**Psycho-Oncology**
*Psycho-Oncology* **21:** 588–593 (2012)
Published online 21 March 2012 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3067

# Mind matters in cancer survival

David Spiegel*
*Stanford University School of Medicine, Stanford, CA 94305, USA*

**Correspondence to: Stanford University School of Medicine, Stanford, CA 94305, USA.*
*E-mail: dspiegel@stanford.edu*

## Abstract

***Objective*: The very name "psycho-oncology" implies interaction between brain and body. One of the most intriguing scientific questions for the field is whether or not living better may also mean living longer.**

***Methods*: Randomized intervention trials examining this question will be reviewed.**

***Results*: The majority show a survival advantage for patients randomized to psychologically effective interventions for individuals with a variety of cancers, including breast, melanoma, gastrointestinal, lymphoma, and lung cancers. Importantly, for breast and other cancers, when aggressive anti-tumor treatments are less effective, supportive approaches appear to become more useful. This is highlighted by a recent randomized clinical trial of palliative care for non-small cell lung cancer patients.There is growing evidence that disruption of circadian rhythms, including rest-activity patterns and hypothalamic–pituitary–adrenal (HPA) axis function, affects cancer risk and progression. Women with metastatic breast cancer have flatter diurnal cortisol patterns than normal, and the degree of loss of daily variation in cortisol predicts earlier mortality. Mechanisms by which abnormal cortisol patterns affect metabolism, gene expression, and immune function are reviewed. The HPA hyperactivity associated with depression can produce elevated levels of cytokines that affect the brain. Tumor cells can, in turn, co-opt certain mediators of inflammation such as NF*k*B, interleukin-6, and angiogenic factors to promote metastasis. Also, exposure to elevated levels of norepinephrine triggers release of vascular endothelial growth factor, which facilitates tumor growth.**

***Conclusions*: Therefore, the stress of advancing cancer and management of it is associated with endocrine, immune, and autonomic dysfunction that has consequences for host resistance to cancer progression.**



Received: 16 February 2012
Accepted: 24 February 2012

**Keywords: cancer; survival; group therapy; psychotherapy; endocrine; cytokine**

## Introduction

The field of psycho-oncology is hung up on the hyphen in its name. How do we understand the link between mind and body? Is that hyphen merely an arrow to the left, indicating that cancer in the body affects the mind? Can it be an arrow to the right as well, mind affecting the course of cancer? We know that social support affects survival [1], including that with cancer [2]. Also, people tend to die after rather than before their birthdays and major holidays [3,4]. Depression worsens survival outcome with cancer [5,6]. Yet, we have been understandably delicate about mind/body influence, not wanting to claim too much, or to provide unwitting support for overstated claims that wishing away cancer or picturing white blood cells killing cancer cells would actually do it. That arrow to the right is a connection, not a superhighway. Yet, in our desire to be respected members of the oncology community, we have often minimized a natural ally in the battle against cancer – the patient's physiological stress-coping mechanisms. Even at the end of life, helping patients face death, making informed decisions about level of care, and controlling pain and distress are not only humane but appears to be medically more effective than simply carrying on with intensive anti-cancer treatment alone [7].

A recent randomized clinical trial of palliative care for non-small cell lung cancer patients [8] makes that case strong. The authors reported a clear but apparently paradoxical finding: "Despite receiving less aggressive end-of-life care, patients in the palliative care group had significantly longer survival than those in the standard care group (median survival, 11.65 vs. 8.9 months; $p = 0.02$)" (p. 738). Those randomized to palliative care became less depressed as well. The palliative care condition consisted of an average of four visits that focused on choices about resuscitation preferences, pain control, and quality of life. The study suggests that at the end of life, less aggressive treatments may be the most effective not only psychologically, but also medically.

How could living better at the end of life lead to living longer? When we began to investigate the effects of support groups for people with cancer in the 1970s, we and others were concerned that watching others die of the same disease would demoralize patients and might even hasten their death. We evaluated mood and discussion content minute-by-minute to determine whether bad news about other group members was depressogenic.

We found that these women with advanced breast cancer talked more seriously about death and dying but showed no signs of depression or panic [9]. Indeed, our initial studies, confirmed by many others, indicated that we reduced distress and pain [10,11].

But now the results are showing something more profound than reduced distress and pain or feeling better: they are showing that facing death better helps people to live longer with cancer. We reported in 1989 the results of a clinical trial demonstrating that women with metastatic breast cancer randomized to a year of weekly group therapy lived 18 months longer than control patients and that the difference was not due to differences in initial disease severity or subsequent chemotherapy and radiotherapy. The result of this 10-year study, cited at last count on Google Scholar 2222 times, was first greeted with great excitement and later skepticism. Now, 21 years later, the findings are being confirmed.

A decade later, we conducted an Institutional Review Board-approved replication study that showed no overall effect of a similar group therapy on breast cancer survival, but a significant interaction with tumor type, such that those with estrogen receptor (ER) negative cancers who were randomized to group therapy lived significantly longer than did ER negative patients receiving standard care alone [12]. As this is a clear disconfirmation of the hypothesis that facing death together could improve survival, major advances in hormonal and chemotherapies had improved overall survival for women with metastatic breast cancer in the interim [13]. However, women with ER negative tumors were largely excluded from the benefit of hormonal treatments, which could account for the difference in findings [13]. Further support for this explanation comes from the fact that overall survival of our cohorts of women with metastatic breast cancer has improved over the decades (Figure 1).

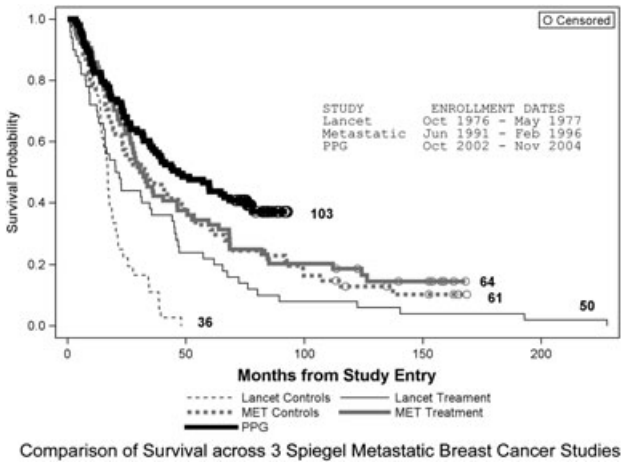


**Figure 1.** Comparison of survival across three Spiegel metastatic breast cancer studies

More recently, a randomized trial of psychoeducational groups for women with primary breast cancer found both significantly reduced rates of relapse and longer survival [14,15]. In addition to this, our original study [16], and the recent palliative care study referred to previously [8], three other published randomized psychotherapy trials [17–20] and one matched cohort trial [21] have reported that psychosocial treatment for patients with a variety of cancers enhanced both psychological and survival outcome (Table 1). However, six other published studies [22–27], four involving breast cancer patients [24–27], found no survival benefit for those treated with psychotherapy (Table 2). Three of these six studies reported no emotional benefit from the interventions [23–25], making enhanced survival unlikely. In another major multicenter replication trial [26], supportive-expressive group psychotherapy did significantly reduce depression but did not improve survival. However, the odd thing about this study is that the women randomized to treatment were more depressed to begin with, making their medical prognosis worse at baseline [6]. Furthermore, the outcome of all these studies is not random: no studies show that gathering cancer patients together in groups and directing their attention to emotional expression and mortality shortens survival [28].

The most provocative but also discordant results have occurred in studies of women with breast cancer, where treatment for ER positive and also human epidermal growth factor receptor 2-positive tumors has improved substantially. Among cancers with poorer medical prognosis, such as ER negative breast cancer, malignant melanoma, non-small cell lung cancer, leukemia, and gastrointestinal cancers, intensive emotional support seems to extend survival. Patients who benefit from a targeted and highly effective chemotherapeutic approach obtain less apparent survival benefit from emotional support than do those with less effective biomedical interventions. Thus, especially in the palliative settling in which aggressive anti-tumor treatments are less

**Table 1.** Randomized trials showing survival benefit from psychotherapy

| Study | Cancer | *N* | Psychological outcome |
|---|---|---|---|
| Spiegel *et al.*, 1989 | Metastatic breast | 86 | Less distress, pain |
| Richardson *et al.*, 1990 | Lymphoma, leukemia | 94 | Better treatment adherence |
| Fawzy *et al.*, 1993 | Melanoma | 66 | Less distress, better coping |
| Kuchler *et al.*, 1999 | Gastrointestinal cancers | 271 | Better stress management |
| McCorkle *et al.*, 2000 | Solid tumors | 375 | Less distress |
| Spiegel *et al.*, 2007 | Metastatic breast | | Less distress, pain<br>*Survival benefit only among ER negatives* |
| Andersen *et al.*, 2010 | Primary breast cancer | 62 | Improved coping |
| Temel *et al.*, 2010 | Non-small cell lung cancer | 107 | Improved Q of L, reduced depression |



**DOI**: 10.1002/pon

**Table 2.** Randomized trials showing no survival benefit of psychotherapy

| Study | Cancer | *N* | Psychological outcome |
|---|---|---|---|
| Linn *et al.*, 1982 | Lung, gastrointestinal | 120 | Less depression, more self-esteem, life satisfaction |
| Ilnyckyj *et al.*, 994 | Breast | 127 | No benefit |
| Cunningham *et al.*, 1998 | Metastatic breast | 66 | No benefit |
| Edelman *et al.*, 1999 | Metastatic breast | 121 | No long-term benefit |
| Goodwin *et al.*, 2001 | Metastatic breast | 235 | Less distress, depression |
| Kissane *et al.*, 2004 | Primary breast | 303 | Less distress |
| Kissane *et al.*, 2007 | Metastatic breast | 227 | Prevented new depression, less hopelessness, trauma sx, improved social functioning |

efficacious, supportive approaches become more useful. One would think that psychosocial support would have the least biomedical effect in more advanced cancers, and yet, our original observation involved women with metastatic breast cancer. By the time someone dies with cancer, they usually have a kilogram of tumor in their body. Yet, this may be when the body's resources for coping with physiological as well as psychological stress matter the most.

## Mind/body interactions and cancer progression

As a large portion of the variance in any disease outcome is accounted for by the specific local pathophysiology of that disease, prognosis must also be explained in part by "host resistance" factors, which include the manner of response to the stress of the illness [29] including the endocrine, neuroimmune, and autonomic nervous systems [30,31]. For example, in a series of classic experiments in animals, Riley [32,33] showed that crowding accelerated the rate of tumor growth and mortality. In an authoritative review of human stress literature, McEwen [34] documented the adverse health effects of cumulative stressors and the body's failure to adapt the stress response to them. Activation of the hypothalamic–pituitary–adrenal axis (HPA) is an adaptive response to acute stress, but over time in response to cumulative stress, the HPA's signal to noise ratio can be degraded, so that it is partially "on" all the time, leading to adverse physiological consequences, including abnormalities of glucose metabolism [35], hippocampal damage [36], accumulation of abdominal fat [37,38], and depression [39,40]. Sapolsky and colleagues found that stressed older animals not only had persistently elevated cortisol levels after the stress was over, but also much more rapid growth of implanted tumors [35,41]. Abnormalities of HPA function, including glucocorticoid receptor hypersensitivity, have also been found to be associated with post-traumatic stress disorder (PTSD) [42,43]. PTSD symptoms, including intrusive preoccupation with the diagnosis, avoidance, and hyperarousal, are common among cancer patients [44–47]. Adverse emotional events, ranging from traumatic stressors to cumulative minor ones, are associated with HPA dysregulation. Persistently elevated or relatively invariant levels of cortisol may, in turn, stimulate tumor proliferation [35] via differential gluconeogenesis in normal and tumor tissue, activation of hormone receptors in tumor, or immunosuppression [35,48–50]. A history of traumatic stress has been found to be associated with shorter disease-free interval and therefore poorer prognosis with breast cancer [51].

Glucocorticoids are potently immunosuppressive, so the effects of acute and chronic stress and related hypercortisolemia may include functional immunosuppression as well. This has been demonstrated clearly in animals [52–54], and there is growing evidence in humans as well [55–57]. This in turn could influence the rate of breast cancer progression [58–61]. Thus, glucocorticoid dysregulation may be associated with other stress-related endocrine and immune dysfunction that could adversely affect host resistance to cancer progression.

Hypothalamic–pituitary–adrenal abnormalities have been demonstrated in cancer patients. Women with metastatic breast cancer have flatter diurnal cortisol patterns than normal [62], and flattened diurnal cortisol predicts earlier mortality with breast cancer [63]. These aberrant glucocorticoid levels throughout the day may represent a failed response to chronic inflammatory aspects of cancer. For example, chronic inflammatory conditions such as colitis and Epstein–Barr virus infection have been associated with colon and nasopharyngeal cancers, respectively [64]. Moreover, tumor cells can co-opt certain mediators of inflammation such as NF*k*B and growth-promoting cytokines and angiogenic factors to promote tumor progression and metastasis. Such chronic inflammation with relatively constant cytokine release into the circulation may trigger a glucocorticoid response that would especially disrupt circadian variation in cortisol levels. This may induce a cycle of glucocorticoid resistance that disrupts negative feedback and glucocorticoid control [65]. The pro-inflammatory cytokine interleukin-6 (IL-6) is associated with smaller hippocampal volume. Thus, there may be an inflammatory cytokine-mediated influence on diurnal cortisol that is associated with breast cancer and its progression. This effect would be worsened by the HPA dysregulation associated with depression, which is also connected to cytokines that trigger "sickness behavior" that overlaps with the symptoms of depression [66] and are coupled with HPA axis hyperactivity [67,68]. Such dysregulation is also associated with sleep and other circadian system disruption [63]. Miller and colleagues have found flattening of diurnal cortisol slope associated with resistance to corticotropin-releasing factor/dexamethasone suppression [69], similar to that found among women with metastatic breast cancer [65]. IL-1 alpha blocks glucocorticoid receptor translocation in a mouse fibroblast



**DOI**: 10.1002/pon

line, reducing the ability of dexamethasone to turn on a reporter gene construct, leading to glucocorticoid resistance [69]. This is reversed with administration of an IL-1 receptor antagonist. This pathway demonstrates how cytokines can contribute to the dysregulation of diurnal cortisol seen in women with breast cancer. Thus, this provides further evidence that cancer and associated inflammatory processes can dysregulate the HPA axis. The abnormal cortisol patterns, in turn, may affect expression of oncogenes such as breast cancer type 1 susceptibility protein (BRCA1), and retard apoptosis of malignantly transformed cells [70]. Cytokine–endocrine interactions are plausibly related to depression and adverse cancer outcome via such mechanisms [71].

There is also growing evidence that the other major hormonal stress-response system in the adrenal gland, the sympathetic-adrenal-system, also affects cancer progression [72]. Epinephrine, produced in the adrenal medulla, is released in the early stress response, increasing heart rate and blood pressure. It also triggers release of vascular endothelial growth factor (VEGF), which stimulates the growth of blood vessels and therefore can provide a blood supply for metastatic cancer cells. This effect is increased by chronic stress in animal models [72]. Blocking the effect of norepinephrine with short inhibitory RNAs or beta-blockers reverses this stress-induced increase in VEGF and reduces tumor growth. Social isolation is associated with higher levels of tumor epinephrine in ovarian cancer patients [73]. The most striking clinical application of this relationship are recent studies demonstrating that breast cancer patients who happen to be taking beta-adrenergic blockers for hypertension or other problems have longer disease-free and overall survival [74–76].

## Conclusion

Thus, it is plausible that interventions that provide emotional and social support, and improve stress management at the end of life might have a positive impact on physiological stress-response systems that affect survival. The line connecting "psycho" social factors to oncology can help to align better stress management and social support with enhanced somatic resistance to tumor growth. Psycho-oncology is a discipline that helps cancer patients mobilize all of their resources to live well with cancer. We know that it is not simply mind over matter, but mind matters.

### Acknowledgement

Preparation of this manuscript was supported by NCI grant RO1CA118567.

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**DOI**: 10.1002/pon