Depression as a Predictor of Disease Progression and Mortality in Cancer Patients

A Meta-Analysis

Jillian R. Satin, MA; Wolfgang Linden, PhD; and Melanie J. Phillips, BSc

BACKGROUND: Cancer patients and oncologists believe that psychological variables influence the course of cancer, but the evidence remains inconclusive. This meta-analysis assessed the extent to which depressive symptoms and major depressive disorder predict disease progression and mortality in cancer patients. **METHODS:** Using the MEDLINE, PsycINFO, CINAHL, and EMBASE online databases, the authors identified prospective studies that examined the association between depressive symptoms or major/minor depression and risk of disease progression or mortality in cancer patients. Two raters independently extracted effect sizes using a random effects model. **RESULTS:** Based on 3 available studies, depressive symptoms were not shown to significantly predict cancer progression (risk ratio [RR] unadjusted = 1.23; 95% confidence interval [CI], 0.85-1.77; $P = .28$). Based on data from 25 independent studies, mortality rates were up to 25% higher in patients experiencing depressive symptoms (RR unadjusted = 1.25; 95% CI, 1.12-1.40; $P < .001$), and up to 39% higher in patients diagnosed with major or minor depression (RR unadjusted = 1.39; 95% CI, 1.10-1.89; $P = .03$). In support of a causal interpretation of results, there was no evidence that adjusting for known clinical prognostic factors diminished the effect of depression on mortality in cancer patients. **CONCLUSIONS:** This meta-analysis presented reasonable evidence that depression predicts mortality, but not progression, in cancer patients. The associated risk was statistically significant but relatively small. The effect of depression remains after adjustment for clinical prognosticators, suggesting that depression may play a causal role. Recommendations were made for future research to more clearly examine the effect of depression on cancer outcomes. **Cancer 2009;115:5349–61. © 2009 American Cancer Society.**

KEY WORDS: cancer, depression, mortality, recurrence, meta-analysis, psychosocial oncology.

Laypersons and oncologists now implicate psychological functioning in the prediction of cancer outcomes. In consequence, the field of psycho-oncology has experienced exponential growth.[1] Eighty-five percent of cancer patients and 71.4% of oncologists endorse the belief that psychological variables affect cancer

Corresponding author: Jillian R. Satin, MA, Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, British Columbia, V6T 1Z4 Canada; Fax: (604) 822-6923; jsatin@psych.ubc.ca

Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada

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progression.[2] The present meta-analysis examines the effect of depression on recurrence and mortality in cancer patients to determine whether these current beliefs are supported by empirical evidence.

Depression, including depressive symptoms and clinical diagnosis of depression, was chosen as the psychological variable of interest for several reasons. First, we found that depression is the most commonly studied psychological variable with respect to cancer progression and mortality in cancer patients. (A literature search was performed using PsycInfo and MEDLINE online databases. A comprehensive list of psychological variables [anger, anxiety, benefit finding, blame, coping, confusion, creativity, depression, emotional suppression, faith, fighting spirit, helplessness, hope, hopelessness, hostility, humor, internal control, self-control, locus of control, life event, meaning, mental disorder, mental health, mental illness, optimism, pessimism, personality, psychological disorder, psychiatric disorder, religiosity, repression, self-efficacy, sense of coherence, sense of purpose, social support, spirituality, stress, tension, quality of life, or well-being] was crossed with [cancer] and with [mortality or survival] or [progression, relapse, recurrence, or metastasis]). Second, depression has been identified as the only psychological problem more commonly found in cancer patients than in the general population, and as the most likely psychological problem to persist throughout the illness trajectory.[3]

Last, a plausible model exists to link depression with cancer progression and mortality through both behavioral and biological pathways.[4-7] Chronic activation of the hypothalamopituitary-adrenal (HPA) axis has been implicated as a possible mediator of the effect of depression on cancer progression.[8] This maladaptive activation may modulate the functioning of the cellular immune system, increasing the potential for malignant tumor progression. Moreover, cytokines, inflammatory molecules involved in immune-mediated mechanisms, are similarly modified by emotion, with dysregulated production and function linked to disrupted HPA activation.[9] Pro-inflammatory cytokines (ie, interleukin 1, 2; tumor necrosis factor-α) have been shown to increase in depression and, combined with modulation of anti-inflammatory cytokines, may influence cancer outcomes.[8,9]

After a landmark study, by Shekelle and colleagues,[10] had demonstrated a 2-fold higher mortality rate in depressed cancer patients at 17 years follow-up, many epidemiological and prospective studies attempted, but most often failed, to replicate this substantial effect.[11,12] A seminal treatment study utilizing a randomized controlled design called attention to the field of psycho-oncology by demonstrating an 18-month survival advantage of supportive-expressive group therapy in metastatic breast cancer patients.[13] Perhaps no other study in psycho-oncology has received as much attention. However, additional high-quality trials have unfortunately failed to replicate the survival effect of this and other types of psychological therapy.[14-18] As such, considerable doubt exists that psychosocial intervention can affect cancer progression and mortality.[19-23] Given that the effects of psychological variables as predictors of mortality and recurrence have not been consistently demonstrated, we believe that the study of the effect of psychological interventions on cancer outcomes is also resting on a weak foundation.

A descriptive review by Milo[24] concluded that the majority of studies examining the effect of depression on mortality in cancer patients show a significant association. However, this review is not comprehensive and includes studies that examined the effect of related yet different psychological constructs, including helplessness and joy. In another review of the effect of depression on cancer progression, Spiegel and Giese-Davis[25] concluded that the literature is mixed with regards to demonstrating that depression is a risk factor for disease progression and mortality. The authors point out that the average sample size was twice as large in the studies that failed to find a significant difference than in the ones that demonstrated an effect, highlighting the importance of weighing study results for sample size in meta-analysis.

The present meta-analysis is a much needed quantitative synthesis of the often under-powered studies, to date, examining depression as a predictor of disease progression and mortality in cancer patients. This was deemed important for theory and practice in determining the risks associated with depression and for informing the plausibility of a survival effect following psychological intervention.

MATERIALS AND METHODS

Research Objective

The primary objective of this study was to assess the impact of depression, including depressive disorders and

depressive symptoms, on disease progression and mortality in diagnosed cancer patients.

Search for Studies

We searched the CINAHL (EBSCO), EMBASE (Elsevier), PsycINFO (American Psychological Association), and MEDLINE (National Library of Medicine) online databases. The following terms were entered as keywords: [depression] and [cancer] and [mortality or survival]/ [progression or relapse or recurrence or metastasis]. We also examined reference lists of review articles[24-29] to ensure that relevant studies were not overlooked.

Selection of Studies

The inclusion criteria required that the identified articles specifically examined the ability of depressive symptoms or a diagnosis of major or minor depressive episode or disorder, assessed after the time of cancer diagnosis, to predict cancer progression or mortality in human participants. Foreign language articles were considered for inclusion provided that an English abstract was available. To lessen publication bias, dissertations retrieved through our electronic search of databases were also considered for inclusion. Articles were excluded when 1) the study measured the effect of an intervention on depression, 2) depression was assessed by nonstandardized self-report, 3) data were insufficient to compute appropriate effect size statistics, and/or 4) depression was assessed before cancer diagnosis, thus combining the effect of depression on cancer incidence and mortality (see Figure 1).

Data Abstraction

Study characteristics and effect sizes were extracted or computed independently by 2 authors (JRS and MJP). Inconsistencies were resolved by all 3 authors.

Quantitative Data Synthesis

The included studies[30-60] varied with respect to the effect size statistic that could be extracted or calculated from the given data. We report risk ratios (RRs) and hazard ratios (HRs). HRs were abstracted from studies that provided these statistics directly, along with upper and lower confidence limits. HRs are employed in studies in which researchers have access to the time of event, such as death,

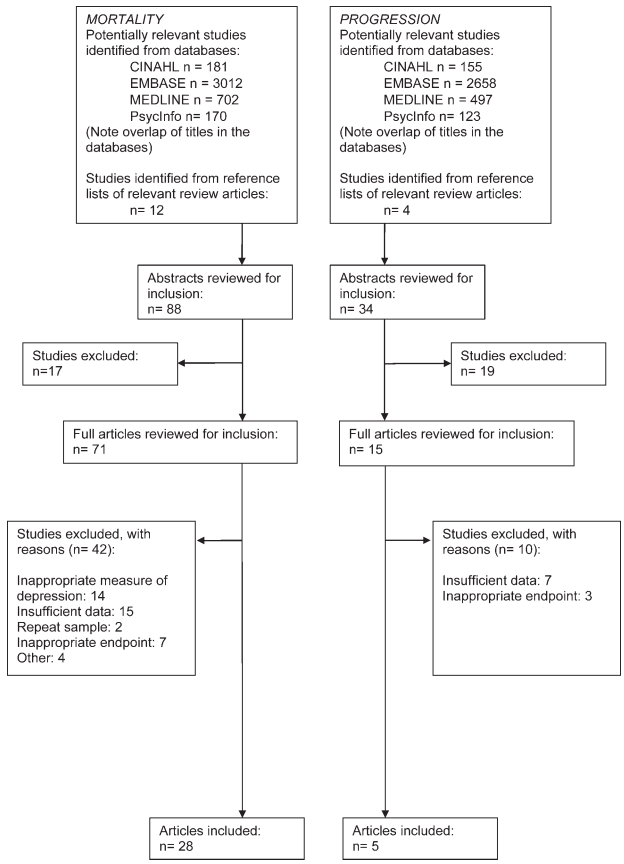

FIGURE 1. The systematic review process is depicted in a flow chart.

for each patient, rather than assessing number of events at 1 time point as is true in the calculation of RRs. In cases where the required data were provided only in a Kaplan-Meier survival curve, RRs were computed from the time of last follow-up.

We divided RRs and HRs into those that adjusted for known clinical prognosticators versus unadjusted values. These factors include, in varying combinations across studies: age, gender, histologic grade, Karnofsky performance status, number of positive lymph nodes, pathologic stage, preoperative percentage forced expiratory volume in 1 second, serum albumin level, smoking status, and treatment status.

The studies have been further dichotomized into those that follow patients for less than 5 years and those that follow patients for more than 5 years. A 5-year time span was chosen as a benchmark because it is conventionally used in defining survival within the cancer literature.

The Comprehensive Meta Analysis (CMA) Version 2.0 software program[61] was used to synthesize the data

Table 1. Characteristics of Included Studies

First Author, Year, Country	No. of Participants, Cancer Type, Sex, Mean Age When Available	Outcome, Length of Follow-Up	Measure of Depression
Andrykowski 1994,[30] United States	42, hematologic, both, 34.0	Mortality, <5 y	POMS
Barraclough 1992,[31] United Kingdom	204, breast, female, 54.3	Progression, <5 y	Interview
Beresford 2006,[32] United States	86, mixed, both, 55.5	Mortality, <5 y	BDI
Bergenmar 2004,[33] Sweden	436, melanoma, both	Progression, <5 y	HADS
Broers 1998,[34] Netherlands	123, hematologic, both, 35.4	Mortality, <5 y	SCL-90R
Brown 2003,[35] Canada	205, mixed, both, 56.3	Mortality, <5 y	CES-D
Buccheri 1998,[36] Italy	133, lung, both, 65.0	Mortality, <5 y	SDS
Chang 2004,[37] United States	114, hematologic, 44.0	Mortality, <5 y	BDI
Faller 2004,[38] Germany	57, lung, both, 65.0	Mortality, ≥5 y	HADS
Graham 2002,[39] United Kingdom	171, breast, female, 48.4	Progression, <5 y	Interview
Gripp 2007,[40] Germany	154, mixed, both	Mortality, <5 y	HADS
Groenvold 2007,[41] Denmark	1588, breast, female, 52.4	Mortality, ≥5 y	HADS
Grulke 2008,[42] Germany	138, hematologic, both, 40.9	Mortality, <5 y	HADS
Lam 2007,[43] Hong Kong	170, mixed, both, 69.0	Mortality, <5 y	HAM-D
Lehto 2007,[44] Finland	59, melanoma, both, 53.8	Mortality, ≥5 y	DEPS
Lloyd-Williams 2009,[45] United Kingdom	87, mixed, both, 69.0	Mortality, <5 y	EDS
Mainio 2006,[46] Finland	101, brain, both, 49.0	Mortality, ≥5 y	BDI
Murphy 1996,[47] United Kingdom	56, hematologic, both, 35.4	Mortality, ≥5 y	CIDI, DSM-III
Nakaya 2006,[48] Japan	229, lung, both	Mortality, ≥5 y	SCID, DSM-III-R
Nakaya 2008,[49] Japan	1178, lung, both, 64.0	Mortality, ≥5 y	HADS
Onitilo 2006,[50] United States	876, mixed, both, 72.25	Mortality, ≥5 y	CES-D
Osborne 2004,[51] Australia	61, breast, female, 55.5	Mortality, ≥5 y	HADS
Phillips 2008,[52] Australia	708, breast, female (mortality) 638, breast, female (progression)	Mortality/progression, ≥5 y	HADS
Pirl 2008,[53] United States	43, lung, mixed, 65.6	Mortality, <5 y	HADS
Prieto 2005,[54] Spain	199, hematologic, both	Mortality, ≥5 y	MSKCC, DSM-IV
Richardson 1990,[55] United States	137, mixed, both	Mortality, <5 y	BDI, SDS
Ringdal 1996,[56] Norway	239, mixed, both, 57	Mortality, <5 y	HADS
Saito-Nakaya 2008,[57] Japan	816, lung, both, 63.9	Mortality, ≥5 y	HADS
Steel 2007,[58] United States	103, hematologic, both, 61.0	Mortality, <5 y	HADS
Stommel 2002,[59] United States	871, mixed, both, 70.1	Mortality, <5 y	CES-D
Watson 2005,[60] United Kingdom	578, breast, female, 55.0	Mortality/progression, ≥5 y	HADS

BDI indicates Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CIDI, Composite International Diagnostic Interview; DAC, Depression Adjective Checklist; DEPS, Depression scale; EDS, Edinburgh Depression Scale; HAM-D, Hamilton Depression Scale; HADS, Hospital Anxiety & Depression Scale; MSKCC, Memorial Sloan-Kettering Cancer Center – modified DSM-IV approach; POMS, Profile of Mood States; PSI, Psychiatric Symptom Index; SCID, Structured Clinical Interview - Depression; SCL-90R, Symptom Checklist 90-R; SDS, Zung's Self-Rating Depression Scale.

into overall effect sizes by weighing the effect sizes for sample size. RRs and HRs above 1.00 indicate a greater risk of death or disease progression in those who are diagnosed with major depression disorder or exhibiting depressive symptoms, while RRs and HRs below 1.00 would indicate that depression is a protective factor in terms of mortality or disease progression.

The random effects model was chosen for between-group comparisons because of 1) the known heterogeneity of study design and participant characteristics as is inherent in epidemiological research,[62] 2) variability between cancer populations in the studies examined, and 3) the finding that the random effects model makes fewer assumptions about shared population characteristics and is therefore more conservative.[63]

Heterogeneity

Between-study heterogeneity was assessed using the I^2 statistic, which reflects the percentage of variation attributable to heterogeneity. p values less than .05 indicate heterogeneity, and I^2 values approximate the proportion of variation of effects due to heterogeneity between studies.[64]

RESULTS

Progression

Description of studies

We report on 5 articles,[31,33,39,52,60] published between 1992 and 2008, that examined the effect of

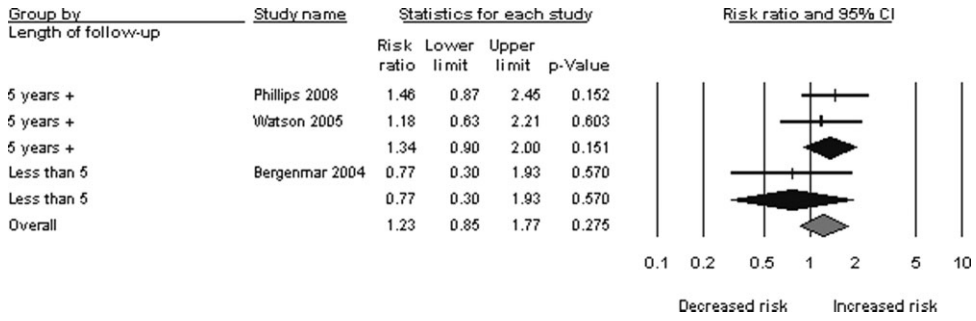

FIGURE 2. Effect of depressive symptoms on recurrence is shown with unadjusted risk ratios.

depression on cancer recurrence and that met all inclusion criteria. Two studies had follow-ups of 5 years or longer, and 3 had a follow-up of less than 5 years. Study characteristics are described in Table 1.

Type of participants

A total of 2097 patients participated in the included studies. The sample sizes of each study range from 171 to 708. Of the 5 articles examining the effect of depression on cancer progression, 4[31,33,37,39,52,60] examined patients with breast cancer and 1 examined patients with melanoma.[33] Average age, based on data available from 4 out of 5 studies, was 47.8 years.

Measurement of Depression

Depressive symptoms

Three studies measured depressive symptoms,[33,52,60] each using the Hospital Anxiety and Depression Scale (HADS).

Clinical depression

Two studies assessed the presence of major or minor depressive episode using clinical interviews based on criteria from the Diagnostic and Statistical Manual (DSM-III and DSM-III-R).[31,39]

Effect of depressive symptoms on cancer progression

The results of the effect of depressive symptoms on cancer recurrence are presented in Figure 2. Effects are presented as unadjusted RRs. Combining across studies that measure depressive symptoms, the resulting RR is 1.23 (95% confidence interval [CI], 0.85-1.77, $P = .275$, $k = 3$). The result is based on homogeneous effects ($P = .483$; $I^2 = 0.0\%$; Fig. 2).

Effect of clinical depression on cancer progression

The 2 available effect sizes cannot be combined with others due to the lack of studies utilizing the same statistics. Graham et al[39] provided an unadjusted RR (RR = 1.179; 95% CI, 0.42-3.24; $P = .764$) and Barraclough et al[31] provided an adjusted HR (HR = 1.26; 95% CI, 0.49-3.25; $P = .633$).

Mortality

Description of studies

Twenty-seven observational studies,[30,32,34-38,40-60] performed between 1990 to 2009, fulfilled inclusion criteria (Table 1). Twenty-five independent studies were based on measures of depressive symptoms, and 3 independent studies measured major or minor depression. Sixteen studies examined survival at less than 5 years postdiagnosis, and 11 studies examined survival at 5 years or longer.

Type of participants

A total of 9417 cancer patients participated in the included studies; the number of participants in each study ranged from 16 to 1588. Populations included: breast cancer ($k = 4$)[41,51,52,60]; lung cancer ($k = 6$)[36,38,48,49,53,57]; brain cancer ($k = 1$)[46]; melanoma ($k = 1$)[44]; and hematological malignancies ($k = 7$).[30,34,39,42,47,54,57] Nine studies included participants with varying cancer diagnoses (ie, mixed).[32,35,40,43,45,50,55,56,59] The 4 studies that included breast cancer patients comprised all female patients, and the remaining studies included both genders. The overall mean age, calculated from studies reporting mean age ($k = 23$), was 55.4 years. The range of available mean ages is 34.0-72.5 years.

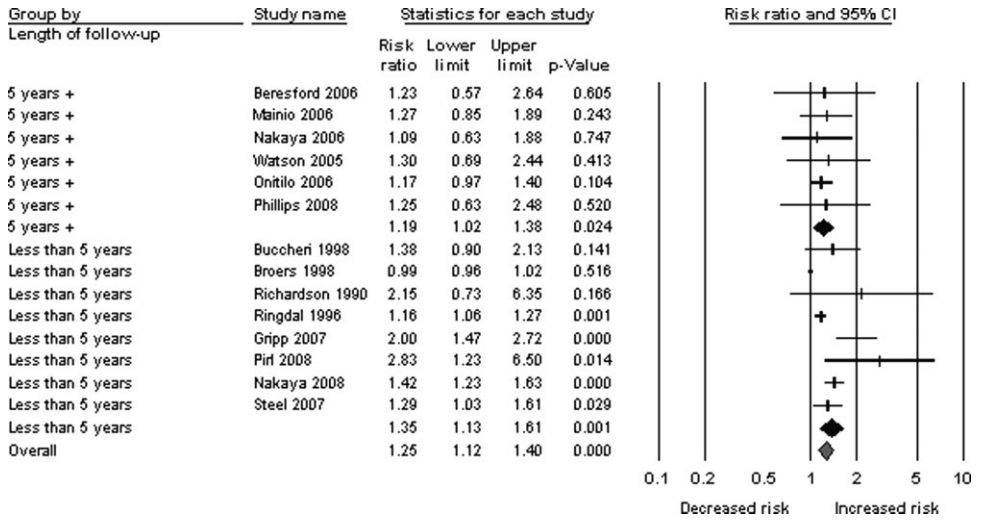

FIGURE 3. Effect of depressive symptoms on mortality is shown with unadjusted risk ratios.

Measurement of Depression

Depressive symptoms

Twenty-four studies measured the effect of clinical symptoms by using standardized self-report questionnaires. Subjects were divided into those scoring high versus those scoring low, which was based on cutoff scores or median splits. The most commonly used diagnostic instrument was the Hospital Anxiety and Depression Scale (HADS; $k = 11$). The variety of other standardized instruments included: Beck Depression Inventory (BDI; $k = 4$); Center for Epidemiologic Studies Depression Scale (CES-D; $k = 4$); Depression Scale (DEPS; $k = 1$); Edinburgh Depression Scale ($k = 1$); Profile of Mood States ($k = 1$); Symptoms Checklist-90-Revised (SCL-90-R; $k = 1$); and Zung Self-Rating Depression Scale (SDS; $k = 1$).

Clinical depression

Three studies examined the effect of current major or minor depressive episode on mortality in cancer patients.[47,48,54] These studies relied on clinical interviews based on the Diagnostic and Statistical Manual (DSM-III-R and DSM-IV) to confirm the presence of major or minor depressive episode.

Effect of depressive symptoms on mortality in cancer patients

The combined RR (unadjusted), including 14 effect sizes from 14 independent studies is 1.25 (95% CI, 1.12-1.40, $P < .001$) (Fig. 3). The result is based on heterogeneous effects ($P < .001$; $I^2 = 80.9\%$).

When analyzed by length of follow-up, studies that assessed mortality after less than 5 years yielded a significant result (RR = 1.35; 95% CI, 1.13 – 1-61; $P = .001$), as did the studies that assessed mortality at 5 years or later (RR = 1.19; 95% CI, 1.02 – 1-38; $P = .024$). Heterogeneity is an issue in the group of studies with follow-ups of less than 5 years ($P < .001$; $I^2 = 89.1\%$), but not in the longer follow-up group ($P = .997$; $I^2 = 0.0\%$).

Two studies[35,41] that adjusted for clinical factors were appropriate for calculating RRs. Their combined effect just failed to reach significance (RR = 1.27; 95% CI, 0.99 – 1.62; $P = .055$).

The combined HR (unadjusted), including 9 effect sizes from 8 independent studies was 1.05 (95% CI, 1.01-1.09, $P = .007$) (Fig. 4). The result is based on moderately heterogeneous effects ($P = .012$; $I^2 = 59.0\%$). When analyzed by length of follow-up, the 7 effects based on follow-up lengths of less than 5 years yielded a significant effect (HR = 1.05; 95% CI, 1.01-1.09; $P = .008$), while the 2 effects that assessed mortality after 5 years or longer did not yield a significant effect (HR = 1.15; 95% CI, 0.70-1.88; $P = .588$). When assessing heterogeneity within length of follow-up, heterogeneity remains in the shorter follow-up group ($P = .004$; $I^2 = 68.9\%$), but not in the longer follow-up group, which included only 2 studies ($P = .831$; $I^2 = 0.0\%$).

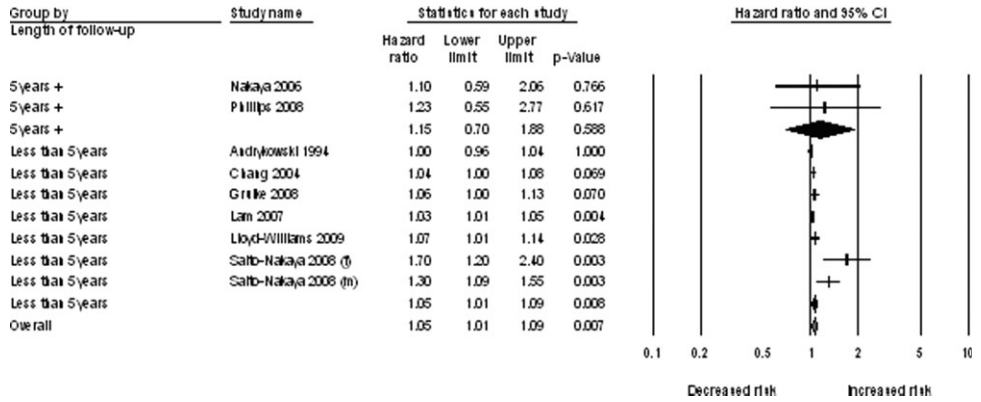

FIGURE 4. Effect of depressive symptoms on mortality is shown with unadjusted hazard ratios.

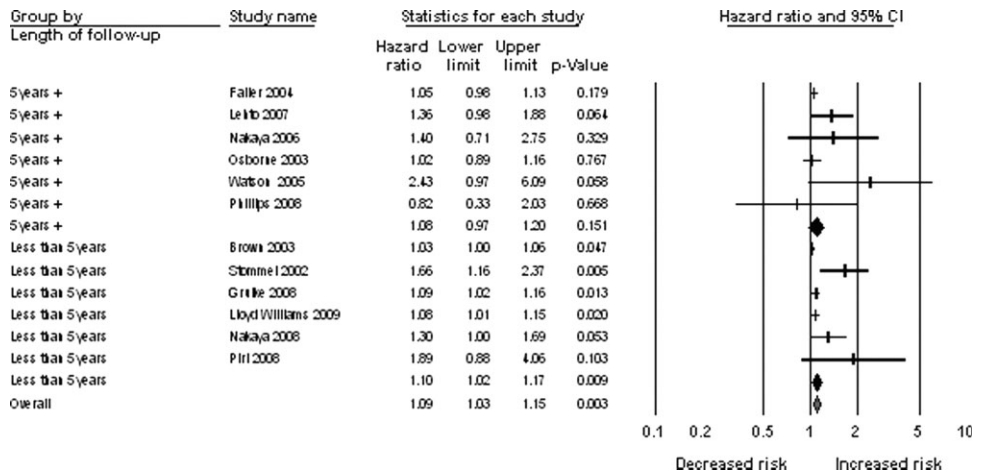

FIGURE 5. Effect of depressive symptoms on mortality is shown with adjusted hazard ratios.

The combined HR (adjusted), including 12 effect sizes from 12 independent studies, is 1.09 (95% CI, 1.03-1.15, $P = .003$). The result is based on moderately heterogeneous effects ($P = .030$; $I^2 = 48.42\%$). When analyzed by length of follow-up, the 6 effects based on follow-up lengths of less than 5 years yielded a significant effect (HR = 1.10; 95% CI, 1.02-1.17; $P = .009$), while the 6 effects after 5 years or longer did not yield a significant effect (HR = 1.08; 95% CI, 0.97-1.20; $P = .151$). Again, heterogeneity was more problematic in the shorter follow-up group ($P = .013$; $I^2 = 63.6\%$) than in the longer follow-up group ($P = .241$; $I^2 = 25.7\%$; Fig. 5).

Effect of clinical depression on mortality in cancer patients

The overall RR (unadjusted), including 3 studies is 1.39 (95% CI, 1.03-1.89, $P = .033$), as displayed in Figure 6. The result is based on heterogeneous effects ($P < .001$; $I^2 = 80.9\%$). The overall HR (adjusted), including 2 studies, is 1.67 (95% CI, 0.96-2.90, $P = .07$). Only Nakaya et al[49] provide an unadjusted HR (HR = 2.0; 95% CI, 0.80-5.00; $P = .138$) (Fig. 6).

Because the studies included in the meta-analyses were few in number and varied in both methodologies and patient samples, there was inadequate power to test potential moderating variables, such as type of cancer, age, gender, and time of measurement (see Table 1 for study characteristics).

Publication bias

Despite efforts to reduce bias through comprehensive review of the existing literature, asymmetrical funnel plots suggest publication bias. Copies of the funnel plots are available from the authors upon request. The classic

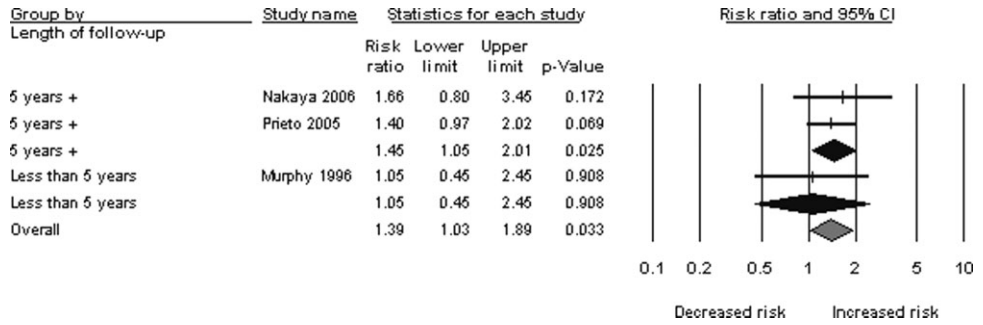

FIGURE 6. Effect of major or minor depressive episode on mortality is shown with unadjusted risk ratios.

fail-safe N's are more promising: fail-safe N = 143 (effect of depressive symptoms on mortality, unadjusted RRs; $k = 14$); fail-safe N = 54 (effect of depressive symptoms on mortality, unadjusted HRs; $k = 9$); and fail-safe N = 83 (effect of depressive symptoms on mortality, adjusted HRs; $k = 12$).

DISCUSSION

The current meta-analysis presents fairly consistent evidence that depression is a small but significant predictor of mortality in cancer patients. Estimates were as high as a 26% greater mortality rate among patients endorsing depressive symptoms and a 39% higher mortality rate among those diagnosed with major depression. There is no evidence that the effect weakens when adjustments are made for other known risk factors, suggesting that depression may be an independent risk factor in cancer mortality, rather than merely correlating with biological factors associated with a poor prognosis.

The association between depression and cancer progression did not emerge as significant, although only 3 studies were available for meta-analysis. It is rather surprising that depression is shown to predict mortality but not disease recurrence, especially given that research based on animal models clearly demonstrated the effect of stress on metastasis and tumor growth.[4] We postulate that this difference is primarily due to the limited numbers of studies and correspondingly low power.

It is somewhat difficult to appreciate the meaning of the overall effect sizes because benchmarks have not been established for describing the magnitude of risk or hazard ratios as small, medium, or large, as has been done with the Cohen *d*, for example. For the sake of comparison, a previous meta-analysis comparable to, in methodology, our meta-analysis found that depressed patients with coronary heart disease have a 2-times greater risk of mortality than nondepressed patients after adjusting for clinical factors,[65] thus revealing a more robust and convincing effect linking depression to mortality in cardiac disease.

Limitations

A limitation of the current meta-analysis is the combining of studies that adjust the effect of depression on mortality for varying clinical factors. It would be more rigorous to combine only those studies that control for the same factors; however, there are simply not enough studies that include the same clinical prognosticators to make comparisons meaningful.

Publication bias is an issue that must be considered in all meta-analyses. Our funnel plots raise this concern; however, as we have demonstrated, a major file-drawer problem is not likely here. A more pertinent concern lies in the exclusion of studies with insufficient data to compute RRs or HRs ($k = 15$).[66-80]

There was evidence of considerable heterogeneity in the overall results, which had a tendency to diminish in the studies of longer follow-ups. The presence of heterogeneity was not surprising considering the variability among studies, especially among cancer type. The random-effects model was, therefore, appropriate so that the summary effect sizes can be conceptualized as average effects, rather than syntheses of effects, as would be reflected using the fixed-effects model.[63]

Last, the meta-analysis can make statements only about the effect of depression on all-cause mortality in cancer patients, rather than cancer-specific deaths, because the majority of studies do not differentiate cause of death.

Recommendations

Our meta-analysis presents reasonable evidence that depression status modestly predicts mortality in cancer patients. The inability to reach firmer conclusions rests in the varied methodologies undertaken in research studies assessing psychological variables, and, hence, it limits the generalizability and translation of these findings into practice. As such, we propose a number of future recommendations:

1) The HR is considered to be a superior measure of effect size compared with the odds ratio or RR by taking multiple endpoints into account. We, therefore, recommend the use of HRs when actual time of death is available.
2) Depression should be measured and analyzed at multiple time-points. This type of analysis was available only in 1 included study,[35] in which both baseline and time-dependent analyses were conducted. A demonstration of the deleterious effect of depression on cancer mortality and recurrence might end up being "watered-down" if some patients are showing signs of depression at diagnosis but then recover on their own. If measuring depression at 1 time-point, we suggest measuring a minimum of a 1-month period post-diagnosis. If depression is assessed during this 1-month period, then a normal reaction to the receipt of a diagnosis of a life-threatening illness may be captured, rather than the onset of a clinically significant problem that may affect health behaviors and outcomes.[81]
3) It is not clear from the present meta-analysis if there is an ideal length of follow-up to capture a survival effect. Our results suggest a tendency for the effect to be present within the first 5 years and to weaken with longer follow-up. This is consistent with a review of the effect of depression on cancer progression, which reported that the average follow-up length for positive findings was 5 years, while the average length of follow-up for negative findings was 10 years.[25] It would be ideal to present results for both early and late follow-ups.
4) Whenever possible, cancer-specific mortality should be reported separately from all-cause mortality to draw conclusions about the direct impact of depression on cancer outcome. Because depression has been shown to be associated with a higher mortality rate in the general population,[82] cancer-specificmortality must be studied to appreciate the effect of depression on cancer outcomes.
5) Studies with large sample sizes for specified cancer subtypes are required to test the potential moderating effects of variables such as cancer stage, cancer grade, gender, and age. Cancer type is perhaps the most important factor to consider because cancer types differ in symptomatology, prognosis, patient profile (eg, age, gender), treatment options and associated side-effects and present unique issues, such as loss of function and disfigurement. Cancer type also varies with respect to the involvement of the immune system, making some cancer sites more susceptible to influences by psychological factors.[8] However, assessing mortality risk inherent in depression separately for different cancer types requires exceptionally large samples that will be difficult and expensive to acquire.

   Cancer stage and grade are other important factors to consider. It is a reasonable assumption that depression would have a greater effect in earlier stages of disease, before the cancer has progressed. In contrast to this assumption, physical vulnerability has been found to increase the effect of stress on immune change, making it possible that a later stage of cancer would actually increase the effect of depression on cancer outcomes.[83] It has been suggested that very early and very advanced tumors as well as cancers with virulent cell histopathology (eg, lung or pancreatic cancer) rarely deviate from their expected course and are, therefore, less likely to be affected by psychological factors.[84] These questions, however, remained unanswered in our analyses.
6) Although depression is the most commonly studied psychological variable with respect to cancer outcomes, it does not follow that it necessarily has the strongest effect on survival or disease severity. In a recent review of the prognostic significance of patient-reported outcomes in cancer clinical trials, quality of life was shown to commonly predict survival perhaps even better than performance status.[85] Because the latter review was not a meta-analysis and used different inclusion criteria, we cannot compare the predictive abilities of quality of life and depression; but, we

recognize that this is an exciting opportunity for research using positive psychology constructs.

Summary

The present meta-analysis synthesized a substantial body of research. The search strategy for this meta-analysis was systematic and inclusive and the analysis is based on high levels of evidence by including only prospective studies. The finding that depressive symptoms and clinical diagnosis of depression predict mortality in cancer patients highlights the need to continue this line of research. However, it is important to acknowledge that the overall effect sizes are relatively small and that causality has not been absolutely established. We would like to highlight that this meta-analysis does not support a need for patients and their families to feel responsible for their disease outcome if they experience depression. It has become accepted in popular culture that cancer patients need to maintain a positive attitude to heroically defeat cancer, a recommendation that Spiegel and Giese-Davis[25] have termed an "emotional straightjacket." Even if one did ascribe to this belief, the magnitude of the effect of depression on mortality does not seem to warrant the assignment of responsibility and blame to cancer patients.

Considering the existing but moderately sized evidence that depression places cancer patients at greater risk of death, it is not surprising that studies assessing the impact of psychological treatment often fail to find significant effects on cancer mortality. Nevertheless, our meta-analysis provides an empirical justification for systematic screening of psychological distress and subsequent treatments. We know that psychological treatment can reduce subjective distress but if the psychological treatment is proposed to affect mortality by ameliorating depression, it can do so only when treatment successfully reduces this risk. This implies a mediator model that needs to be tested, a crucial step that is often omitted in behavioral medicine research.[86] Although psychological treatment should be available to distressed cancer patients for assistance in coping with the burden of a chronic life-threatening illness, an impressive improvement in survival is unlikely unless a subgroup is identified that could benefit more than others.

Conflict of Interest Disclosures

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