Depression and Cancer: Mechanisms and Disease Progression

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Depression and cancer commonly co-occur. The prevalence of depression among cancer patients increases with disease severity and symptoms such as pain and fatigue. The literature on depression as a predictor of cancer incidence is mixed, although chronic and severe depression may be associated with elevated cancer risk. There is divided but stronger evidence that depression predicts cancer progression and mortality, although disentangling the deleterious effects of disease progression on mood complicates this research, as does the fact that some symptoms of cancer and its treatment mimic depression. There is evidence that providing psychosocial support reduces depression, anxiety, and pain, and may increase survival time with cancer, although studies in this latter area are also divided. Psychophysiological mechanisms linking depression and cancer progression include dysregulation of the hypothalamic-pituitary-adrenal axis, especially diurnal variation in cortisol and melatonin. Depression also affects components of immune function that may affect cancer surveillance. Thus, there is evidence of a bidirectional relationship between cancer and depression, offering new opportunities for therapeutic intervention. Biol Psychiatry 2003;54:269-282 © 2003 Society of Biological Psychiatry

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Introduction

Depression in patients with cancer has been underdiagnosed and undertreated due, in part, to the belief that depression is a normal and universal reaction to serious disease (Newport and Nemeroff 1998; Rodin and Voshart 1986; Spiegel 1996) and, in part, because the neurovegetative signs (weight loss, sleep disturbance) or emotional/cognitive signs of depression are often attributed to the medical illness itself (Craig and Abeloff 1974; McDaniel et al 1995). Thus, serious medical and psychi-

atric comorbidity is often overlooked, leading to undertreatment that complicates cancer and depression and at the least adversely affects patients' quality of life.

Depression Among Cancer Patients

Rates of depressive states reported for cancer inpatients are roughly comparable to similarly ill patients with other medical diagnoses (Evans et al 1999). Studies of medical inpatients show that one third report mild or moderate symptoms of depression, and up to one fourth may suffer from major depression (McDaniel et al 1995) or a depressive syndrome (Katon and Sullivan 1990; Atkinson et al 1988). However, some studies show that rates of major depression among cancer patients are similar to those in the general population (Lansky et al 1985). Comorbid depression, in turn, is associated with increased functional impairment and poorer quality of life over the course of chronic illness (Katon and Sullivan 1990; Weitzner et al 1997), as well as reduced optimism about the effectiveness of medical treatment (Cohen et al 2001). Cancer and depression severity have interactive and deleterious effects on quality of life. More rapid progression and increased symptoms of cancer, especially pain (Spiegel and Bloom 1983b), are associated with more severe depression (Bukberg et al 1984; Spiegel et al 1994).

These studies suggest that the severity of the medical illness, irrespective of its underlying cause, is the factor most closely associated with the frequency of both depressive symptoms and syndromes. Indeed, major depression is diagnosable in as many as 58.5% of terminally ill patients requesting assisted suicide (Chochinov et al 1995) and was a major determinant of the will to live among 585 cancer patients in palliative care (Chochinov et al 1999). In a study of 988 terminally ill patients, depressive symptoms were significantly associated with interest in euthanasia or physician-assisted suicide (odds ratio [OR] 5.29; 95% confidence interval [CI], 1.21-23.2), an effect size similar to that of pain (OR 1.26; 95% CI, 1.02-1.56) (Emanuel et al 2000). One encouraging finding from a meta-analysis of 58 studies is that the prevalence of depression among cancer patients has decreased during the

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past two decades (van't Spijker et al 1997). This may reflect improvements in treatment, including less mutilating surgical interventions (e.g., lumpectomy vs. mastectomy for breast cancer) (Wellisch and Carr 1991; Pozo et al 1992; Levy et al 1992), improved medical outcomes (Peto et al 2000), and an improved atmosphere of social support for cancer patients (Spiegel 2001).

However, an even more interesting question is the relationship between depression and cancer progression—to what extent does depression not merely complicate the emotional course of cancer but affect its medical course?

Depression as a Predictor of Cancer Incidence, Progression, and Mortality

The literature on the association between depression and subsequent cancer incidence, progression, and mortality is divided, although a preponderance of the studies demonstrate a connection, and only one (Derogatis 1979) showed that depression seemed to have a protective effect against cancer (see review Giese-Davis and Spiegel 2003). At the time of the Giese-Davis and Spiegel (2003) review, the evidence linking depression to cancer incidence was weaker than that connecting it to progression. There were 30 studies examining a possible link between depression and cancer incidence, with only 6 finding a positive association. There were 24 published studies testing whether depression was linked with cancer progression, and 15 reported positive associations. In our previous chapter, we review in detail 9 of the cancer incidence and 12 of the cancer progression studies. Here, we review several early classical and major studies published in the last 10 years examining the connection between depression and cancer. Unfortunately, in the majority of these studies, depression is not assessed with diagnostic interviews, the quality of self-report measures vary, and longitudinal assessment of depression is rare. Thus, resulting conclusions are best attributed to general distress or a mixture of depression and anxiety symptoms. Conclusions about diagnosable depression cannot be drawn from the literature currently available.

Recent Major Studies

In six major studies within the last 5 years, depression was found to predict cancer incidence, progression, or mortality, consistent with the Shekelle et al (1981) early classical study (Persky et al 1987; Everson et al 1996; Penninx et al 1998; Loberiza et al 2002; Stommel et al 2002; Herrmann et al 1998; Watson et al 1999) (see Table 1).

In the Everson et al (1996) study, they assessed hopelessness, disease history, and biological, behavioral, and socioeconomic measures of 2428 men from the Kuopio region in Eastern Finland. All-cause as well as specific mortality was tested over 6 years. This was a population-based study, with about 83% of those eligible enrolled. They used a Finnish Cancer Registry to confirm cancer incidence and a national death registry to confirm and categorize death. They found a dose-response relationship with levels of hopelessness, with moderate and high scorers having more than a twofold increase in risk of cancer death.

Penninx et al (1998) assessed subjects at interviews in 1982, 1985, and 1988 in a well-designed prospective study of 4825 male and female subjects aged 71 and older from East Boston, Iowa, and New Haven, Connecticut. Participants who scored above 20 on the Center for Epidemiological Studies-Depression Scale (CES-D) at each of the three time points met criteria for depression (n=146). This chronic depression significantly predicted cancer incidence. In this study, they separated smoking and chronic depression. In fact, the risk for developing cancer was higher for the nonsmokers than for the smokers.

In the Loberiza et al (2002) study, patients receiving hematopoietic stem-cell transplantation (HSCT) were followed from before transplantation to 24 months post-HSCT with questionnaires; however, depressive syndrome was not assessed until the 6-month follow-up. Therefore, depression related to survival beyond 6 months was tested and was found to be predictive of early death when patients lived less than 12 months from transplantation. This study is limited by the use of a measure of "depressive syndrome" rather than a validated measure of depression. Their measure (a checklist authors created of depression symptoms) was highly correlated with the Medical Outcomes Study (MOS) 36-Item Short Form (SF-36) (Ware and Sherbourne 1992) and with poorer quality of life on the Spitzer Quality of Life Index Scale (Spitzer et al 1981). In addition, effect of depressive symptoms on survival held when medical factors such as graft-versushost disease were controlled. Thus, while the depression measure lacked specificity and there could have been error variance associated with it, depression strongly predicted higher mortality 1 year later.

Stommel et al (2002) elected to equate negative health status with a prior history of depression or emotional problems or physical limitations and used it to predict cancer mortality in a sample of 871 cancer patients in Michigan. They found that those with either a prior history of emotional problems or physical limitations were at increased risk of early death, but the combination of the two increased risk by 2.6 times. Contrary to these findings, those people experiencing a new depression or physical

limitation subsequent to diagnosis were at no greater risk of early death than those who reported none.

Herrmann et al (1998) utilized the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) as a routine screening tool when patients were admitted to general medical wards at a hospital in Gottingen, Germany. This study examined the odds of death for all-cause mortality but included separate subgroup analyses of cardiopulmonary disease and hematologic diseases or cancer. Higher HADS depression scores significantly predicted higher mortality in all groups.

Lastly, Watson et al (1999) assessed 578 women with early stage breast cancer for depression and coping style 4 to 12 weeks after diagnosis. Helpless/hopelessness significantly predicted shorter event-free but not overall survival at 5 years. High depression (HADS) significantly predicted overall survival and became stronger when adjusted for prognostic factors. However, depression did not predict event-free survival.

In five major studies, no association between depression and disease progression was found (Zonderman et al 1989; Bleiker et al 1996; Kaplan and Reynolds 1988; Teno et al 2000; Tross et al 1996) (Table 2).

One possible reason for the disparity in findings is follow-up time. The average follow-up time in the positive studies is 5 years, while that in the negative studies is 10 years. One might conclude that the studies with longer follow-up are more definitive, but this is not necessarily the case. Longer follow-up may be possible in less lethal forms of cancer. Alternatively, different factors may predict shorter versus longer-term mortality. Other factors may supplant but not eliminate the predictive importance of depression as follow-up time is extended. As survival time is extended, other intervening health factors are more likely to account for mortality, thereby obscuring any possible specific relationship between depression and specific disease-related mortality. Furthermore, the fact that the associations in many of these studies are predictive over a substantial time period reduces the likelihood that the associations are based on an effect of disease on mood rather than the other way around. Nonetheless, studies that more completely account for ultimate survival time with high proportions of mortality are more likely to be definitive.

The average sample size was twice as large in the null studies as in the positive ones (5002 vs. 2424). This would also seem to lend greater weight to the null findings, but there is an asymmetry in statistics such that a larger sample is needed to prove the absence rather than the presence of an association—a significant relationship in a small population is notable, while the absence of one is less definitive in a relatively small population. Nonetheless, the null studies were in general adequately powered to detect a difference.

There are three other recent studies with ambiguous results. The Dalton et al (2002) study merits further discussion, and this large sample (89,491) was not included in the above size estimates. They found an elevated rate of cancer in a large systematic study of all patients hospitalized with depression in Denmark over a 24-year period but concluded that depression per se had no effect on cancer rates. On subanalysis, they attributed the overall relationship to an association with tobacco-related cancers; however, they had no data regarding possible differences in tobacco use among depressed patients, so the effect could not automatically be attributed to differential use of tobacco products. Indeed, several studies have found that cancer risk is elevated in depressed heavy smokers more than in nondepressed heavy smokers (Linkins and Comstock 1990; Knekt et al 1996), indicating an interaction in which depression potentiates cancer risk from smoking. Methodologically, it is questionable to attribute a main effect finding to a subgroup relationship, unless it was specifically hypothesized before the overall analysis. While their interpretation of their data is plausible, they do not necessarily explain the finding.

While Bleiker et al (1996) found in a large case control trial that depression did not predict cancer incidence, anti-emotionality did. This finding is consistent with that from a prospective cohort study of 939 men born between 1900 and 1920 which found that control of depression was related to cancer incidence (fully adjusted relative risk [RR] = 1.7; 95% CI, 1.0-2.8) and mortality (RR = 2.2; 95% CI, 1.1-4.6) (Tijhuis et al 2000). In this study, overall emotional control was not related to disease progression, but control of depression was related.

Thus, one factor that may moderate the relationship between depression and cancer is the management of it, with emotional overcontrol adding to the deleterious effect of the disease itself. The tendency to overcontrol emotion has also been linked to elevated risk of cancer incidence or progression (Greer 1993; Greer and Morris 1975). Greer and Morris (1975) found that patients who reported extreme suppression were at higher risk for cancer. These people "had never or not more than twice during their adult lives openly shown anger and nearly always concealed other feelings," which are statements very similar to statements common for repressors (Weinberger 1990). A recent meta-analysis has confirmed that emotional repressiveness is a predictor of cancer incidence (McKenna et al 1999). While this repressive emotional style, often dubbed the cancer personality (Watson et al 1991; Baltrusch et al 1991), may mask self-report of depression and other symptoms, physiologic assessments in repressors are consistent with distress (Weinberger et al 1979). In addition, studies show that those who tend to deliberately suppress such emotions are more likely to be

Table 1. Studies Linking Depression to Cancer Incidence, Progression, and Mortality

Authors and Year	Sample	n	Design	Measure of Depression	
Shekelle et al 1981	Random sample of 5397 men, Western Electric employees		Prospective	MMPI	
Persky et al 1987	Random sample of 5397 men, Western Electric employees	2020	Prospective	ММРІ	
Everson et al 1996	Men from Kuopio (Finland) Ischemic Heart Disease Study	2428	Prospective	Hopelessness Scale	
Penninx et al 1998	Elderly cohort	4825	Prospective	CES-D, depressed at three time points	
Loberiza et al 2002	Hematopoetic stem cell transplant recipients	193	Prospective	"Depressive syndrome"	
Stommel et al 2002	Cancer patients	871	Prospective	CES-D	
Herrmann et al 1998	rrmann et al 1998 Consecutive medical admissions (Hematology/Oncology $n = 96$)		Prospective	HADS	
Watson et al 1999	Women with primary breast cancer	578	Prospective	HADS depression	
Dalton et al 2002	lton et al 2002 All adults in Denmark psychiatrically hospitalized with depression		Retrospective	Hospital diagnosis	
Felitti et al 1998	Adverse Childhood Experiences (ACE)	9508 HMO patients	Retrospective	NIMH Diagnostic Interview Schedule	
Tijhuis et al 2000	Elderly men	939	Prospective	CECS	

MMPI, Minnesota Multiphasic Personality Inventory; RH, relative hazard; CI, confidence interval; CES-D, Center for Epidemiological Studies-Depression Scale; RR, relative risk; HADS, Hospital Anxiety and Depression Scale; OR, odds ratio; HMO, health maintenance organization; NIMH, National Institute of Mental Health; CECS, Courtald Emotional Control Scale.

overtly anxious and depressed (Classen et al 1996). Indeed, recent work indicates that there are at least four separable constructs in regard to emotion management among cancer patients: repressive-defensiveness, suppression, restraint, and distress (Giese-Davis and Spiegel 2001). While some, such as repressive-defensiveness, may be relatively fixed patterns of affect management or defense, we demonstrated in a recent randomized trial that supportive-expressive group psychotherapy for metastatic breast cancer patients resulted in a reduction of suppression and increased restraint of hostility (Giese-Davis et al 2002). Thus, cancer patients' styles of handling and reporting emotional distress may contribute additional variance to attempts to relate the distress itself, such as depression, to disease progression.

Lastly, a recent study found an indirect link between depression and cancer by examining the effect of adverse childhood experiences on the prevalence of both psychiatric and medical illness. Felitti et al (1998) found that the number of adverse childhood experiences was associated with relative risk of both depression and cancer, e.g., four or more such events were associated with a relative risk of

4.6 (95% CI, 3.8-5.6) of depression for 2 or more weeks in the past year and an RR of 1.9 (95% CI, 1.3-2.7) of having any cancer.

Methodological Factors Relevant to Differences in Results

What can one conclude from this literature? When researchers have made use of multiple measures of depression over time, thus establishing a chronic course for depression, it is more likely to be positively associated with cancer incidence. Most studies fail on this criterion, however, utilizing a single baseline measure of depression to predict cancer incidence many years later. Because this one-time measurement is likely to reflect transient shifts in mood or adjustment disorders that readily resolve, we are not surprised that so few cancer incidence studies find positive associations with depression. Of these studies, Penninx et al (1998) stands out as a model. The authors did not find higher cancer incidence when they used the one-time measurement of depression symptoms in 1988, methodology more similar to that employed in the remaining studies. We conclude that the evidence does not

Length of Follow-up	Cancer Incidence	Cancer Progression	Cancer Mortality	
17 years	17 years —		2.3-fold increase in odds of cancer death $(p < .001)$	
20 years	Relative hazard $= 1.40$	_	Relative hazard = 1.90	
6 years	Relative hazard = 1.80 95% CI 1.11, 2.92	_	Moderate RH = 2.25 95% CI 1.10, 4.58 High RH = 2.61 95% CI 1.03, 6.64	
3.8 years	RR = 1.88, 95% CI 1.13–3.14	_	_	
1 year	_	_	RR = 3, 95% CI 1.07, 8.30	
19 months	_	_	New depressive sx RH = 1.66, 95% CI 1.16–2.37 Prior emotional problems RH = 2.04, 95% CI 1.14–2.65	
22 months	_	_	Depression predicted mortality OR = 3.2, 95% CI 1.9–5.5	
5 years	_	p < .01, 65% alive with no recurrence	RH 3.59 (Watson et al 1999)	
24 years	RR = 1.05, 95% CI 1.03, 1.07; Non-tobacco-related cancers RR = 1.0, 95% CI .97, 1.03	_	_	
9 years	Elevated risk of depression and cancer related to severity of ACE Intermediate control of depression RR = 1.7, 95% CI 1.0–2.8	_	Intermediate and high control of depression RR = 2.1, 95% CI	
	1.7, 93% CI 1.0-2.0		1.0–4.3	

strongly support a link with cancer incidence, though methodological differences, especially involving the severity and chronicity of depression, may obscure results.

Stronger evidence links sustained depression after diagnosis to faster cancer progression or shorter survival. Depression at diagnosis that subsequently resolves may be a normal process that has no effect on cancer progression; however, both denial of depression at diagnosis (Dean and Surtees 1989) and depression that does not readily resolve (Levy et al 1991) have been linked with faster progression. On balance, the link between depression and cancer progression appears stronger. However, Whitlock and Siskund (1979) caution that these associations may merely reflect underlying physiologic processes mimicking depression symptoms but that are markers for tumor burden or cancer progression. Tumors can cause endocrine or cytokine changes that include disturbed sleep, greater fatigue or malaise, and reduced energy or vigor (Fife et al 1996). In addition, studies that control for vegetative symptoms of depression and still find associations between depression and cancer survival (Ehlers and Christiensen 2003) may not account for other symptoms or contingencies. For instance, greater pain may cause greater depression (Spiegel 1994), but this higher level of depression may be a marker of faster cancer progression. In addition, depression may reduce adherence to treatment, which could speed cancer progression. Lastly, most patients may experience greater distress when they are within a year of death (Butler et al 2003). We conclude that although there is support in the literature for an association between lingering depression and faster cancer progression, the field has yet to sort out the overlapping symptoms of increased tumor burden and vegetative depression.

This literature provides no support for the popular notion that people "give" themselves cancer. This misrepresentation can have the effect of creating an unwarranted sense of guilt. Nonetheless, depression may be one among a number of risk factors for cancer progression and warrants future prospective research.

Medical Effects of Psychosocial Treatment of Depression

These findings raise the possibility that effective treatment of depression and/or anxiety may affect the course of the disease as well as the patient's distress (McDaniel et al 1995; Clarke 1998). There are 10 published randomized

Table 2. Studies Showing No Effect of Depression on Cancer

Authors and Year	Sample	n	Type of Study	Depression Measure
Zonderman et al 1989	National Health and Nutrition representative sample	6913	Prospective	CES-D and General Well- Being Questionnaire
Bleiker et al 1996	Residents of Nijmegen (Netherlands) 43 or older	9705	Case-control	Self-Assessment Questionnaire- Nijmegen
Kaplan and Reynolds 1988	Population sample	6848 men and women	Prospective	HPL (Human Population Laboratory) Questionnaire
Teno et al 2000	Hospitalized medical patients (321—25% with cancer)	1266	Prospective	POMS
Tross et al 1996	Women with stage II breast cancer	280	Prospective	SCL-90-R

CES-D, Center for Epidemiological Studies-Depression Scale; RR, relative risk; CI, confidence interval; OR, odds ratio; POMS, Profile of Mood States; SCL-90-R, Symptom Checklist-90-Revised.

trials that examine this hypothesis (see Table 3). In all of them, both control and intervention groups received standard medical cancer treatment. While they were designed to reduce distress in general and enhance coping rather than treat depressive symptoms per se, in a number of cases there was a significant reduction in depressive symptoms on measures such as the Profile of Mood States' depression subscale (Spiegel et al 1981; Fawzy et al 1990; Goodwin et al 2001), most notably among patients who showed significantly elevated symptoms of mood disturbance at baseline (Goodwin et al 2001; Classen et al 2001). Since many effective treatments for depression involve cognitive and behavioral components that affect mood (Beck et al 1979; Dobson 1989), it is possible that a variety of interventions directed at behavior change and cognitive restructuring might also affect depressive and other related symptoms, such as anxiety, which commonly co-occur with depression in cancer patients (Kissane et al 1998; Payne et al 1999; von Essen et al 2000).

We found to our initial surprise that a year of Supportive/Expressive group psychotherapy not only reduced anxiety and depression, improved coping (Spiegel et al 1981), and reduced pain (Spiegel and Bloom 1983a) among metastatic breast cancer patients but also increased survival time by an average of 18 months (Spiegel et al 1989). Four other published randomized trials (Fawzy et al 1993; Richardson et al 1990; Kuchler et al 1999; McCorkle et al 2000) also found that various psychotherapies for cancer patients were associated with significantly longer survival time, as well as reduced psychiatric symptomatology. McCorkle et al (2000) conducted a large randomized trial of nursing home care intervention fol-

lowing cancer surgery. Three hundred seventy-five patients aged 60 to 92 were identified within 2 months of diagnosis of solid tumors. The intervention consisted of three home visits and five telephone calls. Analysis of the program indicated that it involved patient education (43%), monitoring physical and emotional status (25%), psychological support and reassurance (16%), referrals (11%), and other tasks (5%). While there were no survival differences among early stage patients (not surprising since the mean follow-up time was only 24 months), there was a treatment-related survival advantage for patients diagnosed with advanced disease ($\chi^2 = 9.2$, p < .002), with 67% 2-year survival in the intervention group and 40% in the control sample. Thus, this study indicates that even a brief home-based nursing intervention affected survival for more seriously ill older cancer patients.

While it could be argued that the Richardson et al (1990) and McCorkle et al (2000) interventions may have affected survival by improving medical treatment adherence, there was direct evidence in the Richardson et al (1990) study that treatment effects on survival time occurred independent of positive changes in adherence, and an analysis of adherence data after intervention from the Spiegel et al (1989) study indicated no differences in subsequent medical care that could account for the observed survival differences (Kogon et al 1997).

However, five randomized trials found no effect of psychotherapy on survival time of cancer patients. In two of the five studies, there were substantial psychological benefits but no survival advantage (Linn et al 1982; Goodwin et al 2001). The Goodwin et al (2001) study is

Follow-up	Cancer Incidence	Cancer Progression	Cancer Mortality
10 years	No prediction of cancer incidence RR = 1.1, 95% CI .9–1.4	-	No prediction of cancer mortality RR = 1.2, 95% CI .8–1.8
5 years	Depression not related antiemotionality OR 1.16, 95% CI 1.05–1.35	_	_
17 years	No difference depressed vs. nondepressed	_	No difference depressed vs. nondepressed
2 years	_	_	Depression did not add to prediction of mortality $(p = 6)$
15 years	_	Distress did not predict relapse RR = 1.01, 95% CI .622-1.66	Distress did not predict mortality RR = 1.03, 95% CI .58-1.82

notable for its large sample size (n=235), multicenter design, use of Supportive/Expressive group therapy, and beneficial effect on anxiety and depression as well as pain. The other three studies reported transient or no psychological benefit (Ilnyckyj et al 1994; Edelman et al 1999; Cunningham et al 1998) and no survival advantage. Thus, the literature is divided, with 5 of 10 published trials showing a survival effect of psychotherapeutic support. At the least, none show a survival deficit for those who receive emotional support, suggesting that the positive findings are not likely to be just random variation (Spiegel 2002). That five studies have been published indicating no survival advantage provides some evidence against the idea of positive publication bias.

What are the aspects of psychosocial intervention that seem to be most effective in reducing depression or potentially improving survival? It would seem that even brief interventions early in the course of cancer may be quite helpful (Kuchler et al 1999; Fawzy et al 2003; Richardson et al 1990; McCorkle et al 2000). These four trials produced remarkable psychological and medical results, with six or fewer patient interventions timed early in the course of disease, two right after initial surgical intervention (McCorkle et al 2000; Kuchler et al 1999). By contrast, those that have been psychologically and medically effective in late stage disease have been far longer, requiring a year or more to be effective in reducing distress (Spiegel et al 1981; Goodwin et al 2001). It is difficult to know when would be the right time to withdraw support for cancer patients with progressive terminal illness, so continuing psychosocial support until death would seem most helpful and would likely be most effective. This is one difference between the Spiegel et al (1989) and Goodwin et al (2001) studies. In the former, group intervention continued until death, with many patients participating in support groups for years, while in the Goodwin trial, the intervention ended after 1 year. Thus, parameters that include intervention timing, type, and duration are important variables in outcome. Though these interventions reduce distress, we cannot assume that this reduction mediated survival.

Depression and Cancer Progression: Physiologic Mechanisms

Depression and Treatment Adherence

How might depression affect the incidence or progression of cancer? Depression might affect behavior and adherence to medical treatment (Pirl and Roth 1999). Psychological distress interferes with adherence to screening procedures such as mammography (Lerman et al 1994). Interventions specifically designed to improve adherence have done so (Richardson et al 1990); however, in some studies higher depression and anxiety scores have been found to be associated with increased adherence to chemotherapy and other forms of cancer treatment (Ayres et al 1994). There is also evidence that the large cancer patient appetite for complementary therapies (Eisenberg et al 1997; Kao and Devine 2000) is an attempt to cope with hopelessness and other depressive symptoms (Sollner et al 1997; Coyne et al 1999). While most patients utilizing complementary treatments also utilize conventional care (Eisenberg et al 1997), there is the potential for interference as well. On balance, depressive symptoms may impair rather than improve adherence to conventional medical treatment, which could account for worse medical outcome.

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Table 3. Randomized Trials Examining the Hypothesis that Psychosocial Treatment Affects Cancer Survival Time

Authors	Year	Cancer Type	n	Intervention	Psychological Outcome	Survival Outcome
Linn et al	1982	Lung, pancreatic, skin, sarcoma, leukemia, lymphoma	120	Individual existential psychotherapy	Improvement in depression, self-esteem, life satisfaction, alienation, locus of control	No difference
Spiegel et al	1989	Metastatic breast	86	Supportive/expressive group therapy	Reduced anxiety/depression (POMS), improved coping, reduced pain	Hazard ratio for treatment .51, 95% CI .31–.82
Richardson et al	1990	Lymphoma, leukemia	94	Education, home visiting	Improved treatment adherence	RR = .39, independent of adherence
Fawzy et al	1993	Malignant melanoma	66	Cognitive-behavioral group therapy	Reduced anxiety/depression (POMS), improved coping	Improved at 4- and 10-year follow-up
Ilnyckyj et al	1994	Breast, lymphoma, colon, ovarian	127	Heterogeneous group therapies, some leaderless	No improvement	No difference
Cunningham et al	1998	Metastatic breast	66	Cognitive-behavioral combined with supportive/expressive	Increased anxious preoccupation and decreased helplessness in treatment group	No difference
Kuchler et al	1999	Gastro-intestinal cancers	271	Individual psychotherapy at the time of diagnosis	Unreported	Hazard ratio for intervention group .6 (95% CI .45–.84)
Edelman et al	1999	Metastatic breast	124	Cognitive-behavioral	Transient improvement in POMS	Interquartile range 0.97 (.59–1.46) No difference
McCorkle et al	2000	Solid cancers	375	Disease management and psychological support via 3 home visits and 5 telephone contacts	Unreported	RR of death for controls 2.04, 95% CI 1.33–3.12
Goodwin et al	2001	Metastatic breast	235	Supportive/expressive	Improvement in distress (POMS), reduced pain	Hazard ratio 1.06 for treatment, 95% CI .78-1.45

POMS, Profile of Mood States; CI, confidence interval; RR, relative risk.

Depression and Hypothalamic-Pituitary-Adrenal Function

The use of biomarkers of depression in cancer patients has been recommended because of the ease with which depressive symptoms can be confounded with symptoms of cancer and side effects of its treatment (McDaniel et al 1995). The cortisol profile is one of the best-studied indicators of hypothalamic-pituitary-adrenal (HPA) function in depressed populations. Cortisol is a glucocorticoid hormone produced by the adrenal cortex whose circulating levels and circadian rhythm are regulated by the hypothalamus and pituitary gland (McEwen 1987). It mobilizes glucose into the blood to fuel the "fight or flight" reaction, but chronically higher levels are potently immunosuppressive. Cross-sectional comparisons of depressed and nondepressed individuals have identified elevated 24-hour mean cortisol levels and a flattened circadian cortisol rhythm in depressed subjects (Deuschle et al 1997; Thompson et al 1992; Yehuda et al 1996). Preclinical studies have also documented suppressive effects of chronic HPA axis activation on T-cell mediated immune responses (Mc-Ewen 1987).

Breast and ovarian cancer patients have abnormalities in the circadian rhythm of cortisol (Touitou et al 1995). Among breast cancer patients, these abnormalities include high basal levels along the 24-hour scale (van der Pompe et al 1996; Touitou et al 1995), erratic peaks and troughs, and flattened circadian profiles (Touitou et al 1995). Loss of normal circadian variation in cortisol, similar to that observed in depression, predicts earlier mortality among metastatic breast cancer patients (Sephton et al 2000). We found that this abnormality in HPA function involved peaks late in the day and was associated with loss of marital support through bereavement or divorce and lower numbers of natural killer cells. Other recent studies have shown that female night shift workers are at higher risk for breast cancer (Davis et al 2001; Schernhammer et al 2001). While these authors attribute this effect to suppressed melatonin levels (Shafii and Shafii 1998), disruption of circadian cortisol rhythms is also a possible mechanism (Spiegel and Sephton 2002). Indeed, there is also evidence that in certain prostate cancer cell lines, the androgen receptor becomes cortisol-sensitive, thereby allowing physiologic levels of cortisol to stimulate tumor growth (Zhao et al 2000); however, Mormont et al (2002) did not observe a significant effect of blunted diurnal cortisol rhythms in patients with gastrointestinal tumors. However, there was a trend in their data suggesting earlier mortality in patients with blunted rhythms, and they utilized a categorical rather than continuous test of significance, which restricted statistical power. Recently, Filipski et al (2002) advanced this area of research by dysregulating diurnal cortisol in an animal model. They ablated the suprachiasmatic nucleus in mice, demonstrated that circadian cortisol rhythm was blunted, and observed that implanted osteosarcomas and pancreatic adenocarcinomas grew significantly more rapidly than in shamoperated animals. Thus, the clinical observations in humans have been supported in an experimental model.

There is even evidence that psychotherapeutic treatment may normalize cortisol levels in cancer patients. Cruess et al (2000) randomly assigned 34 early stage breast cancer patients to cognitive-behavioral stress management therapy (CBT) or a control condition. After the 10-week intervention, cortisol levels were significantly lower in the intervention group. This drop in cortisol was associated with greater benefit finding during CBT (Antoni and Carver 2003). Similarly, early stage breast cancer patients who participated in a 13-week experiential-existential group therapy (van der Pompe et al 1997) showed lower levels of plasma cortisol and prolactin. Thus disruption in diurnal cortisol patterns is associated with more rapid cancer progression, and there is some evidence that supportive interventions that may reduce distress may normalize cortisol levels.

Potential Mechanisms of Endocrine Effects on Disease Progression

Mechanisms have been proposed whereby the neuroendocrine correlates of stress may promote neoplastic growth. Stress hormones may suppress immune resistance to tumors (Callewaert et al 1991; Landmann et al 1984) or act via differential effects on gluconeogenesis in healthy versus tumor cells (Rowse et al 1992; Sapolsky and Donnelly 1985). Tumor cells may become resistant to the catabolic action of cortisol, which inhibits the uptake of glucose in numerous cell types. In such cases, energy would be preferentially shunted to the tumor and away from normal cells by cortisol (Romero et al 1992). Several studies have found an association between stress-related elevation of glucocorticoids and more rapid tumor growth in animals (Ben-Eliyahu et al 1991; Rowse et al 1992; Sapolsky and Donnelly 1985). Another hypothesis suggests that hormones of the HPA axis may actually promote the expression of breast cancer oncogenes due to activation of proopiomelanocortin (POMC) genes by corticotropin releasing hormone (CRH). The POMC promoter has homology with POMC transcription factors that bind to human MAT-1 breast cancer oncogenes (Licinio et al 1995). In addition, since stress-related increases in sympathetic nervous system and HPA activity are known to have generally suppressive effects on immune function, it is plausible that immune functions important in resistance

to breast tumor growth are thereby suppressed (Andersen et al 1994; Bergsma 1994; Bovbjerg 1989; Souberbielle and Dalgleish 1994). Elevation of glucocorticoids is associated with clinically significant immunosuppression, and enhanced secretion of norepinephrine during stress has also been associated with suppression of lymphocyte function (Felten and Olschowka 1987). Thus, there are a variety of means by which depression-related abnormalities in HPA function could affect the rate of cancer progression. One leading hypothesis is an association between HPA and immune dysfunction, since glucocorticoids are potently immunosuppressive.

Depression and Immunity in Cancer

The severity of depression and related repressive coping in response to it may have a deleterious effect on immunocompetence in cancer patients (Baltrusch et al 1991). For example, clinician-rated symptoms of depression significantly predict both lower white blood cell counts and natural killer (NK) cell numbers in this population (Andersen et al 1994). Symptoms of chronic depression and a lack of social support predicted reduced NK cell cytotoxicity measured at a 3-month follow-up in breast cancer patients (Levy et al 1987a). Natural killer cells attack transformed or dying cells in the absence of any particular antigen and may provide cancer surveillance. It is noteworthy that a reduction in NK cytotoxicity is associated with the progression of metastatic breast cancer (Levy et al 1987b, 1991, 1985). There are, however, data suggesting that acute stress is associated with short-term increases in NK and T-cell responses in women with breast cancer (Andersen et al 1998; Levy et al 1990). Depression can be understood as a chronic and maladaptive stress response (Gold et al 1988). Andersen et al (1998) studied 116 breast cancer patients shortly after surgical treatment. They found that the level of stress was associated with lower NK cell cytotoxicity, even when supplemented by gamma interferon. Stress was also associated with lower lymphocyte proliferative responses. Acute stress may have rather different effects on the HPA and immune function than the chronic stress often associated with cancer.

These studies on depression provide preliminary evidence for a directional relationship between depressive symptoms and aspects of the immune system in groups homogeneous for gender and type of disease; however, the link between such enumerative measures of immunity and clinically meaningful immune function is unclear. More research is needed which examines specific endocrine and immunologic correlates of depression for their effects on the health status of cancer patients.

Conclusion

There is growing evidence of a relationship between depression and cancer incidence and progression. Depression complicates not only coping with cancer and adherence to medical treatment but also affects aspects of endocrine and immune function that plausibly affect resistance to tumor progression. Some studies of psychotherapeutic interventions that reduce depression have shown that they normalize potential mediators such as cortisol and may slow disease progression. There is good reason to identify and treat the substantial minority of cancer patients who suffer from depression with therapies designed to improve their quality of life and ability to cope with the cancer. Importantly, further exploration of possible effects of depression and its treatment on endocrine and immune function on cancer progression itself represents an exciting research and clinical opportunity. Mind matters in cancer treatment.

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