HHS Public Access

Author manuscript

Psychosom Med. Author manuscript; available in PMC 2022 June 01.

Published in final edited form as:

Psychosom Med. 2021 June 01; 83(5): 417–422. doi:10.1097/PSY.0000000000000935.

POSITIVE PSYCHOSOCIAL FACTORS AND OXYTOCIN IN THE OVARIAN TUMOR MICROENVIRONMENT

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Abstract

OBJECTIVE: Clinical ovarian cancer research shows relationships between psychosocial factors and disease-promoting aspects of the stress response (e.g., norepinephrine, cortisol). However, little is known about how psychosocial factors might relate to beneficial hormones in the ovarian tumor microenvironment. Here we examine relationships between psychosocial factors and tumor-associated oxytocin, a hormone linked to survival and anti-tumor processes in ovarian cancer.

METHODS: Ovarian cancer patients (N=96) completed assessments of positive psychosocial factors (social support, positive affect and purpose in life) and distress (perceived stress and depression) at the time of surgery. Levels of oxytocin and IL-6 in ascites fluid were obtained during surgery and analyzed by ELISA. Multiple regression analyses adjusting *a priori* for patient age and disease stage examined associations between psychosocial factors and ascites oxytocin. IL-6 was used as a covariate in secondary analyses to examine the potentially confounding effects of inflammation in these relationships.

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RESULTS: Higher levels of positive affect (β=.22, *p*=.034), purpose in life (β=.31, *p*=.021), and social nurturance (β=.24, *p*=.024) were all related to higher levels of tumor-associated oxytocin at the time of surgery. In contrast, we found no effects for distress or social attachment. Relationships between oxytocin, purpose in life and social nurturance were independent of IL-6, whereas positive affect was no longer significant with IL-6 in the model.

CONCLUSIONS: Tumor-associated oxytocin may be a previously uninvestigated link in the relationship between psychosocial factors and health in ovarian cancer. Future studies should examine causal mechanisms of relationships observed in this study.

Keywords

Ovarian Cancer; Oxytocin; Positive Affect; Psychological Well-being; Social nurturance; Tumor Microenvironment

Background

Substantial mechanistic and clinical research has demonstrated relationships between psychosocial factors and disease-promoting sequelae of the stress response in ovarian cancer (1). Risk factors such as social isolation and poor psychological well-being have been associated with greater tumor aggressiveness (2) and poorer clinical outcomes (3) along with alterations in neuroendocrine hormones including higher levels of tumor norepinephrine (4) or dysregulated cortisol (5). Effectors of the sympathetic nervous system (e.g., norepinephrine) have been identified in the ovarian tumor microenvironment and have been shown to influence key tumor-promoting cellular processes, including angiogenesis, invasion, apoptosis, and secretion of pro-inflammatory cytokines (1). Although hypothalamic and neurohypopheseal oxytocin have been widely studied in relationship to psychosocial factors, virtually nothing is known about how oxytocin in the periphery, such as tumor-associated oxytocin, is related to psychosocial factors.

Oxytocin is a hormone frequently linked with the health benefits of psychological well-being, due to its association with stress-buffering, social support, and positive affective states (6–8). Central oxytocin is synthesized in the hypothalamus and secreted by the posterior pituitary (9). Oxytocin is also synthesized and released at a number of sites peripherally, including the heart, adrenal medulla, gastrointestinal tract, thymus, and ovary (9). Both centrally-released and externally administered oxytocin have been shown to buffer against psychological and physiological stress (7, 8, 10, 11) and to mediate or enhance the stress-buffering effects of social support (7, 8, 11–14). Oxytocin can exert calming effects on the body including activating the parasympathetic nervous system, increasing vagal tone, and lowering blood pressure (7, 15).

Oxytocin has been shown to have anti-inflammatory and anti-tumor effects in ovarian cancer in multiple studies including anti-proliferative, anti-migratory, and anti-invasive effects (16–19). Healthy ovarian cells secrete oxytocin as a part of normal ovarian function (20, 21). Recent work from our laboratory reported that ovarian tumor cells secreted oxytocin *in vitro,* and also identified oxytocin in malignant effusions (ascites) in the ovarian tumor microenvironment (16). Levels of ascites oxytocin reached concentrations over 200-fold

higher than levels in plasma and were not correlated with plasma oxytocin. These observations suggest that oxytocin in the ovarian tumor microenvironment is most likely a distinct biological compartment from plasma oxytocin, which reflects oxytocin released from the posterior pituitary (16). Additionally, patients with higher levels of ascites oxytocin had a significant survival advantage compared to those with lower levels of ascites oxytocin, adjusting for clinical and demographic variables (16).

In previous research, stress-related psychosocial factors have been shown to influence tumor progression through a variety of pathways, including sympathetic innervation of tumors and beta-adrenergic signaling (1). Given research linking oxytocin to parasympathetic activity and to stress-buffering and positive psychosocial factors, here we examined relationships between tumor-associated (ascites) oxytocin, distress, and psychosocial factors considered to be protective or positive in a cohort of ovarian cancer patients at the time of their primary surgery. We hypothesized that higher levels of oxytocin in ascites would be related to lower levels of distress (perceived stress and depressed mood) and to higher levels of positive factors (social support, positive affect, and purpose in life). Follow-up analyses adjusting for ascites interleukin-6 were performed on observed relationships between oxytocin and psychosocial factors as oxytocin has been shown to have anti-inflammatory effects (13, 16, 22, 23) and as peripheral inflammation has been shown to influence both tumor progression and the central nervous system (24, 25).

Methods

Participants

Women with suspected ovarian cancer were recruited from two large midwestern university medical centers during a pre-surgical clinic visit as part of a larger IRB-approved study on biobehavioral factors and tumor progression. Patients were recruited between December 2003 and August 2013. Eligibility for the study was restricted to patients with primary epithelial ovarian, peritoneal or fallopian tube carcinoma. Histological diagnosis was confirmed by pathology. Exclusion criteria included: age under 18 years, history of previous cancer, comorbid condition with known immune system effects, current pregnancy, and inability to accurately answer questions (dementia). Of 183 patients meeting these conditions, 105 had ascites samples available for oxytocin analysis. Of these 105 patients, 96 completed psychosocial questionnaires. The final sample included 96 patients with epithelial ovarian cancer. A subset of 57 patients completed the Psychological Well-Being Scale (26) which was introduced later in the study.

Procedure

The institutional review boards of the participating institutions approved all procedures. Informed consent was obtained during the patients' pre-surgical visit. Psychosocial surveys were completed between the pre-surgical visit and surgery. Samples of ascites were obtained during surgery and were processed immediately. All samples were centrifuged at 2200 rpm at 20°C for 10 minutes. Ascites was stored at −80°C until analyzed.

Assessments

Psychosocial Measures—The Center for Epidemiological Studies-Depression Scale (CES-D) is a 20 item self-report scale that measures frequency of depressive symptoms over the past seven days (27). The CES-D contains four subscales: depressed mood, vegetative depression, interpersonal relations and positive affect. As cancer symptoms can resemble vegetative depression, we used the depressed mood subscale. Examples of depressed mood items include “I felt depressed” and “I thought my life had been a failure”. The positive affect subscale was also used. Examples of positive affect items include “I was happy” and “I enjoyed life.”

The Perceived Stress Scale (PSS) is a 14 item self-report measure that assesses the degree to which individuals perceive events in their life as stressful or uncontrollable over the past month (28). Examples of items include, and “in the last month, how often have you felt nervous or stressed” and “in the last month, how often have you felt you were effectively coping with important changes that were occurring in your life.”

The Social Provisions Scale (SPS) is a 24-item self-report scale measuring the extent to which social relationships are perceived as supportive (29). The SPS has six subscales: reliable alliance, reassurance of worth, social integration, guidance, attachment and nurturance. The social attachment and nurturance subscales were used in this study. Social attachment, a facet of social support encompassing emotional closeness and connectedness (e.g., “I feel a strong emotional bond with at least one other person,” “I have close relationships that make me feel good”), was selected because attachment is associated with oxytocin in the literature (30, 31) and because social attachment is the facet of social support most linked to biological processes or survival in previous ovarian cancer research (5, 32). Nurturance, a facet of social support involving providing care to others (e.g., “I feel responsible for taking care of someone else,” “There is no one who needs me to take care of them” [reverse scored]), was examined because caring for others has been shown to elicit oxytocin and is hypothesized to be a mechanism of stress-buffering, particularly in women (7, 8). For reasons of parsimony, the two subscales with the strongest theoretical or empirical relationship to oxytocin or aspects of tumor biology were examined.

Purpose in life was assessed using the Psychological Well-Being Scale (33), a 42-item scale which measures six facets of well-being: environmental mastery, self-acceptance, autonomy, personal growth, positive relations, and purpose in life. Purpose in life is defined as the extent to which an individual believes their current and past life has meaning, direction and purpose (e.g., “I have a sense of direction and purpose in life,” “My daily activities often seem trivial and unimportant to me [reverse scored]”). Purpose in life was chosen for this investigation because it has been shown to be related to stress and inflammatory biomarkers (6, 34) and is frequently investigated in the context of disease outcomes and mortality (33).

Biological Assays

Oxytocin immunoreactivity in ascites was analyzed by ELISA (Arbor Assays, Ann Arbor, MI) following extraction of samples using C18 Sep-Pak columns (Waters; Milford, MA) as described (35). The oxytocin immunoassay was performed following manufacturer’s

instructions; the lower limit of detection was approximately 1 pg/well and the intra and inter-assay coefficient of variance (CV) were < 8% and < 12%, respectively.

Interleukin-6 in ascites was analyzed by ELISA (R&D Systems, Minneapolis, MN). The minimum detectable level was less than 3.1 pg/mL and inter-assay CV ranged from 3.3% to 6.4%.

Statistical Analyses

The Statistical Package for the Social Sciences (V.24, Armonk, NY) was used for data analysis. Distributions were examined for violations of normality and potential outliers. Oxytocin and interleukin-6 values were $\log_{10}$ transformed to normalize their distributions. Distress or stress-buffering variables correlated above r=.50 were combined into composite scores to avoid construct overlap/redundant analyses (36). Perceived stress and depressed mood (r= .565) were combined into a composite score hereafter referred to as the "*distress composite*" (N=94). The distress composite had good internal reliability (Cronbach's alpha= .863). The stress-buffering variables of social support, positive affect and purpose in life were not correlated above .500 (highest correlation r= .358) and thus were retained as separate variables in analyses.

All analyses adjusted *a priori* for patient age and disease stage. Potentially confounding factors that may have been associated with oxytocin and were examined and included as covariates if significantly related to ascites oxytocin. Multiple regression models were constructed to examine relationships between oxytocin and psychosocial factors, adjusting for the covariates described above. Follow-up analyses of significant observed relationships were performed adjusting for ascites interleukin-6 to clarify the possible role of inflammation in these associations, as interleukin-6 has been strongly related to ascites oxytocin (16) and psychosocial variables (37) in previous work.

Results

Participant characteristics

Clinical characteristics of patients can be found in Table 1. Eighty-nine patients (92.7%) had advanced stage disease (Stages III and IV) and seven patients (7.3%) had early stage disease (Stages I and II). Mean age was 59.4±11.3 (range: 27– 83) years. Neither cancer stage (p=.73) nor patient age (p=.15) was significantly related to ascites oxytocin in this group; however, these variables were included *a priori* as covariates in analyses as a conservative measure. Ascites oxytocin was not associated with disease comorbidity, BMI, education, smoking, alcohol use, medication use, number of children or menopausal status (p>.16). Means and standard deviations of clinical, biological, and psychosocial variables are seen in Table 1. For reference, typical blood levels of oxytocin in healthy, non-pregnant, non - lactating women are between 1–5pg/mL (38, 39) and typical blood levels of interleukin-6 in healthy adults are approximately 2.6 pg/mL (40). Simple correlations between oxytocin, interleukin-6 and psychosocial variables can be found in Table 2.

Distress, positive psychosocial factors, and oxytocin

The distress composite score was not associated with ascites oxytocin (β=−.14, *p*=.14). In contrast, greater positive affect (β=.22, *p*=.03) and purpose in life (β=.31, *p*=.02) were significantly associated with higher levels of ascites oxytocin, adjusting for patient age and disease stage (Table 3). Greater nurturance/providing care to others was also associated with significantly higher levels of ascites oxytocin (β=.24, *p*=.024; Table 2); however, social attachment was not associated with ascites oxytocin levels (β=.02, *p*=.82).

To adjust for potentially confounding effects of inflammation on observed relationships between psychosocial factors and oxytocin, follow-up analyses adjusting for ascites interleukin-6 were conducted for significant relationships observed above. When interleukin-6 was added into the regression along with covariates, relationships between ascites oxytocin and purpose in life (β=.31, *p*=.02) and social nurturance (β=.21, *p*=.04) remained significant. However, the relationship between oxytocin and positive affect was no longer significant with ascites interleukin-6 in the model (β=.17, *p*=.11), suggesting that inflammatory processes in the tumor microenvironment may have contributed to this relationship.

Discussion

A key finding of this study is that ovarian cancer patients who reported higher levels of positive psychosocial factors (purpose in life, positive affect and social nurturance) had higher levels of tumor-associated oxytocin, a hormone linked to anti-tumor processes and survival in ovarian cancer (16–19). Beta values for relationships between ascites oxytocin and positive affect, social nurturance and purpose in life were all in the medium range (41), suggesting moderate associations between these variables. The findings of this study are consistent with other reports that positive psychosocial factors are associated with favorable biological profiles and reduced mortality in healthy and chronic illness populations (42, 43). Positive psychosocial factors have been related to improved immune response, lower levels of inflammatory markers (e.g., IL-6, CRP), healthier diurnal cortisol rhythms, lower blood pressure, and faster cardiovascular recovery from stress in other studies (44). This study is the first to show a relationship between positive psychosocial factors and tumor-associated oxytocin in a clinical cancer population.

In contrast, psychological distress was not associated with ascites oxytocin. This observation is consistent with previous research showing the beneficial health-related associations of positive psychosocial factors to be independent of distress or negative affect (4, 45). Surprisingly, tumor associated oxytocin was not related to social attachment, but only to social nurturance. Social attachment has been the factor most linked to biological processes in our prior ovarian cancer research (3, 37, 46, 47). However, the relevance of nurturance is consistent with the oxytocin-focused “tend and befriend” hypothesis of female coping and stress response, which highlights the integral nature of caring for and nurturing others in eliciting oxytocin and facilitating physiological and psychological recovery from stress (7). Thus, it is possible that nurturance may be more important in eliciting oxytocin than feeling a sense of connectedness to others.

Several studies implicate oxytocin as a mechanism by which positive psychosocial factors might impact health. In the present study, positive psychosocial factors were found to be associated with higher levels of tumor-associated oxytocin, which have been linked to survival and lower tumor-associated inflammation in previous research (16). Thus, it is possible that oxytocin pathways may link positive emotions and health in ovarian cancer patients. This hypothesis is consistent with studies showing that oxytocin mediates the physiological benefits of social support in animals (13, 14) and enhances the stress-buffering effects of social support in humans (11, 12). The present study suggests the relevance of further research on whether endogenous or exogenous oxytocin can bolster the protective effects of social support or reduce behavioral or physiological stress in ovarian cancer patients.

The putative mechanistic pathways linking positive psychosocial factors and tumor-associated oxytocin remain to be elucidated. Both “top-down” and “bottom-up” pathways may be involved. Stress-related psychosocial factors have been shown to influence ovarian tumors via beta-adrenergic signaling and sympathetic innervation of tumors (1). Recent research suggests that parasympathetic innervation of tumors may have a suppressive effect on tumor progression (48). Central oxytocin has been shown to activate the parasympathetic nervous system, decrease sympathetic activation and subjective stress, facilitate faster recovery from stressors, lower blood pressure, and increase vagal tone (7, 15). It is possible that psychosocial factors that elicit central oxytocin are similarly linked to oxytocin in the tumor microenvironment through reduced sympathetic or increased parasympathetic innervation of tumors. However, this hypothesis remains to be investigated.

Although we did not observe relationships between stress or distress and oxytocin in ovarian cancer patients, it is still possible that psychosocial factors are connected to tumor-associated oxytocin through physiological stress pathways. Engert et al. (15) found that higher plasma oxytocin levels following an experimental stressor were initially associated with HPA axis co-activation (measured by salivary cortisol). However, individuals who had the highest initial plasma oxytocin response to stress also had fastest return from the decreased level to baseline vagal activity, leading the authors to suggest that oxytocin aids in stress recovery rather than a buffering of the initial stress response. If oxytocin aids in stress recovery versus a buffering of the initial stress response, this could explain the correlation between oxytocin and positive psychosocial variables associated with coping in absence of a relationship between oxytocin and distress. It is also possible that connections between positive psychosocial factors and health behaviors (49, 50) could have indirect effects that influence oxytocin in the tumor microenvironment. For example, positive affect has been related to exercise frequency (44) and oxytocin has been found to mediate the anti-tumor effects of exercise in a murine model of breast cancer (51).

In addition to the “top-down” mechanisms that may be driving relationships between psychosocial factors and tumor-associated oxytocin, it also possible that the reverse is true, that higher levels of oxytocin in the ovarian tumor microenvironment are influencing patient experience of positive psychosocial factors. In our previous research, oxytocin reduced interleukin-6 secretion from ovarian tumor cells in vitro, and higher levels of tumor-associated oxytocin were related to lower levels of systemic inflammation in ovarian cancer

patients (16). Although mechanisms were not examined in the present study, it is possible that tumor-associated oxytocin reduces inflammatory signaling in a variety of cells in the tumor microenvironment. This potentially could lead to less availability of inflammatory cytokines for diffusion into peripheral circulation. Systemic inflammation has known effects on the central nervous system, inducing “sickness behaviors” such as fatigue and anhedonia (24). It is therefore possible that the suppressive effects of oxytocin on systemic inflammation may contribute to the observed relationships. We explored this possibility by adjusting for interleukin-6 in follow-up analyses of psychosocial variables and oxytocin. Relationships between oxytocin, purpose in life, and social nurturance were independent of interleukin-6, suggesting that oxytocin is associated with psychosocial factors above and beyond relationships with inflammation. In contrast, the relationship between oxytocin and positive affect was no longer significant with interleukin-6 in the model. It is possible that the physical symptoms associated with inflammation are more likely to influence transient positive emotions, such as positive affect (e.g., “I am happy”), than more stable and or eudaimonic psychosocial factors like purpose in life and social nurturance. The relationship between oxytocin, interleukin-6, and psychosocial factors remains to be explored further using more mechanistic methodology. For example, it would be valuable to examine the impact of peripheral oxytocin on systemic and central inflammatory cytokines and inflammation-associated behavior in pre-clinical cancer models.

The purpose of oxytocin production by neoplastic ovarian cells is unclear. We have previously speculated that it is possible that tumor cells derived from ovarian tissue may continue to express oxytocin as a retained function of the original cells (16). However, the production of oxytocin by tumor cells along with data that oxytocin can inhibit the growth, migration, and proliferation of ovarian tumor cells (17–19) is indeed puzzling and remains to be answered by future research.

Study Limitations and Future Directions.

The correlational design of this study does not allow us to address the critical questions of how and why psychosocial factors are related to tumor-associated oxytocin. Pre-clinical studies are needed to better understand the casual mechanisms underlying relationships observed in this study. For example, animal models utilizing chronic stress or social housing paradigms could examine the potential role of stress or socialization on levels of tumor-associated oxytocin, including potential involvement of sympathetic or parasympathetic activation. Oxytocin receptor knock out models could also be used to examine the importance of oxytocin receptors on mediating the effects of social support or buffering against the effects of stress on disease progression.

Clinical Implications

These findings highlight a link between positive emotions, purpose in life, nurturance, and tumor-associated oxytocin, a biomarker predictive of survival and tumor inflammatory processes in prior research. These findings suggest the potential benefit of clinical interventions utilizing positive psychology strategies such as enhancing meaning, gratitude, and creating opportunities for social nurturance for ovarian cancer patients. Interventions

such as acceptance and commitment therapy, which has been used to enhance a sense of meaning in cancer patients, may be particularly useful for further exploration.

Conclusions

This study shows a novel association between positive psychosocial factors and oxytocin, a hormone associated with survival and anti-tumor effects in ovarian cancer (16–19). Findings from this study suggest tumor-associated oxytocin is a previously uninvestigated link in the complicated relationship between psychosocial factors, health and well-being in ovarian cancer. Understanding the biological pathways linking positive psychosocial factors and tumor-associated oxytocin could contribute to a better understanding of psychosocial influences on disease progression in cancer.

Acknowledgments

Conflicts of Interest and Source of Funding:

This project was supported in part by NIH grants CA193249 and CA140933 (SL), T32GM108540 (SL), CA109298 (AKS), R35 CA209904 (AKS), AG017265 and AG043404 (SC), HL-116387 (PMM), P30CA086862 (PI George Weiner) and the American Cancer Society (AKS). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of interest disclosure statement: Dr. Thaker has done consulting and/or speaking for Stryker, Iovance Biotherapeutics, Abbvie/Stemcentrx, Clovis Oncology, Unleash Immunolytics, Celsion, Merck, and Glaxo Smith Kline and Astra Zeneca, has research funding from Merck and Glaxo Smith Kline, and is a Celsion shareholder; Dr. Sood has done consulting for Merck and Kiyatec, has had research funding from M-Trap, and is a Biopath shareholder; other authors declare no potential conflicts of interest.

Acronyms:

CES-D	Center for Epidemiological Studies-Depression Scale
PSS	Perceived Stress Scale
SPS	Social Provisions Scale
ELISA	enzyme-linked immunosorbent assay
CV	coefficient of variance
HPA	Hypothalamic pituitary adrenal axis

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Table 1.

Participant Characteristics

Characteristic	**Ovarian Cancer Patients (*N*=96)**
Age, Years, Mean (S.D.; range)	59.4±11.3 (27– 83)
Race	***N* (Percent)**
White	92 (95.8%)
Black/African America	3 (3.1%)
Native American	1 (1.0%)
Ethnicity	
Non-Hispanic	91 (94.8%)
Declined to answer	5 (5.2%)
Cancer Stage	
Advanced	89 (92.7%)
Early	7 (7.3%)
Histology	
Serous	81 (84.4%)
Endometrioid	3 (3.1%)
Mucinous	1 (1.0%)
Clear Cell	4 (4.2%)
Other/Mixed	7 (7.3%)
Biological Assays: Mean (SD)[†]	
Ascites Oxytocin (pg/mL)	196.8 (±339.7)
Ascites IL-6 (pg/mL; N=94)	7504.4 (±8447.4)
Psychosocial Distress Measures: Mean (*SD*)	
Depressed Mood (CESD, N=94)	3.8 (±3.5)
Perceived Stress Scale (PSS, N=94)	21.6 (±6.5)
Positive Psychosocial Measures: Mean (*SD*)	
Social Support (SPS)	
Attachment	14.5 (±2.2)
Nurturance	12.6 (±2.9)
Positive Affect (CESD)	7.2 (±2.9)
Purpose in Life (PWBS; N=56)	37.6 (±7.3)

Table 2:

Simple unadjusted correlations between psychosocial variables and log-transformed ascites oxytocin and interleukin-6

Variable		Ascites Oxytocin (log $_{10}$)	Ascites IL-6 (log $_{10}$)
Disease Stage	*r*	−.098	−.004
	N	96	93
Age	*r*	−.036	−.071
	N	96	93
Distress Composite	*r*	−.047	.161
	N	90	88
Positive Affect	*r*	.231 *	−.262 *
	N	96	93
Social Nurturance	*r*	.245 *	.067
	N	96	93
Social Attachment	*r*	.023	.002
	N	96	93
Purpose in Life	*r*	.315 *	−.095
	N	56	55

* p<.05

Table 3:

Regression analyses predicting levels of ascites oxytocin from psychosocial variables in ovarian cancer patients at the time of surgery

Variable	Positive Affect (N=96)			Social Nurturance (N=96)			Purpose in Life (N=56)		
	B	***SE B***	**β**	***B***	***B SE***	**β**	***B***	***B SE***	**β**
Age	−.002	.007	−.031	−.001	.007	−.021	−.005	.009	−.075
Stage	−.198	.291	−.681	−.200	.289	−.071	.048	.369	.017
Psychosocial Predictor	.057	.026	.220*	.059	.026	.235*	.031	.013	.312*
R^2	.059			.065			.105		
F	1.911			2.136			2.039		

*p<.05