Physical symptoms, coping styles and quality of life in recurrent ovarian cancer: a prospective population-based study over the last year of life

M.A. Price\textsuperscript{a,b}, M.L. Bell\textsuperscript{b}, D.W. Sommeijer\textsuperscript{c}, M. Friedlander\textsuperscript{c,d}, M.R. Stockler\textsuperscript{c,e}, A. deFazio\textsuperscript{f}, P.M. Webb\textsuperscript{g}, The Australian Ovarian Cancer Study Group\textsuperscript{f,g,h}, The Australian Ovarian Cancer Study - Quality of Life Study Investigators\textsuperscript{a,b,h}, P.N. Butow\textsuperscript{a,b}

a. Centre for Medical Psychology and Evidence-based Decision-making (CeMPED), School of Psychology, The University of Sydney, Sydney, Australia

b. Psycho-oncology Co-operative Research Group (PoCoG), The University of Sydney, Australia

c. Australia New Zealand Gynaecological Oncology Group (ANZGOG), NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, Australia

d. Department of Medical Oncology, Prince of Wales Hospital, Randwick, Australia

e. Sydney Cancer Centre, RPA and Concord Hospitals, Concord, Australia

f. Department of Gynaecological Oncology, Westmead Hospital and Westmead Institute for Cancer Research, The University of Sydney at Westmead Millennium Institute, Westmead, Australia

g. Queensland Institute of Medical Research, Gynaecological Cancers Group, Brisbane, Australia

h. Peter MacCallum Cancer Centre, Melbourne, Australia
Corresponding address

Dr M. Price, Centre for Medical Psychology and Evidence-based Decision-making (CeMPED), School of Psychology, Transient Building (F12), The University of Sydney, NSW 2006, Australia. T: +61 2 93513916 F: +61 2 90365292 E: melanie.price@sydney.edu.au
Abstract

Objective

The aim of this study was to describe the trajectory of physical symptoms, coping styles and quality of life (QoL) and the relationship between coping and QoL over the last year of life in women with recurrent ovarian cancer.

Methods

The patient cohort were women recruited to the Australian Ovarian Cancer Study who subsequently experienced recurrent, invasive ovarian cancer and completed at least one psychosocial assessment (optimism, minimisation, hopelessness/helplessness, QoL) during the last year of life (n=217).

Results

QoL declined sharply from six months before death. Lack of energy was the most prevalent symptom over three measurement periods (67-92%) and also the most severe. Anorexia (36-55%), abdominal swelling (33-58%), nausea (26-47%) and pain (26-43%) all increased in prevalence and severity towards the end of life. Higher optimism ($p=0.009$), higher minimisation ($p=0.003$) and lower helplessness/hopelessness ($p=0.03$) at baseline were significant predictors of subsequent higher QoL.

Conclusions

Progressive deterioration in quality of life may be an indicator of death within about six months and therefore should be an important consideration in decisions about subsequent treatment. Coping styles which independently predicted subsequent changes in QoL could potentially be targeted by interventions to minimise worsening QoL.

(Word 2007 - 196 words)

Keywords: coping, end of life, ovarian cancer, psychosocial, quality of life, symptoms
Introduction

Despite improvements in surgery, chemotherapy and targeted therapy, women with advanced ovarian cancer face a poor prognosis, with more than 50% dying within five years of diagnosis [1]. Patients and their families have to bear the increase in disease burden at the terminal stage of ovarian cancer, reflected in increasing physical symptoms and hospitalisations for complications such as ascites, bowel obstruction, pain and pleural effusion [2-3]. One of the most challenging clinical goals in caring for women with recurrent ovarian cancer is achieving the delicate balance between managing distressing cancer-related symptoms and optimising quality of life (QoL) and knowing when to cease chemotherapy. Although it is well known that increased symptom severity has a negative impact on QoL in patients with cancer [4-5], including ovarian cancer [6], there is a paucity of data about symptoms and QoL in patients with recurrent ovarian cancer, especially in the terminal phase of the disease.

The psychological and social impacts of recurrent and progressive disease, and how they inter-relate, also need to be better understood to guide optimal end of life care. There is increasing evidence that psychological morbidity at the end of life can be influenced by individual coping styles such as acceptance, avoidance and help seeking [7]. An active or accepting coping style, rather than an avoiding copying style, has been associated with better QoL [7-8], while there is some evidence that optimism and minimisation are associated with improved QoL [9] and longer survival [9-10]. Recent evidence suggests that social support, in particular social attachment, is associated with longer survival [11].

Few studies have explored changes in, and the relationship between, symptoms of disease, coping styles and QoL in patients with terminal disease, and none in women with recurrent ovarian cancer. Therefore, the aims of the current study were to:

(a) describe the most common and severe physical symptoms reported by women with recurrent ovarian cancer in the last year of life;
(b) describe the trajectory of coping styles and QoL in these women; and

c) evaluate the predictive relationship between coping styles one year prior to death and the
subsequent trajectory of QoL in the final months of life.

Methods

Sample

The Australian Ovarian Cancer Study (AOCS) is 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 cancers) between 2002 and 2006. Details of
the study have been described elsewhere [12]. In brief, women were recruited through major
treatment centres and the state-based cancer-registries. The AOCS has collected detailed
epidemiological data, pathology and initial treatment data, as well as ongoing treatment and
clinical outcome data [12].

The AOCS Quality of Life (AOCS-QoL) study has investigated the role of psychosocial
factors in predicting outcomes, recruiting AOCS participants with invasive cancer who were
alive in May 2005 or recruited to AOCS after this date [13]. 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. Quality of Life and
psychosocial data were collected by validated questionnaire measures at three-monthly
intervals for up to two years, beginning 3-55 months post-diagnosis (mean 25.8 months) [13-14]. 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 current analyses include women in the AOCS-QoL study who completed at least one
questionnaire assessment within their last year of life and who died before 1 May 2012. The
study was approved and conducted in accordance with the ethical standards of the
Measures

Primary outcome

Quality of Life was assessed using the Functional Assessment of Cancer Therapy-Ovarian scale (FACT-O-version 4) [15] every three months. The FACT-O is a multi-dimensional, ovarian cancer-specific, quality of life instrument, assessing the four core QoL domains that together comprise the FACT-G: physical wellbeing (7 items); social wellbeing (7 items); emotional wellbeing (6 items); and functional wellbeing (7 items); together with 11 additional items assessing disease and treatment issues specific to ovarian cancer (symptom burden) (note: the item regarding interest in sex was excluded from analyses due to the high number of missing responses). Individual item responses range from 0 (not at all) to 4 (very much). FACT-O and domain scores are the sum of individual item responses. The physical, social, emotional and functional well-being domain scores range between 0-30, the symptom burden scores range between 0-50, and the overall FACT-O scores is standardised to range between 0-100. Higher scores reflect greater wellbeing. The minimally important difference (MID) for the FACT-G is six points on a standardised scale [16] and we expect this MID to be appropriate also for our standardised FACT-O scores.

Descriptive and predictor variables

Socio-demographics: Age, education, work and marital status were accessed via AOCS. Regional area (metropolitan/regional/remote) was calculated using the postcode of residential addresses. The Duke UNC Functional Social Support Questionnaire, measuring satisfaction with the functional and affective aspects of social support, was assessed every three months [17]. Scores range between 8-40 with higher scores indicating better social support.
Disease and treatment: Time between diagnosis and completion of the baseline questionnaire, surgical stage (I–IV, International Federation of Gynecology and Obstetrics (FIGO) classification) and date of death were accessed through AOCS. Current treatment information (chemotherapy, radiotherapy and/or hormonal treatment) was collected within each questionnaire, or from AOCS if missing.

Coping variables: Optimism was assessed using the Life Orientation Test–Revised [18], a widely used 6-item measure of dispositional optimism. Scores range between 0-24 with a higher score indicating higher optimism. Two sub-scales of the Mental Adjustment to Cancer (MAC) scale [19] were used to measure helplessness/hopelessness and minimisation [20]. The six-item helplessness/hopelessness (HH) scores range between 6-24, with higher scores reflecting greater HH, and the 5-item minimisation scores range between 5-20, with higher scores reflecting greater minimisation. These three variables were measured every three months.

Statistical analyses

Months to death was calculated as the date of death minus the assessment date, rounded to the nearest month. The top five most severe symptoms from the FACT-O were identified for each of the three time periods (7-9, 4-6, and 0-3 months) separately. Prevalence for these symptoms was calculated as the percent who reported that symptoms bothered them “quite a bit” or “very much”. The following 16 variables were graphed over time (months to death), with 95% confidence intervals (CI): global QoL (FACT-O), physical wellbeing, social wellbeing, emotional wellbeing, functional wellbeing, symptom burden, optimism, minimisation, helplessness/hopelessness scores, and the seven individual symptom items identified within the top five symptom list.

To assess trajectories over time, mixed models, which included months to death and its square as fixed effects, and a random participant effect, were fitted for each of the 16 variables listed above. A statistically significant linear term for time indicates a steady
change in the outcome. A statistically significant linear and quadratic (non-linear) term for
time indicates an increase or decrease as well as a change in the rate of increase or
decrease over time. If neither linear nor quadratic (non-linear) terms are significant there is
no evidence for change over time.

The association between psychosocial coping variables (optimism, minimisation and
helplessness/hopelessness) and global QoL (FACT-O) was investigated using mixed models
among participants completing more than one assessment (n=158). Each participant’s
earliest assessment observation in the year preceding death was used to predict all
subsequent assessments of QoL. In addition to the coping variables, fixed effects of age,
months to death, current social support and current treatment (yes/no: radiotherapy or
chemotherapy); and a random effect of patient were included in the model. Current social
support and treatment were included to control for potential influence on QoL at each time
point. Mixed models account for the within participant correlation due to repeated measures
and give unbiased estimation for data missing completely at random and missing at random
[21]. All statistical analyses were performed in SAS version 9.3 (Cary, NC).

Results

Two hundred and seventeen AOCS-QoL study participants, with a total of 502 assessments
completed during the last year of life, met the criteria for this analysis. Fifty-nine completed
one (27%), 61 completed two (28%), 67 completed three (31%), and 30 completed four
assessments (14%). Eighty-nine assessments were completed within the last three months
of life, 130 between 4-6 months before death, 152 between 7-9 months before death and
131 assessments between 10-12 months before death.

Patient characteristics are presented in Table 1. The mean age of participants was 63 years,
most were living as married (74%) and had advanced stage disease at diagnosis (93%,
FIGO III/IV). Fifty-three percent of patients who completed an assessment between 10-12 months before death were receiving chemotherapy at the time, decreasing to 39% of patients who completed an assessment within the last three months of life.

**Physical symptoms and their trajectory in the last year of life**

The five most severe and common physical symptoms, from among individual FACT-O items, at three time frames within the last year of life (7-9 months, 4-6 months, 0-3 months before death), are displayed in Table 2. These included: lack of energy, poor appetite, stomach swelling, loss of bowel control, nausea, pain, and weight loss. All of these symptoms increased in prevalence and severity towards the end of life (see Figure 1).

Prevalence was defined as the percentage of patients reporting a specific symptom as ‘quite a bit’ or ‘very much’. Severity was defined as the average score on the 0-4 scale, with higher scores reflecting greater severity. Lack of energy was both the most prevalent and most severe symptom reported in the last year of life, reported by 67% of women at 7-9 months before death, 78% at 4-6 months before death, increasing to 92% in the last three months of life. Loss of appetite was the second most severe symptom during the last year of life, while swollen abdomen was the second most prevalent symptom, present in 33% of patients at 7-9 months before death increasing to 58% in the last three months of life. Losing weight appeared among the top five symptoms only within the last three months of life, overtaking pain which, although increasing in severity and prevalence, was not among the top five symptoms within the last three months of life (Figure 1). Exploratory analyses showed that currently receiving chemotherapy was significantly associated with increases in nausea (p<0.0001), vomiting (p=0.004) and lack of energy (p=0.06).

Figure 2 displays the individual trajectories for FACT-O, physical wellbeing, social wellbeing, emotional wellbeing, functional wellbeing, symptom burden, optimism, minimisation and helplessness/hopelessness over the last year of life. Physical wellbeing and emotional wellbeing steadily decreased and helplessness/hopelessness steadily increased over time, reflected by significant p-values for the linear time terms. Not surprisingly, the physical
wellbeing decline was steepest, and can be attributed to three individual items (lack of energy, nausea and pain) not only being within the most prevalent and severe symptoms reported, but also steadily increasing as time to death decreased.

Global QoL, functional wellbeing, symptom burden and minimisation scores also changed significantly over time, but the rates of change over time were variable rather than steady, as demonstrated by statistically significant non-linear (quadratic) time terms (Figure 2). Three of the most prevalent symptom items, all among the ovarian-specific symptom burden domain, also had a variable rate of change over time. Appetite decreased more steeply over the last six months of life, weight loss sharply increased in the last three months of life, and abdominal swelling sharply increased in the last two months of life.

In contrast, there was no evidence of change over time in social wellbeing, optimism and minimisation scores, with both linear and non-linear (quadratic) terms non-significant. Of note, bowel control, which was among the top five most severe symptoms at 7-9 months before death, was approximately constant rather than increasing or decreasing over time.

**Coping and QoL trajectory in the last year of life**

The results of the linear mixed models analysis examining whether coping variables predicted subsequent quality of life are displayed in Table 3. Both older age \( (p=0.02) \) and better social support \( (p=0.002) \) were positively associated with subsequent QoL, while current treatment was not \( (p=0.2) \). Optimism \( (p=0.009) \), minimisation \( (p=0.003) \) and helplessness/hopelessness \( (p=0.03) \) were all statistically significant predictors of subsequent QoL. A one-point increase in optimism was associated with an increase in QoL of 0.6 (95% CI: 0.2, 1.1); a one-point increase in minimisation was associated with an increase in QoL of 1.1 (95% CI: 0.4, 1.8) and a one-point increase in helplessness/hopelessness was associated with a decrease in QoL of 0.8 (95% CI: -1.5, -0.1).
Discussion

This large prospective study of women with recurrent ovarian cancer documents the changes in physical symptoms, coping styles and QoL over the last year of life and clearly demonstrates a substantial deterioration in symptoms and QoL in the six months before death. The findings raise important questions as well as illustrating the challenges in identifying these patients and how best to intervene to improve their end of life care.

The most prevalent and most severe symptom was lack of energy, reported by 67% of patients 7-9 months before death and increasing to 92% in the last three months of life. Although fatigue is well recognised as a burdensome symptom in advanced cancer patients in general [4, 22] and ovarian cancer specifically [3], treatment options are limited. There is some evidence that a stimulant drug, methylphenidate may be effective [23], while physical exercise and psychosocial interventions have been shown to be effective in reducing fatigue in breast cancer survivors, and may be of benefit in patients in the terminal phase [24].

Anorexia, abdominal swelling and nausea were also prevalent and severe, worsening towards the end of life. Options to palliate these symptoms include drainage of ascites, percutaneous gastosomes, stent placing, as well as symptomatic treatment of bowel obstruction with steroids and somatostatin [25]. There is evidence that bevacizumab and aflibercept targeting vascular endothelial growth factor, and catumaxomab, targeting EpCAM and anti-CD3, reduce ascites and could reduce the need for repetitive paracenteses [26-29].

Pain is a prevalent symptom at the end of life, highly prioritised by patients [30-31]. In our study, while other symptoms were more prevalent, pain remained an important symptom, with 46% of women reporting pain in the last three months of life (data not shown). While substantially less than the 85% of patients with ovarian cancer who had pain mentioned in their medical records during the last six months of life in the Rolnick et al. [32] study, given the substantial evidence available for the treatment and management of pain, the prevalence of patients reporting pain is unacceptably high [33-34].
The QoL trajectory in the last year of life was variable, but invariably declined. In the first six months, the downward slope was gradual and took on average about four months to decrease by the minimal important difference of six. From about six months before death the QoL decline sharply steepened, mainly determined by declining physical and functional wellbeing and increasing single symptom severity. Although there are few data with which to compare our findings, a small study of 62 patients with recurrent ovarian cancer also showed that patients experienced increasing significant clinical events from six months before death [2].

The progressive deterioration in quality of life evident in our data may be an indicator of death within about six months and therefore should be an important consideration in decisions about subsequent treatment. There is evidence from clinical trials that QoL is an independent prognostic factor for survival in patients with various types of cancer [35], including ovarian cancer [36]. A dip in patient QoL may be a useful clinical warning that the patient is entering the terminal phase of life, and may aid clinician and patient decision-making regarding futile chemotherapy, thus reducing the number of patients who receive chemotherapy shortly before they die [2].

Notably, we found no evidence that being on chemotherapy was associated with an additional improvement or deterioration in QoL. However, the observational nature of our study design does not enable us to determine whether chemotherapy was able to palliate symptoms, the main goal of treatment in patients with platinum-resistant, recurrent ovarian cancer. Research specifically designed to evaluate whether palliative chemotherapy improves symptoms in women with recurrent ovarian cancer is currently being conducted by the Australia New Zealand Gynaecological Oncology Group [37].

Parallel with an increase in physical disease burden, hopelessness/helplessness increased and minimisation decreased in the last year of life, as coping resources were increasingly strained. While it may not be surprising that cancer has an increasing impact at the end of
life, this may not only be a negative process. It may be necessary for patients and their
families to move from hoping for a dramatic improvement to accepting and preparing for their
approaching death [38]. More research into the nuances of hope and meaning at the end of
life would enable greater understanding of the role of coping.

A major finding of this study is that optimism, minimisation and hopelessness/helplessness
at the beginning of the last year of life were related to QoL as death approached. Vos et al.
[39-40] found that some level of denial, although more extreme than minimisation, was
associated with improved QoL in patients with lung cancer, independent of disease burden,
suggesting a protective effect on social and emotional outcomes, while Van Laarhoven et al.
[7] reported venting emotions was a negative predictor of emotional functioning at the end of
life. These results do suggest that at least early in the last year of life, minimisation may help
patients to retain a sense of joy and meaning in life independent of their cancer. Of clinical
relevance, the potential benefit of interventions targeting specific aspects of coping, such as
Mindfulness-based interventions or Acceptance/Commitment Therapy [41-43], in addition to
symptoms such as anxiety, depression and insomnia, may offer some protection against the
steepness of declining QoL in patients approaching the end of life.

In conclusion, this study described the trajectory of physical symptoms, coping styles and
QoL of women with recurrent ovarian cancer in their last year of life. Progressive
deterioration in quality of life may be a reliable indicator of death within about six months and
therefore should be an important consideration in decisions about subsequent treatment and
help to identify patients who require supportive care rather than more chemotherapy. Coping
styles independently predicted subsequent changes in QoL and provide additional
psychosocial targets for intervention that have potential to impede some aspects of
worsening QoL. Further research is required to elucidate the role of coping on QoL in the
last year of life and whether early intervention can improve coping and QoL.

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Disclosures

The authors have declared no conflict of interest.
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456 Adjustment Among Late-Stage Ovarian Cancer Patients: Examining the Role of
457 Avoidance in Treatment. Cogn Behav Pract 2012; 19(4); 508-517.
Table 1. Descriptive statistics for patient demographics, disease stage at diagnosis, and treatment status at the first assessment during the last year of life.

<table>
<thead>
<tr>
<th>Variables (N=217(^1))</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (Standard Deviation)</td>
</tr>
<tr>
<td>Age (in years)</td>
<td>62.6 (10.0)</td>
</tr>
<tr>
<td>Months since diagnosis</td>
<td>25.8 (13.9)</td>
</tr>
<tr>
<td>Marital status</td>
<td>N (%)</td>
</tr>
<tr>
<td>Current partner</td>
<td>153 (74)</td>
</tr>
<tr>
<td>Ex partner</td>
<td>43 (21)</td>
</tr>
<tr>
<td>Never married</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>School only (≤12 years)</td>
<td>100 (46)</td>
</tr>
<tr>
<td>Trade/Technical</td>
<td>66 (30)</td>
</tr>
<tr>
<td>University</td>
<td>47 (22)</td>
</tr>
<tr>
<td>Residential location</td>
<td></td>
</tr>
<tr>
<td>Major city</td>
<td>134 (62)</td>
</tr>
<tr>
<td>Regional/remote</td>
<td>83 (38)</td>
</tr>
<tr>
<td>FIGO stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Early (I/II)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Advanced (III/IV)</td>
<td>199 (93)</td>
</tr>
<tr>
<td>Current chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>102 (47)</td>
</tr>
<tr>
<td>No</td>
<td>115 (53)</td>
</tr>
<tr>
<td>Current radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (1)</td>
</tr>
<tr>
<td>No</td>
<td>215 (99)</td>
</tr>
</tbody>
</table>

\(^1\)Numbers may not add up to total due to missing data
Table 2. Prevalence of the five most severe symptoms from the FACT-O reported during each of three time periods (7-9 months before death, 4-6 months before death, and 0-3 months before death).

<table>
<thead>
<tr>
<th>Months before death</th>
<th>Symptom 1</th>
<th>Mean severity (95% CI)</th>
<th>Percent prevalence* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-9 months</td>
<td>I have a lack of energy</td>
<td>2.2 (2.0, 2.4)</td>
<td>67 (59, 74)</td>
</tr>
<tr>
<td></td>
<td>I have a good appetite²</td>
<td>1.4 (1.1, 1.6)</td>
<td>36 (28, 43)</td>
</tr>
<tr>
<td></td>
<td>I have swelling in my stomach area</td>
<td>1.3 (1.1, 1.5)</td>
<td>33 (26, 41)</td>
</tr>
<tr>
<td></td>
<td>I have control of my bowels³</td>
<td>1.2 (1.0, 1.4)</td>
<td>36 (28, 43)</td>
</tr>
<tr>
<td></td>
<td>I have nausea</td>
<td>1.0 (0.8, 1.2)</td>
<td>26 (19, 33)</td>
</tr>
<tr>
<td></td>
<td>I have pain</td>
<td>1.0 (0.8, 1.2)</td>
<td>26 (19, 34)</td>
</tr>
<tr>
<td>4-6 months</td>
<td>I have a lack of energy</td>
<td>2.6 (2.4, 2.8)</td>
<td>78 (71, 86)</td>
</tr>
<tr>
<td></td>
<td>I have a good appetite²</td>
<td>1.9 (1.7, 2.1)</td>
<td>37 (29, 49)</td>
</tr>
<tr>
<td></td>
<td>I have swelling in my stomach area</td>
<td>1.7 (1.4, 1.9)</td>
<td>46 (37, 55)</td>
</tr>
<tr>
<td></td>
<td>I have pain</td>
<td>1.4 (1.2, 1.7)</td>
<td>43 (34, 51)</td>
</tr>
<tr>
<td></td>
<td>I have nausea</td>
<td>1.3 (1.0, 1.5)</td>
<td>38 (30, 47)</td>
</tr>
<tr>
<td>0-3 months</td>
<td>I have a lack of energy</td>
<td>3.0 (2.8, 3.2)</td>
<td>92 (86, 98)</td>
</tr>
<tr>
<td></td>
<td>I have a good appetite²</td>
<td>2.5 (2.2, 2.8)</td>
<td>55 (45, 66)</td>
</tr>
<tr>
<td></td>
<td>I have swelling in my stomach area</td>
<td>2.1 (1.7, 2.4)</td>
<td>58 (47, 68)</td>
</tr>
<tr>
<td></td>
<td>I am losing weight</td>
<td>1.8 (1.5, 2.1)</td>
<td>55 (45, 66)</td>
</tr>
<tr>
<td></td>
<td>I have nausea</td>
<td>1.5 (1.2, 1.8)</td>
<td>47 (37, 58)</td>
</tr>
</tbody>
</table>

1 Symptom response options 0 = "not at all", 1 = "a little bit", 2 = "somewhat", 3 = "quite a bit", 4 = "very much"

2 Prevalence is the percentage of women reporting 3 or 4.

3 Item has been reverse coded so that higher scores reflect worsening appetite.

4 = "very much"
Table 3. Association of quality of life (FACT-O) with coping variables while controlling for months to death, age, social support, and current treatment. Regression coefficient estimates and 95% confidence intervals (CIs) from a mixed model are shown. Each participant’s first observation in the year preceding death for coping variables was used to predict all subsequent observations of QoL.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimism</td>
<td>0.6 (0.2, 1.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>Minimisation</td>
<td>1.1 (0.4, 1.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Helplessness/hopelessness</td>
<td>-0.8 (-1.5, -0.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>0.22 (0.04, 0.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Months to death</td>
<td>2.6 (2.1, 3.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current social support†</td>
<td>0.5 (0.2, 0.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Current treatment‡</td>
<td>-1.8 (-4.5, 0.9)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

†Optimism, minimisation, helplessness/hopelessness and age at the first assessment only were entered into the model; ‡Current social support and treatment were entered as time-varying covariates.
Figure 1. Mean symptom scores over months to death, with 95% confidence intervals. Statistically significant $p$ values for the linear and non-linear (quadratic) terms for time (from a mixed model) indicate an increase or decrease in the outcome, as well as a change in the rate of increase or decrease. If the linear term only is statistically significant there is evidence for a steady change. If neither linear nor non-linear (quadratic) terms are significant there is no evidence for change over time.

Figure 2. Mean global QoL, physical, emotional, social, functional domains, symptom burden, optimism, minimisation, and helplessness/hopelessness, over months to death, with 95% confidence intervals. Statistically significant $p$ values for the linear and non-linear (quadratic) terms for time (from a mixed model) indicate an increase or decrease in the outcome, as well as a change in the rate of increase or decrease. If the linear term only is statistically significant there is evidence for a steady change. If neither linear nor non-linear (quadratic) terms are significant there is no evidence for change over time.