Title: Helplessness/hopelessness, minimization, and optimism predict survival in women with invasive ovarian cancer: A role for targeted support during initial treatment decision-making?

Short title: Psychosocial predictors of survival in invasive ovarian cancer

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ABSTRACT

Objectives: Women with advanced ovarian cancer generally have a poor prognosis but there is significant variability in survival despite similar disease characteristics and treatment regimens. The aim of this study was to determine whether psychosocial factors predict survival in women with ovarian cancer, controlling for potential confounders.

Methods: The sample comprised 798 women with invasive ovarian cancer recruited into the Australian Ovarian Cancer Study and a subsequent Quality of Life study. Validated measures of depression, optimism, minimization, helplessness/hopelessness and social support were completed 3-6 monthly for up to two years. 419 women (52.5%) died over the follow-up period. Associations between time-varying psychosocial variables and survival were tested using adjusted Cox proportional hazard models.

Results: There was a significant interaction of psychosocial variables measured prior to first progression and overall survival, with higher optimism (adjusted Hazard Ratio per 1 standard deviation (HR) = 0.80, 95% Confidence Interval (CI): 0.65-0.97), higher minimization (HR=0.79, CI: 0.66-0.94) and lower helplessness/hopelessness (HR=1.40, CI: 1.15-1.71) associated with longer survival. After disease progression these variables were not associated with survival, (optimism HR=1.10, CI: 0.95-1.27; minimization HR=1.12, CI: 0.95-1.31; and helplessness/hopelessness HR=0.86, CI: 0.74-1.00). Depression and social support were not associated with survival.

Conclusions: In women with invasive ovarian cancer, psychosocial variables prior to disease progression appear to impact on overall survival, suggesting a preventive rather than modifying role. Addressing psychosocial responses to cancer and their potential impact on treatment decision-making early in the disease trajectory may benefit survival and quality of life.

Background

Epithelial ovarian cancer is the second most commonly diagnosed gynaecological cancer and the leading cause of death from gynaecological malignancies in western countries [1-2]. Despite improvements in surgery, chemotherapy and targeted therapy, women with invasive ovarian cancer face a poor prognosis, with a median time of 16 months from diagnosis to first progression, and a greater than 50% chance of dying within five years [2]. However, there is wide variability in survival between women with similar disease characteristics and treatment regimens that is not well explained by established prognostic factors such as patient age, BRCA mutation status and optimal surgery. One factor that may contribute to this variability is the impact of individual psychosocial response to a diagnosis of cancer and treatment.

It is well documented that psychosocial factors have a significant impact on subsequent psychological wellbeing and quality of life [3-4]. Less clear is whether psychosocial factors impact on cancer survival. The mechanisms by which such factors may influence cancer survival potentially include a direct effect on immune and/or neuro-endocrine systems [5], or an indirect effect via changes in behavior, such as diet, exercise and adherence to treatment [6]. It is also possible that people with positive emotions and coping styles obtain more information regarding their disease and treatment, which in turn, may enhance their self-care or may lead to better treatment decisions or seeking treatment at centers of excellence [7-8].

Antoni et. al. have propose an integrative bio-behavioral stress-response model, noting that chronic stress, negative affect and social adversity have been associated with increased sympathetic nervous system signaling, hypothalamic pituitary adrenal axis dysregulation, inflammation and decreased cellular immunity, which could interact with the tumor micro-environment to promote factors favoring tumor growth [5,9-10]. It is also possible that some psychosocial factors may impact on survival differently, depending on the disease site and stage, as we previously reported among patients with early and metastatic breast cancer and melanoma [11-14].

While there is some evidence to support a relationship between negative emotional responses, unfavorable coping styles, optimism, depression and social support with cancer recurrence and survival [7,15-21], results are inconsistent. Interpreting many of these studies is difficult as they fail to effectively control for prognostic factors and do not adequately consider potential interactions between psychosocial and disease or treatment variables over time.

Similarly, while psychosocial interventions have demonstrated marked benefits for patient psychological wellbeing and quality of life, the probability of finding survival benefits from such interventions diminishes as methodological rigor increases, particularly in patients with advanced cancer [22-23] Nevertheless, the possibility of a psychosocial impact on outcome remains an intriguing one.

Of direct relevance to ovarian cancer, Lutgendorf et. al. found that perceived social support was correlated with disease related biomarkers, including NK cell activity [26] and interleukin-6 [27] in women with ovarian cancer. This group have directly linked social support and survival in ovarian cancer, specifying a particular aspect of social support, lower social attachment pre-surgery, predicting shorter survival in 168 women controlling for disease characteristics [21]. Depression and practical social support were not related to survival, while other coping factors were not considered.

Therefore the aim of this large population-based study of women with invasive ovarian cancer was to determine if psychosocial factors, in particular depression, optimism, minimization, helplessness/hopelessness and social support, were predictors of survival. We hypothesised that:

1) higher optimism, lower depression, a positive coping style (higher minimization and lower helplessness-hopelessness) and higher perceived social support over time would predict longer survival, controlling for demographic, disease and treatment variables; and

2) psychosocial predictors of survival would vary over time and with progression status.

METHODS

The sample comprised women who participated in the Quality of Life (QoL) sub-study of the Australian Ovarian Cancer Study (AOCS), a prospective population-based study that recruited women aged 18-79 years newly diagnosed with primary epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) between 2002 and 2006. Women were recruited through major treatment centres and the state-based cancer-registries. AOCS collected detailed epidemiological, pathology and initial treatment data, as well as ongoing treatment and clinical outcome data [28]. The AOCS Quality of Life (AOCS-QoL) study was

established to investigate the role of psychosocial factors in predicting outcomes, recruiting AOCS participants with invasive cancer who were alive in May 2005 or recruited into AOCS after this date [29-30]. AOCS clinical follow-up extended beyond the completion of the AOCS-QoL study, and for the cohort described in this analysis, survival was censored at 31 October 2011.

Initial contact was made by AOCS to preserve confidentiality. Consenting women were mailed an information statement, consent form, questionnaire booklet and a reply-paid envelope. Psychosocial variables were measured by validated questionnaires at three-monthly intervals for those diagnosed with stage III/IV disease and over the first year for those diagnosed with stage I/II; or six-monthly intervals for those diagnosed with stage I/II and more than 12 months post-diagnosis; for up to two years, beginning between 3-55 months post-diagnosis (median 17 months). The frequency of data collection for patients with stage I/II disease was reduced, as little was expected to change in the intervening period, as a means of promoting study retention [29-30]. If more than one item on any questionnaire was missing, the participant was contacted to complete the items; missing psychosocial data are therefore minimal. The study was approved and conducted in accordance with the Human Research Ethics Committees of The University of Sydney, QIMR Berghofer Medical Research Institute and all participating sites across Australia.

Measures

Primary outcome: Survival time was calculated as the number of days between recruitment into the QoL study (baseline assessment) and death from any cause, or censoring (31 October 2011). Survival was calculated from time of entry into the QoL study due to the variability in time between diagnosis and study entry; and time between diagnosis and QoL study entry was treated as a covariate.

Descriptive and predictor variables

Socio-demographics: Age, education and marital status were accessed via AOCS.

Disease and treatment: Time between diagnosis and the QoL study baseline assessment, stage of disease at diagnosis (I–IV, International Federation of Gynecology and Obstetrics (FIGO classification, re-categorised as late stage (II-IV) versus stage I), histological grade (1 versus >1), date of first disease progression (according to Gynecological Cancer Intergroup

(GCIG) criteria based on CA125, imaging, clinical criteria, or death).(31) Dates of diagnosis were accessed through AOCS. Dates of death were accessed through AOCS and data linkage with the Australian Institute of Health and Welfares' National Death Index (NDI). Current treatment information (chemotherapy or radiotherapy) was collected within each questionnaire assessment, or from AOCS if missing.

Psychosocial variables:

i) Depression was assessed using the 7-item subscale of the Hospital Anxiety and Depression Scale (HADS) [32]. Possible scores range between 0-21, with higher scores reflecting greater depression.

ii) Helplessness/Hopelessness (HH) was measured using the 6-item subscale of the Mental Adjustment to Cancer (MAC) scale [33]. Possible scores range between 6-24, with higher scores reflecting greater helplessness/hopelessness.

iii) Minimization was measured using a sub-scale of the Osborne et al (1999) rescaled Australian version [34] of the original Mental Adjustment to Cancer (MAC) scale [33], specifically the 5-item Fighting Spirit–Minimizing the Illness sub-scale (hereafter referred to as minimization). Possible scores range between 5-20 with higher scores reflecting greater minimization.

iv) Optimism was assessed using the Life Orientation Test–Revised [35] a widely used 6-item measure of dispositional optimism. Possible scores range between 0-24, with higher scores indicating higher optimism.

v) Social Support was assessed using the 8-item Duke UNC Functional Social Support Questionnaire, measuring satisfaction with the functional and affective aspects of social support [36]. Possible scores range between 8-40, with higher scores indicating better social support.

Statistical Methods

The associations of depression, optimism, coping (minimization, helplessness/hopelessness) and social support with survival were tested using Cox proportional hazard models. Time-varying models, using data collected at all time points during the two year QoL study assessment period, were utilised in order to assess the on-going effects of psychosocial

variables. For example, treating depression as time-varying enables any changes in depression over time (which may improve or worsen) to be considered in assessing the impact of depression on survival.

To investigate whether the effects of psychosocial variables were modified by disease progression, interactions were included. Three approaches were used: 1) unadjusted time-varying models including only the psychosocial variable, first disease progression status (occurred or not at each time point), and their interaction; 2) adjusted time-varying models including each of the individual psychosocial variables, first disease progression status and their interaction, while adjusting for age at diagnosis, stage of disease at diagnosis (FIGO II-IV versus I), grade at diagnosis (grade 1 versus others), time since diagnosis, and current treatment (chemotherapy/radiotherapy versus none), with all variables (except for age, stage and grade) treated as time-varying covariates; and 3) adjusted baseline models where each of the baseline variables, except for first disease progression status and current treatment, were used to predict later outcomes. If the interaction was not significant at the 0.01 level the interaction was excluded. The models were pre-specified and the choice of covariates was based on background knowledge. The proportional hazards assumption was checked using standard methods.

To illustrate the effect of the psychosocial variables and the interaction with disease progression on survival, helplessness/hopelessness was categorised (median split of 9) for creation of a Kaplan-Meier plot. The difference between strata was tested using a log-rank test, with a Sidak adjustment for multiple comparisons.

Results

Among the 798 participants (response rate 66%), 628 (79%) had advanced disease (FIGO II-IV) at diagnosis. Participants were recruited and completed the baseline AOCS-QoL study assessment at a median of 17 months post diagnosis (inter-quartile range 10-27). The majority were married (73%) and aged between 40-60 years (65%) at AOCS-QoL study entry. Over half (51%) had post-school education and two thirds lived in metropolitan centres. One hundred and eighty seven women (23%) had their first disease progression before AOCS-QoL study entry; 168 women (21%) had their first disease progression within the AOCS-QoL study period; and 96 women (12%) progressed after the AOCS-QoL study

period but prior to censoring. There were 419 deaths between entry into the AOCS-QoL study and censoring (31/10/2011), including 14 (3%) among women with early stage (FIGO I) disease at diagnosis. Further demographic and disease variables are shown in Table 1.

Psychosocial scores over time are shown in Table 2. Over the eight assessment periods, average scores remained stable, with overall a low level of psychological morbidity, high social support and moderate optimism. Correlations between some of the psychosocial variables were moderate to high (for example, -0.53 between optimism and helplessness/hopelessness and -0.23 between helplessness/hopelessness and minimization), however as we were specifically interested in exploring the impact of these separate variables, they were all retained in the models.

Unadjusted and adjusted time varying models of predictors of survival are shown in Table 3. Neither depression (adjusted HR per 1 standard deviation (HR)=1.00; 95% Confidence Interval (CI) 0.89-1.12), social support (HR=1.01; CI 0.90-1.14), nor their interactions with first disease progression status, were associated with survival. However, there was a significant interaction between optimism and progression status, with *higher optimism* prior to progression associated with longer survival (HR=0.80; CI 0.65- 0.97), whereas after progression, optimism was not associated with survival (HR=1.10; CI 0.95-1.27). There was also a significant interaction between minimization and progression status, with *higher minimization* prior to progression associated with longer survival (HR=0.79; CI 0.66- 0.94), whereas after progression, minimization was not associated with survival (HR=1.12; CI 0.95-1.31). Similarly, there was a significant interaction between helplessness/hopelessness and progression status, with *higher helplessness/hopelessness* prior to progression associated with shorter survival (HR=1.40; CI: 1.15-1.71), whereas helplessness/hopelessness after progression was not associated with survival (HR= .86; CI 0.74-1.00). Figure 1 displays the unadjusted Kaplan-Meier survival curves for helplessness/hopelessness and disease progression status.

In sensitivity analyses, with only baseline psychosocial measures included in the model, the importance of considering changes in psychosocial variables over time was clearly demonstrated. While the association between baseline helplessness/hopelessness before disease progression and shorter survival was maintained (HR=1.37; CI: 1.32-1.66), neither baseline optimism nor baseline minimization (or their interactions with disease progression status) were associated with survival (see Table 3).

Conclusions

This large prospective, population-based study is the first to comprehensively examine the relationship between psychosocial factors and survival among women with invasive ovarian cancer. Our results clearly indicate that prior to the progression of ovarian cancer, coping strategies of helplessness/hopelessness, minimization and optimism independently predicted survival. These results reinforce the conclusions of earlier meta-analyses that reported a significant role for these psychological factors in predicting cancer survival [15,18,37] and our own previous study [11-14]. This suggests that these coping responses are possible targets for intervention that may have the potential to improve both psychological and medical outcomes in these women.

Notably, only prior to disease progression were coping strategies predictive of survival, suggesting that these factors have a preventive, rather than modifying role. Once ovarian cancer has progressed, it appears that the disease burden may overwhelm any contribution made by psychosocial factors. The most likely mechanisms underlying the observed relationship between these psychosocial factors and survival are an important influence on treatment decision-making, possibly affecting adherence to optimal rigorous treatment regimens, and/or coping with difficult treatment side-effects and optimal self-care, over significant periods of time. These hypotheses are worthy of further investigation.

In contrast to previous studies, and our hypotheses, we found no evidence for depression or social support being associated with survival. This may simply be explained by some bias in our sample, who reported surprisingly low rates of clinical depression on average over time, moderate levels of use of psychological and other supportive care services, and generally high levels of social support [30]. However, given the methodological rigor of our research design, the alternative explanation, that depression and social support may not be significant predictors of survival in ovarian cancer, appears more likely.

As shown in Table 2, our own data indicate that *on average,* psychosocial measures remained fairly stable over time. However, it is important to note that the number of participants at each time-point declined steadily as women died or were too unwell to continue with study questionnaires; for women closer to death, psychosocial variables are likely to be different, and these current data cannot inform our understanding of their experience. There was a spread of coping styles across the women, with about one third reporting low helplessness/

hopelessness and high minimization (arguably the optimal approach) and one third reporting high helplessness/ hopelessness and low minimization (arguably the least helpful approach), and the remainder utilising a combination of more and less helpful approaches. Thus there appears ample opportunity for intervention to optimise coping approaches.

A strength of our study was the inclusion of repeated assessments and the inclusion of time-varying variables in the analyses, since the assumption that people's mood and coping style remain constant over the cancer trajectory is unsupported by the literature [38-39] Thus, use of baseline or cross-sectional assessment of psychosocial variables only, can represent a flaw in the study design. Our analyses using baseline variables only produced quite different findings to those including time varying variables, with optimism and minimization no longer significant in these models, reinforcing the importance of considering variables over time. Given the many factors that contribute to survival in these women and changes in these contributing factors over-time, that helplessness/hopelessness prior to disease progression remained significant in the baseline only model confirms this is a powerful predictor.

We note some limitations, such as the modest (66%) response rate, and with respondents being somewhat more educated and with earlier stage disease, it is possible that these data do not fully reflect outcomes for those less educated and with late stage disease. Our sample was recruited across stages of disease and at varying times since diagnosis; however, as our primary outcome was survival, this heterogeneity had little impact on the analyses, and outweighs the advantage of closely track these women over a two year period, monitoring change in psychosocial and disease progression status.

In conclusion, despite our prospective design and careful control of prognostic factors, it is still possible that women's psychosocial responses were reflecting unmeasured signs and symptoms of disease progression; thus we cannot conclude that psychosocial factors *cause* reduced survival. However, guidelines for the care of women with ovarian cancer emphasise that the focus of management should be minimization of the physical *and* psychosocial impacts of the cancer and its treatment [40] and our findings reinforce the importance of addressing women's psychosocial responses to their cancer early in their disease trajectory as they may have an impact not only on quality of life but also on survival. Future research should focus on the relationship between psychosocial factors, specifically around these coping variables, initial treatment decision-making, variations in adherence to treatment protocols, and treatment side-effects. This may well inform the development of interventions

targeting coping strategies early in the disease trajectory in women with ovarian cancer with the potential to maximise not only psychological well-being and quality of life, but also survival.

Table 1. Patient demographics, disease and treatment variables at AOCS-QoL study entry (baseline)

	Median (Inter-Quartile Range)
Age (years)	61 (53, 67)
Months post diagnosis	17 (10, 27)
	Number of patients (%)[1]
Age group (years)	
<40	119 (15)
41-50	254 (32)
51-60	264 (33)
>60	161 (20)
Education	
High school or less	384 (49)
Trade/technical	268 (34)
University and higher	129 (16)
Married or partnered	563 (73)
Residential location	
Major city	507 (64)
Regional/remote	291 (36)
FIGO stage (at diagnosis)	
I	156 (19)
II	81 (10)
III	488 (62)
IV	59 (8)
Tumor grade (at diagnosis)	
1	57 (7)
> 1	732 (93)
Time of first disease progression	
Before QoL study entry	187 (23)
During QoL study[2]	168 (21)

After AOCS-QoL study[3]	96 (12)
No progression	347 (43)
On treatment (at baseline)	179 (23)
Died prior to census (31 Oct 2011)	419 (52)

[1] Numbers may not add up to total due to missing data

[2] Baseline assessment and up to two years of QoL study data collection

[3] After completing QoL study data collection and before census

Table 2. Mean (SD) psychosocial variables over time

QoL assessment number	n[1]	Months since diagnosis	Depression (0-21)[2]	Optimism (0-24)[2]	Helplessness/ Hopelessness (6-24)[2]	Minimization (5-20)[2]	Social support (8-40)[2]
1	798	18.6 (10.3)	3.7 (3.5)	15.9 (4.5)	9.3 (3.4)	16.1 (2.8)	34.2 (6.2)
2	727	22.6 (10.6)	3.8 (3.6)	15.9 (4.5)	9.4 (3.4)	16.0 (2.8)	34.0 (6.9)
3	675	26.4 (10.9)	3.7 (3.4)	16.2 (4.5)	9.6(3.3)	16.1 (2.6)	34.3 (6.7)
4	624	30.3 (11.3)	3.7 (3.6)	16.2 (4.8)	9.7 (3.4)	16.1 (2.5)	34.0 (7.0)
5	558	33.9 (11.7)	3.6 (3.7)	16.5 (4.6)	9.6 (3.3)	16.1 (2.4)	34.4 (6.9)
6	445	35.6 (11.3)	4.0 (3.9)	16.4 (4.8)	9.8 (3.5)	16.0 (2.7)	34.4 (6.9)
7	401	38.3 (11.3)	3.8 (3.7)	16.4 (4.8)	9.7 (3.4)	16.0 (2.8)	34.9 (6.5)
8	371	41.9 (11.4)	3.5 (3.6)	16.5 (4.9)	9.4 (3.3)	16.2 (2.6)	35.0 (6.4)

[1] Women remaining in the study over time are survivors, while those who died during the study period are not represented at later time points

[2] Possible score range

Table 3. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for overall survival from 10 time-varying covariate Cox proportional hazards models. Hazard ratios are given per standard deviation (SD).

	Unadjusted[1]			Adjusted[1,2]			Adjusted, baseline predictors[1,2,4]		
Variable	HR	95% CI	p-value[3]	HR	95% CI	p-value[3]	HR	95% CI	p-value[3]
Depression (per SD=3.6 points)	1.03	0.92, 1.15	0.6	1.00	0.89, 1.12	1.0	1.04	0.91, 1.18	0.6
Optimism (per SD=4.7 points)			0.03			0.01			0.1
No progression[5]	0.81	0.66, 0.99		0.80	0.65, 0.97		0.87	0.70, 1.07	
Progression	1.06	0.92, 1.22		1.10	0.95, 1.27		1.07	0.92, 1.26	
Minimization (per SD=2.7 points)			0.04			0.005			0.6
No progression	0.81	0.67, 0.97		0.79	0.66, 0.94		0.99	0.81, 1.20	
Progression	1.04	0.89, 1.21		1.12	0.95, 1.31		1.04	0.91, 1.19	
Helplessness/hopelessness (per SD=3.4 points)			0.002			0.0001			0.02
No progression	1.35	1.12, 1.63		1.40	1.15, 1.71		1.37	1.32, 1.66	
Progression	0.92	0.80, 1.06		0.86	0.74, 1.00		1.02	0.86, 1.20	
Social support (per SD=6.7 points)	1.01	0.90, 1.14	0.9	1.01	0.90, 1.14	0.7	0.96	0.84, 1.09	0.5

[1] Models included the psychosocial variable, progression status, and their interaction, if significant at $p<0.01$.

[2] Adjusted models included age at diagnosis, late stage at diagnosis, high grade at diagnosis, time post diagnosis to QoL study entry, current treatment status.

[3] The p-value is for the interaction with first disease progression status.

[4] Progression status and current treatment status are time varying, all other variables are measured at Qol study entry (baseline).

[5] Progression status at each time point (no progression or progression).

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