Published in final edited form as:
Head Neck. 2014 August ; 36(8): 1113–1119. doi:10.1002/hed.23421.

A pilot study of psychosocial functioning and vascular endothelial growth factor in head and neck cancer patients

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Abstract

Background—Psychosocial functioning is associated with vascular endothelial growth factor (VEGF) in various patient populations. This study examined whether psychosocial functioning in patients with head and neck squamous cell carcinoma (HNSCC) is associated with tumor VEGF expression, a protein that stimulates angiogenesis and is associated with poor prognosis.

Methods—Forty-two newly diagnosed patients completed assessments of psychosocial functioning (i.e. depressive symptoms, perceived stress, anxiety, social support) prior to surgery. Tumor samples were obtained for VEGF analysis and HPV-typing.

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This work was presented at the 32nd Annual Meeting of the Society of Behavioral Medicine (abstract #2051).

Results—Poorer psychosocial functioning was associated with greater VEGF expression controlling for disease stage (OR=4.55, 95% CI = 1.72, 12.0, $p < 0.01$). When examined by HPV-status, the association between psychosocial functioning and VEGF remained significant among HPV-negative patients (OR=5.50, 95% CI = 1.68, 17.3, $p < 0.01$), but not among HPV-positive patients.

Conclusions—These findings inform our understanding of the biobehavioral pathways that may contribute to poor outcomes in non-HPV-associated HNSCCs.

Keywords

depressive symptoms; perceived stress; anxiety; social support; human papillomavirus

INTRODUCTION

Patients with head and neck squamous cell carcinoma (HNSCC), which includes cancers of the oral cavity, pharynx, and larynx, have one of the highest rates of depression[1, 2] and psychological distress,[3] relative to other cancer patient populations. Although treatment-related side effects likely contribute to distress,[4] high levels of depressive symptoms[5] and psychological distress[3, 6] have also been observed in newly diagnosed patients prior to treatment. Psychological distress and depressive symptoms in HNSCC patients have not only been reported to be associated with deficits in quality of life,[5, 7] but also with poorer prognosis and higher mortality,[8, 9] although the potential biological mechanisms that may underlie such associations have not been identified.

Several studies have reported that various measures of psychosocial functioning are associated with biological processes, such as angiogenesis,[10-12] that may be relevant to cancer progression and outcomes. Angiogenesis has long been recognized to promote tumor growth and metastases[13] and can be stimulated by various proteins including vascular endothelial growth factor (VEGF).[14-17] Importantly, associations between psychosocial functioning and VEGF have been reported in some cancer patient populations. For example, in a cross-sectional study of 24 women with ovarian cancer, higher levels of social well-being were associated with lower levels of serum VEGF, whereas feelings of worthlessness and helplessness were associated with higher levels of VEGF.[10] Similarly, among 51 newly diagnosed colorectal cancer patients, higher levels of loneliness assessed 1-2 days prior to surgery were associated with stronger immunohistochemical expression of VEGF in tumor obtained at surgery.[11] Depression was also found to be significantly associated with serum levels of VEGF in a cross-sectional study of newly diagnosed colorectal cancer patients prior to undergoing surgical treatment.[18]

Depression, mood disorders, and chronic stress are associated with dysregulation of hypothalamic-pituitary-adrenal (HPA) axis functioning,[19, 20] which can lead to increased secretion of cortisol[21] and increased levels of pro-inflammatory cytokines, including IL-6.[22, 23] VEGF can be regulated by stress hormones (such as norepinephrine, epinephrine, and cortisol),[24, 25] and studies have demonstrated that IL-6 has pro-angiogenic effects including increased VEGF production.[26] As a result, VEGF may be dysregulated in individuals with mood disorders or depression, as observed in a cross-sectional study in

which levels of serum VEGF were significantly higher in 12 women with major depressive disorder compared with 12 healthy women.[27]

In the context of HNSCC, these findings may have clinical relevance given empirical data demonstrating that VEGF is associated with tumor aggressiveness[28] and decreased survival.[29-31] Among patients with oral or oropharyngeal squamous cell carcinoma, greater VEGF expression in tumor was the most significant predictor of poorer disease-free survival and poorer overall survival.[30] Similarly, a meta-analysis estimated the risk of death within 2 years to be 1.88-fold higher among HNSCC patients with strong VEGF expression.[29]

However, the study of biobehavioral mechanisms in HNSCC is complex, most notably because a subgroup of HNSCCs appears to arise from a different etiology.[32-34] Although HNSCC is a disease that is primarily attributed to environmental exposures (i.e. tobacco use and alcohol consumption), accumulating data suggest that human papillomavirus (HPV) infection of the upper airway is associated with the development of a subset of head and neck cancers.[34] These HPV-related cancers arise from distinct risk factors,[35] have different biomolecular signatures, [34, 36, 37] and are highly treatment-responsive with improved survival outcomes.[38-41]

Due to the distinct molecular mechanisms involved,[34, 36, 37] biobehavioral pathways are likely to differ between HPV-related and non-HPV-related HNSCCs as well.[42] Notably, viral oncogenes of HPV16 (such as E6 and E7) have assorted biological effects, including dysregulation of VEGF[43] via various promoter regions.[44, 45] As a result, associations that may exist between psychosocial functioning and VEGF might be obscured in HPV-related HNSCC given that other co-occurring molecular mechanisms can impact VEGF expression.

To date, few studies have examined potential associations between psychosocial functioning and biological processes in HNSCC patients, and none have examined whether such associations might differ in HPV- and non-HPV-related HNSCCs, as far as we are aware. Thus, the aim of the present study was to examine psychosocial functioning assessed prior to treatment in relation to VEGF expression in tumors of newly diagnosed HNSCC patients. Based on prior findings,[10, 11, 27] it was hypothesized that poorer psychosocial functioning (as characterized by high levels of depressive symptoms, perceived stress, and anxiety and low social support) would be associated with greater VEGF expression in tumor. In addition, given increasing evidence that differential pathways underlie HPV- and non-HPV-related disease,[34] we also explored whether associations between psychosocial functioning and VEGF expression would vary by HPV-status.

MATERIALS AND METHODS

Participants and procedures

Newly diagnosed HNSCC patients, age 18 or older, who were undergoing surgical procedures, were eligible for the study. Exclusion criteria included prior cancer treatment, presence of immune disorder or known HIV+ status. Patients who were deemed unable to provide informed consent by collaborating oncologists due to neurological issues or cognitive impairment were also excluded. Eligible patients were identified by oncologists

prior to surgery and referred to a study research assistant who obtained written informed consent. Forty-two patients participated in the study. One to three days prior to surgery, participants completed questionnaires assessing demographic characteristics, health behaviors, and psychosocial functioning. During surgery, a section of tumor was obtained for HPV-typing analyses. Archival tissue from the resected primary tumor was retrieved from the Tumor Bank for immunohistochemical analysis of VEGF expression. Finally, medical chart review was conducted to ascertain patient clinical characteristics including tumor site and TNM classification. Disease stage was determined according to the American Joint Committee on Cancer Staging Manual, 7th edition.[46] This study was approved by the Institutional Review Board, and all participants provided written informed consent to participate.

Measures

Demographic variables and health behaviors—Demographic characteristics, including age, gender, marital/partner status, and education, were obtained. Health behaviors assessed include smoking status, number of years smoked (for current or former smokers), and frequency of alcohol consumption. According to USDA dietary guidelines[47] and prior studies,[48] alcohol use was categorized as “Never” (0 drinks per week), “Occasional” (≤ 2 drinks per week), “Moderate” (3-6 drinks per week for women; 3-14 drinks per week for men), or “Heavy” (> 6 drinks per week for women; > 14 drinks per week for men).

HPV-status—HPV-typing of tumor was performed using polymerase chain reaction (PCR) techniques. Specifically, tissue specimens were quick frozen and stored at –20°C or fixed in 95% ethanol. DNA was extracted from frozen or fixed tissue by using the QIAamp DNA kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. 100ng of DNA were used in each PCR amplification reaction to amplify HPV DNA. PCR was performed using consensus, HPV6 and HPV16 primers and platinum Taq-polymerase (Invitrogen, Carlsbad, CA) as previously described.[49]

Psychosocial functioning—Participants completed measures of depressive symptoms, perceived stress, state anxiety, and social support. Depressive symptoms were assessed using the 20-item Center for Epidemiological Studies-Depression (CES-D) scale,[50] which is a well-established measure that has been extensively used in cancer patient populations including HNSCC patients.[51, 52] Items were summed to obtain a total score, with higher scores reflecting higher levels of depressive symptoms. Cronbach's α in the present sample was 0.82.

Perceived stress was measured using the 14-item Perceived Stress Scale (PSS).[53, 54] This instrument is designed to measure the degree to which life situations are appraised as stressful. Items were summed to obtain a total score, with higher scores reflecting higher perceived stress. Cronbach's α in the present sample was 0.77.

State levels of anxiety were measured using the 20-item state anxiety scale of the Spielberger State-Trait Anxiety Inventory (STAI),[55] which has been previously utilized with HNSCC patients.[8] A total score was obtained by summing the item responses. Higher scores

reflected higher levels of state anxiety. Cronbach's α was 0.92 indicating high internal consistency.

Social support was assessed using the general population version of the Interpersonal Support Evaluation List (ISEL).[56, 57] This scale consists of 40 statements regarding the perceived availability and quality of potential social support and has often been related to indices of physical health.[58] Items were summed to create an overall total support score whereby a higher score indicated greater social support. In the present sample, Cronbach's α for the total social support score was 0.91.

VEGF expression—VEGF immunostaining was performed on the primary tumor using the following methods: Archival tissue samples (fixed in 10% phosphate-buffered formaldehyde and embedded in paraffin) were obtained from the Tumor Bank for immunohistochemical analysis of VEGF expression using standard procedures previously published.[59] In brief, one tissue section contiguous to a hematoxylin-eosin stained section previously used for clinical diagnostic purposes was used for VEGF immunostaining. Antigen retrieval was performed by boiling deparaffinized 5-μm-thick sections for 10 min in citrate buffer (pH6) using a 750 W microwave oven at low setting. After pre-incubation in serum and peroxidase blocking, the sections were incubated overnight at 40°C with anti-VEGF antibodies at 1:50 to 1:100 dilution.[59] A corresponding tissue section without primary antibody Ab-3 served as a negative control. Negative controls were incubated overnight in phosphate buffered saline (PBS). After washing with PBS for 10 min, the immunohistochemical reaction was detected using a commercial avidin-biotin-peroxidase kit (Vectastain Elite, Vector, Burlingame, CA) with diaminobenzidine as chromogen. As in prior studies,[28, 31, 60] a pathologist blinded to other study variables scored VEGF expression as: 1 = weak; 2 = moderate; or 3 = high/intense using the following guidelines: a mild stain of 5–25% of cells was graded as weak (1); staining of 25%-50% of cells was graded as moderate (2); and intense staining comprising >50% of the cells was classified as high/intense. This score was reached by scanning the entire slide at low to medium magnification (X2-X10 objective), thus determining semi-quantitatively the extent of positive stain in the selected section.

Statistical Analyses

Descriptive analyses were used to characterize the study sample. Correlational analyses were conducted to examine associations among the psychosocial functioning variables. To examine whether demographic, clinical, or behavioral variables were associated with VEGF expression and should be included as covariates in subsequent models, separate ordinal logistic regressions assuming proportional odds (i.e. cumulative logit models) were performed with each variable. Ordinal logistic regression models were also used to examine associations between individual psychosocial variables with VEGF expression. In addition, to evaluate whether overall psychosocial functioning was associated with VEGF expression, a composite factor of poor psychosocial functioning was created by computing a z-score for each of the four psychosocial variables. For the purpose of the composite score, social support was re-scored so that higher scores reflected lower social support. Z-scores were then combined across the four measures, resulting in a composite measure of poor

psychosocial functioning. This composite measure was examined in relation to VEGF expression using ordinal logistic regression models.

Two participants had missing data on the psychosocial measures. Multiple imputation was used to account for missing data in the ordinal logistic regression analyses via the methods of Raghunathan and colleagues[61] with 100 imputed datasets. Findings from the models using multiple imputation did not substantially differ from the findings obtained from non-imputed analyses, and therefore, the data presented are from the models using multiple imputation. We set the criteria for statistical significance to $p < 0.05$ (2-sided). The statistical analyses were conducted using STATA 12 (StataCorp, College Station, Texas). The imputation datasets were created using Raghunathan and colleagues' macro developed for SAS (SAS, version 9.2, SAS Institute, Cary, NC).

RESULTS

Characteristics of the Study Sample

Participants were predominantly male (76%) with a mean age of 57.7 years. Demographic and tumor characteristics, as well as psychosocial variables, are presented in Table 1. Overall, participants reported relatively modest levels of psychological distress, as the sample means for perceived stress and state anxiety were generally lower than those reported in the general population[54, 55] and below the clinical cutoff score of 16 for depressive symptoms.[50] With respect to HPV status, HPV DNA was detected in 33% of patients (14/42); of those patients with HPV DNA detected in the tumor sample, the majority was HPV16-positive (85.7% or 12/14). VEGF staining was assessed as weak in 26% of tumor samples, moderate in 50%, and high/intense in 24% of samples.

Factors associated with VEGF

Separate ordinal logistic regression models were evaluated and indicated that demographic (age, gender, education, marital status) and behavioral variables (smoking, alcohol consumption) were not associated with VEGF expression after adjusting for disease stage. HPV-status, disease stage, and tumor site were also not associated with VEGF expression. Although disease stage was not associated with VEGF expression, we included stage as a covariate in subsequent ordinal logistic regression models consistent with prior studies of VEGF in cancer patients.[10, 11]

Correlational analyses were performed to examine associations among the psychosocial variables. Measures of depressive symptoms, perceived stress, and anxiety were highly correlated with *r*-values ranging from 0.67 to 0.78, *p*s < 0.01 (see Table 2), whereas social support was not significantly associated with depressive symptoms, perceived stress, or anxiety (all *p*s > 0.05). Due to the high intercorrelations observed among the distress variables, potential associations between psychosocial variables and tumor VEGF expression were initially examined using separate models (see Table 3). Controlling for disease stage, which remained non-significant in the following multivariable analyses, higher levels of depressive symptoms were associated with greater VEGF expression (OR = 1.31, 95% CI = 1.08, 1.59, $p < 0.01$). Similarly, higher levels of perceived stress (OR = 1.15,

95% CI = 1.04, 1.27, $p < 0.01$) and anxiety (OR = 1.09, 95% CI = 1.03, 1.16, $p < 0.01$) were also associated with greater VEGF expression. In contrast, social support was not significantly associated with VEGF expression.

Because HPV-associated and non-associated HNSCCs are considered to be distinct diseases with different biomolecular signatures, patients were divided into two groups: those with HPV-negative tumors and those with HPV-positive tumors. As above, associations between psychosocial variables and tumor VEGF expression were individually tested using separate models and controlling for disease stage. Among HPV-negative patients, depressive symptoms, perceived stress, and anxiety were positively associated with VEGF expression (ps < 0.01). However, among HPV-positive patients, depressive symptoms, perceived stress, and anxiety were not significantly associated with VEGF expression (ps > 0.29).

In order to examine the association between overall psychosocial functioning and VEGF expression, a composite variable representing poor psychosocial functioning (e.g., depressive symptoms, perceived stress, anxiety, and low social support) was created for use in subsequent analyses as described above. Controlling for disease stage, overall poor psychosocial functioning was associated with greater VEGF expression (OR = 4.55, 95% CI = 1.72, 12.0, $p < 0.01$). As above, upon further examination, the association of poor psychosocial functioning with VEGF expression was statistically significant among HPV-negative patients (OR = 5.40, 95% CI = 1.68, 17.3, $p < 0.01$), but not among HPV-positive patients (OR = 3.20, 95% CI = 0.55, 18.53, $p = 0.20$). It should be noted that the association of psychosocial variables with VEGF was very similar when using a three-item composite distress measure (excluding social support).

DISCUSSION

The present findings suggest that poor psychosocial functioning is associated with greater tumor expression of VEGF, a signaling protein that promotes angiogenesis and tumor aggressiveness[28] and is associated with poor clinical outcomes in HNSCC.[29-31] These findings, which are the first to be reported in HNSCC patients, are of particular interest when considered in the context of prior studies suggesting that psychosocial functioning is associated with survival in HNSCC patients.[8, 62-64] Indeed, depression and mood disorders are generally associated with poorer outcomes in cancer patients[65] including reduced survival in HNSCC,[8] whereas reductions in depression have been associated with longer survival in women with metastatic breast cancer.[66] Thus, these data highlight one plausible biological pathway that might underlie such observations and add to the growing body of research suggesting that psychosocial functioning is associated with biological processes that can contribute to cancer progression.[67, 68]

Further, exploratory analyses suggest that associations between psychosocial functioning and VEGF are more likely to be observed among patients with non-HPV-related disease. It is widely acknowledged that HPV-related HNSCC represents a distinct entity with different risk factors and improved outcomes.[34] Given how patient characteristics and risk factors differ between HPV-related and non-HPV-related disease, it is perhaps not surprising that the associations were observed primarily in HPV-negative patients. Behavioral risk factors

(such as smoking and heavy alcohol consumption) tend to be more prevalent in HPV-negative HNSCC,[35] and these behaviors are often strongly correlated with psychosocial functioning and mood disorders.[69, 70] Such behaviors may also contribute to VEGF overexpression,[71] although we did not observe such associations between behavioral risk factors and VEGF expression in the present study. Further, HPV-related disease is characterized by molecular and genetic alterations that reflect the oncogenic function of the E6 and E7 proteins.[33] These oncoproteins not only lead to genomic instability,[34] but also contribute to aberrant expression of VEGF.[43] Hence, interrelations of psychosocial functioning and VEGF may be more ambiguous in the context of HPV-related disease.

In contrast to our hypotheses, social support was not significantly associated with VEGF expression. This may be due to a variety of reasons. One possibility is that the level of perceived support reported at the time of cancer diagnosis may not reflect the extent of support present during the months and years preceding the cancer diagnosis. It is likely that patients receive more support during the stressful period when learning of a new cancer diagnosis, when our study assessments were obtained. Thus, the level of support reported at diagnosis may not reflect levels of support available during the period preceding such a diagnosis. Although data from various intervals prior to cancer diagnosis are not available for comparison purposes, a recent study of HNSCC patients reported that perceived support decreased from pretreatment to post-treatment,[72] indicating that levels of support do fluctuate over time and may be higher at certain times surrounding an unique event (i.e. cancer diagnosis).

Another potential factor that may be contributing to differences between the present findings and prior study findings is the use of diverse measures that may be sensitive to distinct aspects of social support. For example, Nausheen and colleagues utilized measures of loneliness,[11] and Lutgendorf and colleagues assessed components of social well-being.[10] Differences across measures may be capturing differential aspects of support, social integration, or connectedness, which may be more or less biologically meaningful. It should also be noted that women are more likely than men to receive social support from multiple sources;[73, 74] and while social support has demonstrated benefits among women with cancer,[75-78] less is known regarding social support and cancer outcomes among men. Therefore, differences between the present findings and prior study findings may be attributed, in part, to the fact that the present study sample was comprised predominantly of men, for whom the benefits of social support have been less consistently demonstrated within the cancer context.

In addition, variations in how VEGF was assessed may explain some of the discrepancies across studies. Although serum VEGF levels may provide an indirect estimate of tumor VEGF expression,[79] systemic levels are also impacted by other variables including platelet count[80] and tumor-derived IL-6, which can upregulate platelet VEGF expression.[81] In addition, our approach directly assessed tumor VEGF expression and not nodal metastatic tissue. Potential differences that exist in VEGF expression across primary tumor and nodal tissue may explain some of the differences observed across studies.

The present study has several limitations. First, the sample size is limited, which made it less likely that we would detect the hypothesized associations. Second, the cross-sectional nature of the associations between psychosocial functioning and VEGF expression precludes any causal inferences regarding the direction of the observed associations. We cannot exclude the possibility that, at the time of surgery, patients who have more severe disease may also feel more distressed, although we attempted to address this possible confound by controlling for disease stage in the analyses. Third, it should be noted that the effect sizes were generally quite modest. This may be due, in part, to a variety of factors including the heterogeneity in disease sites or the assessment of acute distress as opposed to chronic stress, which may have greater physiological consequences. Finally, this pilot study did not include any neuroendocrine measures (e.g., norepinephrine, cortisol) that could inform the possible mechanisms linking psychosocial functioning with VEGF expression. Despite these limitations, the present findings add to the extant literature on psychosocial functioning and pro-angiogenic factors in HNSCC patients and suggest that additional study of biobehavioral mechanisms in HNSCC is warranted in this complex patient population. Future studies that focus on specific subgroups of HNSCC patients are needed to elucidate the biobehavioral mechanisms underlying psychosocial functioning and clinically-relevant biomarkers in this patient population.

In conclusion, our findings suggest that poorer psychosocial functioning prior to surgery is associated with greater VEGF expression in tumor, which is a clinically relevant biomarker among HNSCC patients. These findings may have implications for patient outcomes given that greater VEGF expression in tumor is predictive of poorer overall and disease-free survival.[29-31] Further, it was noted that such associations were primarily evident in patients with non-HPV-related disease. These findings contribute to a greater appreciation of the distinct biobehavioral pathways that may be involved in HPV- and non-HPV-related HNSCCs and offer a novel example of how existing biobehavioral frameworks can be refined by incorporating new developments in the biology of HNSCC.

Acknowledgments

This research was supported by National Institutes of Health grants P30CA006927, R41CA144100, and K22CA107115. The authors would like to thank Denise Cothren and Colleen McKeown for their assistance and Dr. Robert Ferris for providing helpful comments on an earlier version of this manuscript. We acknowledge the FCCC Tumor Bank Facility, Biosample Repository, Histopathology Facility, High Throughput Screening and Translational Research Facility, Population Studies Facility, and the Biostatistics and Bioinformatics Facility for their services.

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Table 1

Participant Characteristics

Variable	No. of patients (%)	Mean ± SD
Age in years		57.7 ± 12.85
Gender		
Men	32 (76%)	
Women	10 (24%)	
Race/Ethnicity		
Non-Hispanic White	40 (95%)	
African American	2 (5%)	
Marital status		
Single (never married)	4 (9%)	
Married/living as married	28 (67%)	
Divorced or widowed	10 (24%)	
Education[a]		
High school or less	19 (45%)	
Some college	7 (17%)	
College or post-grad degree	13 (31%)	
Smoking history[b]		
Never	11 (26%)	
1-30 years	15 (36%)	
31+ years	15 (36%)	
HPV-positive	14 (33%)	
VEGF expression		
Weak	11 (26%)	
Moderate	21 (50%)	
Intense	10 (24%)	
Primary site		
Oral cavity	26 (61%)	
Larynx	7 (17%)	
Oropharynx	7 (17%)	
Hypopharynx	2 (5%)	
T classification		
T1	11 (26%)	
T2	14 (33%)	
T3	10 (24%)	
T4	7 (17%)	
N classification		
N0	24 (57%)	
N1	6 (14%)	
N2	12 (29%)	
Stage		

Variable	No. of patients (%)	Mean ± SD
I	9 (21%)	
II	7 (17%)	
III	9 (21%)	
IVA	17 (41%)	
Planned Treatment		
Surgery only	19 (45%)	
Surgery plus radiation	13 (31%)	
Surgery plus chemotherapy	1 (2%)	
Surgery, radiation, and chemotherapy	9 (21%)	
Depressive symptoms[c] (CES-D)		6.60 ± 3.69
Perceived stress[c] (PSS)		9.95 ± 6.79
Anxiety[c] (STAI)		20.73 ± 11.64
Social support[c] (ISEL)		89.95 ± 13.74

Abbreviation: SD = standard deviation.

Note:

[a] Three participants (7%) had missing data on education level

[b] One participant (2%) was noted as a smoker, but information regarding length of smoking history was missing

[c] Two participants had missing data on psychosocial measures.

Table 2

Intercorrelations of Psychosocial Variables

Variable	1	2	3	4
1. Depressive symptoms	--	0.74**	0.78**	0.07
2. Perceived stress		--	0.67**	0.04
3. State anxiety			--	0.13
4. Social support				--

Note:

** $p < 0.01$.

Table 3

Associations between Psychosocial Functioning and VEGF Expression in All Patients and by HPV-status

	All patients			*HPV-negative*			*HPV-positive*		
Measure	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Depressive symptoms	**1.35**	**1.11, 1.65**	**<0.01**	**1.44**	**1.14, 1.83**	**<0.01**	1.23	0.84, 1.78	0.29
Perceived stress	**1.15**	**1.04, 1.27**	**<0.01**	**1.20**	**1.06, 1.37**	**<0.01**	1.07	0.89, 1.27	0.47
State anxiety	**1.09**	**1.03, 1.16**	**<0.01**	**1.12**	**1.04, 1.21**	**<0.01**	1.04	0.93, 1.16	0.48
Social support	1.00	0.96, 1.04	0.86	0.99	0.94, 1.04	0.74	1.04	0.96, 1.12	0.37
Poor psychosocial functioning	**4.55**	**1.72, 12.0**	**<0.01**	**5.40**	**1.68, 17.3**	**<0.01**	3.20	0.55, 18.53	0.20

Abbreviations: OR = odds ratio; CI = confidence interval.

Note: Associations were assessed with multivariable ordinal logistic regression analyses controlling for disease stage. Estimates from these models can be interpreted as the odds of falling into a higher vs. lower category of VEGF expression with each unit increase in the psychosocial variable.