate susceptibility for prostate cancer, as previous demonstrated. This study evaluates the interplay among three highly variant genes (i.e., IL-10, TGFbetaR-1, VEGF), their receptors and their influence on PCa within a case-control study consisting of an under-served population. METHODS: This study evaluated single gene and joint modifying effects on PCa risk in a case-control study comprised of 859 AA men (193 cases and 666 controls) using TaqMan qPCR. Interaction among polymorphic IL-10, TGFbetaR-1 and VEGF was analyzed using conventional logistic regression analysis (LR) models, multi-dimensionality reduction (MDR) and interaction entropy graphs. Symbolic modeling allowed validation of gene-gene interaction findings identified by MDR. RESULTS: No significant single gene effects were demonstrated in relation to PCa risk. However, carriers of the VEGF 2482T allele had a threefold increase in the risk of developing aggressive PCa. The presence of VEGF 2482T combined with VEGFR IVS6 + 54 loci were highly significant for the risk of PCa based on MDR and symbolic modeling analyses. These findings were substantiated by 1,000-fold cross validation permutation testing (P = 0.04), respectively. CONCLUSION: These findings suggest the inheritance of VEGF and VEGFR IVS6 + 54 sequence variants may jointly modify PCa susceptibility through their influence on angiogenesis. Larger sub-population studies are needed to validate these findings and evaluate whether the VEGF-VEGR axis may serve as predictors of disease prognosis and ultimately clinical response to available treatment strategies.

Wagner, A. D., et al. (2012). "Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer." Cochrane Database Syst Rev(7): CD008941.

BACKGROUND: Vascular-endothelial-growth-factor (VEGF) is a key mediator of angiogenesis. VEGF-targeting therapies have shown significant benefits and been successfully integrated in routine clinical practice for other types of cancer, such as metastatic colorectal cancer. By contrast, individual trial results in metastatic breast cancer (MBC) are highly variable and their value is controversial. OBJECTIVES: To evaluate the benefits (in progression-free survival (PFS) and overall survival (OS)) and harms (toxicity) of VEGF-targeting therapies in patients with hormone-refractory or hormone-receptor negative metastatic breast cancer. SEARCH METHODS: Searches of CENTRAL, MEDLINE, EMBASE, the Cochrane Breast Cancer Group's Specialised Register, registers of ongoing trials and proceedings of conferences were conducted in January and September 2011, starting in 2000. Reference lists were scanned and members of the Cochrane Breast Cancer Group, experts and manufacturers of relevant drug were contacted to obtain further information. No language restrictions were applied. SELECTION CRITERIA: Randomised controlled trials (RCTs) to evaluate treatment benefit and non-randomised studies in the routine oncology practice setting to evaluate treatment harms. DATA COLLECTION AND ANALYSIS: We performed data collection and analysis according to the published protocol. Individual patient data was sought but not provided. Therefore, the meta-analysis had to be based on published data. Summary statistics for the primary endpoint (PFS) were hazard ratios (HRs). MAIN RESULTS: We identified seven RCTs, one register, and five ongoing trials from a total of 347 references. The published trials for VEGF-targeting drugs in MBC were limited to bevacizumab. Four trials, including a total of 2886 patients, were available for the comparison of first-line chemotherapy, with versus without bevacizumab. PFS (HR 0.67; 95% confidence interval (CI) 0.61 to 0.73) and response rate were significantly better for patients treated with bevacizumab, with moderate heterogeneity regarding the magnitude of the effect on PFS. For

second-line chemotherapy, a smaller, but still significant benefit in terms of PFS could be demonstrated for patients treated with bevacizumab (HR 0.85; 95% CI 0.73 to 0.98), as well as a benefit in tumour response. However, OS did not differ significantly, neither in first- (HR 0.93; 95% CI 0.84 to 1.04), nor second-line therapy (HR 0.98; 95% CI 0.83 to 1.16). Quality of life (QoL) was evaluated in four trials but results were published for only two of these with no relevant impact. Subgroup analysis stated a significant greater benefit for patients with previous (taxane) chemotherapy and patients with hormone-receptor negative status. Regarding toxicity, data from RCTs and registry data were consistent and in line with the known toxicity profile of bevacizumab. While significantly higher rates of adverse events (AEs) grade III/IV (odds ratio (OR) 1.77; 95% CI 1.44 to 2.18) and serious adverse events (SAEs) (OR 1.41; 95% CI 1.13 to 1.75) were observed in patients treated with bevacizumab, rates of treatment-related deaths were lower in patients treated with bevacizumab (OR 0.60; 95% CI 0.36 to 0.99). AUTHORS' CONCLUSIONS: The overall patient benefit from adding bevacizumab to first- and second-line chemotherapy in metastatic breast cancer can at best be considered as modest. It is dependent on the type of chemotherapy used and limited to a prolongation of PFS and response rates in both first- and second-line therapy, both surrogate parameters. In contrast, bevacizumab has no significant impact on the patient-related secondary outcomes of OS or QoL, which indicate a direct patient benefit. For this reason, the clinical value of bevacizumab for metastatic breast cancer remains controversial.

Wang, K., et al. (2011). "Five polymorphisms of vascular endothelial growth factor (VEGF) and risk of breast cancer: a meta-analysis involving 16,703 individuals." Cytokine **56**(2): 167-173.

Associations between five polymorphisms of vascular endothelial growth factor (i.e., VEGF +936C/T, -1154A/G, -2578C/A, -634G/C and -460T/C) and risk of breast cancer have been extensively studied, and the currently available results are inconclusive. Therefore, we performed this meta-analysis to further study the associations. The databases of Pubmed, Embase and CNKI were retrieved up to April 1st, 2010. The pooled ORs and 95% CIs were used to assess the strength of the associations. A total of 10 case-control studies with 8175 cases and 8528 controls were included in this study. The overall results of combined analyses showed that five polymorphisms of VEGF were not associated with risk of breast cancer [ORs (95% CIs): 1.03 (0.84-1.27) for CC vs. TT for +936C/T, 0.95 (0.81-1.12) for AA vs. GG for -1154A/G, 1.01 (0.90-1.14) for CC vs. AA for -2578C/A, 1.02 (0.90-1.16) for GG vs. CC for -634G/C and 0.86 (0.68-1.09) for TT vs. CC for -460T/C]. When subgroup analyses by ethnicity for VEGF +936C/T and -634G/C, the results suggested that +936C/T was not associated with the risk of breast cancer for either Asians [1.40 (0.92-2.13) for CC vs. TT and CC+CT vs. TT: 1.38 (0.91-2.10) for CC+CT vs. TT] or Caucasians [0.93 (0.73-1.19) for CC vs. TT and 0.91 (0.72-1.16) for CC+CT vs. TT], and -634G/C was not associated with the breast cancer for Caucasians [1.07 (0.92-1.24) for GG vs. CC and 1.05 (0.91-1.21) for GG+GC vs. CC]. In addition, when excluding one study, which was out of Hardy-Weinberg equilibrium for VEGF +963C/T and whose controls were from both patients and healthy people, the negative results were also persistent, and ORs (95% CIs) were 1.04 (0.84-1.29) for CC vs. TT, 1.03 (0.83-1.27) for (CC+CT) vs. TT. This meta-analysis suggests that the VEGF +936C/T, -1154A/G, -2578C/A, -634G/C and -460T/C may be not associated with risk of breast cancer development based on the currently available studies, especially for Caucasians. More well designed studies with larger sample size on different ethnicities are needed to further assess the associations.

Wang, Y., et al. (2013). "Effects of autocrine vascular endothelial growth factor (VEGF) in non-small cell lung cancer cell line A549." Mol Biol Rep **40**(4): 3093-3099.

It is reported that the autocrine loop of the vascular endothelial growth factor (VEGF) is crucial for the survival and proliferation of non-small cell lung cancer (NSCLC) tumors. In this study we aimed to systematically investigate the role of autocrine vascular VEGF in NSCLC cell line A549 through inhibition of endogenous VEGF. A549 cells were transfected with florescence-labeled VEGF oligodeoxynucleotide with lipofectamine. For the experimental group, cells were transfected with VEGF anti-sense oligodeoxynucleotide (ASODN), sense oligodeoxynucleotide (SODN) and mutant oligodeoxynuleotide (MODN) respectively. For the control group cells were mock transfected with lipofectamine or culture medium. At indicated time point after transfection, the expression levels of VEGF mRNA and protein in A549 cells were analyzed by RT-PCR and ELISA respectively. Cell viability was measured by the MTT assay. Cell cycle distribution was detected by flow cytometry. As revealed by RT-PCR assay, the mRNA level of VEGF in cells transfected with ASDON was significantly lower than the other four groups ($P < 0.05$) at 24 and 48 h after transfection. ELISA assay yielded similar result with significantly decreased level of VEGF protein expression ($P < 0.05$). The survival fraction of A549 cells transfected with ASDON was significantly lower than the other four groups ($P < 0.05$) at 24 h after transfection. Also the percentage of G2 phase cells of ASODN group was significantly lower than other four

groups. Our data indicate that VEGF expression is efficiently inhibited in A549 cells by ASODN transfection and this inhibition leads to inhibited cell growth and impaired cell cycle distribution.

Wang, Y. Z. and Y. C. Wong (1998). "Sex hormone-induced prostatic carcinogenesis in the noble rat: the role of insulin-like growth factor-I (IGF-I) and vascular endothelial growth factor (VEGF) in the development of prostate cancer." Prostate **35**(3): 165-177.

BACKGROUND: Despite extensive effort, the mechanisms of prostate carcinogenesis are still unknown. We report on a modified method which enabled us to induce a high incidence of prostate carcinogenesis in the Noble rat and examined the role of insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) and their receptors during sex hormone-induced prostate carcinogenesis. METHODS: Noble rats were implanted subcutaneously with a combination of testosterone and estradiol capsules for up to 12 months. Animals were sacrificed starting at 2 months after implantation, and the prostate gland was removed for histopathological and immunohistochemical studies. RESULTS: The results showed that hyperplasia/dysplasia was detected as early as 2 months after treatment, while carcinoma in situ was induced in 4 months and adenocarcinoma in 7 months. Our data suggest that IGF-1, produced by stromal cells in hyperplasia, exerted its effects, through a paracrine mode, on epithelial cells which were IGF-1 receptor (IGF-1R)-positive. The production of IGF-1 appeared to switch to epithelial cells in adenocarcinoma, through which it regulated tumor cell growth via autocrine mode by binding to IGF-1R of carcinoma cells. On the other hand, VEGF was overexpressed in hyperplastic/dysplastic and carcinoma cells, while VEGF-R was detected in endothelial cells. The results suggest that overexpression of VEGF in deranged epithelia and arterial muscle cells may exert its influence on stromal angiogenesis and abnormal growth of prostate gland. CONCLUSIONS: A modified Noble rat model with a high incidence of prostate carcinogenesis has been developed. Using this model, we have further established that IGF-1 and VEGF may be the critical regulators in mediating epithelial-stromal interactions in sex hormone-induced prostate carcinogenesis.

Wei, X., et al. (2014). "Evaluation of thyroid cancer in Chinese females with breast cancer by vascular endothelial growth factor (VEGF), microvessel density, and contrast-enhanced ultrasound (CEUS)." Tumour Biol **35**(7): 6521-6529.

To evaluate thyroid cancer in Chinese females with breast cancer by VEGF, MVD, and contrast-enhanced ultrasound (CEUS), 34 of 2,278 female inpatients with breast diseases who underwent routine thyroid ultrasonography were pathologically proved as thyroid cancer and enrolled into two groups: a breast cancer group and a non-breast cancer group. CEUS was performed and enhancement patterns were classified. Time-intensity curve parameters were analyzed to correlate with MVD CD34 and VEGF expression. Fourteen (2.6 %) and 20 (1.1 %) patients in breast cancer and non-breast cancer group were pathologically diagnosed as thyroid cancer. Six (42.8 %) and 0(0 %) patients showed high enhancement CEUS patterns of thyroid cancer in these two groups, respectively. The arrival time of time-intense curve was shorter, and the mean and peak intensity were higher in thyroid cancer in breast cancer group. The mean MVD counts and VEGF expression were significantly higher in thyroid and breast carcinomas in breast cancer group ($P < 0.01$). We also found that the mean and peak intensity were significantly associated with MVD counts and VEGF expression ($P < 0.01$). CEUS is recommended in evaluating the microcirculation of thyroid cancer in women with breast cancer and has the significant relationship with MVD counts and VEGF expression.

Whynott, R. M., et al. (2016). "Vascular endothelial growth factor (VEGF) and cyclooxygenase 2 (COX 2) immunostaining in ovarian cancer." Eur J Gynaecol Oncol **37**(2): 164-166.

PURPOSE OF INVESTIGATION: Vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX 2) are markers of angiogenesis and potential therapeutic targets. Previous studies demonstrate that VEGF is upregulated in some ovarian cancers. The purpose of this study was to determine the correlation of VEGF and COX 2 staining with survival in ovarian cancer patients. MATERIALS AND METHODS: One hundred forty-three consecutive patients with ovarian carcinoma underwent primary staging or cytoreduction prior to platinum-based chemotherapy. Their tumors were immunohistochemically stained for expression of VEGF and COX 2. FIGO stage, grade, cytoreduction status, and histology were also analyzed as prognostic factors. RESULTS: Twenty-seven patients had Stage I tumors, three Stage II, 87 Stage III, and 26 Stage IV. Median follow-up was 74 months (mean 79 months). One hundred nineteen patients (83.2%) had tumors that were positive for VEGF and 110 patients (76.9%) had tumors that were positive for COX 2. Patients with tumors staining positive for both VEGF and COX 2 (68.5%) had a significantly increased risk of dying from their ovarian cancer (Chi-square $p = 0.011$, Log rank $p = 0.037$). Multivariate logistic regression analysis revealed FIGO stage, grade, cytoreduction status, and VEGF/COX 2 expression to be independent prognostic indicators of survival. Conclusion: VEGF and COX 2 staining are frequently positive in ovarian

cancer. Patients whose tumors are positive for both VEGF and COX 2 have a decreased survival. These patients may benefit from anti-angiogenesis targeted therapy.

Wood, J. M. (2000). "Inhibition of vascular endothelial growth factor (VEGF) as a novel approach for cancer therapy." Medicina (B Aires) **60 Suppl 2**: 41-47.

Of the numerous growth factors and cytokines that have been shown to have angiogenic effects, vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF), appears to be a key factor in pathological situations which involve neovascularization as well as enhanced vascular permeability. Our aim was to design a low molecular weight synthetic molecule that potently and selectively blocks the VEGF/VEGF receptor system after oral administration, suitable for the chronic therapy of VEGF-dependent pathological neovascularization. PTK787/ZK 222584 is a potent inhibitor of VEGF receptor tyrosine kinases, active in the submicromolar range. It also inhibits other class III kinases, like the PDGFR-beta tyrosine kinase, c-Kit and c-Fms, but at higher concentrations. It is not active against kinases from other receptor families such as EGFR, FGFR-1, c-Met and Tie-2 or intracellular kinases like c-Src, c-Abl, PKC-alpha. PTK787/ZK 222584 inhibits VEGF-induced autophosphorylation of KDR, and endothelial cell proliferation, migration and survival in the nanomolar range in cell based assays. In concentrations up to 1 microM, PTK787/ZK 222584 does not have any cytotoxic or anti-proliferative effect on cells that do not express VEGF receptors. After oral dosing (50 mg/kg) to mice, plasma concentrations of PTK787/ZK 222584 remain above 1 microM for more than 8 h. PTK787/ZK 222584 induces dose-dependent inhibition of VEGF- and PDGF-induced angiogenesis in a growth factor implant model, as well as a tumor cell-driven angiogenesis model after once daily oral dosing (25-100 mg/kg). In the same dose range, it also inhibits the growth of several human carcinomas, grown subcutaneously in nude mice, as well as a murine renal carcinoma and its metastases in syngeneic, orthotopic models. Histological examination of tumors reveals inhibition of microvessel formation in the interior of the tumor. PTK787/ZK 222584 also significantly inhibits ascites formation induced by a human ovarian carcinoma grown in the peritoneum of nude mice as well as pleural effusion induced by a human lung adenocarcinoma in nude mice. PTK787/ZK 222584 is very well tolerated and does not impair wound healing. It also does not have any significant effects on circulating blood cells or bone marrow leukocytes as a single agent, or impair hematopoetic recovery following concomitant cytotoxic anti-cancer agent challenge. These studies indicate that compounds that inhibit the effects of VEGF, such as PTK787/ZK 222584, have the potential to provide a novel, effective and well-tolerated therapy for the treatment of solid tumors. These agents may also provide a new therapeutic approach for the treatment of other diseases where angiogenesis plays an important role.

Xiang, F. and Y. Shen (2006). "[Expression of vascular endothelial growth factor (VEGF) and its receptors KDR, Flt1 in lung cancer and their relationship to prognosis]." Zhongguo Fei Ai Za Zhi **9**(6): 511-515.

BACKGROUND: It is well known that vascular endothelial growth factor (VEGF) and its receptors are closely related to tumor angiogenesis, but the exact relationship with patients' prognosis is unclear till now. The aim of this study is to explore the expression of VEGF and its receptors KDR, Flt1 in pulmonary carcinoma and their relationship with patients' prognosis. METHODS: The expression of VEGF, KDR and Flt1 was examined immunohistochemically by PV-9000 method in 75 cases of pulmonary carcinoma with complete follow-up records. RESULTS: There was an extensive expression of VEGF, KDR and Flt1, mainly in the cytoplasm of tumor cells (TCs), fibroblasts (FBs), and endothelial cells. The distribution of VEGF, KDR and Flt1 was heterogeneous, mainly located at periphery of the tumor mass or necrosis. The positive rate of VEGF, KDR and Flt1 in the TCs was all significantly higher than that in the FBs ($P < 0.01$, $P < 0.02$, $P < 0.02$). Both in TCs and FBs, the positive expression of VEGF, KDR and Flt1 was related to the postoperative survival of patients ($P < 0.01$, $P < 0.01$, $P < 0.01$; $P < 0.01$, $P < 0.01$, $P < 0.05$). The survival time in patients with positive VEGF, KDR or Flt-1 in TCs was significantly lower than that in those with corresponding negative one respectively ($P < 0.0001$, $P < 0.0005$, $P < 0.0005$). There was a positive correlation between VEGF and Flt1 in TCs ($P < 0.01$), between VEGF in FBs and Flt1 in TCs ($P < 0.01$), and also between VEGF and KDR or Flt1 in FBs ($P < 0.01$, $P < 0.01$). CONCLUSIONS: VEGF may act as a considerable promoting growth factor on tumor cells via Flt1, mainly in autocrine and less in paracrine manner. VEGF, KDR and Flt1 may exert important roles in prognosis of patients with pulmonary carcinoma.

Xie, B., et al. (1999). "Co-expression of vascular endothelial growth factor (VEGF) and its receptors (flk-1 and flt-1) in hormone-induced mammary cancer in the Noble rat." Br J Cancer **81**(8): 1335-1343.

Vascular endothelial growth factor (VEGF) is recognized to play a predominant role in breast cancer prognosis. The action of VEGF is mediated by two high-affinity receptors with ligand-stimulated tyrosine kinase activity: VEGFR-1/flt-1 and VEGFR-2/flk-1, which are expressed mainly in vascular endothelial

cells. To the best of our knowledge, no previous studies on the expression of these receptors in breast cancer cells has been made. We have established a new animal model for breast cancer, using a combination of 17beta-oestradiol and testosterone as 'carcinogens'. Taking advantage of the animal model, we have demonstrated that mammary cancer cells expressed not only high levels of VEGF but also, surprisingly, its receptors (fit-1 and flk-1) in mammary cancer cells. Intense reactivities to VEGF, flt-1 and flk-1 were observed in mammary cancer cells, especially in invasive mammary carcinoma. Western blot analysis confirmed the increase in flk-1 and flt-1 proteins in induced mammary cancers. Based on these observations, we hypothesize that in mammary cancer, VEGF regulates, in addition to endothelial proliferation and angiogenesis, also growth of cancer cells by an autocrine mechanism mediated through its receptors. To further verify this hypothesis, we investigated the correlation between cellular proliferation and the expression of VEGF, flt-1 and flk-1. Using double-labelling immunocytochemistry, we have shown a correlation between high VEGF activity and Ki-67 expression. The Ki-67 indices in the areas of strong and weak VEGF reactivities were 58.3% and 3.7% respectively. Similarly, there was also a correlation of strong flk-1 and Ki-67 reactivity. The Ki-67 indices for areas of strong and weak flk-1 reactivities were 53.9% and 3.1% respectively. On the other hand, there was a reverse correlation between fit-1 and Ki-67 activities. These results indicate that overexpression of VEGF and flk-1 is correlated with high Ki-67 index. The data, therefore, suggest that VEGF may act as an autocrine growth factor for mammary cancer cells in vivo and this autocrine regulatory role may be mediated through flk-1. The present study is the first report showing that VEGF may act as a growth stimulator for mammary cancer cells.

Xing, X., et al. (2015). "Biglycan up-regulated vascular endothelial growth factor (VEGF) expression and promoted angiogenesis in colon cancer." Tumour Biol **36**(3): 1773-1780.

Biglycan is an important component of the extracellular matrix, which belongs to the small leucine-rich proteoglycan family. Recent studies have shown that biglycan expression is elevated in many tumor tissues and implies poor prognosis, such as colon cancer. However, the molecular mechanism of biglycan in colon cancer has not been investigated. The present study aimed to investigate the effects of biglycan on vascular endothelial growth factor (VEGF) expression in colon cancer cells and on tumor angiogenesis in vivo. Biglycan overexpression vectors were constructed, and the stable biglycan overexpression in human colon cancer cell lines (HCT116 cells) was established by G418 screening. The stable cell clones were subsequently used to initiate tumor xenografts in nude mice. Our results showed that biglycan overexpression notably up-regulated the levels of VEGF in colon cancer cells, which was further confirmed by immunohistochemistry analysis in the xenograft colon tumors. Moreover, high levels of biglycan promoted angiogenesis and colon tumor growth, as evidenced by the increased cell viability, colon tumor size, and weight, as well as the CD34 expression. Additionally, we found that the extracellular signal-regulated kinase (ERK) signaling pathway was activated by biglycan in colon cancer cells. The ERK inhibitor PD98059 dramatically reversed the increased expression of VEGF induced by biglycan. Taken together, our results indicated that biglycan up-regulated VEGF expression in colon cancer cells and promoted tumor angiogenesis. Biglycan-mediated VEGF regulation may correlate with the activation of the ERK signaling pathway. Therefore, biglycan may be a promising target for anti-angiogenic therapy for cancer.

Xu, Q., et al. (2013). "Ultrasound-mediated vascular endothelial growth factor C (VEGF-C) gene microbubble transfection inhibits growth of MCF-7 breast cancer cells." Oncol Res **20**(7): 297-301.

We evaluated the effects of ultrasound-mediated microbubble transfection of VEGF-C siRNA on breast cancer cells in vitro and in vivo. MCF-7 cells were transfected with VEGF-C siRNA and the protein and mRNA expression of VEGF-C was tested using Western blot and qRT-PCR. Twenty nude mice tumors were established by injecting with MCF-7 cells, and were randomized into four groups when palpable tumors reached 190 mm3. The length and width of MCF-7 tumors in mice were measured every 3 days. After 20 days, all mice were killed and the expression of VEGF-C in tumor tissue was also detected by Western blot and qRT-PCR. Results showed that VEGF-C siRNA effectively suppressed the protein and mRNA expression of VEGF-C in MCF-7 cells in vitro. VEGF-C siRNA inhibited the growth of human lymphatic endothelial cells (LECs) and MCF-7 cells. The volume and weight of MCF-7 tumor in VEGF-C siRNA microbubble with irradiation group were reduced with more extent than that in other groups in vivo. The present study highlights that VEGF-C siRNA in combination with ultrasound-mediated microbubble destruction (UMMD) could be a powerful, promising nonviral technology for breast cancer gene therapy.

Yang, J., et al. (2006). "Increased expressions of vascular endothelial growth factor (VEGF), VEGF-C and VEGF receptor-3 in prostate cancer tissue are associated with tumor progression." Asian J Androl **8**(2): 169-175.

AIM: To investigate the differences in microvessel densities (MVD) and the expressions of

vascular endothelial growth factor (VEGF), VEGF-C and VEGF receptor-3 (VEGFR-3) between prostate cancer (PCa) tissues and adjacent benign tissues, and to explore the correlations among MVD, Jewett-Whitmore staging, Gleason scores and expressions of VEGF, VEGF-C and VEGFR-3 in the progression of PCa. METHODS: An immunohistochemical approach was adopted to detect the expressions of CD34, VEGF, VEGF-C and VEGFR-3 in both cancer areas and peripheral benign areas of 71 primary prostatic adenocarcinoma specimens. A statistic analysis was then performed according to the experimental and clinic data. RESULTS: Significantly upregulated expressions of VEGF, VEGF-C and VEGFR-3 were all found in malignant epithelium/cancer cells compared with adjacent benign epithelium (P<0.01). Patients in stage D had a significantly higher score than patients in stage A, B or C when comparing the expression of VEGF-C or VEGFR-3 in the tumor area (P<0.01). In addition, significant correlations were observed between Jewett-Whitmore staging and VEGF-C (r(s)=0.738, P<0.01), clinical staging and VEGFR-3 (r(s)=0.410, P<0.01), VEGF-C and Gleason scores (r(s)=0.401, P<0.01), VEGFR-3 and Gleason scores (r(s)=0.581, P<0.001) and MVD and VEGF (r(s)=0.492, P<0.001). CONCLUSION: Increased expressions of VEGF and VEGF-C were closely associated with progression of PCa. The main contribution of increased VEGF expression for PCa progression was to upregulate MVD, which maintained the growth advantage of tumor tissue. However, the chief role of increased expressions of VEGF-C and VEGFR-3 was to enhance lymphangiogenesis and provide a main pathway for cancer cells to disseminate.

Yi, J. and T. Pan (2004). "[Expression of vascular endothelial growth factor C and its receptor VEGF-R3 and their significance in non-small cell lung cancer]." Zhongguo Fei Ai Za Zhi **7**(6): 488-492.

BACKGROUND: To determine the relationship between VEGF-C/VEGF-R3 expression and clinicopathologic factors and prognosis of patients with non-small cell lung cancer (NSCLC). METHODS: VEGF-C and VEGF-R3 expression was detected in 84 patients with NSCLC by immunohistochemical staining. The significance of VEGF-C and VEGF-R3 expression was analyzed statistically. RESULTS: In the immunoreactive cells, staining was mainly located in cytoplasm and membrane. VEGF-C and VEGF-R3 were highly expressed in lung cancer tissues (55.9% and 59.5%, respectively) while negative in the normal lung tissues. The expression of VEGF-C significantly correlated with histology (P=0.013). VEGF-R3 expression was associated with lymph node metastasis (P=0.002) and TNM stage (P=0.020). Multivariate analysis showed that VEGF-R3 (P < 0.001) and histology (P=0.020) were independent prognostic factors. CONCLUSIONS: Detection of VEGF-R3 in lung cancer tissues might be helpful to predict prognosis of patients with lung cancer.

Yu, D. H., et al. (2002). "[Relationship among expression of vascular endothelial growth factor-C(VEGF-C), angiogenesis, lymphangiogenesis, and lymphatic metastasis in oral cancer]." Ai Zheng **21**(3): 319-322.

BACKGROUND & OBJECTIVE: There may be a close relationship among the vascular endothelial growth factor-C (VEGF-C) expression, peritumour lymphatic vessels, and lymph node metastasis. The purpose of this study was to compare the relationship among VEGF-C mRNA expression, density of lymphatic and blood vessels, and lymphatic metastasis in oral squamous carcinoma. METHODS: VEGF-C mRNA was determined by RT-PCR. Lymphatic and blood vessel differential stain was determined by enzyme-histochemical technique. Automated image analysis quantification was applied to determine the number of total lymphatic and blood vessels in unit area (TNa). RESULTS: The peri-tumor lymphatic TNa of oral carcinoma was significantly higher in VEGF-C-positive group than those in VEGF-C-negative group(26.42 +/- 5.85: 17.34 +/- 6.48) (P < 0.01), but the blood TNa was a few higher(35.16 +/- 15.55: 33.49 +/- 13.73) (P > 0.05). Lymphatic TNa (30.67 +/- 5.76: 21.94 +/- 5.84) (P < 0.01) and blood TNa (44.19 +/- 14.29: 30.61 +/- 11.82) (P < 0.01) were significantly higher in lymph node metastasis group than those in no-metastasis group. CONCLUSION: VEGF-C mainly promotes peri-tumor lymphangiogenesis and has a little effect on angiogenesis. Simultaneous increase of lymphatic and blood vessels may be related to the synergic expression of VEGF, VEGF-C and their receptors.

Zhang, C., et al. (2011). "Vascular endothelial growth factor (VEGF) +936 C/T gene polymorphism and gastric cancer risk: appraisal of a recent meta-analysis." Int J Biol Markers **26**(4): 274-275.

Zhang, J., et al. (2005). "Regulation of vascular endothelial growth factor (VEGF) production and angiogenesis by tissue Factor (TF) in SGC-7901 gastric cancer cells." Cancer Biol Ther **4**(7): 769-772.

Tissue factor (TF), an initiator of the extrinsic coagulation cascade, is expressed in a wide range of cancer cells and plays important roles in cancer progression and metastasis. We demonstrated between TF and vascular endothelial growth factor (VEGF) production differences in four human gastric cell lines. One of these cell lines, SGC-7901, a high TF and VEGF producer, was grown subcutaneously in severe combined immuno-deficient (SCID) mice. The SCID mice generated solid tumors characterized by intense vascularity. In contrast, SGC-7901 cells transfected

with antisense TF cDNA generated relatively avascular tumors in SCID mice, as determined by immunohistochemical staining of tumor vascular endothelial cells with anti-VIII factor antibody. To investigate the structure-function relationship between TF and VEGF, the SGC-7901 cell line was transfected with antisense a full-length TF cDNA, a cytoplasmic deletion mutant lacking the distal three serine residues (potential substrates for protein kinase C), or an extracellular domain mutant, which has markedly diminished function for activation of factor X. Cells transfected with the full-length antisense TF sequence produced decreased levels of both TF and VEGF. Transfectants with the extracellular domain mutant produced high levels of VEGF mRNA. However, cells transfected with the cytoplasmic deletion mutant construct produced increased levels of TF, but little or no VEGF. Thus, the cytoplasmic tail of TF may signal VEGF expression in some tumor cells.

Zhao, Z., et al. (2012). "Vascular endothelial growth factor (VEGF) gene polymorphisms and colorectal cancer: a meta-analysis of epidemiologic studies." Genet Test Mol Biomarkers **16**(12): 1390-1394.

BACKGROUND: Studies investigating the association between vascular endothelial growth factor (VEGF) polymorphisms and colorectal cancer (CRC) risk report conflicting results. To clarify the effect of four VEGF (-460T/C, -634G/C, +936C/T, and -2578C/A) gene polymorphisms on the risk of developing CRC, we carried out a meta-analysis using published data to obtain more precise estimates of risk. METHODS: Electronic searches of PubMed and EMBASE were conducted to select studies for this meta-analysis. The principal outcome measure was the odds ratio (OR) with 95% confidence interval (CI) for the risk of CRC associated with four VEGF (-460T/C, -634G/C, +936C/T, and -2578C/A) gene polymorphisms. RESULTS: We identified 12 epidemiologic studies, which included 2770 CRC cases and 2568 controls. The combined results based on all studies showed that CRC cases had a significantly higher frequency of VEGF -634GG (OR=1.24, 95% CI=1.06, 1.44) and -2578AA (OR=1.37, 95% CI=1.12, 1.66) genotype and a lower frequency of -634CG (OR=0.82, 95% CI=0.71, 0.95) than controls. When stratifying for race, we found that patients with CRC had a significantly higher frequency of -460TC (OR=1.54, 95% CI=1.22, 1.94), -460CC (OR=2.00, 95% CI=1.50, 2.67), and -2578AA (OR=1.38, 95% CI=1.12, 1.69) and a lower frequency of -2578AA (OR=0.78, 95% CI=0.65, 0.93) genotypes of VEGF than controls, among Caucasians. We also found that patients with CRC had a significantly higher frequency of -634GG (OR=1.61, 95% CI=1.20, 2.15) and a lower frequency of -634CG (OR=0.60, 95% CI=0.46, 0.79) genotypes of VEGF than controls, among Asians. CONCLUSIONS: Our meta-analysis suggests that the VEGF -460T/C, -634G/C, and -2578C/A gene polymorphisms are associated with a risk of CRC.

Zhou, Y., et al. (2010). "Vascular endothelial growth factor (VEGF) +936 C/T gene polymorphisms and gastric cancer risk: a meta-analysis involving 4,138 subjects." Int J Biol Markers **25**(4): 213-218.

The association between vascular endothelial growth factor (VEGF) +936 C/T gene polymorphisms and gastric cancer risk is still controversial and ambiguous. The objective of our study was to investigate this association. The Medline and Embase databases were searched by two investigators. Crude odds ratios (OR) and 95% confidence intervals (CI) were used to test the association between VEGF +936 C/T polymorphisms and gastric cancer risk. Our meta-analysis comprised seven case-control studies, which included 1,893 gastric cancer cases and 2,245 controls. The combined results showed that there was no relationship between VEGF +936 C/T gene polymorphisms and gastric cancer risk (CC: OR 0.97, 95% CI 0.85, 1.11; CT: OR 1.01, 95% CI 0.88, 1.16; TT: OR 1.10, 95% CI 0.79, 1.55). Subgroup analysis by ethnicity and stage, location, and Lauren classification of gastric cancer did not change the results. This meta-analysis suggests that there is no association between VEGF +936 C/T polymorphisms and gastric cancer risk. Further studies should pay attention to other potentially functional SNPs.

Zhou, Y., et al. (2011). "Vascular endothelial growth factor (VEGF) gene polymorphisms and gastric cancer risk in a Chinese Han population." Mol Carcinog **50**(3): 184-188.

The association between vascular endothelial growth factor (VEGF) gene polymorphisms and gastric cancer risk is still controversial and ambiguous. The objective of this study was to investigate the association between VEGF gene polymorphisms and gastric cancer risk in Chinese Han patients. We extracted the peripheral blood samples in 150 patients with gastric cancer and 150 controls. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis was performed to detect three VEGF gene polymorphisms (-634 G/C, +936 C/T, and +1612 G/A) in these patients. Patients with gastric cancer had a significantly higher frequency of 1612 AA genotype (OR=6.26, 95% CI=1.80, 21.85; P=0.004) than controls. Patients with cardia gastric cancer had a significantly lower frequency of AA (OR=0.11, 95% CI=0.01, 0.89; P=0.04) than those with noncardia gastric cancer. Patients with Lauren's diffuse-type gastric cancer had a significantly higher frequency of AA (OR=3.41, 95% CI=1.22, 9.55; P=0.02) than those with Lauren's intestinal-type gastric cancer. The -634 G/C and +936 C/T gene polymorphisms were not

associated with a risk of GC and its progression. This study suggests that the VEGF +1612 G/A gene polymorphisms may be associated with gastric cancer in Chinese Han patients, and that difference in genotype distribution may be associated with the location and Lauren's classification of gastric cancer.

Zygalaki, E., et al. (2007). "Quantitative real-time reverse transcription PCR study of the expression of vascular endothelial growth factor (VEGF) splice variants and VEGF receptors (VEGFR-1 and VEGFR-2) in non small cell lung cancer." Clin Chem **53**(8): 1433-1439.

BACKGROUND: Vascular endothelial growth factor (VEGF) is a major regulator of angiogenesis and its expression is increased in non-small cell lung cancer (NSCLC). We aimed to determine the expression pattern of VEGF splice variants in NSCLC and its correlation with the clinicopathological characteristics of tumors. METHODS: We used real-time reverse transcription PCR to quantify the mRNA expression of total VEGF, 4 VEGF splice variants (VEGF(121), VEGF(165), VEGF(183), and VEGF(189)), and 2 VEGF receptors (VEGFR-1 and VEGFR-2) in 27 pairs of cancerous and adjacent noncancerous tissues originating from patients with NSCLC. RESULTS: Total VEGF, VEGF(121), and VEGF(165) were expressed in all specimens, whereas VEGF(183) and VEGF(189) were present in small amounts in certain samples. Total VEGF, VEGF(121), and VEGF(165) mRNA was upregulated in cancerous compared with healthy tissues, whereas VEGF(183) and VEGF(189) expression tended to be higher in healthy tissues. The expression of VEGFRs was similar between matched specimens. No correlation was found between the expression of total VEGF or VEGF splice variants and the clinicopathological characteristics of tumors. The expression patterns of VEGF splice variants differed between tissue pairs. VEGF(121) was the major variant expressed in all samples; however, its relative expression was higher in cancerous tissues. The relative expression of VEGF(183) and VEGF(189) was upregulated in healthy lung tissues, whereas the ratio of VEGF(165) to total VEGF was similar between matched specimens. CONCLUSIONS: The expression pattern of certain VEGF splice variants is altered during tumorigenesis. Our data support the hypothesis that during malignant progression an angiogenic switch favoring the shorter diffusible isoforms occurs.

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