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Psychological distress and its correlates in ovarian cancer: a systematic review

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Abstract

Objectives: Ovarian cancer is often diagnosed at an advanced stage, and consequently high levels of distress are often experienced. It is necessary to understand the factors associated with psychological distress in order to guide interventions to target those factors. The purpose of this systematic review was therefore, to identify correlates of psychological distress in ovarian cancer.

Method: Included studies had to be quantitative and empirical, with standardized measures of psychological distress (anxiety or depression), and to present results for ovarian cancer patients specifically. Standard systematic search methods were used. Information about design, ovarian cancer sample size, disease stage, time since diagnosis, measures of distress used and findings was extracted from each study. The studies were quality assessed using experimenter-defined criteria as good, average and poor quality. Strength of the evidence (strong, some, inconclusive) was based on the quality and consistency of findings.

Results Eighteen studies meeting the inclusion criteria were identified. There was strong evidence for a relationship between younger age, being diagnosed with more advanced disease, more physical symptoms and shorter time since diagnosis with increased levels of anxiety and/or depression. Additional factors (e.g., immune) tested in few studies also emerged as correlates of distress.

Conclusions Demographic, disease and quality of life factors correlated with distress. However, too few studies assessed possible psychological and immunological correlates, which could be potentially modified and should be assessed in future studies.

Keywords: cancer, oncology, ovarian cancer, anxiety, depression

Ovarian cancer is usually diagnosed at an advanced stage and the overall 5-year survival rate is approximately 40% [1]. Treatment usually involves radical surgery and chemotherapy, which can have a significant impact on quality of life, and risk of recurrence is high [1]. Not surprisingly, a number of studies have found elevated levels of anxiety and depression in patients with ovarian cancer [2-4]. However, one longitudinal study [5] found that 23% of ovarian cancer patients experienced little or no distress. Thus, the psychological sequelae of ovarian cancer is quite heterogeneous. Identifying systematic and reliable research-based risk factors of psychological distress/reduced quality of life could help to guide psychological support and/ or interventions to those who require them the most.

This is a significant issue. A study of 143 women with ovarian cancer found that although 55% of participants had experienced some depressive symptoms, very few had been offered counselling [3]. Further, a search of the literature from 1980 – 2005 revealed only five psychological intervention studies for patients with gynaecologic cancers [6-10]. To further this research, it is necessary to identify correlates of psychological distress. This will allow us to improve screening for interventions, guide their therapeutic contents and improve their efficacy. In order to identify such correlates, it is necessary to review the literature carefully, assessing articles for study quality. The latter could vary widely and significantly affect the inferences that can be drawn.

A review on quality of life in ovarian cancer [11] noted several methodological limitations. First, the absence of a clear-cut definition of quality of life led to uncertainties in theoretical and operational concepts. Second, very few studies controlled for disease stage and other prognostic factors. Third, many studies modified valid versions of psychometric instruments. Fourth, many studies used small samples with possible insufficient statistical power. Some studies included patients with a variety of cancers, without presenting results for ovarian cancer patients separately, making inferences about ovarian cancer nearly impossible. Since many different measures were used, it was not possible to do a meta-analysis. Overall, only limited conclusions could be drawn. **Although many of these issues have been addressed in subsequent studies, others, such as the ratio of variables to participants, use of non-standardized questionnaires, and failure to report results by type of cancer are still prevalent.**

However, during the past decade there has been a substantial increase in research assessing levels of psychological distress and factors affecting psychological adjustment in ovarian cancer. Although Pearman [12] carried out a review on quality of life and

psychosocial adjustment in gynaecologic cancer survivors, several issues limit the conclusions that can be drawn by this review. First, no specific period for the literature search was provided. Second, the only database searched was Medline. Third, gynaecologic cancer patients were not differentiated, although factors that may affect psychological adjustment can differ considerably depending on diagnosis. For example, ovarian cancer generally has a worse prognosis than cervical and endometrial cancers, since it is more likely to be diagnosed at a later stage. Furthermore, in recent years new articles on distress in ovarian cancer have been published. Fourth, the strength of evidence could not be assessed, as studies were not quality assessed.

The purpose of this review was to assess correlates of psychological distress (conceptualized as levels of anxiety and depressive symptoms) in ovarian cancer. This review covered the period from January 1994 (to include any articles missed by the previous review on quality of life in ovarian cancer) to May 2007. The studies were quality assessed, and divided into good, average and poor quality, in order to assess the strength of evidence.

Method

Four methods were used to locate relevant studies: a keyword search, a backward search, a manual search of relevant journals, and a manual conference program search. Using the keyword search method, we searched the databases Medline, PsycInfo and Embase for articles published in the English language covering the period from January 1994 to May 2007, with the provision that any articles published in 1994 and included in the previous review [11] were not included. The search included the following terms: *ovarian cancer NOT genetic (because the review was concerned with women who already had ovarian cancer), ovarian carcinoma, gynaecologic cancer, gynecologic cancer, psych$, depression, major depression, anxiety, anxiety disorders, distress, and stress.* After each term had been entered into the keyword function, the cancer-related terms were combined using the OR function, and so were the psychological terms. A further search was then conducted, whereby the results of the previous searches were combined using the AND function. This generated 798 hits. Overall, the keyword search yielded 49 articles.

Following the keyword search, we carried out a backward search, in which we located papers by examining the reference lists of all papers obtained from the first step (as well as a recent non-systematic literature review; Pearman, 2003). This did not identify any further articles.

We then carried out a manual search of the journals *Gynecologic Oncology* (from which we had identified a number of articles) and *Psycho-Oncology* for the period January 1994 – May 2007. This did not identify further articles.

Following this, we contacted the authors of unpublished dissertations, to enquire whether they had written any relevant articles based on their dissertation. This method identified a further two manuscripts.

We also examined the abstracts of the 2006 World Congress of Psycho-Oncology. This identified a further 3 studies. Overall, 49 published studies and 5 unpublished studies were identified.

Following this, we e-mailed the authors of the unpublished studies to request manuscripts. One author was not contactable at the email address provided. A further two authors did not respond with sufficient information to enable inclusion of their studies in this review. Therefore, only 2 unpublished studies were obtained.

Inclusion and exclusion criteria

To be included, studies had to meet the following criteria:

1) Either include ovarian cancer patients only, or to present the results for ovarian cancer patients separately. Twenty-one studies were excluded according to this criterion, either because they were concerned only with patients with cervical and endometrial cancer (3 studies), or because ovarian cancer results were not presented separately (18 studies).
2) Be a quantitative study with standardized or validated measures of psychological distress. Nine studies with qualitative methods were excluded.
3) Present new data not already reported in an earlier source. Three articles were excluded according to this criterion.

Extracted information

The following information was extracted from each study: report information (authors, year of study, source of study), ovarian cancer sample size, age of participants, disease stage at diagnosis, time since diagnosis, measures used (including whether they were standardized), design and major findings.

Ratings of study quality

A methodological quality assessment list was used to assess the studies. This was devised based on reviewing existing quality assessment lists, [13,14] extracting those criteria that were considered relevant, and devising further ones based on consultation, to cover all sections of the articles. Since quality assessment was generic, the criteria could be applied to a variety of different types of study design. These criteria are summarized and elaborated on in Table 1. To reduce subjectivity in ratings, most criteria (10/12) could be assessed objectively with little interpretation. Each criterion was assessed out of 3 points (poor, medium and good). Appendix 1 provides a full account of the quality assessment tool.

Overall assessment

The studies are summarized in Table 2 together with their findings. They were assessed out of 36 points. Studies that scored 30 points or above (> 80%) were classified as good, those that scored 26-29 points were classified as average, and those scoring 25 points or lower were classified as poor.

When collating the findings, the strength of evidence for a relationship between demographic and other factors and psychological adjustment was assessed by defining three levels of evidence. Levels of evidence were based on those set out by Ariens et al. [13], and related to both quantity and quality, and are as follows: 1. Strong evidence: Consistent findings across two or more good studies; 2. Some evidence: Consistent findings across two or more studies, where at least 1 must be average; 3. Inconclusive evidence: Consistent findings in multiple poor studies, inconsistent findings, or only one study is available, irrespective of quality.

Results

Eighteen studies were identified in this systematic review. The majority were carried out in the USA (11 studies). Other studies were carried out in Australia (3 studies), Canada (1 study), Hong Kong (2 studies), and the UK (1 study). Thirteen of the studies dealt with ovarian cancer patients only (2 of those studies focused on survivors), and 5 dealt with women with a variety of gynaecologic cancers including ovarian cancer, for which the pertinent results could be interpreted.

The quality assessment highlighted a number of limitations with the studies. First, psychological studies were less likely to report biomedical variables, such as type of treatment, and medical studies were less likely to report other demographic variables, such as socioeconomic status (SES), and marital status. Second, some studies that compared the prevalence of anxiety and depression in ovarian cancer patients to the general population did not have a control group. Third, there were a few issues with the statistical tests - dividing data into quartiles to address the issue of skew, rather than transforming variables (1 study) and doing Pearson correlations only, rather than regression (2 studies). Fourth, means and standard deviations were not always reported. Fifth, many studies had rather small samples – eight failed to meet the criterion of 10 participants per independent variable required for 3 points. Finally, some of the studies used non-standardized assessment tools (that had not been validated and published) to assess secondary outcomes. Table 1 provides the major limitations of each study.

Overall, twelve of the studies were rated as methodologically good, five were rated average, and one was rated poor. Levels of depression in ovarian cancer groups tended to be higher than in community samples, with percentages of those scoring above the clinical cut-off ranging from 21-25% in the good studies, to 33% in the poor study [5] (though, interestingly, this study found that 23% of individuals experienced little or no distress). Notably, the prevalence of depression decreased after the three month period following completion of treatment [21], although it does not appear to differ across the first 6 weeks post-diagnosis [27]. However, it is

important to note that studies involving patients who were at varying stages of their cancer journey found approximately that approximately 25% of participants scored above the clinical cut-off, suggesting that depressive symptoms may remain a significant problem for some patients. Studies that looked at ovarian cancer survivors found that 6% of ovarian cancer survivors, defined as those who had been 2 years or more without evidence of active disease, scored above the clinical cut-off for depression [29], which is comparable to the general population and survivors scored higher on the Mental Health Inventory than population norms, indicating better mental health than the general population [28]. Overall, levels of anxiety tended to be higher than levels of depressive symptoms [3]. Hipkins et al. [21] reported that the prevalence of clinical levels of anxiety was 47% 3 months after finishing treatment, and that anxiety increased from completion of treatment to 3 month follow-up. Correlates of levels of anxiety and depressive symptoms are reported in Table 3.

One factor constantly associated with increased levels of distress in ovarian cancer patients included younger age, where evidence was found in five good studies [3,4,15,16,26] and one average study [21]. In contrast, 1 average study [28] found no relationship between age and depressive symptoms in ovarian cancer survivors, and one good study [25] found lower levels of distress in women under 45 years old. The weight of the evidence therefore strongly suggests that younger patients experience more anxiety/depression.

Being diagnosed with advanced stage disease was associated with increased levels of psychological distress in three good studies [3,16,25] and one poor study [5], although two average studies found no relationship between disease stage and levels of distress (Hipkins et al., 2004; Stewart et. al, 2001 – ovarian cancer survivors). Based on these results, there is strong evidence that having advanced stage disease at diagnosis is associated with higher levels of psychological distress. Shorter time since diagnosis was associated with increased levels of distress in three good studies [3,17,22], although it is important to note that this was not assessed in a large number of studies, since participants were often recruited when they were newly diagnosed.

Worse performance status was associated with increased levels of psychological distress in one good study [15] and one poor study [5], although one average study [21], found no relationship between Karnofsky performance status and levels of depression/anxiety. This suggests inconclusive evidence for a relationship between Karnofsky performance status and levels of psychological distress.

Increased levels of physical impairment was related to increased levels of psychological distress in two good studies [4,22] and one poor study [5]. Related to this, 1 average study on ovarian cancer survivors [29] found that increased levels of self-reported neurotoxicity was associated with increased levels of depression. From these findings, it was concluded that there is **strong** evidence for a relationship between increased levels of physical symptoms and increased levels of psychological distress. Phase of treatment (active/ follow-up) was not associated with levels of depression/anxiety, in the one good study that addressed this issue [16]. Also no differences in psychological distress were found between those with newly diagnosed and recurrent cancer in one average study [20], suggesting that both cancer phases are psychologically equally difficult.

Regarding cancer site, three studies assessed several different types of gynaecologic cancers. Two good studies [16,17] and one average study [27] found no differences between patients with ovarian cancer and those with other types of gynaecologic cancers. However, one good study [25] found that women with ovarian cancer experienced lower levels of depressive symptoms than those with cervical and endometrial cancer. This study included very few participants with advanced stage disease, which may account for this difference. These results do not suggest any clear relation between cancer site and levels of psychological distress.

Poor perceived social support was associated with increased levels of anxiety and depression in one good study [4] and two average studies [21,27]. This was assessed in different ways across the studies i.e. perceived social support [27], perceived emotional support [21], and perceived unsupportive family/friend behaviours [4], which adds to the robustness of the evidence. These findings suggest moderate evidence for a relationship between perceived social support and levels of

psychological distress. Also, depression at time of diagnosis was a significant predictor of depressive symptoms 3 months later, and levels of anxiety and intrusive thoughts at time of diagnosis were significant predictors of levels of anxiety 3 months later in one average study [21].

Increased levels of distress were associated with worse quality of life in two good studies [22,25]. However, these results should be viewed with caution, because although Molassiotis et al. [25] found that depression accounted for 45% of the variance in quality of life, the scale used contained mood items.

Finally, some interesting issues were assessed in single studies. The relationship between levels of distress and immune factors was assessed in three good studies [18,23,24]. Costanzo et al., [18] found that a history of depression and increased depressed mood were associated with higher levels of interleukin-6 in ascitic fluid. Lutgendorf et al. [23], found that higher levels of helplessness were associated with higher levels of vascular endothelial growth factor, a pro-angiogenic factor which is associated with poorer survival. Lutgendorf et al. [24], found increased levels of distress were associated with lower levels of natural killer cells in tumour-infiltrating lymphocytes. Thus, various indices of distress are correlated with biomarkers of important prognostic factors in ovarian cancer. Parker et al. [26], in a good study, found that lower levels of knowledge about ovarian cancer and higher CA 125 levels were associated with increased levels of **depressive symptoms**. Furthermore, the latter association was moderated by knowledge levels, such that it did not occur if knowledge about ovarian cancer was low, suggesting that depth of understanding of the illness links CA125 with depression. Increased anxiety was associated with lower levels of knowledge about ovarian cancer, and with higher levels of preoccupation with CA 125. de Moor et al. (2006), in a longitudinal study, found that CA 125 positively correlated with anxiety and depression at baseline, but no prospective relations were found. Boscaglia et al. [16], in a good study, found that increased levels of negative religious coping (i.e., confusion and dissatisfaction with God, redefining the illness as a punishment) were associated with higher levels of anxiety

and depression. The results from these studies point at possible complex relations between information-seeking, coping and distress in ovarian cancer.

Discussion

In order to identify correlates of psychological distress in ovarian cancer, a systematic review of the literature was carried out. The results showed strong evidence for a relationship between younger age, being diagnosed with more advanced disease, more physical symptoms and shorter time since diagnosis with increased levels of anxiety and depression; some evidence for a relationship between low perceived social support and worse performance status and increased levels of anxiety/depression was also found. There was inconclusive evidence for a relationship between being on active chemotherapy, having a recurrence and having ovarian cancer (compared to other gynaecologic cancers) and levels of anxiety/depression. While the evidence for a relationship between quality of life and distress could be viewed as strong based on our criteria, the issue of item overlap (quality of life instruments often include measures of mood) spuriously inflated this relationship.

Overall, a consistent relationship was found between younger age and increased levels of anxiety/ depression. Similar findings have been reported in other cancers i.e., Strong et al. [30]. Individuals diagnosed at a younger age have several issues to contend with, including the impact of their diagnosis on those around them (e.g., spouses, children), issues about childbearing, multiple unfulfilled goals, and the possibility of an early death. Although younger women are more likely to be married (than widowed), and possibly have a wider social network, the disease is more likely to impact on their everyday life. The evidence presented here suggests that younger women should be carefully assessed for symptoms of anxiety and depression.

Physical symptoms and impairment were also associated with increased levels of anxiety and depression, possibly because they are viewed as indicators of disease progression. In addition, some treatment-induced physical symptoms (e.g., nausea) may either induce or be associated with altered mood state as part of the “sickness

response" [31]. Similarly, lower performance status was associated with increased levels of anxiety/ depression. This evidence suggests that individuals with limited ability to perform daily activities may benefit from psychological interventions, and that psychological interventions should be tailored to accommodate their limitations (i.e., by phone for people who are unable to travel). Alternatively, depression or anxiety may lead to poorer performance status because depressed patients have reduced motivation [32] leading to reductions in energy expenditure required for daily activities. It is also plausible that relations between self-reported physical symptoms and distress may reflect the underlying personality trait of neuroticism [33], manifested by corresponding scores on both outcomes. Objective measures of physical health or statistically controlling for neuroticism may be required to test the true relation between impairment and distress.

More advanced disease was associated with increased levels of distress in newly diagnosed patients. Advanced stage disease is associated with poorer survival and more symptoms, and patients are obviously aware of these threats. This evidence suggests that individuals diagnosed with advanced disease should be carefully assessed for anxiety and depression.

As in other cancers [34], levels of anxiety/ depression tended to decrease as time since diagnosis increased. A cancer diagnosis is a traumatic event, and coming to terms with it requires a significant shift in perspective, which could explain these findings. This may reflect an adaptation process.

As expected, poorer quality of life was significantly associated with increased levels of anxiety/ depression. Experiencing more physical symptoms and reduced ability to engage in leisure activities/ work is likely to decrease self-esteem, possibly leading to greater distress. Future studies need to test whether self-esteem mediates such a relation. This evidence suggests that interventions targeting quality of life are a high priority area for future research, and should be made widely available, particularly given the relations between quality of life and distress/ survival [35, 36]. However, as mentioned above, these relations may partly stem from item overlap and need to be tested by removing distress items from quality of life instruments.

As expected, given previous studies on other types of cancer, i.e., Helgeson & Cohen, [37] poor perceived social support was associated with increased levels of anxiety and depression. This may result from patients not receiving sufficient emotional or instrumental support from close friends/ relatives. Alternatively, high patient distress may lead to reduced social support due to significant others not having the skills to manage such distress.

The evidence assessed here suggests no differences in levels of anxiety and depression between patients with ovarian cancer and those with other gynaecologic cancers. Similar findings were observed in two excluded studies [38, 39]. Ovarian cancer has a worse prognosis as it is more likely to be diagnosed at an advanced stage, and consequently requires more aggressive treatment, both of which are distressing. However, provided disease stage was controlled for in these studies, this lack of difference is expected since cancer can be life threatening and all gynaecologic cancers may affect sexual relations and intimacy. Thus, other factors related to the disease mentioned above, rather than the mere diagnosis of ovarian cancer, should be considered when assessing anxiety and depression [5].

Being on active chemotherapy treatment was not associated with increased risk of anxiety and depression. This was surprising since chemotherapy can cause a number of unpleasant side effects, often greatly reducing life satisfaction and inducing the sickness response. A number of the studies here included only newly diagnosed individuals. However, patients undergoing chemotherapy are aware that their condition is being treated, which may reflect an important source of medical support. Upon completion of treatment, some patients experience anxiety that their progress is not being monitored, and that they will be unaware of a recurrence (particularly since ovarian cancer can be asymptomatic). Similar “separation anxiety” is found in patients leaving the intensive coronary care unit for less intensive monitoring and care in other parts of hospitals [40]. Also surprisingly, having a recurrence was not associated with increased levels of anxiety and depression. In these studies, individuals who had a recurrence were compared with newly diagnosed patients. Comparing patients who had a recurrence with disease-free individuals at a similar

time since diagnosis may yield different results. Alternatively, this result could be explained in the following way: by the time of recurrence, some individuals have been living with their illness for several years, and may have come to terms with their diagnosis and treatment – news of a recurrence may be less surprising than the initial diagnosis. This issue requires further research.

A few well-designed studies found that various indices of distress were correlated with biomarkers of prognostic factors in ovarian cancer (e.g., VEGF, IL-6). Since distress may lead to altered immune function, interventions to reduce distress need to be made a priority. These studies are important since they point at potential mediators linking psychological factors with prognosis in ovarian cancer e.g.[41]. However, this needs to be tested in longitudinal studies and randomized controlled trials, which would provide a better understanding of the direction of the relation between immune factors and psychological distress.

Regarding methodology/ reporting, several issues need to be addressed in future studies. First, information should be collected on whether the individual is living alone or with a partner, socioeconomic status, type of treatment received and whether the patient has had a recurrence. Second, more prospective studies and randomized-controlled trials are needed, the latter enabling causal inferences and having potential clinical value. In addition, longitudinal studies should test trajectories of change in distress following diagnosis and treatment. Third, more attention should be given to sample size. Fourth, questionnaires should be validated prior to usage if possible. Fifth, importantly, studies should use models to structure their research questions – to date, most studies have not been based on theory regarding adjustment to illness [42, 43]. Finally, limitations and possible future directions for research should be provided. Although some of these conclusions echo those of Montazeri et al. [11], which would suggest lack of progress in recent years, the studies published in the current decade were rated 'average' or better, in contrast with the study published in the 1990s. It is also encouraging to see that the volume of published research on ovarian cancer has been increasing in recent years – over half the studies included in this review were published after 2003. In addition, the studies revealing relationships

between distress and disease biomarkers indicate promising avenues and call for testing whether treating distress could alter such biomarkers and improve prognosis in ovarian cancer. Also, some studies point to a number of modifiable factors affecting levels of distress, such as levels of knowledge and coping strategies, which were not assessed in the ovarian cancer literature before the late 1990s. Given recent reviews on psychological interventions and prognosis in cancer [44], future studies need to design alternative interventions for modifying psychosocial factors.

This systematic review had a few limitations. A number of authors were reluctant to provide details of unpublished studies, which consequently could not be included. Some correlates of distress (e.g., immune factors, coping) were tested in too few studies to enable firm conclusions.

Overall, this review has provided a first step towards identifying factors that may impact on psychological distress in ovarian cancer, a disease that has often been neglected in psycho-oncology research until recently. This is also the first review to quality assess studies, and therefore provides a more stringent test of the evidence than previous reviews on ovarian cancer. The evidence here can be used as a preliminary guide when deciding which patients to assess for anxiety and depression and whom to target when designing psychological interventions.

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Table 1: Criteria for Quality Assessment

	Item definition
Rationale	Was there sufficient theoretical background to justify the study aims?
Disease variables	Was time since diagnosis reported?
	Was disease stage reported?
	Were background biomedical and demographic variables reported?
Study design	Was the study cross-sectional/ case-control, prospective or a RCT?
	Was the choice of design adequate for the research question
Analysis and data presentation	Were adequate statistical tests carried out (of sufficient complexity)? Were important biomedical & demographic variables considered?
	Were the descriptive and inferential statistics presented adequately?
	Was the sample size sufficient in relation to the number of independent variables (at least 10 times the number of IVs in the analysis)?
Measures used	Were reliable and valid measures used to assess psychological distress?
Discussion	Were the conclusions justified based on the design and research findings?
	Were the limitations reported?

Table 2: Prevalence and correlates of distress, and quality assessment of studies

Ref no.	Article reference	Design	Ovarian cancer (N)	Disease stage (I – IV)	Time since diagnosis (months)	Measures of distress used	Findings	Quality Assessment score (12-36) and major limitations
1	[15] (Bodurka Bevers et al., 2000)	CR	246	181 – III/ IV 65 – I/II	0.3-364 (median 28.5)	CES-D; STAI – state anxiety	1) 21% had probable clinical depression 2) Poor performance status a/w high depression, anxiety, low QoL 3) Younger age related to greater likelihood of depression	30 disease stage/ time since diagnosis, study design, limitations
2	[16] (Boscaglia et al., 2005)	CR	100	60 – I; 11 – II; 28 – III; 1 – IV	Under 1 year (mean 22.21 weeks, **SD** = 14.58)	BDI for Primary Care; STAI – state anxiety;	1) 24% at least mild symptoms of depression, mean anxiety higher than general population 2) Younger age, advanced stage of disease, greater level of negative religious coping: a/w higher level of depression 3) Negative spiritual coping correlated with higher anxiety 4) Phase of treatment (active versus not active) and site of cancer (ovarian versus not ovarian) unrelated to depression or anxiety	30 sample size, data, demographics
3	[17] (Chan et al., 2005)	RCT	39 intervention (T), 36 control (C)	88 – I; 18 – II; 40 –III; 9 – IV	Newly diagnosed	BDI; Beck Anxiety Inventory;	1) No effect of the intervention on any measure 2) Lower educational level a/w less anxiety 3) No significant differences between ovarian cancer and other gynaecologic cancers in levels of anxiety and depression	31 introduction, data, sample size, limitations
4	[18] (Costanzo et al., 2005)	CR	61	45 - III, 16 –IV	Newly diagnosed	POMS-SF; CES-D;	1) Elevated levels of distress in advanced-stage cancer compared to community samples 2) History of depression a/w higher levels of IL-6 in ascitic fluid	33 demographics
5	[19] (de Moor et al., 2006)	LN	90 (complete follow-up)	8% - I, 7% - II, 66% - III, 17% - IV	Mean 2.60 years (**SD** 3.11)	PSS; STAI; CES-D	1) Optimism negatively a/w anxiety, stress and depression at baseline and follow-up 2) CA 125 a/w anxiety at baseline but not follow-up	35
6	[20] (Donovan et al., 2002)	CR	151 (81 initial cancer, 70 recurrent)	77% -III/ IV	Recently diagnosed/ being treated for a recurrence	POMS-SF	1) No differences in POMS between those with newly diagnosed and recurrent cancer	28 intro, time since diagnosis, demographics, stats, sample size, limitations

7	[21] (Hipkins et al., 2004)	LN	57	65% -III/ IV	Mean 6.1 months	HADS	1) Anxiety at T1, perceived emotional support and younger age a/w anxiety at T2 2) IES-intrusions at T1 a/w anxiety at T2 3) Depression at T1 and perceived emotional support associated with depression at T2 4) Increase in anxiety, decrease in depression over 3 months	28 demographics, data, questionnaire, limitations
8	[22] (Hodgkinson et al., 2007)	CR	54 (27%)	59% - I, 17% - II, 22.6% - III, 1.5% - IV	Mean 3.7 years (**SD** 2.3)	SF-12; HADS	1) 5.5% cases of depression, 14% anxiety (higher than general population) 2)Correlates of distress: poorer physical and mental QoL, PTSD, higher total needs 3) Extended survival a/w lower anxiety	31 intro, time since diagnosis, limitations
9	[5] (Kornblith et al., 1995)	LN	151 at start	86% III/IV	Not reported	MHI	1) In 1/3 of patients, symptoms of anxiety and depression occurred at levels of moderate to very severe intensity 2) 33% had high levels of psychological distress 3) High distress a/w more physical symptoms, worse physical functioning, worse current well-being, advanced disease, being an inpatient on study entry 4) Physical symptoms, physical functioning and performance status -predictors of psychological distress 5) 23% - little or no distress	25 intro, time since diagnosis, disease stage, demographics, stats, data, sample, questionnaires, limitations
10	[23] (Lutgendorf et al., 2002)	CR	24	19 III/IV	New diagnosis (before surgery)	POMS	1) Higher levels of helplessness a/w higher VEGF	31 sample size, data
11	[24] (Lutgendorf et al., 2005)	CR	42	83% III/ IV	Newly diagnosed (after surgery)	POMS (SF)	1) No significant differences in distress, depressed mood between groups 2) More distress associated with poorer NKCC in TIL	33 sample size
12	[25] (Molassiotis et al., 2000)	CR	35 (56.5%)	3- borderline 21 – I, 19 –II, 3 –III, 1 – IV	52.3 months (***SD*** 45.1, range 6 months – 13 years)	POMS	1) Lower levels of mood disturbance, lower levels of depression in ovarian than cervical cancer 2) Younger age, early stage disease a/w better psychological health 4) Depression accounted for 45% of variance in QoL	30 intro, study design, sample size, questionnaire
13	[3] (Norton et al., 2004)	CR	143	39% - III	Mean 22 mths (49% diagnosed within 6 mths)	BDI (not somatic items); MHI	1) Higher levels of depression than community samples 2) Higher levels of anxiety than depressive symptoms 3) Younger age, less time since diagnosis and more advanced disease stage a/w more psychological distress	31 design, questionnaire, limitations

14	[4] (Norton et al., 2005)	CR	143	46% - III	18 months (***SD*** 2.3 years)	MHI	1) Older age a/w less anxiety and depression, 2) Higher levels of physical impairment a/w lower perceived control over the illness , which a/w greater psychological distress 3) Higher levels of unsupportive behaviours from family/ friends a/w lower self-esteem, which a/w greater psychological distress	33 questionnaire
15	[26] (Parker et al., 2006)	CR	126	85% - III/IV	Mean 2.7 years (**SD** 3.4)	CES-D; STAI;	1) 25% scored above clinical cut-off 2) Age negatively a/w depressive symptoms and anxiety 3) CA125-preoccupation significantly a/w anxiety; 4) Lower knowledge scores and higher CA125 preoccupation scores a/w more depressive symptoms - knowledge moderated association of CA125- preoccupation with depressive symptoms 5) Anxiety negatively a/w knowledge, positively a/w CA125 preoccupation	31 demographics, questionnaires, conclusions
16	[27] (Petersen et al., 2005)	LN	9 (35%)	61% - I, 12% - II, 27% - III	Newly diagnosed	Hopkins Symptom Checklist-90;	1) Levels of distress did not change over first 6 weeks 2) No significant differences in levels of distress between ovarian cancer and other sites 3) Distress a/w poor perceived social support	26 intro, disease stage, demographics, design, stats, data, sample, limitations
17	[28] (Stewart et al., 2001)	CR	200	Not reported	7.2 years (**SD** = 4.9)	MHI	1) Mental health not affected by age, education, time since diagnosis	26 intro, disease stage, stats, data, questionnaires, limitations
18	[29] (Wenzel et al., 2002)	CR	49	38 – I; 11 – II	5 years or more (5-10)	SF-36; CES-D;	1) Neurotoxicity a/w psychological well-being, depression	26 demographics, stats, data, sample, questionnaires, conclusions, limitations

Glossary: CR –cross-sectional; LN – longitudinal; RCT – randomized controlled trial; CES-D – Center for Epidemiologic Studies – Depression Scale; STAI – State Trait Anxiety Inventory; BDI – Beck Depression Inventory; POMS – Profile of Mood States; HADS – Hospital Anxiety and Depression Scale; MHI – Mental Health Inventory;

Table 3: Factors correlated with levels of anxiety and depressive symptoms in ovarian cancer

Factor	Most frequently observed association	Congruent with observations	No relation	Incongruent with observations	Level of evidence
Age	Younger – more distress	Good: 5 Average: 1	Average: 1 (survivors)	Good:1	Strong
Disease stage	More advanced – more distress	Good: 3 Poor: 1	Average: 2 (1 on survivors)		Strong
Time since diagnosis	Shorter – more distress	Good: 3	Good: 1 Average: 1 (survivors)		Strong
Disability status	Worse – more distress	Good: 1 Poor: 1	Average: 1		Some
Physical symptoms	More symptoms – more distress	Good:2 Poor: 1			Strong
Active chemotherapy/ follow-up	Chemotherapy – more distress		Good:1		Inconclusive
Phase of treatment: initial/ recurrent	Recurrent – more distress		Average: 1		Inconclusive
Site of cancer	Ovarian – more distress		Good:1 Average: 1	Good: 1	Inconclusive
Perceived social support	More social support – less distress	Good:1 Average: 2			Some
Previous levels of depression	More – more distress	Average: 1			Inconclusive
Previous levels of anxiety	More – more distress	Average: 1			Inconclusive
Previous levels of intrusive thoughts	More – more distress	Average: 1			Inconclusive
Quality of Life	Poorer quality of life – more distress	Good: 2			Strong

Appendix 1: Details of the quality assessment criteria

Rationale

Good: The introduction contained sufficient theoretical background to justify the study aims
Medium: The introduction contained some theoretical background, but not all study aims were clear
Poor: The introduction contained no theoretical background

Time since diagnosis

Good: All participants newly diagnosed, or time since diagnosis reported
Medium: Time since diagnosis was not reported, but all participants were either newly diagnosed, or at the start of a new course of chemotherapy
Poor: This information was not reported

Disease Stage

Good: This information was reported
Poor: This information was not reported

Background biomedical and demographic variables

Good: Information was reported on whether the individual was living alone or with a partner, socioeconomic status, type of treatment received and whether the patient had had a recurrence.
Medium: Information was not reported on one or more of these variables
Poor: Information was not reported on any of these variables

Study Design

Good: Randomized controlled trial
Medium: Prospective/ longitudinal study
Poor: Cross-sectional study

Suitability of the design to answering the research question:

Good: Best possible design used
Medium: Inappropriate control group used/ no control group when comparing levels of anxiety/ depressive symptoms to the general population
Poor: Hypotheses suggesting causality tested in a cross-sectional design

Were adequate statistical tests carried out?

Good: The best statistical tests possible were used
Medium: The statistical tests could have been better (i.e. data divided into quartiles to address the idea of skew, rather than transforming variables, doing Pearson correlations only, rather than regression)
Poor: Failure to use inferential statistics, or explain the statistical tests properly

Presentation of the statistical tests

Good: Means and standard deviations were fully reported, and the graphs were easy to understand
Medium: Either means only were reported, or the graphs were not very clear
Poor: Means and standard deviations were not reported.

Sample size

Good: More than 10 participants per independent variable
Medium: The sample was adequately powered to assess single variables, but the number of participants per independent variable was less than 10
Poor: A very small sample (under 30 participants)

Measures Used
Good: All the questionnaires used were standardized, defined as questionnaires that had been validated and published
Medium: Some of the questionnaires (that assessed secondary outcomes) had not been standardized
Poor: Reliability and validity information were not reported

Were the conclusions justified based on the research findings?

Good: All conclusions followed on logically from the research findings
Medium: Not all conclusions were supported by the research findings
Poor: Inferences of causality were made based on cross-sectional data

Limitations
Good: All limitations were mentioned
Medium: The authors mentioned some limitations, but failed to point out others that the reviewers noticed
Poor: No limitations of the study/ issues for future research were mentioned