Vascular Endothelial Growth Factor Gene Polymorphisms Are Associated with Prognosis in Ovarian Cancer

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Abstract Purpose: Vascular endothelial growth factor (VEGF), an important regulator of angiogenesis and vascular permeability, is involved in various steps of ovarian carcinogenesis. Gene polymorphisms within the gene encoding VEGF were shown to be independently associated with an adverse outcome in various malignancies. No data are available for ovarian cancer.

Experimental Design: In the present multicenter study, we examined three common polymorphisms within the VEGF gene (−634G/C, −1154G/A, and −2578C/A) known to be associated with an increased VEGF production in 563 Caucasian patients with ovarian cancer from Austria and Germany using pyrosequencing. Results were correlated with clinical data.

Results: The three investigated polymorphisms did not correlate with any of the investigated clinicopathologic variables. In univariate and multivariate models, no significant correlations between any polymorphism and patients’ overall survival were ascertained. Simultaneous carriage of the three homozygous genotypes (i.e., VEGF −634C/C, VEGF −1154G/G, VEGF −2578C/C) known to be associated with increased VEGF expression in an individual patient, however, was independently associated with a shortened overall survival (hazard ratio, 2.1; 95% confidence interval, 1.1-3.9; P = 0.02).

Conclusions: We present the first data on VEGF gene polymorphisms in ovarian cancer. Simultaneous carriage of the three investigated homozygous genotypes was shown to be an independent adverse prognostic factor of overall survival.

Angiogenesis has been established as a crucial factor in carcinogenesis influencing tumor growth, invasion, and the formation of metastases (1, 2). Growth stress such as hypoxia induces connective tissue or tumor cells to secrete angiogenic molecules, thereby influencing the balance between proangiogenic and antiangiogenic factors (2, 3).

Vascular endothelial growth factor (VEGF), a dimeric glycoprotein with four splice variants consisting of 121, 165, 189, and 206 amino acid residues, is a proangiogenic molecule that elicits its effects by acting as an endothelial cell mitogen and a mediator of increased vascular permeability via binding to its receptors VEGF receptor I and kinase domain receptor (4).

In ovarian cancer, in vitro studies showed that VEGF is crucially involved in various steps of ovarian carcinogenesis (5–7). VEGF was shown to be associated with the promotion of angiogenesis in early stage ovarian cancer, suggesting that VEGF-driven angiogenesis might be an early event in ovarian carcinogenesis (8). Recently, immunohistochemically detected VEGF overexpression and elevated serum levels of VEGF were shown to be associated with an impaired prognosis (9, 10).

The VEGF gene is located on chromosome 6p21.3. At least 30 single-nucleotide polymorphisms in this gene have been described in the literature. Among these, the VEGF −634G/C, −1154G/A, and −2578C/A polymorphisms have been shown to be associated with an increased VEGF production (11–13). Recently, VEGF polymorphisms were evaluated in melanoma (14) and bladder (15), lung (16), prostate (17), and breast cancer (18, 19). Patients. A total of 563 patients with ovarian cancer were included in the present study (Medical University of Vienna, Austria: n = 176; Charité, Campus Virchow-Klinikum, Berlin, Germany: n = 157; Medical University of Innsbruck, Innsbruck, Austria; 6 Department of Obstetrics and Gynecology, Friedrich-Alexander-University Erlangen-Nuernberg, Erlangen, Germany; 7 Department of Obstetrics and Gynecology, Johannes Gutenberg-University, Mainz, Germany; and 189, and 206 amino acid residues, is a proangiogenic molecule that elicits its effects by acting as an endothelial cell mitogen and a mediator of increased vascular permeability via binding to its receptors VEGF receptor I and kinase domain receptor (4).

Materials and Methods

Patients. A total of 563 patients with ovarian cancer were included in the present study (Medical University of Vienna, Austria: n = 176; Charité, Campus Virchow-Klinikum, Berlin, Germany: n = 157; Medical
University of Innsbruck, Austria: n = 75; Friedrich-Alexander-University Erlangen-Nuernberg, Germany: n = 84; Johannes Gutenberg-University, Mainz, Germany: n = 71. The respective Institutional Review Boards approved the present study. Patients were treated between November 1988 and August 2004 and followed up according to established protocols of the respective institutions. Patients were treated according to standards of the respective institution with hysterectomy, bilateral salpingo-oophorectomy, pelvic and/or paraaortic lymphadenectomy, appendectomy, and omentectomy. All patients with tumor stages Ic to III and all patients with clear cell carcinoma received six cycles of adjuvant platinum-based chemotherapy. Patients’ characteristics are shown in Table 1.

**DNA extraction.** DNA was isolated from centrifuged blood clots (Vienna, Innsbruck) by a modified DNAzol procedure (20), from EDTA-blood (Berlin, Erlangen, Vienna) using the QiAamp DNA Blood Midi Kit (Qiagen, Inc., Hilden, Germany), or from formalin-fixed paraffin-embedded tissue (Mainz; ref. 21). The extracted DNA was stored at 4°C until analyzed.

**PCR.** The primers \( \text{VEGF}^\prime -634 \text{ SE} 5'\text{\textmd{GGGACAGAGACCGG-GTC-3'}} \), \( \text{VEGF}^\prime -634 \text{ AS} 5'\text{\textmd{GGTACCCTCCAAGACG-3'}} \), \( \text{VEGF}^\prime -634 \text{ AS} 5'\text{\textmd{CTTGAGGTCGGCTGAC-3'}} \), \( \text{VEGF}^\prime -515 \text{ AS} 5'\text{\textmd{CACGCGGTGCTGAC-3'}} \), \( \text{VEGF}^\prime -2578 \text{ SE} 5'\text{\textmd{AGGGCTATGCCAGCTGTAGG-3'}} \), \( \text{VEGF}^\prime -1154 \text{ AS} 5'\text{\textmd{AGAACCTTGCGCCGTTCGAG-3'}} \) were used to amplify fragments of the \( \text{VEGF} \) gene. Antisense primers were biotinylated. PCR was carried out in a total volume of 25 μl including 25 ng template, 5 pmol of each sense and antisense primers and puReTaq Ready-To-Go PCR Beads (Amersham Biosciences, Little Chalfont, United Kingdom), which contain 2.5 units of puReTaq DNA polymerase, 10 mmol/L Tris-HCl (pH 9.0 at room temperature), 50 mmol/L KCl, 1.5 mmol/L MgCl2, 200 μmol/l dATP, dCTP, dGTP, and dTTP, and stabilizers, including bovine serum albumin. PCR was done on a Perkin-Elmer GeneAmp PCR system 9600 with 40 cycles at 94°C for 30 s, at 58°C (\( \text{VEGF}^\prime -2578, \text{VEGF}^\prime -634 \)) or 57°C (\( \text{VEGF}^\prime -634 \)) for 30 s, and 72°C for 30 s. The reaction was preceded by a primary denaturation step at 94°C for 1 min and incubated at 72°C for 7 min.

**Detection of polymorphisms by pyrosequencing.** Three common functional single nucleotide polymorphisms (\(-634 \text{ G/C}, -1154 \text{ G/A}, -2578 \text{ C/A}) within the \( \text{VEGF} \) gene were detected using Pyrosequencer PSQ 96 and the PSQ 96 SNP Reagent Kit (Pyrosequencing AB, Uppsala, Sweden). Twenty-five microliters of PCR product was used for pyrosequencing according to the instruction of the manufacturer. Five picomoles of the sequencing primers \( \text{VEGF}^\prime -634 \text{ SE} 5'\text{\textmd{GGGACAGAGACCGG-GTC-3'}} \), \( \text{VEGF}^\prime -634 \text{ AS} 5'\text{\textmd{GGTACCCTCCAAGACG-3'}} \), \( \text{VEGF}^\prime -634 \text{ AS} 5'\text{\textmd{CTTGAGGTCGGCTGAC-3'}} \), \( \text{VEGF}^\prime -1154 \text{ SE} 5'\text{\textmd{AGAACCTTGCGCCGTTCGAG-3'}} \), \( \text{VEGF}^\prime -1154 \text{ AS} 5'\text{\textmd{AGAACCTTGCGCCGTTCGAG-3'}} \), \( \text{VEGF}^\prime -2578 \text{ SE} 5'\text{\textmd{AGGGCTATGCCAGCTGTAGG-3'}} \), \( \text{VEGF}^\prime -2578 \text{ AS} 5'\text{\textmd{AGAACCTTGCGCCGTTCGAG-3'}} \) and \( \text{VEGF}^\prime -2578 \text{ AS} 5'\text{\textmd{AGAACCTTGCGCCGTTCGAG-3'}} \) were applied to detect the variations of the polymorphisms.

**Statistics.** After testing for normality using Kolmogorov-Smirnov (version 9.1, SAS Institute) to test, the following values were found to be normally distributed (i.e., \( P > 0.05 \)) and therefore were given as means (SD): age of patients, time to recurrent disease, and time of follow-up. \( \chi^2 \) tests were used to compare frequencies of \( \text{VEGF} \) genotypes between groups defined by clinicopathologic variables. Presence of all three of the homozygous genotypes (i.e., \( \text{VEGF}^\prime -634 \text{ C/C}, \text{VEGF}^\prime -1154 \text{ G/G}, \text{VEGF}^\prime -2578 \text{ C/C} \)) in an individual was shown to be associated with an increased \( \text{VEGF} \) production (11–13). Therefore, further statistical analysis focused at comparing the end point of overall survival of the group of patients with simultaneous carriage of these three genotypes (\( n = 29 \)) with all other patients. Survival times of patients with no evidence of disease, with stable disease, and patients having died of non-cancer-related events were censored with the last follow-up date. Survival times of patients who died of disease and of patients with progressive disease at the time of last follow-up were not censored. Survival probabilities were calculated by the product limit method of Kaplan and Meier and resulting survival curves were compared using the Breslow test.

To evaluate the simultaneous carriage of these three genotypes as an independent predictor of survival, a multivariate Cox regression model was estimated comprising the clinically established Fédération Internationale des Gynécologistes et Obstétristes (FIGO) stage (II–IV versus I), tumor grade (2–3 versus 1), age of patients (>70 versus ≤70 years), and the newly investigated variable simultaneous carriage of these three genotypes as independent variables. Interactions between the simultaneous carriage of these three genotypes and FIGO stage, tumor grade, and age of patient were tested for statistical significance.

The proportional hazards assumption of the Cox model was visually checked by plotting Schoenfeld residuals of each variable against time and tested by evaluating the statistical significance of the interaction of each variable with log time.

As our study was designed as a multicenter study to generate as many DNA samples as possible, we did not carry out any power analysis before the study. Therefore, we cannot report on any original study power. However, we did a post hoc study power, as follows. The power to detect a hazard ratio of a given magnitude for a polymorphism depends on the distribution of the genotypes of that polymorphism, on the distribution of survival time, and on the distribution of follow-up time. Using the distributions as they present in our data, we calculated a post hoc power of 80% for detecting a hazard ratio of 1.55 for \( \text{VEGF}^\prime -634 \text{ G/C}, 1.95 \) for \( \text{VEGF}^\prime -1154 \text{ G/A}, \) and 1.7 for \( \text{VEGF}^\prime -2578 \text{ C/A} \). In comparison, the observed hazard ratios for these polymorphisms were 1.2, 1.25, and 0.92, respectively.

The SAS System (version 9.1, SAS Institute, Inc., Cary, NC) and the SPSS statistical software system (SPSS 11.0, SPSS, Inc., Chicago, IL) were used for statistical computations. We used the SAS/Genetics software (version 9.1, SAS Institute) to test for the presence of any linkage disequilibrium. Two-sided \( P < 0.05 \) was considered statistically significant.

**Results**

The frequencies of the genotypes were 45.1% (GG), 46.8% (GC), and 8.1% (CC) for \( \text{VEGF} -634 \text{ G/C} \); 41.4% (GG), 46.1% (GA), and 12.5% (AA) for \( \text{VEGF} -1154 \text{ G/A} \); and 25.5% (CC),

**Table 1. Patients’ characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>N or mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients enrolled</td>
<td>563</td>
</tr>
<tr>
<td>Age at first diagnosis (y)</td>
<td>56.6 (12.7)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>137</td>
</tr>
<tr>
<td>II</td>
<td>48</td>
</tr>
<tr>
<td>III</td>
<td>298</td>
</tr>
<tr>
<td>IV</td>
<td>73</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>82</td>
</tr>
<tr>
<td>G2</td>
<td>211</td>
</tr>
<tr>
<td>G3</td>
<td>258</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>279</td>
</tr>
<tr>
<td>Mucinous</td>
<td>64</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>62</td>
</tr>
<tr>
<td>Clear cell</td>
<td>13</td>
</tr>
<tr>
<td>Others</td>
<td>131</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
<tr>
<td>No. patients with follow-up information available</td>
<td>510</td>
</tr>
<tr>
<td>Time of follow-up (mo)</td>
<td>43.5 (36.4)</td>
</tr>
<tr>
<td>Recurrence status</td>
<td></td>
</tr>
<tr>
<td>No. patients with recurrent disease</td>
<td>268</td>
</tr>
<tr>
<td>Time to recurrent disease (mo)</td>
<td>17.4 (18.8)</td>
</tr>
<tr>
<td>Status at last observation</td>
<td></td>
</tr>
<tr>
<td>Alive with no evidence of disease</td>
<td>319</td>
</tr>
<tr>
<td>Alive with stable disease</td>
<td>9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>45</td>
</tr>
<tr>
<td>Dead as a result of disease</td>
<td>125</td>
</tr>
<tr>
<td>Dead as a result of other causes</td>
<td>12</td>
</tr>
</tbody>
</table>

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50.5% (CA), and 24.0% (AA) for VEGF −2578C/A; all were in Hardy-Weinberg equilibrium (P = 0.08, P = 0.8, and P = 0.9, respectively). All three VEGF polymorphisms were in linkage disequilibrium \[ \text{VEGF} \rightarrow -634G/C \text{ and VEGF} \rightarrow -1154G/A; \text{ Lewontin's } D' \] = −0.74 (P < 0.001); VEGF −634G/C and VEGF −2578C/A; \( D' = -0.83 \) (P < 0.001); and VEGF −1154G/A and VEGF −2578C/A; \( D' = 0.79 \) (P < 0.001)] within the study population. No significant associations between the three investigated VEGF polymorphisms as well as the simultaneous carriage of the three homozygous genotypes and the clinicopathologic variables FIGO stage, tumor grade, and age of patients at diagnosis were ascertained.

In a univariate analysis, FIGO stage, tumor grade, age of patients at diagnosis, and the simultaneous carriage of the three homozygous genotypes, VEGF −634C/C, VEGF −1154G/G, and VEGF −2578C/C (n = 29), were associated with overall survival (Table 2; Fig. 1). When genotypes were ascertained independently, no significant association was found. In a multivariate Cox regression model, these results remained unchanged (Table 2). No interactions between the simultaneous carriage of the genotypes VEGF −634C/C, VEGF −1154G/G, and VEGF −2578C/C and FIGO stage, tumor grade, or age of patient at diagnosis could be statistically verified (P = 0.9, P = 0.9, and P = 0.7, respectively). Thus, the effect of simultaneous carriage of the genotypes found in multiple Cox regression analysis is independent of the level of a patient's FIGO stage, tumor grade, or age at diagnosis. No significant violations of the proportional hazards assumption could be detected for any of the variables entering the multivariate Cox model.

### Discussion

Various studies have investigated gene polymorphisms in patients with ovarian cancer. Relatively few data have been published on their prognostic effect (22, 23). The present multicenter study was set up to evaluate polymorphisms within candidate genes as prognostic markers in a large series of Caucasian patients with ovarian cancer. Based on the important role of VEGF-driven angiogenesis in ovarian carcinogenesis and based on previously published promising data on VEGF polymorphisms in other malignancies (15, 18, 19), we ascertained the prognostic effect of three common functional polymorphisms within the VEGF gene. We aimed at establishing a critical combination of VEGF genotypes as independent prognostic variables.

To our best knowledge, we are the first to report on VEGF polymorphisms in patients with ovarian cancer. In our series, VEGF genotypes were not associated with any investigated clinicopathologic variable. With respect to patients' prognosis, none of the VEGF genotypes alone showed any statistical significance. The VEGF −634C/C, −1154G/G, and −2578C/C genotypes have been shown to be associated with an increased VEGF production (11–13). Therefore, it can be reasonably speculated that simultaneous carriage of these three homozygous genotypes would lead to the highest circulating VEGF value. In our series, these patients had a significantly impaired overall survival. This finding is biologically plausible. Furthermore, we and others have previously shown that patients with elevated serum VEGF levels have a shortened survival (10).

We found a critical combination of VEGF genotypes to be independently associated with survival in a large series of patients with ovarian cancer. These data are new and biologically plausible. The clinical value of these results in the beginning era of bevacizumab (24–28) and other even newer VEGF inhibitors, such as sorafenib (29) and sunitinib (30), remains to be proved.

### Acknowledgments

We thank Dan Casire Castillo-Tong for selecting PCR and pyrosequencing primer sequences.

### Table 2. Univariate Kaplan-Meier analysis and multivariate Cox regression model of prognostic covariates in patients with ovarian cancer

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate P</th>
<th>HR (95% CI)</th>
<th>Multivariate P</th>
</tr>
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<tbody>
<tr>
<td>FIGO stage (II-IV vs I)</td>
<td>&lt;0.001</td>
<td>8.2 (3.8-17.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor grade (G2-3 vs G1)</td>
<td>0.002</td>
<td>1.8 (1.1-3.2)</td>
<td>0.027</td>
</tr>
<tr>
<td>Age at diagnosis ( &gt;70 vs ≤70 y)</td>
<td>0.044</td>
<td>1.7 (1.2-2.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>VEGF −634G/C</td>
<td>0.08</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>VEGF −1154G/A</td>
<td>0.24</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>VEGF −2578C/A</td>
<td>0.75</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Simultaneous carriage of the three homozygous genotypes² vs others</td>
<td>0.005</td>
<td>2.3 (1.3-4.2)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Multivariate Cox regression analysis.

Table 1. Multivariate analysis of clinicopathologic variables in patients with ovarian cancer.

**Table 2. Univariate Kaplan-Meier analysis and multivariate Cox regression model of prognostic covariates in patients with ovarian cancer**

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<td>0.24</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>VEGF −2578C/A</td>
<td>0.75</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
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<td>0.005</td>
<td>2.3 (1.3-4.2)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Breslow test.

Fig. 1. Kaplan-Meier curves including the 95% confidence bands on overall survival of patients with ovarian cancer. Simultaneous carriage of the three homozygous genotypes, VEGF −634C/C, VEGF −1154G/G, and VEGF −2578C/C (B), was compared with all other combinations of genotypes (A).
References

3. Damert A, Ikeda E, Risau W. Activator protein 1 binding potentiates the hypoxia induced transcriptional activa-
growth factor (VEGF) splice variants. Cancer Metasta-
by anti-vascular endothelial growth factor neutralizing antibody: novel concepts of angostatic therapy from
endothelial growth factor) and its receptors in ovarian borderline and malignant neoplasms. Lab Invest 1996;
transforming growth factor-β associates with angiogenesis in epithelial ovarian cancer. Int J Gynecol Pathol
markers of p53 function and angiogenesis to prognosis of stage I epithelial ovarian cancer. Clin Cancer Res
2005;11:3733 – 42.
11. Mohammadi M, Ollier WE, Hutchinson IV. A func-
tional association study of VEGF gene promoter poly-
morphisms with VEGF expression by stimulated pbm
dothelial growth factor gene polymorphisms are asso-
ciated with acute renal allograft rejection. J Am Soc
morphism in the 5′-untranslated region of the VEGF
factor single nucleotide polymorphisms on tumour de-
velopment in cutaneous malignant melanoma. Genes
15. Kim EJ, Jeong P, Quan C, et al. Genotypes of TFN-α, VEGF, hOGG1, GSTM1, and GSTT1: useful
determinants for clinical outcome of bladder cancer.
16. Kourouakis MI, Papazoglou D, Giatromanolaki A, Bougoukas G, Maltezos E, Sivridis E. VEGF gene se-
quence variation defines VEGF gene expression status
and angiogenic activity in non-small cell lung cancer.
cytokine gene polymorphisms on the development of
polymorphisms in the VEGF gene with breast cancer
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polymorphisms in the VEGF gene with breast cancer
constitutional de novo mutation in exon 8 of the p53
gene in a patient with multiple primary malignancies.
22. Heffer LA, Grimm C, Ackermann S, et al. An inter-
leukin-6 gene promoter polymorphism influences the
biological phenotype of ovarian cancer. Cancer Res
p53 mutations with resistance to platinum-based che-
motherapy and shortened survival in ovarian cancer.
24. Monk BJ, Choi DC, Pugmire G, Burger RA. Activity of
bevacizumab (rhuMAB VEGF) in advanced refrac-
tory epithelial ovarian cancer. Gynecol Oncol 2005;
taxane chemotherapy demonstrates activity in refrac-
26. Wright JD, Hagemann A, Rader JS, et al. Bevaci-
zumab combination therapy in recurrent, platinum-
refractory, epithelial ovarian carcinoma: a retrospec-
27. Monk BJ, Han E, Josephs-Cowan CA, Pugmire G, Burger RA. Salvage bevacizumab (rhuMAB VEGF)-
based therapy after multiple prior cytotoxic regimens
in advanced refractory epithelial ovarian cancer.
Gynecol Oncol 2006;102:140 – 4.
28. Bidus MA, Webb JC, Sedman JD, Rose GS, Boice
CR, Elkas JC. Sustained response to bevacizumab in
refractory well-differentiated ovarian neoplasms.
29. Siu LL, Awada A, Takimoto CH, et al. Phase I trial of
sorafenib and gemcitabine in advanced solid tumors
with an expanded cohort in advanced pancreatic can-
30. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in
patients with metastatic renal cell carcinoma. JAMA
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