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Cancer and Depression

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Half of all cancer patients have a psychiatric disorder, usually an adjustment disorder with depression. Anxiety about illness, such as cancer, often leads to delay in diagnosis, which has been estimated to reduce prospects of long-term cancer survival by 10% to 20%. Although earlier studies showed that depressed individuals were at higher risk for cancer incidence, later studies have not confirmed this predictive relationship. Nonetheless, effective psychotherapeutic treatment for depression has been found to affect the course of cancer. Psychotherapy for medically ill patients results in reduced anxiety and depression, and often pain reduction. In three randomised studies, psychotherapy resulted in longer survival time for patients with breast cancer (18 months), lymphoma, and malignant melanoma. The physiological mechanisms for these findings have not yet been determined, but four fundamental possibilities for psychotherapeutic effects on physiological change include health maintenance behaviour, health-care utilisation, endocrine environment, and immune function. Thus, effective treatment of depression in cancer patients results in better patient adjustment, reduced symptoms, reduced cost of care, and may influence disease course. The treatment of depression in these patients may be considered a part of medical as well as psychiatric treatment.

Comorbidity of psychiatric with medical illness is a common and under-recognised problem. The stress of serious medical disease such as cancer may stimulate reactions that include depression and anxiety. In certain cases, such as pancreatic cancer, depression may occur as an early presenting symptom of medical illness via more specific but poorly understood physiological mechanisms. In addition, since both cancer and depression are common disorders, they will tend to co-occur by chance. Although there is little evidence that psychiatric illness increases the likelihood of developing cancer, there is some suggestion that it may influence the course of the illness, and it undoubtedly affects patient and family adjustment to serious medical disease. This paper reviews the evidence that diagnosis and treatment of depression is an important component of effective management of cancer patients.

Prevalence of depression among cancer patients

There is a high prevalence of psychiatric illness, especially depression and anxiety, among the medically ill. Although these two disorders are the most common psychiatric problems in the population of the US (Myers *et al*, 1984), they are even more common among the medically ill. In a recent review of studies, Katon & Sullivan (1990) concluded that 6% of patients in primary care treatment settings and 11% of medical in-patients have major depression, compared with a 3% incidence in the general population (Fig. 1). In one carefully designed study, 47% of cancer patients were found to have a diagnosable

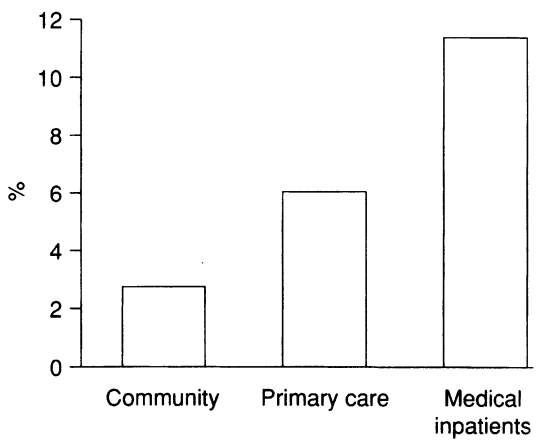


Fig. 1 Prevalence of major depression in three populations. From Katon & Sullivan (1990).

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psychiatric disorder (Derogatis *et al*, 1983) and this proportion of cancer patients with psychiatric disorders has recently been confirmed using the Hospital Anxiety and Depression Scale (Carroll *et al*, 1993). A recent review cites a range of depression among cancer patients from 4.5% to 50% (McDaniel & Nemeroff, 1993). Common symptoms associated with depression in cancer patients are decreased energy, sexual dysfunction, reduced employment (Tross & Holland, 1989), and social isolation (Spiegel, 1990). Anxiety about illness such as cancer leads to delay in diagnosis, which has been estimated to reduce prospects of long-term cancer survival by 10% to 20% (Holland, 1989).

Despite the high prevalence of depression observed in the research literature on cancer patients, it is often underdiagnosed in the medically ill due to: (a) misattribution of depressive symptoms such as energy loss, appetite disturbance and sleep difficulties to symptoms of cancer or side-effects of its treatment; (b) focus on medical signs and symptoms to the exclusion of psychiatric ones; and (c) therapeutic nihilism regarding psychiatric conditions (Spiegel & Sands, 1988; McDaniel & Nemeroff, 1993). This represents a lost opportunity for effective diagnosis and treatment.

Depression and cancer incidence

For many years, depression was thought to be a risk factor for the development of cancer. This belief derived from a widely cited study by Shekelle and colleagues (Shekelle *et al*, 1981; Persky *et al*, 1987), which related higher depression scores on the Minnesota Multiphasic Personality Inventory among 2020 men who worked at a Western Electric plant to a 2.3-fold increase in relative risk of subsequently developing cancer. Fox (1989) concluded that the finding in these studies may be due to a small subsample who worked under very difficult circumstances involving exposure to polychlorinated biphenols, which pose a considerable cancer risk. Job-related stress and increased disease risk might also have contributed to depression.

Furthermore, several more recent studies have failed to find a relationship between depression and cancer incidence (Hahn & Petitti, 1988; Kaplan & Reynolds, 1988). A large study ($n=3980$) by Zonderman *et al* (1989) reported no relationship between scores on the Center for Epidemiological Studies depression scale (CES-D; Radloff, 1977) and cancer morbidity or mortality. (It should be noted that the criterion for depression was a continuum score on the CES-D, and no categorical research or clinical diagnoses of depression were used.) Thus there is little support for the notion of a prospective link between depression and cancer (Fox, 1989).

Depression and pain

Evidence has accumulated that pain and depression co-occur. Bond (1973) and co-workers (Bond & Pearson, 1969) reported higher neuroticism scores among patients with cervical carcinoma who reported pain than among those who did not. Similarly, Woodforde & Fielding (1970) reported that cancer patients who sought treatment in the pain clinic had higher scores on measures of depression, psychosomatic symptoms, gastrointestinal symptoms and hypochondriasis, than those patients who did not. Ahles *et al* (1983) found that cancer patients with pain obtained higher scores on measures of depression, anxiety, hostility and somatisation than patients without pain. Derogatis *et al* (1983) reported that, of cancer patients with a psychiatric diagnosis, 39% reported severe pain, compared with only 19% of such patients who did not have a psychiatric diagnosis. Moreover, 15% of patients with significant pain had symptoms of a major depression. Lanksy *et al* (1985) studied 500 female patients with cancer in any of five sites, and found that the depressed subgroup had significantly more pain and greater physical disability, and was more likely to have had prior episodes of depression. Massie & Holland (1987) concluded that the psychiatric complications most often seen in cancer – depression, anxiety and delirium – are all more likely to occur in the cancer patient who has pain. Spiegel & Bloom (1983*a*) found that mood disturbance was more strongly correlated with cancer pain intensity than site of metastasis.

Multiple observations of co-occurrence of pain and depression do not resolve the question of causality. Some authors (Bond, 1973; Spiegel & Bloom 1983*a*) have emphasised that depression amplifies pain in cancer patients, while others (Hendler, 1984; Massie & Holland, 1987) have asserted that depression is a secondary consequence of chronic pain. Peteet *et al* (1986) suggested that psychiatric disturbance may represent *both* a consequence and a cause of pain in cancer patients. In their study of 30 out-patients at a cancer centre, both patients and physicians acknowledged an appreciable influence of emotional state on pain, and a somewhat greater influence of pain on emotional state.

Our research group (Spiegel & Sands, 1988; Spiegel *et al*, 1994) has found that the proportion of SCID diagnoses of major depression was significantly higher among cancer patients with

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considerable pain (28%) than among those without pain (Fig. 2). However, history of prior major depression was more prominent in the low-pain group, suggesting that pain produces major depression, since by history alone, the low-pain group should have been more likely to have current depression. Although depression and other psychiatric disorders may amplify pain, it is likely that persistent pain contributes to depression.

Treatment of depression in cancer patients

Methods

Psychotherapy for the medically ill, often conducted in conjunction with appropriate psychopharmacological treatment, consists of four basic components (Spiegel, 1993*a*; 1994) (Table 1).

(1) *Social support*. Psychotherapy, especially in groups, provides a new social network composed of individuals facing similar problems. Cancer imposes bidirectional social isolation. Those with the illness often feel removed from the flow of life, whereas those without it feel awkward and frightened, afraid to mention the illness, which leads them to withdraw. Psychotherapeutic support provides a badly needed sense of social connection. There is strong evidence that social contact not only has positive emotional effects, but that it actually reduces the risk of mortality (summarised in Fig. 3) (House *et al*, 1988). Indeed, social isolation is as potent a risk factor for mortality as elevated serum cholesterol levels or smoking. Being married predicts better medical outcome with cancer (Goodwin *et al*, 1987), whereas social stresses such as divorce, loss of a job, or bereavement are associated with a greater likelihood of a relapse of cancer (Ramirez, 1989). Thus, constructing new support group social networks for cancer patients is doubly

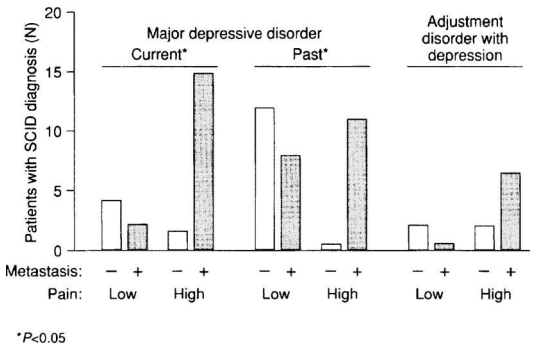


Fig. 2 Psychiatric illness as a function of pain and metastatic status. From Spiegel *et al* (1994).

Table 1
Supportive/expressive group therapy (from Spiegel, 1993*b*)

(1) *Social support*
Building bonds
(2) *Emotional expression*
(3) *Cognitive restructuring*
Detoxifying dying
Taking time
(4) *Coping skills training*
Fortifying families
Dealing with doctors
Pain control

important: it comes at a time in life when natural social support may diminish, and it may confer medical as well as psychological protection.

(2) *Emotional expression*. Cancer elicits strong affects, including fear, anxiety, sadness, depression and anger. Such feelings become less overwhelming and more manageable when dealt with directly in therapy. Many seriously ill individuals feel isolated with their fear and sadness, unable to discuss it with health professionals, family or friends. Ironically, expression of such emotion seems to reduce rather than increase depressive symptoms. Patients often find that psychotherapy organises their dysphoria by providing a time and place to deal with it effectively.

(3) *Cognitive restructuring*. Psychotherapy helps those facing difficult problems to see them from a new point of view. When worked through, life-threatening problems can come to seem real but not overwhelming. New strategies for dealing with them can be developed. Patients can learn to shift from a more passive, emotion-focused coping style, toward problem-focused coping. Many redefine life priorities and values, choosing to spend limited time and energy in new ways. Thus even facing death can result in positive life changes. One woman with metastatic breast cancer described her experience in this way:

> "What I found is that talking about death is like looking down into the Grand Canyon (I don't like heights). You know that if you fell down, it would be a disaster, but you feel better about yourself because you're able to look. I can't say I feel serene, but I can look at it now." (Spiegel, 1993*b*)

(4) *Coping skills training*. Many group and individual psychotherapy programmes teach specific coping skills. These include the means of seeking needed medical information, improving communication with physicians and other health-care staff, and mobilising family and other social

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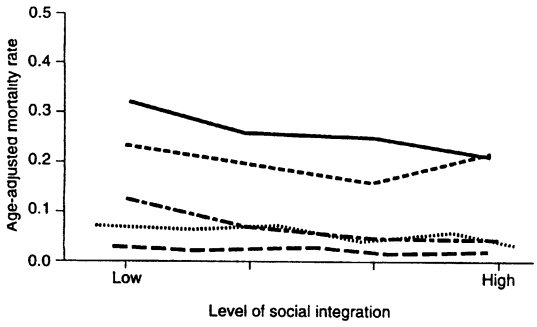


Fig. 3 Level of social integration and age-adjusted mortality for females in five prospective studies. From House *et al* (1988). ——, Evans County Blacks (RR = 1.59); - - - -, Evans County Whites (RR = 1.07); – – – –, Alameda County (RR = 2.81); ·····, Tecumseh (RR = 1.97); – – – –, Eastern Finland (RR = 1.92).

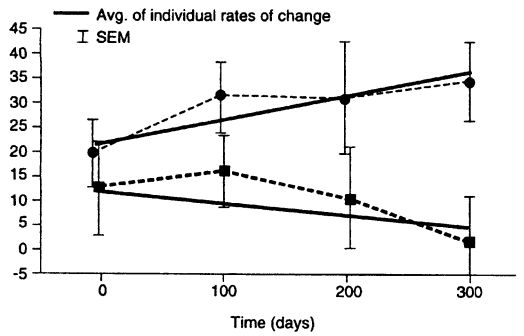


Fig. 4 Total mood disturbance over one year for treatment and control groups. From Spiegel *et al* (1981). ●- - -●, control; ■- - -■, experimental.

support. In addition, many effective programmes teach specific self-regulation skills such as self-hypnosis, meditation, biofeedback, and progressive muscle relaxation (Hilgard & Hilgard, 1975; Burish & Lyles, 1981; Morrow & Morrell, 1982; Zeltzer & LeBaron, 1982; Spiegel & Bloom, 1983*b*; Spiegel, 1990). These can be quite effective in reducing such symptoms as pain and anxiety.

Psychosocial outcome

A number of studies have demonstrated the positive psychological effects of psychotherapeutic interventions for cancer patients, including improvements in mood, adjustment, fatigue and pain (Gustafson & Whitman, 1978; Wood *et al*, 1978; Ferlic *et al*, 1979; Spiegel *et al*, 1981; Spiegel & Bloom 1983*b*). Psychosocial interventions have proven efficacy in helping cancer patients, in particular, to cope better with the illness and live more full lives (Spiegel *et al*, 1981; Turns, 1988; Fawzy *et al*, 1990*a*; Spiegel, 1993*a*). Individual and group psychotherapies are highly effective in reducing depression and anxiety, as well as physical symptoms such as fatigue, nausea, and pain (Forester *et al*, 1985; Cain *et al*, 1986). For example, in our research with metastatic breast cancer patients, those treated with weekly group psychotherapy showed marked reductions in anxiety and depression during the year, while a randomly assigned control group worsened during that period (Fig. 4) (Spiegel *et al*, 1981). Spiegel & Bloom (1983*a*) found that mood disturbance correlated more strongly with cancer pain intensity than the site of metastasis (Table 2). In addition, many interventions show a concomitant reduction in disease-related symptoms such as pain and nausea (Morrow & Morrell, 1982; Spiegel & Bloom, 1983*b*; Forester *et al*, 1985).

Medical outcome

A provocative finding has emerged in the recent literature, indicating that psychotherapy may affect the quantity as well as the quality of life. Our research group found, to our initial surprise, that metastatic breast cancer patients who had been randomly assigned to supportive/expressive group therapy lived, on average, 18 months longer than did the control sample (Tables 3 & 4) (Spiegel *et al*, 1989). This difference proved to be statistically significant by the log-rank test (Fig. 5). By 48 months after the study had begun, all of the control patients had died, but a third of the treatment sample were still alive. These patients had been medically comparable at study entry, including rate and degree of metastatic spread of disease and treatment, with the exception of a non-significant

Table 2
Effect of analgesic use, emotional distress, and pain beliefs on the pain experience of 71 women with metastatic breast cancer (from Spiegel & Bloom, 1983*a*)

Factor	Pain		
	B value	s.e.	Beta
Use of analgesics	0.54	0.10	0.48***
Emotional distress	0.02	0.01	0.20*
Pain beliefs	0.62	0.18	0.31**
Degrees of freedom	3/67[1]		
r^2	0.50		
F	22.17***		

*$P < 0.05$
**$P < 0.001$
***$P < 0.0001$
1. Fifteen observations deleted due to missing data.

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Table 3
Details of control and intervention patients (from Spiegel *et al*, 1989)

Characteristic	Control (*n*=36)		Intervention (*n*=50)	
Age (years)				
at initial diagnosis	49.3	(10.5)	49.9	(10.0)
at study entry	54.6	(10.2)	54.7	(9.9)
Married	25	(69%)	26	(52%)
Type of surgery				
lumpectomy	6	(17%)	3	(6%)
simple mastectomy	2	(6%)	2	(4%)
modified radical mastectomy	11	(31%)	18	(36%)
radical mastectomy	17	(47%)	26	(52%)
Degree of metastatic spread[1]				
soft tissue	0.3	(0.5)	0.5	(0.6)
viscera	0.3	(0.5)	0.3	(0.5)
bone	0.4	(0.7)	0.3	(0.7)
Initial stage[2]				
I	3	(8%)	8	(16%)
II	18	(50%)	16	(32%)
III	5	(14%)	11	(22%)
IV	7	(19%)	2	(4%)
No. of mastectomies[3]	1		1	
Exercise				
hours per week	1.7	(0.8)	1.6	(0.8)
activity level[4]	1.8	(1.1)	1.8	(1.1)
No. of treatment courses at entry[3]				
chemotherapy	1		1	(0,1)
oestrogen	0	(0,1)	0	
androgen	0	(0,1)	0	
steroid	0		0	
irradiation	1	(0,1)	1	(0,1)
days of irradiation	41.7	(81.9)	18.8	(24.8)

Mean (s.d.), or number of cases.
1. Spread of metastasis scaled as: 0, no spread; 1, one site; 2, more than one site of a particular type; and 3 (bone only), four or more sites.
2. χ^2 for trend, $P<0.07$.
3. Median (lower and upper quartiles = median except where indicated).
4. Self-rating 1 to 5.

Table 4
Disease course pre-entry (months) (from Spiegel *et al*, 1989)

	Control mean (s.d.)	Intervention mean (s.d.)
Initial diagnosis to first metastasis	38.0 (44.9)	36.3 (35.6)
First metastasis to entry	24.4 (17.4)	21.9 (21.8)
Initial diagnosis to entry	62.3 (53.5)	58.0 (43.3)

difference in initial staging. The treatment/control difference held even when these differences in staging were controlled.

More recently, Richardson *et al* (1990) found that lymphoma and leukaemia patients who were offered a combination of counselling and home visiting lived longer than control patients, even when treatment-induced differences in adherence to medical treatment were controlled. Fawzy *et al* (1990*a*,*b*) found that malignant melanoma patients randomly assigned to a series of six structured support group meetings were less anxious and depressed than control patients six months later. Follow-up of this study (Fawzy *et al*, 1993) indicated significantly lower rates of recurrence (7/34 *v.* 13/34) and mortality (3/34 *v.* 10/34) at a six-year follow-up. However, one recent study, which used matching rather than random design, indicated no survival advantage for cancer patients trained in the Exceptional Cancer Patient Program (Gellert *et al*, 1993).

Thus there is evidence that psychotherapy may affect not only adjustment to medical illness, but survival time with it. The physiological mechanisms for these findings have not yet been determined, but there are at least four fundamental possibilities for psychotherapeutic effects on physiological change (Bovard, 1985; Spiegel 1991, 1993*a*).

(a) *Health maintenance behaviour*. Diet, sleep and exercise are all affected by depression and anxiety. Since effective treatment of these emotional disorders results in improvement in these symptoms, amelioration of problems in body maintenance activities might facilitate somatic defences against disease progression. However, one recent study of the effects of a specific and rather stringent dietary intervention for cancer patients showed that, if anything, those put through the protocol at the Bristol Cancer Help Centre fared worse than a matched comparison sample (Bagenal *et al*, 1990). Although the comparison may have been weighted against a positive finding (Hayes *et al*, 1990; Sheard, 1990), there is no support for the idea that changing diet improves prognosis.

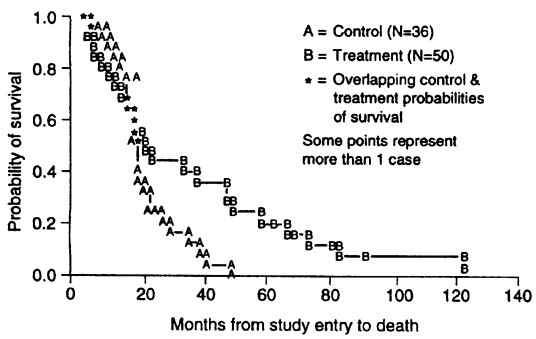


Fig. 5 Kaplan–Meier survival plot, from Spiegel *et al* (1989).

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(b) *Health care utilisation.* It is possible that through better treatment adherence, interaction with physicians, or more aggressive treatment regimens, cancer patients who are less depressed elicit or participate well in more vigorous medical treatment. In our original study, we had no data regarding medical treatment offered subsequent to the intervention year. However, in the study of Richardson *et al* (1990), even when differences in adherence to treatment were controlled, intervention patients had significantly longer survival times. Given the palliative nature of much chemotherapy intervention for metastatic breast cancer, it is unlikely that medical treatment differences alone account for the differences in survival time.

(c) *Endocrine environment.* Hormones known to be influenced by stress and depression, such as cortisol and prolactin (Rose, 1984; Nemeroff, 1991; McDaniel & Nemeroff, 1993), influence tumour proliferation (Shafie & Brooks, 1977; Malarkey *et al*, 1983; Israel, 1989). The hyperactivity of the hypothalamic–pituitary–adrenal axis observed in depression (Evans *et al*, 1986; Chrousos & Gold, 1992; McDaniel & Nemeroff, 1993) among cancer patients could, therefore, stimulate tumour progression, especially among hormone-sensitive cancers, such as breast cancer, for which one of the more effective treatments is a mild oestrogen agonist and receptor blocker, tamoxifen. There is evidence that social support can function as a stress buffer, reducing plasma levels of cortisol elicited by stressors (Fig. 6) (Levine *et al*, 1989). Given that hypercortisolaemia is a well-known phenomenon in depression (Nemeroff, 1991), which can be conceptualised as a state of chronic stress-related hyperarousal and depletion (Gold *et al*, 1988*a*, *b*), it may be that effective treatment of depression and anxiety reduces corticosteroid levels. This in turn could reduce steroid or other hormonal effects on tumour growth via direct receptor stimulation, effects on glucose metabolism or uptake, or via steroid-induced immunosuppression.

(d) *Immune function.* There is substantial and growing evidence that stress and depression influence components of the immune system (Glaser *et al*, 1985; Schleifer *et al*, 1985, 1989; Irwin *et al*, 1987). Major depression is associated with reduced natural killer cell activity (Evans *et al*, 1992), and these cells are a subset of T cells that are involved in cancer surveillance (Herberman & Ortaldo, 1981; Levy *et al*, 1987). Various psychotherapeutic stress management techniques have positive effects on the immune system (Kennedy *et al*, 1988; Ader *et al*, 1990; Irwin & Strausbaugh, 1991). Preliminary results of a stress management intervention, which include relaxation, social support, cognitive restructuring and education, suggest that immune function may be positively affected in both AIDS patients (Antoni *et al*, 1990) and those with malignant melanoma (Fawzy *et al*, 1990*b*). Fawzy found that support group patients had greater activity of natural killer cells (NKA) at six-months but not 12-month follow-up. Furthermore, baseline levels of NKA were significantly predictive of recurrence rates at six-year follow-up, although changes in NKA over time were not predictive of outcome (Fawzy *et al*, 1993). Thus, in these studies, group psychotherapy, which reduced depression and anxiety, also increased NKA and resulted in lower rates of recurrence and mortality. These data suggest that such treatment may influence the course of cancer via an effect on components of the immune system.

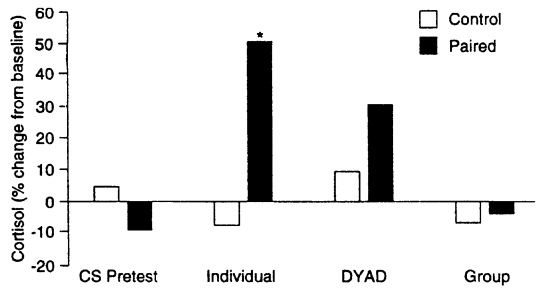


Fig. 6 Cortisol responses to a stressor as a function of social support. Stress-induced cortisol increases (individual) are attenuated by the presence of one other animal (DYAD) and eliminated by the presence of five others (Group). From Levine *et al* (1989).

Conclusions

Depression is a common problem among cancer patients, but is often unrecognised and therefore undertreated because depressive symptoms are misattributed to cancer or its treatment. There is little evidence that depression predisposes to developing cancer, but cancer pain may produce or exacerbate depression. Effective treatment of depression in cancer patients may influence the course of the disease as well as quality of life. Thus clinical attention to depression in cancer patients results in better patient adjustment, reduced symptoms, and may influence disease course. The treatment of depression in these patients may be considered a part of medical as well as psychiatric treatment. The mechanisms underlying such an effect may involve influence on daily activities such as diet, exercise and sleep, on adherence to medical

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treatment, or may involve changes in endocrine and immune function. There is growing evidence that psychiatric therapy for the medically ill is a powerful and important component of treatment, with both psychological and physical effects.

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