

Social Influences on Clinical Outcomes of Patients With Ovarian Cancer

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A B S T R A C T

Purpose

Previous research has demonstrated relationships of social support with disease-related biomarkers in patients with ovarian cancer. However, the clinical relevance of these findings to patient outcomes has not been established. This prospective study examined how social support relates to long-term survival among consecutive patients with ovarian cancer. We focused on two types of social support: social attachment, a type of emotional social support reflecting connections with others, and instrumental social support reflecting the availability of tangible assistance.

Patients and Methods

Patients were prospectively recruited during a presurgical clinic visit and completed surveys before surgery. One hundred sixty-eight patients with histologically confirmed epithelial ovarian cancer were observed from the date of surgery until death or December 2010. Clinical information was obtained from medical records.

Results

In a Cox regression model, adjusting for disease stage, grade, histology, residual disease, and age, greater social attachment was associated with a lower likelihood of death (hazard ratio [HR], 0.87; 95% CI, 0.77 to 0.98; $P = .018$). The median survival time for patients with low social attachment categorized on a median split of 15 was 3.35 years (95% CI, 2.56 to 4.15 years). In contrast, by study completion, 59% of patients with high social attachment were still alive after 4.70 years. No significant association was found between instrumental social support and survival, even after adjustment for covariates.

Conclusion

Social attachment is associated with a survival advantage for patients with ovarian cancer. Clinical implications include the importance of screening for deficits in the social environment and consideration of support activities during adjuvant treatment.

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INTRODUCTION

Epithelial ovarian cancers continue to have a high mortality risk despite advances in treatment regimens, with overall 5-year survival rates of 46% and rates of 28% for patients with metastatic disease.¹ Despite growing recognition of molecular alterations in ovarian cancers, it is becoming clear that other considerations such as biobehavioral factors may also affect patient outcome.² Research on cancer survivorship has highlighted the importance of the social environment in contributing to quality of life as well as morbidity and mortality.^{3,4} Social support, often defined as the degree of perceived satisfaction with social relationships, has been shown to have both direct effects on health outcomes and indirect effects that protect individuals from the neg-

ative influence of stress-related biologic processes.⁵⁻⁸ Several studies⁹⁻¹² have demonstrated the importance of social networks and cancer survival, although not all findings have been consistent.^{13,14} Less is known about quality of perceived social support and cancer survival, particularly in ovarian cancer.

In previous work,¹⁵⁻²⁰ we have found that patients with ovarian cancer with low levels of perceived social support show alterations in several disease-related biomarkers, including markers of inflammation, angiogenesis, invasion, and innate immunity, as well as cellular markers of gene expression. Specifically, patients with ovarian cancer with higher levels of perceived social support demonstrated lower levels of vascular endothelial growth factor,¹⁹ interleukin-6,²⁰ and matrix metalloproteinase-9,¹⁸

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particularly in the tumor microenvironment, and higher levels of natural killer cell activity in both peripheral blood mononuclear cells and in tumor-infiltrating lymphocytes.¹⁵ Conversely, low social support accompanied by a high level of depressive symptoms was characterized by transcriptional changes in the tumor that were suggestive of a proinflammatory fingerprint.¹⁷ Consistent with the hypothesis that beta-adrenergic signaling mediated these effects, intratumor norepinephrine levels were also found to be increased in tissues from patients with low levels of social support.¹⁶

The facet of social support most consistently linked to biologic markers in our previous work has been social attachment, a subtype of emotional support reflecting an individual's experience of emotional connection to others that provides a sense of well-being, intimacy, or security. Although social support has been associated with these intermediate markers of ovarian cancer progression, the clinical relevance of these findings has not yet been established by linking social environmental factors with patient outcomes. To define the clinical significance of previously observed links between social support and disease-related biomarkers, this prospective study examined the relationship of social attachment to long-term survival among consecutive patients with ovarian cancer. We hypothesized that patients reporting higher levels of social attachment at the time of diagnosis would have a survival advantage compared with patients with lower levels of social attachment. Secondary analyses examined the hypothesis that these effects would be independent of other social factors such as instrumental social support (availability of help, information, and advice from other people). Instrumental social support is thought to be valuable because it can increase feelings of control by providing information and practical assistance that may help patients cope more effectively with treatment and other cancer-related life stressors.^{3,21}

PATIENTS AND METHODS

Patients

Women older than age 18 years with a newly diagnosed pelvic or abdominal mass suspected for ovarian cancer were potentially eligible for this research. Participation was confirmed following histologic diagnosis of a primary invasive epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. Patients with previous cancer history, primary cancer of another organ, nonepithelial ovarian malignant tumors, systemic steroid medication in the last 4 months, or comorbidities known to alter the immune response (eg, autoimmune disorders) were excluded. This study was approved by institutional review boards of all participating institutions. The final sample included 168 women with epithelial ovarian cancer recruited between November 2003 and December 2009 from the University of Iowa, the University of Miami, and Mercy Medical Center in Miami, FL (Fig 1).

Procedure

Patients were prospectively recruited during a presurgical clinic visit, and they completed questionnaires between the initial visit and surgery. Patients were observed from the time of surgery until death or December 2010. All surgeries were completed at least 1 year before the censor date. Patients were surgically staged according to the International Federation of Gynecologists and Obstetricians (FIGO) guidelines (stages I to IV). Tumor grade was assessed by pathology (low v high grade). Cytoreduction resulting in residual tumor less than 1 cm was considered optimal, and residual disease \geq 1 cm was considered suboptimal. Following surgery, the majority of patients began adjuvant treatment with platinum and taxane combination chemotherapy and received six or more cycles of therapy. Psychosocial assessments were completed before surgery, at 6 months, and at 1 year.

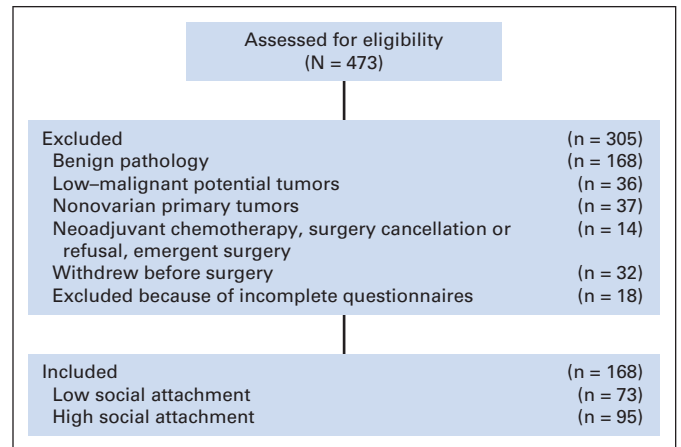


Fig 1. CONSORT diagram showing patient recruitment.

Psychosocial Assessments

Social support/isolation. The Social Provisions Scale (SPS) is a 24-item self-report scale measuring the extent to which social relationships are perceived as supportive.²² Items are rated on a 4-point response from “strongly agree” to “strongly disagree.” Six subscales represent facets of social support conceptualized as representative of distress-buffering features of social relationships. The two subscales included in this research were attachment, which assesses emotional closeness, and reliable alliance, which describes perception of relationships as being able to provide concrete assistance. Attachment was measured by items such as “I feel a strong emotional bond with at least one person” and “I have close relationships which give me a sense of emotional security and well-being.” The reliable alliance subscale was used as a measure of instrumental social support with items including “There are people I can count on in an emergency” and “If something went wrong, no one would come to my assistance” (reverse scored). The SPS has demonstrated adequate reliability and validity in several populations.²²⁻²⁴ Primary analyses examined social support factors as continuous variables since there are no externally validated cut points for these variables and because social support as a continuous variable has been associated with biologic variables in our previous work.^{15,16,18,19} For purposes of illustration and for defining cutoff points with potential clinical relevance, categorical analyses used a median split to define groups as high versus low in attachment. This dichotomy has been associated with biologic differences (eg, gene expression fingerprint associated with metastatic and proinflammatory transcriptional activity in primary ovarian cancers, and levels of the proinflammatory and proangiogenic cytokine interleukin-6 in previous work).^{17,20}

Depression. The Structured Clinical Interview for DSM-IV [Diagnostic and Statistical Manual of Mental Disorders, 4th Edition] Disorders (SCID-I)²⁵ is a semistructured diagnostic interview used to assess patients for DSM-IV Axis I diagnostic disorders. Screening questions and the SCID interview were used to assess presence/absence of major depressive disorder (MDD) at the time of diagnostic surgery as well as history of previous MDD.²⁶ Depression was examined as a covariate to determine whether social support effects could be accounted for by depression.

Demographic and Clinical Information

Demographic information was provided by self-report. Marital status was categorized as single; divorced, widowed, separated; or married/living with partner. Smoking was categorized as never versus ever smoker. Alcohol use was assessed as drinks per week. Clinical and histopathologic information was obtained from medical records. For analyses, stage was dichotomized into early (I to II) versus advanced (III to IV) stage. Date and cause of death were ascertained from patient medical records. Information for seven patients was ascertained through state death records. Survival time was calculated as the number of days between date of tumor resection and date of death or censoring.

Statistical Methods

Distributions were examined for outliers and non-normality. Examination of whether potential covariates differed between social attachment groups was performed by using independent sample *t* tests, Pearson χ^2 tests, and Mantel-Haenszel χ^2 tests. The univariate association of survival time with each potential clinical covariate and with social attachment as a continuous variable was examined by using Cox proportional hazards regression analysis.²⁷ From the fitted Cox models, the unadjusted hazard ratio with 95% CIs was obtained, and significance of the association was tested by using the Wald χ^2 statistic. The covariates that were tested included stage (advanced *v* early), grade (high *v* low), residual disease (suboptimal *v* optimal cytoreduction), body mass index (< 20, 20- < 25, 25- < 30, 30- < 40, \geq 40); smoking (never smoker *v* ever smoker), education, histology (serous *v* nonserous), current and past MDD, and age. The covariates found to have a significant association ($P < .05$) with survival time (age, stage, grade, residual disease, and serous histology) were all included, along with social attachment, as independent variables in a multifactor Cox proportional hazards model to examine the effect of social attachment on time to death after adjusting for these covariates. Standard diagnostics were used to evaluate model adequacy.²⁸ Similar models were examined for instrumental social support. To illustrate the effect of social attachment on survival time by a Kaplan-Meier curve, social attachment was dichotomized at the median of 15.²⁹ Instrumental support and social attachment were entered together in a Cox model to examine the independent contribution of social attachment to survival rate. Ancillary analyses tested whether the effects of social attachment were independent of current depression and history of depression. Social attachment as a time-dependent covariate was used to test the ancillary hypotheses that postsurgery social support levels would be related to survival. Analyses were performed by using SPSS, version 19.0 (SPSS, Chicago, IL) and SAS, version 9.2 (SAS Institute, Cary, NC). The level of significance for all analyses was $P < .05$.

RESULTS

Participant Characteristics

Among the 168 patients enrolled onto this study, the median follow-up time was 2.72 years (range, 1 day to 6.88 years). At the time of diagnosis, 71% of patients had advanced-stage disease, and 86% had high-grade tumor (Table 1). Cause of death for the 63 patients who had died was persistent or recurrent ovarian cancer or complications associated with cancer disease and treatment (eg, bowel obstruction, sepsis, pulmonary emboli). One hundred three patients (61.3%) were still alive at the end of the observation period and were censored on December 15, 2010, for survival analyses. Patients who were low versus high in social attachment did not significantly differ with respect to marital status ($P = .12$), participation in support groups ($P > .54$ at any time-point), or on demographic characteristics (all $P > .27$; Appendix Table A1, online only).

Univariate Cox regression analyses indicated that advanced-stage disease ($P < .001$), high grade ($P = .003$), residual disease ($P = .001$), and age ($P < .001$) were significantly associated with shorter survival time (Table 2). Serous histology was marginally associated with shorter survival time ($P = .056$). Smoking history ($P = .85$), alcohol ($P = .33$), body mass index ($P = .70$), education ($P = .25$), current depression ($P = .42$), and past depression ($P = .97$) were not significantly associated with survival time. Higher levels of social attachment as a continuous variable were significantly associated with longer survival time ($P = .002$).

For purposes of illustration, Kaplan-Meier estimates based on a median split of social attachment showed that at the date of longest follow-up of 6.88 years, 59.1% (95% CI, 58.9% to 59.23%) of patients with high social attachment were still alive. In contrast,

Table 1. Participant Characteristics

Characteristic	No. of Patients	%	Mean	SD
Race				
American Indian/Alaska Native	2	1.19		
Asian	1	0.60		
Black	4	2.38		
Pacific Islander	0	0.00		
White	161	95.83		
Ethnicity				
Non-Hispanic	157	93.45		
Hispanic	11	6.55		
Education				
High school or less	65	39.16		
Some college or trade school	57	34.34		
College degree	30	18.07		
Advanced degree	14	8.43		
Relationship status				
Separated/divorced/widowed	40	23.81		
Single	17	10.11		
Married/living with partner	111	66.07		
Stage				
I	36	21.69		
II	12	7.23		
III	102	61.45		
IV	16	9.64		
Grade				
Low	24	14.37		
High	143	85.63		
Histology				
Nonserous	42	25.15		
Serous	125	74.85		
Residual disease				
Optimal (< 1 cm)	44	73.81		
Suboptimal (\geq 1 cm)	124	26.19		
Smoker				
Never	111	66.07		
Ever	57	33.93		
BMI category at diagnosis				
Underweight	9	5.36		
Normal	35	20.83		
Overweight	65	38.69		
Obese	52	30.95		
Morbidly obese	7	4.17		
Social attachment				
Median		15.00		
Interquartile range		13-16		
Instrumental social support				
Median		16.00		
Interquartile range		14-16		
No. of chemotherapy cycles	168		5.45	2.57
Age, years	168		59.4	12.7

Abbreviations: BMI, body mass index; SD, standard deviation.

only 37.8% (95% CI, 37.66% to 37.94%) of patients with low social attachment were still alive (Fig 2). The median survival time for patients with low social attachment was 3.35 years (95% CI, 2.55 to 4.15 years). Because more than 50% of patients in the high social attachment group were still alive at the end of the study, with the last recorded death at 4.7 years, median survival time could not be calculated for this group.

Table 2. Unadjusted Cox Proportional HRs for Overall Survival in Patients With Ovarian Cancer (N = 168)

Variable	HR	95% CI	P
Stage (advanced v early)	11.66	3.64 to 37.35	< .001
Grade (high relative to low)	8.37	2.04 to 34.30	.003
Histology (serous v nonserous)	1.99	0.98 to 4.03	.056
Residual disease (suboptimal v optimal)	2.42	1.47 to 3.97	.001
Education			
Overall (referent: college/advanced degree)			.25
High school or less	1.40	0.75 to 2.61	.29
Some college or technical school	0.87	0.44 to 1.72	.69
BMI at cancer diagnosis			
Overall (referent: normal 20-< 25)			.70
< 20 (underweight)	0.98	0.32 to 3.02	.98
25-< 30 (overweight)	1.06	0.54 to 2.06	.86
30-< 40 (obese)	1.27	0.59 to 2.39	.63
≥ 40 (morbidly obese)	0.21	0.04 to 2.05	.27
Smoker (ever v never)	1.05	0.62 to 1.77	.85
Current depression (present v absent)	1.21	0.49 to 3.02	.68
Previous depression (present v absent)	0.91	0.48 to 1.75	.79
Age (per 5 years)	1.20	1.07 to 1.35	< .001
Alcohol use (per one drink)	1.30	0.76 to 2.20	.34
Social attachment (per one unit)	0.84	0.75 to 0.93	.002
Instrumental social support (per one unit)	0.93	0.82 to 1.05	.22

Abbreviations: BMI, body mass index; HR, hazard ratio.

In the Cox multivariate model, adjusting for disease stage, grade, histology, volume of residual disease, and age, greater social attachment was associated with a lower likelihood of death (adjusted hazard ratio [HR], 0.87; 95% CI, 0.77 to 0.98; $P = .018$; Table 3). Thus, for example, the adjusted HR of death for a patient whose score was at the 75th percentile of social attachment (score = 16) relative to a patient whose social support was at the 25th percentile (score = 13) was 0.66 (95% CI, 0.46 to 0.93) or a 34% lower hazard of death. To address the question of whether current or past MDD would affect the social

Table 3. Cox Proportional Hazards Model for Overall Survival in Patients With Ovarian Cancer With Social Attachment Adjusted for Covariates

Variable	HR	95% CI	P
Age at cancer diagnosis	1.04	1.01 to 1.06	.002
High grade v low grade	2.06	0.44 to 9.65	.360
Advanced stage v early stage	7.02	1.92 to 25.58	.003
Serous histology v nonserous	0.70	0.33 to 1.50	.840
Suboptimal residual disease v optimal	1.76	1.04 to 2.97	.035
Social attachment at cancer diagnosis*	0.87	0.77 to 0.98	.018

*Social attachment score is used as a continuous variable; thus hazard ratio (HR) is expressed per one unit increase in social attachment score. In multivariate analyses, $n = 166$ because of two patients who could not be staged.

attachment results, multivariate models were examined that included either current or past MDD in the model along with the other covariates. Neither past ($P = .998$) nor current ($P = .43$) MDD significantly predicted survival in the multivariate models, whereas social attachment remained significantly associated with survival in both models (past MDD model: $P = .023$; current MDD model: $P = .037$).

Instrumental Social Support and Survival

Secondary analyses assessed whether attachment-related differences in survival might be attributable to differences in instrumental social support (Table 4). Instrumental social support, however, was not significantly associated with survival time by itself ($P = .22$) or with adjustment for covariates ($P = .31$; Tables 2 and 3). When both instrumental social support and social attachment were included in a Cox model, along with clinical covariates, social attachment remained significantly related to survival (adjusted HR, 0.85; 95% CI, 0.74 to 0.98; $P = .025$) but instrumental social support was not significant (adjusted HR, 1.03; 95% CI, 0.87 to 1.22; $P = .73$).

Social Support Over Time and Survival

To address the question of whether ongoing social support was related to study outcomes, we examined the continuous score of social attachment at the time of surgery, at 6 months, and at 1 year as a time-varying covariate. In this analysis, adjusting for the same covariates as in Table 3, social attachment remained a significant predictor of survival ($P = .049$).

DISCUSSION

The key finding of this prospective study was that social attachment is associated with a survival advantage for patients with ovarian cancer.

Table 4. Cox Proportional Hazards Model for Overall Survival in Patients With Ovarian Cancer With Instrumental Social Attachment Adjusted for Covariates

Variable	HR	95% CI	P
Age at cancer diagnosis	1.04	1.02 to 1.07	.001
High grade v low grade	1.31	0.34 to 5.01	.760
Advanced stage v early stage	8.88	2.08 to 37.88	.003
Serous histology v nonserous	0.67	0.32 to 1.41	.290
Suboptimal residual disease v optimal	1.68	0.99 to 2.84	.053
Instrumental social support at cancer diagnosis*	0.94	0.83 to 1.06	.310

*Instrumental social support score is used as a continuous variable; thus, hazard ratio (HR) is expressed per one unit increase in instrumental social support score. In multivariate analyses, $n = 166$ because of two patients who could not be staged.

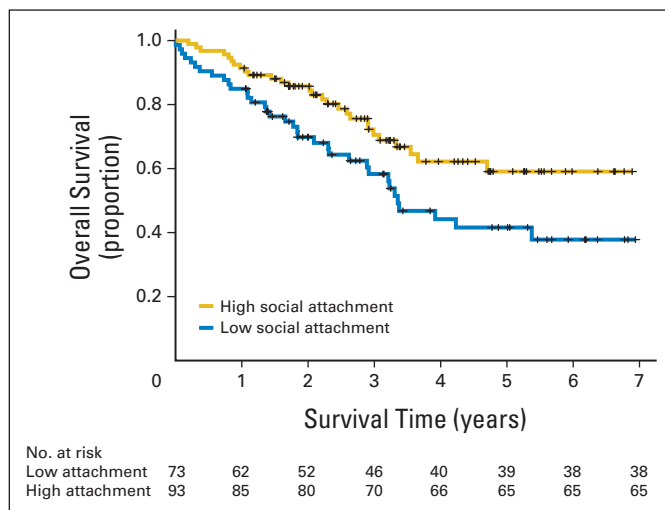


Fig 2. Survival time for patients with high social attachment (Social Provisions Scale attachment subscale ≥ 15) versus patients with low social attachment (score < 15). Cox regression adjusted for covariates indicates that patients with higher social attachment had longer survival times ($P = .018$). Numbers of at-risk (still alive) patients in the low versus high attachment groups are indicated below the x-axis.

This effect was significant when adjusted for disease-related covariates and predominately involved the subjective experience of supportive relationships as opposed to specific functional or instrumental social support. Furthermore, analyses examining changes in social attachment over the first year after diagnosis indicated that social attachment over time was related to survival as well. Instrumental social support was not significantly associated with survival time, either in univariate or multivariate analyses. These findings are the first to link a facet of the social environment with survival in a homogeneous ovarian cancer population and establish the clinical relevance of our previous reports linking social environmental factors with intermediate biomarkers in ovarian cancer.

These results extend findings from previous reports linking the presence of close emotional bonds with survival among women with breast cancer.³⁰⁻³⁵ In addition, these data are consistent with the minimal association of instrumental social support with survival that has previously been reported in other cancer populations,³ with a notable exception in acute myeloid leukemia.³⁶ Several potential mechanisms may underlie these findings. The sympathetic nervous system, one of the major stress response systems, has been shown to promote ovarian cancer growth in preclinical models via beta adrenergic stimulation of angiogenesis, invasion, anoikis, and other metastatic processes.³⁷⁻⁴⁰ Similar processes have been observed in mammary cancer in vivo as well as in other tumor types in vitro.⁴¹⁻⁴⁴ Moreover, social isolation has been linked to inflammatory leukocyte gene expression profiles and related upstream transcription control pathways in other populations.⁴⁵⁻⁴⁷ Glucocorticoids, secreted as the end product of the hypothalamic pituitary adrenal axis, a second stress response system, directly mediate processes promoting tumor growth as well,⁴⁸⁻⁵¹ and may also serve to inhibit chemotherapy-induced apoptosis.⁵²⁻⁵⁴ Other neurohormones such as dopamine, epinephrine, prolactin, and so on are released as part of the stress response and may be implicated in these processes, although their effects have been less well characterized.⁵⁵⁻⁵⁷ Social support is thought to be most critical during times of stress, such as receipt of a cancer diagnosis.³ The social bond relationship in women has been described as a stress regulatory system in which attachment and caregiving behaviors down-regulate the sympathetic nervous system and the hypothalamic pituitary adrenal axis.⁵⁸ The proposed role of social support as a stress buffer^{3,5} would serve to blunt the stimulation of the major stress response systems, thus undercutting processes that would potentially mediate tumor growth. Consistent with the notion of stress buffering, we have found that patients with ovarian cancer with high levels of social attachment have lower levels of norepinephrine in both tumor and ascites at the time of surgery.¹⁶ In addition, social attachment behaviors have been shown to activate oxytocin,⁵⁸ a known inhibitor of tumor growth⁵⁹ in preclinical models.

Inclusion of depression in analyses did not change the relationship of social support and survival, suggesting that the relationship between social support and survival is not accounted for because of its association with either current or past history of depression.

The sources of social attachment and its survival benefits remain a significant topic for future research. We found no significant difference in marital relationship distributions across social attachment groups, suggesting that other objective social factors may play a more dominant role in shaping social attachment experiences. This likely stems from the highly subjective nature of social attachment, which is less strongly related to objective relationship status (eg, marital status) than are other parameters of social support, and which can also be substantially affected by nonmarital relationships (eg, friends, relatives, community relationships, and so on).⁵⁸ Assessment of other nonmarital sources of social support is thus a significant topic for future research in ovarian cancer clinical outcomes.

This study is limited by the fact that we have no information regarding who the primary confidant of the patient is or whether the patient's needs for social support are adequately met. Although these findings are correlational, experimental studies of social isolation in a preclinical ovarian cancer model found faster tumor progression,³⁷ suggesting a potential causal basis for these findings. Additional mechanistic work would be informative to shed light on social influences on tumor biology and disease progression.

Patients generally reported high levels of social attachment. Thus, if they indicated a lack of social support on any item, they would have fallen into the low social support group category. Clinically, this might suggest that if patients indicate moderate concern about an area of emotional social support, they might be considered to be at risk.

In conclusion, this study demonstrates that social attachment appears to confer a survival advantage to patients with ovarian cancer. Clinical implications of this finding include the importance of screening for deficits in the social environment in patients with ovarian cancer and consideration of support activities during adjuvant cancer care and beyond.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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