Original Article

Eudaimonic Well-Being and Tumor Norepinephrine in Patients With Epithelial Ovarian Cancer

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BACKGROUND: The impact of psychological well-being on the physiologic processes involved in cancer progression remains unclear. Prior research has implicated adrenergic signaling in tumor growth and metastasis. Given that adrenergic signaling is influenced by both positive and negative factors, the authors examined how 2 different aspects of well-being (eudaimonic and positive affect) and psychological distress were associated with tumor norepinephrine (NE) in patients with ovarian cancer. **METHODS:** A total of 365 women with suspected ovarian cancer completed psychosocial assessments before surgery and clinical information was obtained from medical records. Study inclusion was confirmed after histological diagnosis. Tumor NE was measured in frozen tissue samples using high-performance liquid chromatography with electrochemical detection. Confirmatory factor analysis was used to model eudaimonic well-being, positive affect, and psychological distress, and structural equation modeling was used to examine associations between these factors and tumor NE. **RESULTS:** Eudaimonic well-being, positive affect, and psychological distress, modeled as distinct but correlated constructs, best fit the data (ie, compared with unitary or 2-factor models) (root mean square error of approximation, 0.048; comparative fit index, 0.982; and standardized root-mean-squared residual, 0.035). Structural equation modeling analysis that included physical well-being, stage of disease, histology, psychological treatment history, beta-blocker use, and caffeine use as covariates was found to have good model fit (root mean square error of approximation, 0.052; comparative fit index, 0.955; and standardized root-mean-squared residual, 0.036) and demonstrated that eudaimonic well-being was related to lower tumor NE ($\beta = -.24$ [$P = .045$]). In contrast, no effects were found for positive affect or psychological distress. **CONCLUSIONS:** Eudaimonic well-being was found to be associated with lower tumor NE, independent of positive affect and psychological distress. Because adrenergic signaling is implicated in tumor progression, increasing eudaimonic well-being may improve both psychological and physiologic resilience in patients with ovarian cancer. ***Cancer*** **2015;121:3543-50.** *© 2015 American Cancer Society.*

KEYWORDS: biological markers, norepinephrine, ovarian neoplasms, psychological resilience, tumor microenvironment.

INTRODUCTION

Ovarian cancer has the highest mortality of all the female reproductive system cancers and an overall 5-year survival rate of 45%.[1] Psychological distress is common among patients with ovarian cancer, with high rates of anxiety and depression reported.[2] Because psychological distress has been associated with both poorer quality of life[3] and disease progression in a variety of cancers,[4] it is important to identify factors that can be targeted to modulate disease-related processes and improve clinical outcomes and quality of life.

Interest in psychological factors that may protect health has grown substantially in recent years.[5] Positive affect, or the well-being associated with pleasurable engagement with one's environment (ie, hedonic well-being),[6] has been related to psychosocial resilience, longevity, and better health in healthy populations, independent of negative affect.[7-9] To the best of our knowledge, the role of positive affect in patients with cancer has been less well characterized. One study found that positive affect was related to biomarkers and survival in patients with renal cell carcinoma,[10] whereas another found

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detrimental effects of positive affect on inflammatory biomarkers.[11] Other studies have shown that eudaimonic well-being, or experiencing a deeper sense of meaning in life, fulfilling one's potential, and accepting oneself,[12] is distinct from positive affect and may be a stronger predictor of health status.[13-15] Eudaimonic well-being has been negatively related to perceived stress, depression, and anxiety in patients with cancer and cancer survivors.[16,17]

In healthy adults, positive affect has been associated with a more normalized diurnal cortisol rhythm and enhanced immune function, although results are inconsistent.[18] Likewise, eudaimonic well-being has generally been related to healthier inflammatory profiles, cortisol rhythms, cardiovascular biomarkers, and sleep patterns.[14,19,20] Differential effects for these constructs have also been shown. For example, eudaimonic well-being (but not positive affect) reportedly predicts better cardiovascular health[15] and lower plasma interleukin-6 levels in older adults.[14] Eudaimonic well-being has also been related to reduced activation of the conserved transcriptional response to adversity, a gene expression signature characterized by upregulation of proinflammatory genes and downregulation of genes associated with antiviral immunity,[21] whereas positive affect (hedonic well-being) was associated with the reverse.[22]

One pathway by which psychosocial factors influence health is via activation of the sympathetic nervous system (SNS), with norepinephrine (NE) as a key neuroeffector molecule.[23] NE-induced adrenergic signaling can regulate multiple downstream biological processes involved in tumor growth and progression,[24-26] including angiogenesis,[27] invasion,[28] and resistance to anoikis.[29] Previous studies have found a relationship between tumor NE levels and negative factors such as stress, depression, and social isolation,[30-32] but to our knowledge little is known regarding the role of positive affect or eudaimonic well-being in patients with cancer. Positive affect and eudaimonic well-being have shown divergent relationships with measures of SNS activation in healthy populations.[15,18] Therefore, the goal of the current study was to examine how positive affect, eudaimonic well-being, and psychological distress relate to tumor NE in patients with ovarian cancer.

MATERIALS AND METHODS

Patients and Procedures

Patients were recruited at a clinic visit 1 to 2 weeks before diagnostic surgery for a pelvic mass suspected to be ovarian cancer. Women with a history of cancer, nonovarian primary tumor site, nonepithelial tumors, tumors of low malignant potential, or a comorbidity known to influence the immune system were excluded. Additional exclusion criteria included age <18 years, systemic corticosteroid use within the previous month, and current pregnancy. Psychosocial assessments were completed at home between the initial clinic visit and surgery. Tumor samples were fresh frozen in the surgical pathology laboratory as soon as possible after surgical resection. The total sample included 365 women diagnosed with invasive primary epithelial ovarian, fallopian tube, or peritoneal cancer. Twelve patients had missing questionnaire data, and therefore tests of the measurement model included 353 patients. Because maximum likelihood estimation uses all available data,[33,34] patients who were missing either tumor NE or questionnaires were still included in the predictive models (see the CONSORT table in Fig. 1). All procedures were approved by Institutional Review Boards at the University of Iowa, Washington University, and University of Miami.

Measures

Psychosocial measures

The Center for Epidemiological Studies-Depression Scale (CES-D) measures the frequency of depressive symptoms over the previous week.[35] A stable 4-factor structure has been identified, including depressed affect, positive affect, vegetative symptoms, and interpersonal relations.[36] Because cancer symptoms can resemble vegetative depression, we used the depressed mood subscale. The positive affect scale was also used. Scores on these subscales range from 0 to 15, with higher scores indicating more depression or positive affect. Adequate reliability was obtained for depression ($\alpha = .83$) and positive affect ($\alpha = .77$).

The Profile of Mood States-Short Form (POMS-SF) measures psychological distress, with subscales for fatigue, vigor, tension/anxiety, depression/dejection, confusion, and anger/hostility.[37] This factor structure has been validated in patients with cancer.[38] The vigor subscale consists of 6 items assessing the frequency of emotions such as "cheerful" and "lively." The vigor and depression/dejection subscales both had excellent reliability ($\alpha = .88$ and .90, respectively).

Cancer-specific intrusive thoughts and avoidance behavior were assessed with the Impact of Event Scale (IES).[39] This 15-item scale has been used to measure psychological distress and anxiety symptoms in patients with cancer.[40] Participants indicated how often within the previous week they experienced intrusive thoughts and avoidance regarding their cancer, with higher scores reflecting greater psychological distress. This scale had excellent reliability ($\alpha = .89$).

Three subscales from the Ryff Psychological Well-Being Scales (PWBS) were used as measures of eudaimonic

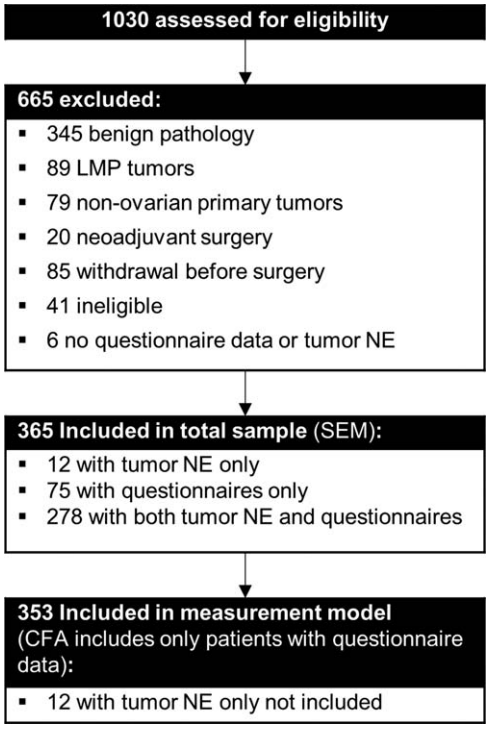

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram displaying patient inclusion. CFA indicates confirmatory factor analysis; LMP, low malignant potential; NE, norepinephrine; SEM, structural equation modeling.

well-being.[12] The personal growth subscale measures whether individuals believe they have psychologically developed and realized their potential. The purpose in life subscale assesses whether one has goals and a sense of meaning in life. The self-acceptance scale assesses positive attitude toward the self and acceptance of both good and bad qualities. Each scale has 7 items, with higher scores indicating greater well-being. Adequate reliability was obtained for each scale (all α were $\geq$.74). This questionnaire was added to the protocol after initiation of the study and therefore fewer participants completed the PWBS.

Self-reported symptoms were measured with the physical well-being subscale of the Functional Assessment of Cancer Therapy (FACT).[41] This subscale assesses 7 somatic symptoms commonly experienced by patients with cancer (eg, lack of energy, pain) and is sensitive to disease stage. Items are rated over the previous week, with higher scores indicating fewer symptoms or greater well-being. This measure demonstrated good reliability ($\alpha = .84$).

Demographic and clinical information

Demographic information was obtained by self-report and clinical information was obtained from medical records.

Tumor NE

Tumor NE was measured as previously described.[42] Briefly, frozen tumor samples were pulverized, homogenized, and extracted before immediate measurement of catecholamine levels using high-performance liquid chromatography with electrochemical detection.[43] Tumor NE was below detectable limits for 31% of patients and was set at the lowest detectable level of the assay (0.1 pg/mg). Tumor epinephrine and dopamine levels were below detectable limits for the majority of the sample; thus, these catecholamines were not included in the analyses.

Statistical Analysis

Initial analyses were conducted using SPSS statistical software (version 21; IBM Corporation, Armonk, NY). Distributions were examined for normality and outliers (>3 times the interquartile range), and no outliers were found. Tumor NE values were log-transformed due to nonnormality. First, the measurement model was examined using confirmatory factor analysis (CFA) with the following indicators: purpose in life, self-acceptance, and personal growth (for eudaimonic well-being); vigor and positive affect (for positive affect); and depressed affect, depression-dejection, and cancer-specific distress (for psychological distress). Physical well-being was included in the CFA as a covariate of each factor to adjust for the influence of physical symptoms on reports of psychological states.[44] To determine whether eudaimonic well-being, psychological distress, and positive affect were independent constructs or opposite poles of a unitary construct,[45] we evaluated a model including only 1 latent variable with all manifest variables as indicators. Similarly, to determine whether positive affect and eudaimonic well-being are independent constructs, a 2-factor model with a general positive/well-being latent variable along with the psychological distress factor was tested.

After a measurement model was adequately specified, a structural equation model (SEM) was assessed with tumor NE as an endogenous outcome regressed on the 3 latent variables. Tumor stage according to the International Federation of Gynecologists and Obstetricians (FIGO) guidelines (stages I/II vs. 3/4), daily caffeine intake, use of beta-blockers, and physical well-being were included as a priori covariates, due to known relationships with adrenergic biomarkers and to control for the potential influences of tumor burden and physical disability. To determine additional covariates, bivariate correlations were examined between tumor NE and body mass index, age, sleep quality, tumor grade assessed by pathology (low vs. high), histology, education, ethnicity, smoking

history, psychological treatment history, and presence of medical comorbidities. Variables significantly correlated with tumor NE were used as covariates and included histology and psychological treatment history. Tumor NE was regressed on these covariates, and correlations between covariates and latent factors were modeled.

All analyses were conducted using Mplus statistical software (version 6.12; Institute for Digital Research and Education, University of California at Los Angeles, Los Angeles, Calif) using maximum likelihood estimation with robust standard errors to account for nonnormality and estimate parameters with missing data present.[46] Maximum likelihood estimation uses all available data, which provides a statistical advantage in terms of both power and reducing bias in parameter estimates.[33,34] Overall model fit was evaluated by examining the comparative fit index (CFI),[47] the root mean square error of approximation (RMSEA),[48] and the standardized root-mean-squared residual (SRMR) and estimates from the standardized model were reported. Recommended cutoff points[49] of 0.95 for CFI, 0.06 for RMSEA, and 0.08 for SRMR were used to evaluate model fit.[49] Nonnested models were compared by evaluating the difference between the Bayesian information criterion (BIC) for each model using the guidelines of Raftery (0-2 indicates weak, 2-6 indicates positive, 6-10 indicates strong, and >10 indicates very strong).[50]

RESULTS

Sample Characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. The average age at the time of diagnosis was 59.8 years. The participants were primarily white, non-Hispanic, and married or living with a partner. Most participants were diagnosed with high-grade (86%; 315 participants) and advanced stage (72%; 263 participants) tumors. Bivariate correlations between study variables are shown in Table 2.

TABLE 1. Participant Demographic and Clinical Characteristics (N=365)

Characteristic	No. (%)
Mean age (SD), y	59.76 (11.71)
Race	
American Indian/Alaska Native	2 (0.5)
Asian	3 (0.8)
Pacific Islander	0
Black/African American	9 (2.5)
White	346 (94.8)
Missing data	5 (1.4)
Ethnicity	
Non-Hispanic	322 (88.2)
Hispanic	15 (4.1)
Unknown/missing data	28 (7.7)
Education	
≤High school	133 (36.5)
Trade school/some college	110 (30.1)
College graduate	73 (20)
Postgraduate degree	31 (8.5)
Missing data	18 (4.9)
Relationship status	
Married or living with partner	235 (64.4)
Single, separated, widowed, or divorced	127 (34.8)
Missing data	3 (0.8)
Cancer stage (FIGO guidelines)	
I	72 (19.7)
II	26 (7.1)
III	229 (62.7)
IV	34 (9.3)
Missing data	4 (1.1)
Grade (assessed by pathology)	
Low	46 (12.6)
High	315 (86.3)
Missing data	4 (1.1)
Histology	
Serous	263 (72.1)
Endometrioid	35 (9.6)
Mucinous	15 (4.1)
Clear cell	24 (6.6)
Other/unknown/missing data	28 (7.7)
Surgical debulking	
Optimal	262 (71.8)
Suboptimal	92 (25.2)
Missing data	11 (3)

Abbreviation: SD, standard deviation.

Measurement Model

The initial CFA testing the hypothesized structure of eudaimonic well-being, positive affect, and psychological distress is presented in Table 3. This model had excellent fit (RMSEA, 0.048; CFI, 0.982; SRMR, 0.035; and BIC, 15740) and all factor loadings were statistically significant ($P < .001$). Moreover, the 3-factor model provided a substantially better fit to the data than the unitary model (RMSEA, 0.177; CFI, 0.71; SRMR, 0.123; and BIC, 16002) and the 2-factor model (RMSEA, 0.113; CFI, 0.891; SRMR, 0.097; and BIC, 15822). These results indicate that eudaimonic well-being, positive affect, and distress are correlated but independent constructs in this population.

SEM Predicting Tumor NE

The final SEM is shown in Figure 2. Before model testing, we examined bivariate correlations between tumor NE and potential covariates. All a priori covariates were found to be significantly related to tumor NE in bivariate correlations, including cancer stage (N = 289; r_{pb} (r_{pb} indicates a point-biserial correlation, where one variable is dichotomous (e.g., high/low grade, yes/no to beta-blocker use)) = 0.16 [$P = .01$]), beta-blockers (N = 290; r_{pb} = -0.14 [$P = .02$]), average daily caffeine intake (N = 272;

TABLE 2. Bivariate Correlations, Means, and SDs of Latent Variable Indicators and Tumor NE

Variable	1	2	3	4	5	6	7	8	9	10
1. Personal growth (PWBS)	–									
2. Purpose in life (PWBS)	0.74[a]	–								
	188									
3. Self-acceptance (PWBS)	0.65[a]	0.63[a]	–							
	188	*188*								
4. Positive affect (CES-D)	0.37[a]	0.35[a]	0.39[a]	–						
	186	*187*	*186*							
5. Vigor (POMS-SF)	0.31[a]	0.32[a]	0.29[a]	0.50[a]	–					
	181	*182*	*181*	*326*						
6. Depressed affect (CES-D)	-0.25[a]	-0.25[a]	-0.34[a]	-0.49[a]	-0.27[a]	–				
	186	*187*	*186*	*345*	*327*					
7. Depression-dejection (POMS-SF)	-0.39[a]	-0.33[a]	-0.38[a]	-0.52[a]	-0.38[a]	0.73[a]	–			
	181	*182*	*181*	*326*	*333*	*327*				
8. Cancer-specific distress (IES)	-0.25[b]	-0.18[b]	-0.23[b]	-0.35[a]	-0.24[a]	0.59[a]	0.63[a]	–		
	179	*180*	*179*	*326*	*328*	*327*	*328*			
9. Physical well-being (FACT)	0.26[a]	0.30[a]	0.26[b]	0.49[a]	0.47[a]	-0.37[a]	-0.48[a]	-0.23[a]	–	
	187	*188*	*187*	*334*	*322*	*335*	*322*	*322*		
10. Tumor NE (log10), pg/mg	-0.21[b]	-0.07	-0.04	-0.06	-0.08	0.04	0.10	0.02	-0.12[c]	–
	151	*151*	*151*	*272*	*263*	*273*	*263*	*262*	*267*	
No.	188	189	188	345	334	346	334	334	339	290
Mean	38.03	38.26	38.21	7.50	8.32	3.49	6.87	26.92	19.41	0.07
SD	6.81	7.33	7.97	3.00	5.45	3.34	6.64	14.79	6.39	1.01

Abbreviations: CES-D, Center for Epidemiological Studies-Depression Scale; FACT, Functional Assessment of Cancer Therapy; IES, Impact of Event Scale; NE, norepinephrine; POMS-SF, Profile of Mood States-Short Form; PWBS, Psychological Well-Being Scales; SDs, standard deviations.
The number for each correlation is displayed below in italic type and varied due to missing data for each pair of measures.
[a] $P<.001$.
[b] $P<.01$.
[c] $P<.05$.

TABLE 3. Factor Loadings of Latent Variables from the Confirmatory Factor Analysis Model

Indicator	Standardized Estimate	Standard Error	R^2
Eudaimonic well-being			
Personal growth	0.87	0.03	0.76
Purpose in life	0.84	0.04	0.70
Self-acceptance	0.77	0.05	0.59
Positive affect			
Positive affect	0.77	0.04	0.60
Vigor	0.64	0.05	0.41
Distress			
Depressed mood	0.80	0.03	0.64
Depressed-dejection	0.93	0.02	0.86
Cancer-specific distress	0.69	0.04	0.47

All factor loadings were significant at $P<.001$.
R^2 is the amount of variance in each indicator that is explained by the latent variable.

$r = 0.16$ [$P = .01$]), and physical well-being ($r = -0.12$ [$P = .05$]). Histology (N = 290; $r_{pb} = 0.19$ [$P = .001$]) and psychological treatment history (N = 274; $r_{pb} = -0.13$ [$P = .03$]) were also related to tumor NE and thus were included in the SEM as covariates. The SEM model had good fit (RMSEA, 0.052; CFI, 0.955; SRMR, 0.036; and BIC, 19816). Of the covariates included, greater daily caffeine use was found to be related to higher tumor NE ($\beta = .16$ [$P = .02$]), whereas psychological treatment history was related to lower tumor NE ($\beta = -.21$ [$P = .002$]). Relations between tumor NE and beta-blocker use ($\beta = -.14$ [$P = .06$]) and physical well-being ($\beta = -.17$ [$P = .09$]) were found to be marginally significant, whereas cancer stage and histology ($\beta = .11$ [$P = .09$]) were unrelated ($\beta = .10$ [$P = .14$]).

Several covariates were also found to be related to the latent constructs. Advanced stage disease was associated with lower positive affect (estimate, -0.16 [$P = .02$]) but not with eudaimonic well-being (estimate, .03 [$P = .74$]) or distress (estimate, 0.09 [$P = .09$]). Beta-blockers and caffeine use were found to be unrelated to all latent variables. Tumor histology was unrelated to eudaimonic well-being and psychological distress, but patients with nonserous tumors reported more positive affect (estimate, -0.17 [$P = .005$]). A history of psychological treatment was found to be related to lower eudaimonic well-being (estimate, -0.19 [$P = .014$]) and greater psychological distress (estimate, 0.23 [$P<.001$]). Physical well-being remained significantly associated with eudaimonic well-being (estimate, 0.33), positive affect (estimate, 0.66), and distress (estimate, -0.48) (all $P<.001$), and the covariances between factors remained statistically significant, with relationships similar to those in the measurement model.

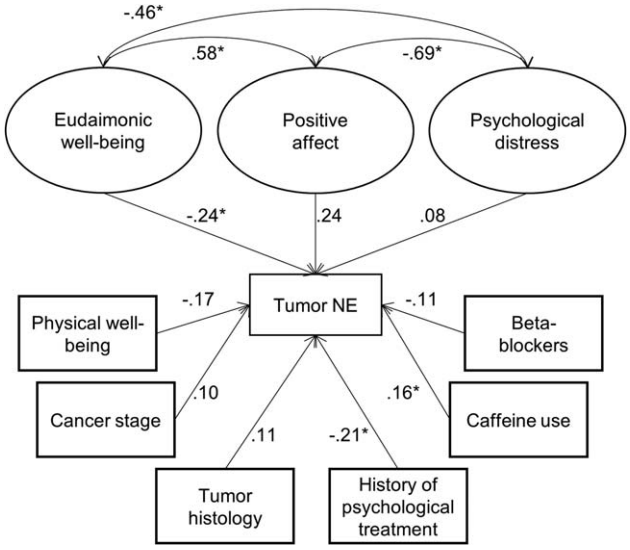

Figure 2. Structural equation model predicting tumor norepinephrine (NE) from latent variables and covariates. Indicators of latent variables, and correlations between control and latent variables, were removed for simplicity.* indicates $P < .05$.

Last, and most important, we examined associations between the latent variables and tumor NE. Eudaimonic well-being was significantly related to lower tumor NE ($\beta = -.24$ [$P = .045$]). In contrast, psychological distress ($\beta = .08$ [$P = .45$]) and positive affect ($\beta = .24$ [$P = .17$]) were both unrelated to tumor NE (Fig. 2).

DISCUSSION

The key finding of the current study was that higher levels of eudaimonic well-being were found to be associated with lower tumor NE in patients with ovarian cancer while controlling for positive affect, psychological distress, and several demographic and clinical covariates. In contrast, positive affect and psychological distress were found to be unrelated to tumor NE. In addition, consistent with prior research,[15,19,22,51] we found that positive affect (hedonic well-being) and eudaimonic well-being were correlated but distinct constructs. This suggests that the beneficial effects of eudaimonic well-being are independent of the influence of other factors, including positive affect. Based on these findings, we concluded that a deeper sense of well-being in patients with cancer may be more physiologically protective than positive or pleasant emotions. A cancer diagnosis often provokes existential concerns, including a struggle to maintain self-identity and meaning in life.[52] Eudaimonic well-being, which entails acting in accordance with one's deepest values, appears to be more indicative of positive adjustment within the context of this struggle.[51] For example, meaning and peace, possible indicators of eudaimonic well-being, have been associated with better quality of life and less depression and anxiety in patients with ovarian cancer.[53]

The findings of the current study may suggest a potential benefit for patients with greater eudaimonic well-being, given that beta-adrenergic signaling upregulates multiple pathways involved in tumor progression.[24] For example, we previously reported associations of elevated tumor NE in patients with ovarian cancer with activated focal adhesion kinase (FAK), which promotes tumor cell survival during metastasis. FAK in turn was found to be associated with poorer overall survival.[29]

These findings extend prior research regarding psychosocial factors and catecholamines in the tumor microenvironment. Data from an orthotopic model of ovarian cancer have indicated that restraint-stressed mice demonstrate elevated tumor NE, along with greater tumor weight and nodules.[54] We have previously reported that patients with ovarian cancer with greater social isolation have higher levels of NE in both tumor and ascites,[55] and that a composite of high depression and low social support is also associated with elevated tumor NE.[42,56] The results of the current study extend this work by demonstrating that a broader sense of well-being predicts lower tumor NE. To the best of our knowledge, the current study is also the first to examine the physiologic relevance of these factors within the context of cancer. The differential effects observed for positive affect and eudaimonic well-being are not surprising given that positive affect can have variable effects on the SNS, depending on both environmental-specific and subject-specific factors.[18] Therefore, the results of the current study add to the literature demonstrating the benefits of eudaimonic well-being, distinct from positive affect.[57]

These findings have potential implications for clinical care. For example, assessing eudaimonic well-being can be done quickly, and individuals with low well-being may be candidates for psychosocial intervention. In addition, the data suggest that interventions targeting eudaimonic well-being, such as acceptance and commitment therapy,[58] mindfulness interventions,[59] and positive psychology approaches emphasizing gratitude and patient strengths,[60] may be more beneficial for enhancing physiological resilience than those targeting positive affect or psychological distress.[57]

Limitations

The findings of the current study do not confirm causality between well-being and tumor NE. However, the methodological strengths, including the simultaneous

examination of eudaimonic well-being, positive affect, and psychological distress, provide a fine-tuned discrimination between these constructs. Although epinephrine and dopamine may also impact processes involved in tumor progression,[25,61] we found negligible levels of both and therefore these catecholamines were not included in the current analyses. The statistical approach enabled patients with missing data to be included.[33] However, 20.5% of this sample had questionnaire but not tumor NE data, which may have affected our ability to detect weaker associations between study variables. Last, although the tumor NE has been indirectly related to survival (eg, via increased FAK), to our knowledge its direct effect on survival is unknown.

The results of the current study demonstrate that eudaimonic well-being, but not positive affect or psychological distress, is associated with tumor NE in patients with ovarian cancer. Because ovarian cancer diagnosis and treatment are often accompanied by psychological distress, and because adrenergic signaling is known to play a role in tumor progression, interventions that increase eudaimonic well-being may have important clinical effects in patients with cancer. Additional research is warranted to examine how eudaimonic well-being influences quality of life and disease progression in patients with ovarian and other cancers.

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CONFLICT OF INTEREST DISCLOSURES

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REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2014. Atlanta, GA: American Cancer Society; 2014.
2. Bodurka-Bevers D, Basen-Engquist K, Carmack CL, et al. Depression, anxiety, and quality of life in patients with epithelial ovarian cancer. *Gynecol Oncol*. 2000;78:302-308.
3. Kornblith AB, Thaler HT, Wong G, et al. Quality of life of women with ovarian cancer. *Gynecol Oncol*. 1995;59:231-242.
4. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Pract Oncol*. 2008;5:466-475.
5. Aspinwall LG, Tedeschi RG. The value of positive psychology for health psychology: progress and pitfalls in examining the relation of positive phenomena to health. *Ann Behav Med*. 2010;39:4-15.
6. Clark LA, Watson D, Leeka J. Diurnal variation in the positive affects. *Motiv Emot*. 1989;13:205-234.
7. Ryan RM, Deci EL. On happiness and human potentials: a review of research on hedonic and eudaimonic well-being. *Annu Rev Psychol*. 2001;52:141-166.
8. Cohen S, Pressman SD. Positive affect and health. *Curr Dir Psychol Sci*. 2006;15:122-125.
9. Fredrickson BL. The role of positive emotions in positive psychology: the broaden-and-build theory of positive emotions. *Am Psychol*. 2001;56:218-226.
10. Prinsloo S, Wei Q, Scott SM, et al. Psychological states, serum markers and survival: associations and predictors of survival in patients with renal cell carcinoma. *J Behav Med*. 2015;38:48-56.
11. Sepah SC, Bower JE. Positive affect and inflammation during radiation treatment for breast and prostate cancer. *Brain Behav Immun*. 2009;23:1068-1072.
12. Ryff CD. Happiness is everything, or is it? Explorations on the meaning of psychological well-being. *J Pers Soc Psychol*. 1989;57:1069-1081.
13. Keyes CL, Shmotkin D, Ryff CD. Optimizing well-being: the empirical encounter of 2 traditions. *J Pers Soc Psychol*. 2002;82:1007-1022.
14. Friedman EM, Hayney M, Love GD, Singer BH, Ryff CD. Plasma interleukin-6 and soluble IL-6 receptors are associated with psychological well-being in aging women. *Health Psychol*. 2007;26:305-313.
15. Ryff CD, Dienberg Love G, Urry HL, et al. Psychological well-being and ill-being: do they have distinct or mirrored biological correlates? *Psychother Psychosom*. 2006;75:85-95.
16. Costa RV, Pakenham KI. Associations between benefit finding and adjustment outcomes in thyroid cancer. *Psychooncology*. 2012;21:737-744.
17. Dukes Holland K, Holahan CK. The relation of social support and coping to positive adaptation to breast cancer. *Psychol Health*. 2003; 18:15-29.
18. Pressman SD, Cohen S. Does positive affect influence health? *Psychol Bull*. 2005;131:925-971.
19. Ryff CD, Singer BH, Dienberg Love G. Positive health: connecting well-being with biology. *Philos Trans R Soc Lond B Biol Sci*. 2004; 359:1383-1394.
20. Lindfors P, Lundberg U. Is low cortisol release an indicator of positive health? *Stress Health*. 2002;18:153-160.
21. Slavich GM, Cole SW. The emerging field of human social genomics. *Clin Psychol Sci*. 2013;1:331-348.
22. Fredrickson BL, Grewen KM, Coffey KA, et al. A functional genomic perspective on human well-being. *Proc Natl Acad Sci U S A*. 2013;110:13684-13689.
23. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Ann N Y Acad Sci*. 1999;896:30-47.
24. Armaiz-Pena GN, Cole SW, Lutgendorf SK, Sood AK. Neuroendocrine influences on cancer progression. *Brain Behav Immun*. 2013; 30(suppl):S19-S25.
25. Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. *Clin Cancer Res*. 2012;18:1201-1206.
26. Armaiz-Pena GN, Allen JK, Cruz A, et al. Src activation by β-adrenoreceptors is a key switch for tumour metastasis. *Nat Commun*. 2013;4:1403.
27. Lutgendorf SK, Cole S, Costanzo E, et al. Stress-related mediators stimulate vascular endothelial growth factor secretion by 2 ovarian cancer cell lines. *Clin Cancer Res*. 2003;9:4514-4521.
28. Sood AK, Bhatty R, Kamat AA, et al. Stress hormone-mediated invasion of ovarian cancer cells. *Clin Cancer Res*. 2006;12:369-375.
29. Sood AK, Armaiz-Pena GN, Halder J, et al. Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. *J Clin Invest*. 2010;120:1515-1523.
30. Lutgendorf SK, Sood AK, Antoni MH. Host factors and cancer progression: biobehavioral signaling pathways and interventions. *J Clin Oncol*. 2010;28:4094-4099.
31. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. *Psychol Med*. 2010;40:1797-1810.
32. Cohen L, Cole SW, Sood AK, et al. Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: role of inflammatory signaling. *PLoS One*. 2012;7:e42324.
33. Anderson TW. Maximum likelihood estimates for a multivariate normal distribution when some observations are missing. *J Am Stat Assoc*. 1957;52:200-203.

34. Enders CK, Bandalos DL. The relative performance of full information maximum likelihood estimation for missing data in structural equation models. *Struct Equ Model A Multidiscip J*. 2001;8:430-457.
35. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.
36. Sheehan TJ, Fifield J, Reisine S, Tennen H. The measurement structure of the Center for Epidemiologic Studies Depression Scale. *J Pers Assess*. 1995;64:507-521.
37. Shacham S. A shortened version of the Profile of Mood States. *J Pers Assess*. 1983;47:305-306.
38. Baker F, Denniston M, Zabora J, Polland A, Dudley WN. A POMS short form for cancer patients: psychometric and structural evaluation. *Psychooncology*. 2002;11:273-281.
39. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. *Psychosom Med*. 1979;41:209-218.
40. Kangas M, Henry JL, Bryant RA. Posttraumatic stress disorder following cancer: a conceptual and empirical review. *Clin Psychol Rev*. 2002;22:499-524.
41. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570-579.
42. Lutgendorf SK, DeGeest K, Sung CY, et al. Depression, social support, and beta-adrenergic transcription control in human ovarian cancer. *Brain Behav Immun*. 2009;23:176-183.
43. Hoffman RP, Sinkey CA, Dopp JM, Phillips BG. Systemic and local adrenergic regulation of muscle glucose utilization during hypoglycemia in healthy subjects. *Diabetes*. 2002;51:734-742.
44. Arden-Close E, Gidron Y, Moss-Morris R. Psychological distress and its correlates in ovarian cancer: a systematic review. *Psychooncology*. 2008;17:1061-1072.
45. Green DP, Goldman SL, Salovey P. Measurement error masks bipolarity in affect ratings. *J Pers Soc Psychol*. 1993;64:1029-1041.
46. Yuan K, Bentler PM. Three likelihood-based methods for mean and covariance structure analysis with nonnormal missing data. *Sociol Methodol*. 2000;30:165-200.
47. Bentler PM. Comparative fit indexes in structural models. *Psychol Bull*. 1990;107:238-246.
48. Steiger JH. Structural model evaluation and modification: an interval estimation approach. *Multivariate Behav Res*. 1990;25:173-180.
49. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct Equ Model A Multidiscip J*. 1999;6:1-55.
50. Raftery AE. Bayesian model selection in social research. *Sociol Methodol*. 1995;25:111-163.
51. Waterman AS. Two conceptions of happiness: contrasts of personal expressiveness (eudaimonia) and hedonic enjoyment. *J Pers Soc Psychol*. 1993;64:678-691.
52. Henoch I, Danielson E. Existential concerns among patients with cancer and interventions to meet them: an integrative literature review. *Psychooncology*. 2009;18:225-236.
53. Brown AJ, Sun CC, Urbauer D, et al. Targeting those with decreased meaning and peace: a supportive care opportunity [published online ahead of print December 18, 2014]. *Support Care Cancer*.
54. Thaker PH, Han LY, Kamat AA, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med*. 2006;12:939-944.
55. Lutgendorf SK, DeGeest K, Dahmoush L, et al. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. *Brain Behav Immun*. 2011;25:250-255.
56. Lutgendorf SK, Lamkin DM, DeGeest K, et al. Depressed and anxious mood and T-cell cytokine expressing populations in ovarian cancer patients. *Brain Behav Immun*. 2008;22:890-900.
57. Ryff CD. Psychological well-being revisited: advances in the science and practice of eudaimonia. *Psychother Psychosom*. 2014;83:10-28.
58. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behav Res Ther*. 2006;44:1-25.
59. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. *J Pers Soc Psychol*. 2003;84:822-848.
60. Seligman MEP, Steen T, Park N, Peterson C. Positive psychology progress: empirical validation of interventions. *Am Psychol*. 2005;60:410-421.
61. Moreno-Smith M, Lee SJ, Lu C, et al. Biologic effects of dopamine on tumor vasculature in ovarian carcinoma. *Neoplasia*. 2013;15:502-510.