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Chapter 11

EFFECT OF PSYCHOSOCIAL INTERVENTIONS ON PSYCHOENUROENDOCRINE OUTCOMES IN CANCER PATIENTS: WHERE DO WE GO FROM HERE?

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ABSTRACT

A significant literature exists on the role of psychosocial factors in cancer initiation and progression, and effects of psychosocial interventions on eventual survival, but research investigating the effects of psychosocial interventions on psychoneuroendocrine and psychoneuroimmune outcomes in cancer patients is rare. There is some evidence that stress-reduction interventions may affect cortisol secretion profiles and aspects of cellular immunity, but the clinical significance of any observed effects is not known. Questions that require additional investigation concern: 1) the significance of various endocrine and immune outcome measures for predicting disease outcome in cancer patients (i.e. disease recurrence and/or survival); 2) the optimal timing of psychosocial interventions to affect biological outcomes (i.e. pre- or post-surgery, chemotherapy); 3) the type and stage of cancers that are potentially most responsive to psychosocial interventions (e.g. early vs. late stage, tumour type), and; 4) consideration of other factors that may be mediating any biological changes seen as a result of psychosocial interventions (i.e. health behaviours). The research in these areas will be reviewed and fruitful directions for future research outlined.

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OVERVIEW

The study of interactions between psychological and social factors and eventual disease initiation and progression in psychosocial oncology has been a hot-button issue for several decades. Controversy began with the introduction of the "Type C" personality style, purported to lead to higher incidence of cancer diseases [1,2]. The "Type C" personality was characterized by emotional repression, agreeableness, passivity and patience combined with a helpless/hopeless coping style that deferred to authority – the type of person often referred to as a "good patient" [1]. The theory holds that this type of person often unconsciously represses or purposively suppresses their emotions and turns them inward, resulting in pathophysiological internal changes that could contribute to the development of cancer. The psychoneuroimmunological (PNI) or psychoneuroendocrinological (PNE) routes by which this process was thought to occur were relatively unspecified. However, a good deal of research over the last two decades has explored these questions with increasing rigour. Another large body of literature exists detailing the associations between chronic stress and health outcomes as diverse as colds, heart disease, asthma, allergies, rheumatoid arthritis and wound healing [3-7] – the question now is - does the same apply to cancer?

The underlying rationale for this type of research is based on an understanding of the stress response and its physiological concomitants – the research on stress is also illustrative of how other psychosocial factors such as depression and social support may affect disease. Essentially, psychosocial processes which result in the perception of psychological or physical threat trigger a cascade of events in the central nervous system (CNS) and periphery that result in stress responses in the autonomic nervous system (ANS) and through the hypothalamic-pituitary-adrenal (HPA) axis. HPA responses are mediated by production of corticotrophin-releasing factor (CRF) and arginine vasopression in the hypothalamus. These releasing factors activate the pituitary gland to secrete hormones such as adrenocorticotrophic hormone (ACTH), enkephalins and endorphins. ACTH then triggers the release of glucocorticoids (cortisol in humans) from the adrenal glands, situated atop the kidneys. Glucocorticoids have a whole host of effects throughout the body, many of which are necessary for regulatory functions, but can also cause downregulation of immune function when exposure is prolonged or chronic [8]. Often in disease states such as cancer or depression, HPA feedback is dysregulated, which can result in chronic hyper-arousal of the HPA axis, or eventual collapse and exhaustion [9]. ANS responses to stress are mediated primarily through the sympathetic nervous system (SNS) through release of catecholamines (epinephrine (EP) and norepinepherine (NE)) both from sympathetic nerve endings and through the medulla of the adrenal glands. In short time frames under acute stressors, elevations in cortisol and catecholamines are adaptive, but if they become chronically elevated as a consequence of exposure to chronic stress, many physiological systems can be negatively affected, resulting in increased risk for viral infections such as common colds [4], increased risk for cardiac disease [6], and slower wound healing [7]. There is also a growing body of evidence, primarily from animal research, that chronic alterations in neuroendocrine feedback dynamics and balance can alter an array of physiological parameters related to cancer tumour development [10]. This research will be reviewed later in this chapter.

A general biopsychosocial or biobehavioral model of cancer development and progression can be helpful to tie together the different inputs and outcomes often measured in

PNI and PNE research. Such a model has been proposed by a number of researchers [11-13] – Figure 1 is their adaptation showing in simple terms their understanding of interactions among a number of key elements, many of which will be discussed in this chapter. It includes the influence of psychological, social and biological background variables such as temperament, social support, and heredity, as well as health behaviours such as diet, exercise and smoking, on health outcomes. These factors interact with the experience of life stress, which can in turn influence neuroendocrine, immune and central nervous system processes that effect disease course and recovery. Psychosocial interventions can act to affect psychological processes as indicated, and change health behaviours, both of which may impact biological processes. These in turn affect disease processes and subsequent morbidity and mortality. This model will be used as a guide to understand the areas in the field that have been relatively well researched, and highlight areas and associations where little empirical understanding exists.

Returning to the clinical study of these potential effects in humans, however, it is important to consider how such relationships can accurately be investigated. Several types of research methodologies have been applied to studying relationships between psychological and social factors and cancer initiation and progression. The question of disease etiology has been addressed primarily through long-term prospective (or retrospective) epidemiological cohort studies that have tracked large groups of initially healthy individuals over time to determine if social, personality or psychological variables predict later cancer incidence in the small proportion who do go on to develop cancers. Very rarely have biomarkers been collected in these studies that might also be associated with disease initiation, so little can be said about potential pathways to disease that any psychosocial factors may affect.

Other methodology has been applied to determine the effects of psychosocial factors on disease progression, recurrence and survival in people once they have been diagnosed with cancer. Because the time-frame is shorter and sample sizes are smaller, this research is substantially less expensive, time consuming and difficult to conduct than large-scale prospective cohort studies with initially healthy populations, and hence there is a much larger body of research in this area. Again, however, the pathways by which psychosocial factors may influence disease outcome are rarely investigated, and research methodology in general has not been of very good quality. However, these studies do provide some tantalizing findings that suggest psychosocial factors may be influencing relevant endocrine and immune markers that may be important in cancer progression [14-16].

Other researchers have begun to investigate the effects of manipulation of psychosocial factors, through different supportive and stress reductive interventions, on outcomes as diverse as quality of life, psychological well-being and symptomatology, endocrine and immune measures, and eventual survival. This work is well known and the survival literature has been extensively reviewed on numerous occasions, with equivocal results [17-21]. There have been a small number of reviews of studies looking at immune and endocrine changes as a result of psychosocial interventions in cancer [22,23], and much speculation about potential pathways [23,24]. Hence, the picture is far from complete.

This chapter will review studies of the above two types (predicting cancer incidence and progression from psychosocial factors, and effects of interventions on survival and psychological, immune and endocrine outcomes). This will not be an exhaustive review but carried out from the perspective of providing a general overview of the field. This chapter will then address several outstanding, relatively unresearched and unresolved areas of inquiry

that may help to direct the thinking of the field regarding the larger questions. These include addressing the specific usefulness of various endocrine and immune measures for predicting disease outcome in cancer patients (i.e. disease recurrence and/or survival). This question in many cases can only be addressed indirectly through noting associations between psychosocial and immune or endocrine measures and linking this with any existing research documenting pathways between certain immune or endocrine measures and disease status.

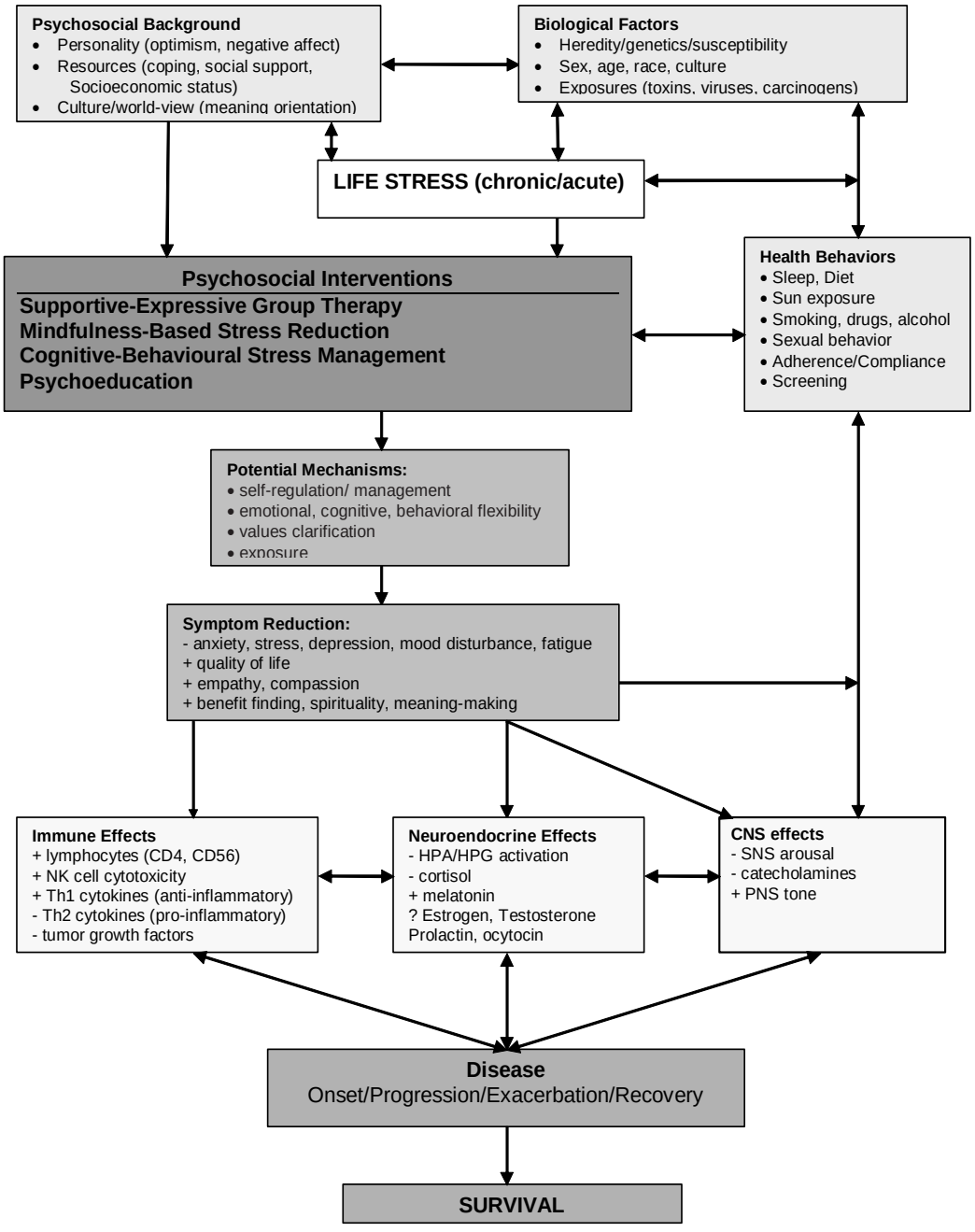

Figure 1. Biobehavioral Model of Cancer Progression.

Other more specific questions of interest for those considering the implementation of psychosocial interventions designed to alter immune/endocrine function or survival include the optimal timing of psychosocial interventions to affect biological outcomes (i.e. pre- or post-surgery, chemotherapy), the type and stage of cancers that are potentially most biologically responsive to psychosocial interventions (e.g. early vs. late stage, solid vs. hematological vs. virally-mediated tumours), and consideration of other factors that may be mediating any biological changes seen as a result of psychosocial interventions (i.e. health behaviours).

The quality and quantity of research available to be drawn upon to address each of these issues varies, and hence this review will also vary in terms of the level of detail and certainty of the conclusions that can be put forth.

Finally, before reviewing the area of psychosocial effects on cancer, the research should be put into perspective: although all the risk factors for different cancers are not definitively known, and because cancer is a term which encompasses over 200 different diseases, it is difficult to determine the relative weight associated with various risk factors. Information on specific risk factors for the major types of cancer is readily available, but it has proven more difficult to obtain actual percentage values in terms of the risk carried for the various factors. One estimate of this data suggests that 30-32% of the variability in incidence for all cancers is related to tobacco, 30-35% to diet, 10% to viruses and infection and so on (including alcohol, sexual factors, heredity, and occupational and environmental exposures), without the inclusion of any psychosocial factors and approximately 5% left unexplained [25]. Hence, the maximum amount of variance in the incidence of cancers that could be accounted for by psychosocial factors would be up to but not likely much beyond five percent. This is not insignificant, and about on par with the effects of alcohol consumption overall. Of course, these values are different for different forms of cancer; for example smoking accounts for approximately 85% of lung cancer cases but is not a risk factor for colon cancer or melanoma. Hence, it may be the case that psychosocial factors play a larger role in some cancers and are inconsequential in others. This possibility has only begun to be investigated.

PSYCHOSOCIAL FACTORS AND DISEASE INITIATION

The research in this area spans 30 years and has been reviewed on several occasions [9,26-33]. The most recent and rigorous review included only studies that used true prospective longitudinal designs, and excluded all those that were cross-sectional, comparisons between groups or semi-prospective, as these study designs do not allow conclusions about causality – 38 studies of this type were excluded [30]. Seventy studies were included in the review, but only 25 of these looked specifically at cancer initiation (while the others focussed on disease progression – reviewed below). Psychosocial factors were divided into several commonly-studied categories: stressful life events; bereavement and other losses; social relations (i.e social support); negative emotions (distress, psychiatric diagnoses); repression of emotions; and personality. Another critical review of studies looking only at disease initiation focussed on similar factors but assessed a broader base of studies, including retrospective cohort studies and case-controlled studies [28]. Several studies published after

these most recent reviews also addressed issues of the association between perceived stress and breast cancer incidence, in particular [34-37].

In terms of major life events and bereavement, a meta-analytic review by Petticrew et al [38] of 15 studies looking at only breast cancer patients found that patients reported adverse life events more than twice as often as control subjects. However, they included studied of low quality including group comparisons and semi-prospective studies. Two more rigorous reviews conclude that large population-based studies using independently collected registry data failed to support the link between major life events and increased risk for cancer [28,30]. Garssen [30] did suggest, however, that negative life events in combination with other risk factors, such as social support or hopelessness, could interact to potentially effect cancer initiation. Bereavement too was concluded not to have a clear-cut effect on cancer incidence [28], but perhaps a stronger effect on death from cancer [30]. This conclusion is based on several large-scale studies which looked at the effects of death of a spouse in the UK [39], widowhood [40] and death of a child [41] in Norway, and loss of a son through war in Israel [42] – findings were suggestive of associations but effects were small or inconclusive in most cases. In the Levav study [42], there were no effects on incidence of all cancers together, but the odds of being diagnosed with lymphoma for bereaved parents compared to the rest of the population was 1.5 times higher, and for melanoma it was 1.7 times higher.

Methodologically, it is important to note that these studies use major life events as surrogate markers for the experience of stress, but none of the studies took into account how the individuals actually perceived these events and subsequently reacted to them. For example, widowhood may be perceived very differently by a young woman with small children and a happy marriage, compared to an older woman with an unsatisfactory relationship. Hence, the subjective stressfulness of these life events rather than their mere presence or absence may be more important in determining psychophysiological responses, but this was not measured in these studies. Newer studies not covered in the most recent review have looked at specific reports of subjective life stress, and found further conflicting results. In a report from the Nurses' Health Study of a subsample of 665 women, subjective stress associated with caregiving did not predict incidence of breast cancer, but women who spent a lot of time caregiving had lower circulating levels of estradiol, which may be significant as major risk factors for breast cancer are related to estrogen exposure – in fact lower estrogen levels may be a protective factor against the growth of breast neoplasms [35]. Hence, in this case, the stress of caregiving may have the opposite effect, of lowering estradiol levels and decreasing cancer risk. Another report from the Nurses' Health Study cohort found that job stress was not related to development of breast cancer in 37, 562 women followed for up to 8 years [43]. Hence, the role of major life events and even subjective stress is likely minor in terms of the development of cancers, but the research is not conclusive.

The research evidence for the role of social support is stronger for disease progression than for cancer incidence, with fewer studies in the area of social support and incidence – some reviews of cancer incidence don't even consider this factor (e.g. 28;33). Of those that were conducted and considered of high methodological quality, one failed to find associations [44] but one found that women with few friends who experienced feelings of social isolation were at higher risk for developing cancer [45]. Issues around how to measure social support and the differential effects of structural measures of support (i.e. number of people in the social network) and perceived emotional support (i.e. satisfaction with the network) continue to make interpretation of the data difficult [30].

Negative emotions associated with mood disturbance or more serious psychiatric illness such as major depressive disorder have also been investigated, and again the results are equivocal. Specifically looking at depression, Dalton [28] found of 10 major prospective studies and two retrospective studies that the support for a link between depression and cancer incidence was strongest for specific types of cancers (i.e. breast; lung) and that the duration of depression was also an important, yet not often assessed factor. In studies that did look at the duration of depression through repeated measurements over a period of years, those who suffered more chronic and stable depression were more likely to be diagnosed with cancer [28]. There was also a moderating effect of smoking, such that smokers who were also depressed were more likely to get cancer than similarly heavy smokers who were not depressed. Garsson [30] expressed the most support for the strength of the evidence associating depression with cancer initiation, but two earlier reviewers [32,33] were less convinced. McKenna [33] failed to find a convincing link between depression or anxiety and breast cancer initiation, and McGee [32] reported a small but marginally statistically significant association, which amounted to an almost negligible effect.

It is important to note, also, that the measures of depression were quite varied and not necessarily the most up-to-date instruments that are known to be valid and reliable in this context. Summarizing the evidence, Garssen [30] noted that of nine studies looking at formal psychiatric diagnosis and incidence of cancer, four studies found a relationship as predicted, whereas five did not. Similarly, of 14 studies on measures of depressive affect and disease initiation, six studies found no effect, seven found an association between depression and cancer incidence, and one study even found depression to be a protective factor against cancer incidence. An additional newer study adds to their knowledge in this area: in a large sample of 81,612 women from the Nurses' Health Study in the USA, depressive symptoms were associated with increased risk for colorectal cancer 4-8 years later, in that those women in the highest quartile of depressive symptoms were at higher risk than those with the lowest levels [46]. Hence, the research is mixed, but there are indicators that chronic levels of depression may be associated with higher risk for cancer initiation, particularly in the case of lung cancer.

Finally, returning to the initial question of the effect of certain personality characteristics on cancer initiation, the cancer-prone or "Type C" personality (described as cooperative, unassertive, patient, suppressing negative emotions and accepting external authority) was investigated as a causal factor in several studies. Because no one theory of personality is universally accepted, many different methods for measuring personality have been utilized in this research. Results in this area have again been varied, with two of four high-quality studies finding positive associations. However, the measures of this construct have varied considerably. The most well-designed study found that men classified as "acting out/emotional" were less likely to develop cancer than those classified as normal, healthy/sensitive, loners, or having a personality characteristic of interpersonal conflict [47]. There was little direct support for a role of the entire Type C personality cluster as defined previously in cancer initiation [28,30].

Emotional repression is a characteristic of the Type C personality described as a tendency to consciously suppress or unconsciously repress negative emotions, often accompanied with denial that difficult emotions even exist. It has been studied independently of other aspects of the personality style. Again, this is a difficult construct to measure, and has been operationally defined in some studies by combining a low score on a measure of anxiety with

a high score on a measure of defensiveness. Hence, the typical highly repressive person would report low levels of anxiety and have a tendency to refuse to acknowledge any emotional difficulties. There are also specific measures for emotional repression that have been developed. In terms of the initiation of cancer, the role of repression is considered questionable, as only two high quality studies support the association, while three others refute it [28,30]. One study that did support an association found that "anti-emotionality" was associated with a 19% increase in breast cancer diagnoses in a group of over 9,000 women in the Netherlands [48].

In summary, it is clear from this overview that there are a tremendous number of conflicting results regarding the role of various psychosocial factors in cancer initiation. For each factor reviewed, there were both supporting and refuting studies published. None can be ruled out as important, and the degree of support for the different factors, from strongest to weakest, can be summarized as: chronic depression, social support, emotional repression, major life events and Type C personality. The issue of how these conditions or characteristics could lead to cancer development will be addressed in subsequent sections. First however, we will consider issues around psychosocial factors and disease progression and survival, in order to better understand the nuances of this research.

PSYCHOSOCIAL FACTORS AND DISEASE PROGRESSION/SURVIVAL

Research in this area mirrors in some ways the results of studies on psychosocial factors and cancer initiation; however in some cases the effects are much stronger when looking at disease progression. This may have as much to do with research methodology as actual effects, but it does inspire greater confidence in the results. Reviews have also been conducted in this area [49,50] and some of the reviews of factors related to cancer incidence also studied progression and survival [9,30,31,51]. Factors considered include bereavement and stressful life events, perceived stress, social support, depression, hopelessness/ helplessness, emotional repression, and also the coping strategies one uses to deal with cancer and its treatments.

Considering the effect of stressful life events on disease outcome, only one study of major life events found a negative relationship between higher total number of life events and shorter disease-free interval and survival [52], where five other studies found no associations (reviewed in Garssen 2004 [30]). Specifically regarding bereavement studies, mixed results have been reported, with large population-based studies showing conflicting results. For example, in a study of 84,000 participants, no effect of losing a partner was found in women, but men were more likely to die from lung cancer and "other cancers", but not from stomach cancer – this effect was highest in younger men (aged 35-64 years) [53]. However, another study of 20,000 people found no increase in death from cancer in people who had lost a spouse [54]. Garssen concluded a weak effect exists for the impact of loss events on death from cancer, based on two studies of child-loss and one bereavement study, but the effect seems stronger for men than women [30].

Twelve studies reviewed by Garssen [30] investigated the relationships between social support and disease progression. In seven reports experiencing social support, having confidantes and a sufficient network of relatives and friends were related to a longer disease-

free interval and longer survival. An example of a well-conducted study in this area is Maunsell et al (1995) [55] who identified the presence of different types confidantes in 224 newly diagnosed breast cancer patients. The larger number of categories in which women had close confidantes (i.e. spouse, children, friends, colleagues, etc), the higher the survival rate 7 years later. Fifty-six percent of women without a confidante had survived compared to 72% of those with one or more confidantes – a dose-response relationship was also seen, in that having more confidantes improved the survival rate.

There were also five negative reports reviewed that found no associations between measures of social support and cancer progression. Reasons for these discrepancies may include the specific ways that social support has been measured – structural versus functional. It may be the case that the quality of the support sytem is more important than its size, as indicated in one study which found no relationships between structural measures of support and survival, but did find associations between the subjective judgment of experienced social support and mortality [56]. A more recent report of 2,835 women who were diagnosed with breast cancer from the Nurses' Health Study in the USA found that women who were socially isolated before the diagnosis of cancer had a 66% increased risk of mortality from any cause, and twice the chance of dying from breast cancer [57]. Women without close relatives, friends or children also had elevated risks of death from breast cancer. Added to the data reviewed by Garssen in 2004 [30], this recent study suggests that women who feel less isolated and have a larger support network may have better outcomes.

The case of depression is yet another in which the evidence for a relationship with survival may be stronger than with incidence, with a good deal of research having been conducted in this area. Garssen [30] summarized that of 33 well-conducted studies in this area, six found that negative emotions predicted a more favorable disease outcome, 11 found a negative relationship, and 16 failed to find a relationship at all. When looking at studies that considered only psychiatric diagnoses, a similar pattern is seen, with two studies finding that having a psychiatric diagnosis was a favourable prognostic indicator, three studies finding the opposite, and no relationship in an additional two.

A well-conducted study published in 2003 and not included in earlier reviews followed similar methodology [58]. Measures were collected on a range of emotional and cognitive factors in the early postdiagnostic period and at 4-month intervals up to 15 months after diagnosis. These were used to predict survival time up to 10 years among 205 cancer patients heterogeneous in disease site, status, and progression. Depressive symptomology was the most consistent psychological predictor of shortened survival time using both baseline and repeated measures, after controlling for several known demographic and medical risk factors. Although controversy remains, most reviewers state that the evidence for an effect of depression on disease course is still inconclusive [23,30,50] although one major review concluded more strongly that depression likely plays a role in cancer survival [9]. These authours noted also that emotional overcontrol or repression of emotions likely adds to the deleterious effect of the depression itself.

Indeed, considering more specifically emotional repression and survival, five studies found that "repressors" had shorter disease-free intervals and shorter survival time. However, three others found no associations. Nonetheless, the role of emotional repression finds more support in terms of cancer progression than for initial cancer etiology and is described as one of the more "promising factors" for further investigation [30].

The final area that was evaluated as a factor in disease progression is coping style and adjustment to illness. Several hypothesized coping styles loosely related to the Type-C personality have been investigated. These include having a "fighting spirit", denial or minimization of the impact of the illness, stoic acceptance or fatalism, and a helpless/hopeless or pessimistic coping style. This latter type of response to cancer is also linked with depression, as some of the symptoms of depression are hopelessness and pessimism. The most support is found for a negative role of this factor in disease progression, with six of 10 studies finding patients with more hopelessness and pessimism had shorter survival times. For the other factors, little support was found for the importance of fighting spirit (1/6 studies), denial (0/5 studies), or fatalism (1/5 studies) [30].

Hence, overall a poor prognostic profile emerges of a person prone to feelings of helplessness, hopelessness and pessimism, with a tendency to repress emotions, and with the perception of little social support. The question then arises of what the physiological consequences of having a predominance of these psychological characteristics may be, and how this profile might promote cancer development. The question also arises of whether psychosocial interventions can, though altering these psychological characteristics, change this internal state and arrest cancer promoting processes already set in motion. The latter question regarding survival will be addressed next.

PSYCHOSOCIAL INTERVENTIONS AND SURVIVAL

This type of research investigates more specifically whether it is possible to manipulate some of the factors identified in the research reviewed previously that seem important for disease outcome, and subsequently change the course of the illness. This is an ambitious undertaking that many researchers would consider the final test for the role of psychosocial factors in disease processes. Again, this work has been reviewed on numerous occasions [17-21].

A recent review used the technique of meta-analysis to quantify the relative effect of psychosocial interventions on survival across all studies in the area that met criteria for good methodological quality [21]. There were 14 studies included in the review; interventions included components such as supportive therapy, emotional expression, cognitive behavioural therapy, psychoeducation, coping skills training, stress management, mental imagery, psychotherapy and hypnotherapy. Most were in formats of weekly group meetings from 6 weeks to one year in duration with follow-up periods ranging from 9-months to 20 years. When hazard ratios (HR) were calculated for each study and aggregated, the average HR was 0.85 (with a confidence interval (CI) of 0.65-1.11). In meta-analytic terminology, a HR of 1.0 means there is no advantage of the intervention over the control condition on survival – both the control patients and those who got the intervention lived about the same length of time. Values below 1.0 favour the interventions, over 1.0 favour the control group. Only if the value is below 1.0 and the confidence interval is entirely above or below 1.0 can the results be considered statistically significant. Hence, even though the HR is below one, the range of the CI includes 1.0, so one cannot conclude with certainty that the interventions prolonged survival. When interventions were analyzed separately by group vs. individual delivery, there was no effect of group programs on survival (HR=0.97, CI=0.73-1.27). However,

individually-delivered interventions did have a positive effect on survival time (HR=0.55, CI=0.43-0.70). What this value means is that the odds of dying first were 35% greater for patients in no-treatment groups compared to those receiving the individual interventions.

As a well-known example of research in this area, consider the case of the Spiegel at al Supportive Expressive Group Therapy (SEGT) study [59,60]. SEGT is a form of professionally-led group psychosocial intervention that evolved specifically to address the support needs of seriously ill medical patients. Two key interrelated goals of SEGT are to build social bonds and to facilitate the expression of emotion. Thus, the group creates a context for the expression, containment, and processing of current distress. This enables patients and their families to proactively address foreseeable challenges, to marshal appropriate resources and to make the most of whatever life remains [59]. Given that lack of social support and emotional repression were two of the strongest predictive factors for poor disease outcomes, this type of approach makes intuitive sense.

The Spiegel study of SEGT, published in 1989, reported on 10-year follow-up of women with metastatic breast cancer randomly assigned to weekly SEGT meetings over the course of an entire year, or care-as-usual, which in the late 1970s included no formal psychosocial support. They found that after 10 years, the women in the treatment group lived an average of 18-months longer than those assigned to the control condition [60]. This caused a great deal of interest internationally and a large replication study was carried out in Canada, known as the Breast Expressive-Supportive Therapy pan-Canadian trial (BEST; [61]). However, that study failed to find any survival advantage for the SEGT group, although it was successful in alleviating pain and suffering, as well as enriching the lives of patients diagnosed with metastatic cancer.

Another long-awaited replication by the original group at Stanford released the results in an abstract format in 2006 [62]: 125 women with metastatic (n = 122) or locally recurrent (n = 3) breast cancer were randomly assigned to the SEGT condition (n = 64), or to the control condition (n = 61) receiving only educational materials for a minimum of 1 year. No overall statistically significant effect of treatment on survival was found for treatment compared to control patients, but there was a statistically significant site by treatment interaction such that estrogen receptor (ER) negative participants randomized to treatment survived longer (median = 29.8 months) than ER negative controls (median = 9.3 months), while the ER positive participants showed no treatment effect (this was a secondary post-hoc unplanned analysis and hence the results must be considered cautiously).. Hence there was no overall effect of the intervention on survival, except perhaps for those whose cancers were *not* responsive to estrogens These cancers also typically have a poorer prognosis than ER positive cancers. If this result were bourne out, it can be speculated that because ER positive cancers respond well to hormonal therapies which may also have effects on HPA functioning, that any putative effect of psychosocial support on survival among ER positive women has been superseded. However, outcome among ER negative women is less affected by hormonal treatments, perhaps leaving room for the impact of other treatments including psychosocial interventions. This study illustrates well the ongoing controversy about the possible life-extending properties of psychosocial interventions and hints at some of the potential neuroendocrine moderators of potential survival effects of psychosocial interventions.

PSYCHOSOCIAL INTERVENTIONS AND IMMUNE AND ENDOCRINE OUTCOMES

There is surprisingly little known about the effects of psychosocial interventions on immune and endocrine outcomes in cancer patients. A small number of narrative reviews speculated on these associations in the 1990s [22,23], but little of a conclusive nature has been discussed. Given the dearth of information, we conducted a systematic review of studies in this area by searching every combination of the following search terms in Medline, Pubmed and PsychInfo: cancer, neoplasm, psychosocial, intervention, treatment, outcomes, immune, endocrine, psychoneuroimmunology, psychoneuroendocrinology, PNI, PNE, biological, cortisol, natural killer, lymphocyte as well as searching the reference lists of selected articles in a snowball technique. Details of the sample, methods, interventions, and outcomes of each study are presented in Table 1. Papers were not vetted or rated on their methodological quality, as relatively few (17 studies) were identified, so all are included in the review. Hence the list includes study designs ranging from pre-post observational studies to larger randomized controlled trials (RCTs). Sample sizes vary from a low of 13 [63] to a high of 227 participants [64]. Of the 17 studies, 11 were RCTs with one or more comparison groups [63,65-67] [64,68-72], another 2 had nonrandomized assignment to one or more comparison groups [73,74], and 4 were pre-post assessments of one intervention only without a control group [75-78]. This distribution is not optimal, as the only study design that allows inferences of causality between participation in interventions and outcome measures is the RCT, but almost two-thirds of the studies did utilize this design. The other study designs can provide provocative preliminary evidence for promising avenues of future research.

Intervention types also varied considerably across studies, as did outcome measures. Interventions ranged from existential psychotherapy [67] to cognitive-behavioural stress management [70], mindfulness-based stress reduction [77,78] (an intervention involving intensive training in meditation and yoga), support groups [66], music therapy [76] and biofeedback [63]. Outcomes, as well, included a range of measures, mostly cortisol (measured both in saliva and blood), and indices of immune functioning (white blood cells, lymphocytes, NK cells, proliferative responses, immunogloblulins, cytokines). A broad range of psychological outcome measures were also used to assess an array of constructs, including stress, depression, anxiety, quality of life, mood, coping strategies, personality, loneliness, optimism and benefit finding. Studies primarily looked at women with breast cancer (13/17) with 2 studies investigating prostate cancer [63-71,73,77-79], 2 with mixed participants [75,76] and one each in malignant melanoma [72] and ovarian cancer [74]. In addition, the stage of cancer also was varied, as was the timing of the intervention. Most participants were diagnosed with non-metastatic disease (stages I=III) in 12/17 studies [63,64,66-68,70-73,77-79], two studies investigated metastatic cancer patients only [65,75], and three included patients with any stage of cancer [69,74,76]. Finally, in terms of timing, the majority of studies were conducted after the completion of surgery and adjuvant treatment (8/17) [63,66,67,71,75-78], followed by during the post-surgical phase (5) [72] [64,70,73,79], during treatment (3) [65] [68,74] and one was conducted pre-surgery [69].

Table 1.

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
1.	1989	Length of survival and lymphocyte percentage in women with mammary cancer as a function of psychotherapy [65]	100 women with metastatic breast cancer were randomly assigned to concurrent psychotherapy and chemotherapy (25 in each group: chemo, no chemo, therapy, no therapy). The groups were matched on age, social background, cancer stage, and medical treatments received.	Patients in the therapy group were randomly assigned to 1 of 3 therapies (creative novation therapy, depth psychotherapy, and relaxation therapy with desensitization). Total psychotherapy time was 30 hours. The chemotherapy group received Doxorubicin and 1 of 3 other combination of agents (cyclophosphamide, fluoruracil and vincristine, cyclophosphamide and prednisolone). Chemotherapy was given in 3-4 week cycles and was repeated 4-9 times	Leucocyte concentration and lymphocyte percentage was measured in the women in the chemotherapy group. Measurements were taken prior to chemo, two weeks after treatment initiation, and one month after for all consecutive cycles resulting in 7 samples. *Patients with no psychotherapy showed a steady decrease in lymphocyte production. Patients in therapy showed an initial decrease but then demonstrated an increase past levels at treatment initiation.*	Psychological outcomes not included
2.	1990	A structured psychiatric intervention for cancer patients: II. Changes over time in immunological measures [72]	61 patients (28 mean and 33 women, mean age = 42) with stage I or II malignant melanoma were randomly assigned to a standard care (n=35) or intervention (n=26) group. Immunological and psychological assessments were taken at baseline, 6 weeks, and 6 months. All patients had completed surgery	A short term structured psychiatric group, 9 hours in duration was provided for the treatment group. The intervention was delivered to groups of 7-10 patients for 11/2 hours for 6 weeks. The intervention consisted of health education, enhancement of problem solving skills, stress management and relaxation, and psychological support	Immune outcomes included NK cells, LGLs, major T-cell subsets, CD8 and CD4 T-cells. Groups did not differ at baseline on immunological variables. *At 6 weeks, the treatment group had higher levels of LGLs. At 6 months, the treatment group remained higher in LGLs but also had higher levels of NK cells. The majority of patients in the treatment group had increases in the percent of LDLs, NK cell and NK function and decreased in CD4 t-cells compared to the control group*	The POMS and the Dealing with Illness-Coping Inventory were used to assess affective state and coping. Coping and affective state were improved after the intervention but no significant correlations were found between affective state and immune changes when groups were analyzed independently.

Table 1. (Continued)

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
3.	1993	Immunological responses of breast cancer patients to behavioral interventions [63]	13 stage I breast cancer patients were enrolled in the study, mean age of 45 years. 7 patients were randomly assigned to immediate treatment and 6 patients to delayed treatment (6 months into the study). All patients had undergone surgery and completed adjuvant treatment.	The intervention was a 9 week sequence of relaxation training, guided imagery and biofeedback training in group format. The first 3 weeks were focused on relaxation and guided imagery with biofeedback being introduced in week 4. Participants were given relaxation tapes and were asked to practice twice daily. After completion of the 9 week intervention, monthly brush up sessions were held.	Blood samples were provided at baseline, throughout treatment and during 3 month follow up for both groups. Immune assays performed included NK cell activity, Con-A, MLR, IL-2, plasma IgA, IgG and IgM, total WBC and PBL. Baseline measures of psychophysiological stress response was taken to evaluate biofeedback training effects. *Between group comparisons demonstrated significant differences in PBL, WBC, Con-A, and MLR. Within group comparisons demonstrated significant effects for PBL, Con-A, MLR, and IgM.*	Psychological tests were administered at baseline and following training. Measurements includ-ed the MMPI, Millon Behavioral Health Inventory, Sarason Social Support Scale, Rotter Locus of control, the Affects Balance Scale, and the MAC Scale. *There were no significant changes demonstrated on the psychological measures from pre- to post-training.*
4.	1994	Effects of behavioral interventions on plasma cortisol and lymphocytes in breast cancer patients: An exploratory study [73]	24 women with stage I and II breast cancer. All patients had surgery and were not undergoing additional treatment. 14 patients volunteered to participate in the treatment and 10 chose to wait and serve as controls (non-randomized)	The intervention consisted of 2 hour session, once a week for 10 weeks. The intervention consisted of relaxation techniques based on autogentic principles and guided imagery, health education, development of stress and illness coping skills	Blood samples were obtained to determine plasma concentration of cortisol and WBC before and after the 2^{nd} and 10^{th} sessions. *There was a significant reduction in cortisol after the 2^{nd} session and were further decreased after the 10^{th} session, totaling a 23% decrease in cortisol levels. No significant differences were seen in numbers of leukocytes and monocytes. Lymphocyte numbers increased overall and specifically after the second session, but not after the 10^{th} session.* There were no correlations between biological outcomes.	A German questionnaire assessed coping with severe bodily disease. Personality factors were controlled for using the Freiburger Personality Inventory. *There were no significant differences in personality factors or coping strategies*

Table 1. (Continued)

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
5.	1997	Coping, life attitudes, and immune responses to imagery and group support after breast cancer treatment [66]	47 women who completed treatment for stage 1-3 breast cancer with a mean age of 46. Patients were randomly assigned to a standard care control group (n=15), standard care plus six weekly 1 hour support session (n=16), or imagery/relaxation sessions (n=16).	Themes for both groups were of giving and receiving support and preparing for the future. The support group focused on the exploration of feelings, returning to normal, the impact of relationships, fears of recurrence, loss and saying goodbye. The imagery group focused on relaxation, setting goals and finding purpose, the impact of beliefs on health, coping with fears, giving and receiving support and concluding.	NK cytotoxicity, cytokines (IL-1α, IL-1β, IL-2 and IFN-γ), and beta endorphins were assessed. *Quality of imagery and frequency of practice was associated with increased NK activity and improved psychical quality of life. No significant differences were found between the groups on any of the immune measures. Neopterin decreased and IFN-γ increased for all the women.*	Assessment instruments included the FACT-B, POMS-Brief, Ways of Coping with Cancer, and the Duke-UNC Functional Social Support Questionnaire. *Coping skills improved for the support and imagery groups. The treatment groups also sought more support from others.* No significant differences were found between treatment groups
6.	1997	Effectiveness of a short-term group psychotherapy program on endocrine and immune function in breast cancer patients: An exploratory study [67]	The sample consisted of women with early stage breast cancer and distant or lymph metastases (mean age = 59). Patients were randomly assigned to an intervention group (11 patients) or a control group (12 patients). A healthy age matched control group of 15 women (mean age = 56) was included for comparison	Patients were randomly assigned to either the existential-experiential group psychotherapy or a wait list control group. The group was semi-structured and focused on fears of death, limitations of freedom, existential isolation, relationships with family, relatives and the medical professions, autonomy, helplessness and dependence and the meaning of life. Sessions were held once a week for 2.5 hours.	*Patients provided 2 blood samples before and after the intervention or at concurrent time periods for the control group. Biological measures included cortisol, ACTH, peripheral blood cells, NK cell activity and proliferative responses. Women with breast cancer had significantly higher cortisol levels than healthy matched women and lower levels of CD3 and CD4 cells. When baseline levels were adjusted, women in the treatment group had lower levels of prolactin and cortisol and lower levels of NK cells, CD4 and CD8 cells.*	*Measures were com-pleted before and after program participation and included the BDI, the STAI, and the POMS. No correlations were found for psychological and endocrine outcomes. Trait anxiety was positively related to changes in CD4 levels. BDI scores were posi-ively related to percent-age of NK cells. Mood disturbance was related to proliferative responses*

Table 1. (Continued)

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
7.	1997	Immune effects of relaxation during chemotherapy for ovarian cancer [74]	22 patients (Mean age= 57) receiving 4 cycles postoperative chemotherapy for stage 1-4 ovarian cancer. 12 patients were in the relaxation group, 10 patients were in the control group. Allocation was based on hospital ward and non-random.	Intervention was designed to train patients how to use cue controlled progressive relaxation skills rapidly and apply them when needed. Audiotapes were provided for practice and patients were asked to practice twice a day. Patients received 3 relaxation training sessions with a clinical psychologist. The relaxation sessions were delivered prior to initiation of treatment, during treatment and prior to the second course of treatment	Venous blood sampling was performed 2 days before chemotherapy and on the morning of their 3rd or 4th cycle. Routine hematological date was assessed (white blood cells, lymphocytes, granulocytes, monocytes, Con-A and NK). Groups were not different at baseline. *After intervention, the relaxation group had higher white blood cell counts and more lymphocytes.* Nonsignificant trends were observed for monocyte levels and proliferative responses to Con-A. NK levels were similar between groups.	The STAI was completed immediately before each blood sampling. No results were reported for psychological outcomes.
8.	1997	Phase II study of psychotherapeutic intervention in advanced cancer [75]	35 patients (16 males, 19 females) enrolled in the study with a mean age of 55 years. The group was heterogeneous but the primary tumor site was colorectal. No control group.	Patients were offered 12, 1.5-2 hour sessions once a week of individual counselling. They also attended twice monthly group meetings lasting 2.5 hours. Psychotherapy was experiential-existentially based and focused on feelings, needs, aims and potential of the individual.	NK cell cytotoxicity and activity was measured prior to the intervention, at 6 weeks and 12 weeks of the intervention and at 6 and 12 months following intake. *5 patients experienced an arrest in tumour growth. No effect of treatment on NK cell activity was observed. No significant relationships were found between NK and psychological outcomes.*	*Patients completed the Purpose in Life Test, Zung's Depression Scale, the Loneliness Inventory and the Cancer Locus of Control scale at the same time as blood sampling. No changes were observed on measures of loneliness, depression or locus of control. Purpose in life increased significantly.*

Table 1. (Continued)

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
9.	2000	Cognitive-behavioral stress management reduces serum cortisol by enhancing benefit finding among women being treated for early stage breast cancer [70]	34 women (mean age = 46) with stage I or II breast cancer recruited within 8 weeks post surgery. 24 women were randomized to the intervention group and 10 to a waitlist control group.	Cognitive behavioral stress management was delivered in 2 hour classes over the course of 10 weeks. Class material consisted of progressive muscle relaxation, meditation, abdominal breathing, guided imagery, cognitive restructuring and techniques to improve coping, assertiveness, anger management and the use of social support.	Blood samples were provided pre and post intervention or control period to assess cortisol levels. There were no significant differences between groups at baseline. *Significant decreases in cortisol were produced for the intervention group compared to the control. Cortisol reductions were significantly associated with improvements in benefit finding.*	Perceived positive contribution for women experiencing breast cancer were measured by the Benefit Finding Scale. Distress was measured by the POMS. *Significant improvements were observed in benefit finding but not in distress levels after program participation.*
10.	2000	A presurgical psychosocial intervention for breast cancer patients: psychological distress and the immune response [69]	41 women (mean age=56). All women were awaiting either surgery or surgery plus adjuvant therapy at enrolment. Patients were randomly assigned to standard care or standard care plus a 2 session psychosocial intervention. Assessments and blood draws were performed before surgery and prior to intervention, before surgery and following intervention, and 1 week following surgery.	The intervention was delivered by two clinical psychologists to individuals or small groups of 2-3. Duration was 90 minutes. The intervention had 3 objectives: psychoeducation about somatic and emotional responses to stress, problems solving skills for use in crisis, relaxation techniques and psychosocial support	NK cell activity and IFN-γ were measured. No significant time or interaction effects were observed in NK cell activity. *A significant interaction was seen for IFN-γ levels, whereby the levels of IFN-γ in the control group decreased steadily and the levels in the therapy group remained constant.* This was no longer significant when baseline measures were included as a covariate	Patients completed the CES-D scale; the Differential Emotions Scale-IV, the IES and the Life Orientation Test. *The therapy group experienced an increase on measures of overall interest and enjoyment and a decrease in sadness compared to the control group.* Optimism increased regardless of group

Table 1. (Continued)

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
11.	2001	Effects of stress management on testosterone levels in women with early stage breast cancer [79]	34 women (mean age = 46) with stage I or II breast cancer recruited within 8 weeks post surgery. 24 women were randomized to the intervention group and 10 to a waitlist control group.	Cognitive behavioral stress management was delivered in 2 hour classes over the course of 10 weeks. Class material consisted of progressive muscle relaxation, meditation, abdominal breathing, guided imagery, cognitive restructuring and techniques to improve coping, assertiveness, anger management and the use of social support.	Blood samples were provided pre and post intervention or control period to assess total testosterone levels. There were no significant differences between groups at baseline. *Post intervention, there were significant reductions in free testosterone and total testosterone. Reduction in testosterone were positively correlated to increases in benefit finding.*	Perceived positive contribution for women experiencing breast cancer were measured by the Benefit Finding Scale
12.	2001	A pilot study into the therapeutic effects of music therapy at a cancer help center [76]	29 patients (21 women and 8 men) participated in a residential 1 week course at the care center with an average age of 49 years (no control group). Cancer type and stage was mixed but breast cancer was predominant. All were in the process or had completed treatment Physiological and psychological assessments were conducted before and after each session.	The intervention was completed over 3 days. Day 1 included listening to 1 hour of music in a relaxed state. Day 2 included active playing of instruments for 1.5 hours in a group format. Day 3 included a 1 hour focus group meeting to discuss, compare and contract their experiences in both the listening and playing sessions.	Two salivary measures were examined: Salivary cortisol and sIgA. *Listening to music resulted in increased levels of sIgA compared to levels before music listening session. Cortisol levels decreased significantly from Day 1 to Day 2, but were not significantly affected by either music treatment.* No significant correlations were found between the physiological and psychological measures	The University of Wales Institute of Science and Technology (UWIST) Mood Adjective Checklist provided information on hedonic tone (well-being), tense arousal and energetic arousal. *Listening to music produced significant decreases in tense arousal and increases in hedonic tone. Active playing of music produced a significant increase in energetic arousal.*

Table 1. (Continued)

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
13.	2003	Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients [77]	49 women with breast and 10 men with prostate cancer. The sample had a mean age of 55 years and were diagnosed with early stage cancer a median of 1.1 years prior. Treatment was completed a median of 6 months prior (excluding hormonal). The sample was mostly comprised of patients with stage II cancer. No control group.	Mindfulness-based Stress Reduction was delivered over 8 weeks with weekly 90 minute group sessions and 1 3 hour silent retreat. Primary components of the program are: mindfulness meditation and yoga practice, psychoeducation regading stress and the stress response and group support.	Biological measurements included all leukocyte subclasses and intracellular cytokines. *Increases in eosinophils and IL-4 production in T-cells were observed as well as decreases in monocytes, T-cell production of IFN-γ, and NK cell production of IL-10.* There were no significant relationships between psychological and immunological measures	Psychological outcomes were measured with the EORTC-QLQ-30, POMS, and the SOSI. *Improvements were observed in quality of life, mood disturbance (13% reduction) and symptoms of stress (19.3% reduction).*
14.	2004	Psychological, behavioral, and immune changes after a psychological intervention: A clinical trial [64]	227 women (mean age = 51) with stage II or III breast cancer who can completed surgery but were awaiting adjuvant therapy were accrued. 113 were randomly assigned to the assessment only group and 114 were assigned to the intervention group. At 4 month assessment, the sample sizes were 91 in the assessment group and 107 in the intervention group.	The intervention was provided to small groups of 8-12 patients and led by 2 clinical psychologists. Groups met for 1.5 hours for 18 sessions. Therapy content included stress management, emotional distress and social adjustment, health behaviors and adherence to treatment.	Immune assays investigated were T lymphocytes, T-cell subsets and NK cells, NK cell cytotoxicity and blastogetnic response to PHA and Con-A. No significant group effects were found for T-lymphocyte counts. *A significant effects was reported for Con-A and PHA induced T-cell blastogenesis in the intervention group.* NK cell count and cell lysis were not significant	Psychological measures were the IES, the POMS, the Social Network Index, the Perceived Social Support Scale, the Food Habits Questionnaire and the Seven Day exercise Recall. *Patients in the intervention group showed a reduction in anxiety and for patients with higher cancer stress, the group produced reduction in mood disturbance and fatigue.* The intervention group also perceived more support

Table 1. (Continued)

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
						whereas the assessment only group reported a reduction in support. Health behaviors (diet and smoking) improved for the intervention group only
15.	2004	A pilot randomiz-ed trial assessing the effects of auto-genic training in early stage cancer patients in relation to psychological status and immune system responses [71]	31 women with early stage breast cancer post surgery and radiotherapy, not undergoing further treatment were randomized to autogentic relaxation training or a wait list control	Autogenic relaxation training was taught in groups and focused on heaviness of limbs, warmth of limbs, calm regular heart beat, easy breathing, abdominal warmth and cooling of the forehead. Measurements were taken before and after the intervention.	CD4, CD8, B cells, NK cells, neutrophils and monocytes were examined. *There was a statistically significant difference in CD8 and NK cells after the intervention.* Caution in interpretation is warranted due to small sample size.	Anxiety and depression were measured using the HADS. *Intervention and control groups were significantly different on measures of anxiety and depression after the intervention*
16.	2004	Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrost erone sulphate (DHEAS) and melatonin in breast and prostate cancer outpatients [78]	49 women with breast and 10 men with pros-tate cancer. The sample had a mean age of 55 years and were diagnosed with early stage cancer a median of 1.1 years prior. Treatment was completed a median of 6 months prior (excluding hormonal). The sample was mostly comprised of patients with stage II cancer. No control group.	Mindfulness-based Stress Reduction was delivered over 8 weeks with weekly 90 minute group sessions and 1 3 hour silent retreat. Primary components of the program are: mindfulness meditation and yoga practice, psychoeducation regading stress and the stress response and group support.	A blood sample was taken for DHEAS testing and saliva samples for melatonin and cortisol. Cortisol samples were provided at 8am, 2pm, and 8pm. Melatonin samples were provided at 2pm. Patients with abnormal cortisol profiles at baseline also had higher stress scores. *No changes were observed in mean cortisol levels, but patients with higher initial cortisol levels decreased over time on mean cortisol levels as well as morning, afternoon and evening levels.* No significant changes were seen in DHEAS or melatonin levels	Psychological outcomes were measured with the EORTC-QLQ-30, POMS, and the SOSI. Psychological data is presented in the paper by Carlson, Speca, Patel and Goodey (2003) [77]

Table 1. (Continued)

	Year	Reference	Sample and Methods	Intervention	Biological Outcomes	Psychological Outcomes
17.	2006	A randomized controlled trial of psychological interventions using the psychophysiological framework for Chinese breast cancer patients [68]	76 participants (mean age = 49) were randomly assigned to a body-mind-spirit (BMS; n=27), supportive-expressive (SE; n=16), social support self help group (SS; n=16), or a no intervention group (n=17). Psychological and physiological measurements were administered at baseline, 4 months and 8 months post intervention.	The BMS group and integrated western psychotherapeutic elements with eastern philosophy and Chinese health practices. It focused on the normalization of traumatic experiences, letting go of attachments, forgiveness and self love and social support and commitment to others (15 total hours). The SE group was designed to build social support, deal with concerns of death, dying and body image, reorder life priorities, improve relationships, communication and symptom control (16 total hours). The SS group was unstructured and members decided topics (15 total hours).	The physiological outcome measure was salivary cortisol. Samples were taken at 5 times thoughout the day (waking, 45 min after waking, 12pm, 5pm, and 9pm). *Only the BMS group showed a significant reduction in total salivary cortisol level after 8 months. Mean cortisol concentration was significantly related to positive social support in that higher support was associated with lower cortisol at 8 months.*	psychological outcome measures included the General Health Questionnaire, the PSS, the Mini MAC Scale, the Courtauld Emotional Control Scale, and the Yale Social Support Index. *After 4 months, a significant reduction in health concerns, emotionality, negative emotion, and positive support was reported for the BMS group. The SS group showed and increase in negative emotion after 8 months. The control group showed a reduction in positive support after 4 months*

What can be concluded from this broad array of study designs, samples, interventions and outcome measures? Overall, 6 studies found some effect of the intervention on measures of cortisol [67,68,70,73,76,78], 14 reported positive effects on immune function [63-67,69,71-74,76-79], and one study reported no effect on immune function [75]. It might not be expected that biological changes would occur in the absence of psychological changes; hence it's important to note that 13 studies found positive effects of the intervention on psychological outcomes [64,66-72,75-78] but 2 studies did not [63,73]. The numbers don't always add up to 17 as some studies included both cortisol and immune measures, and other did not report psychological outcomes at all. It is also important to take into account publication bias, as most papers with negative results either aren't submitted for publication or are rejected at peer review. Also, most studies conducted multiple comparisons and had multiple outcome measures – hence, the finding of one of two positive outcomes inflates the error rate and perhaps exaggerates the effects of these interventions. If the percent positive outcomes were to be assessed on the basis of how many comparisons of all those conducted were statistically significant, the number would be far lower. However, this data does serve as "proof of principle" that it is possible to affect changes, particularly in measures of immune function and cortisol levels, through psychosocial intervention.

As mentioned previously, the quality of the studies varied considerably, with some of quite low quality, so perhaps it is useful to review one or two of the best studies in detail, to illustrate the potential effects. The largest study, conducted by Andersen et al (2004) [64] randomly assigned 227 women with stage II or III breast cancer who had completed surgery to either usual care or group therapy consisting of techniques for stress management, social support, emotional and social adjustment to cancer, enhancing health behaviours and adherence to treatment. After four months during which participants received chemotherapy, retention was good (80-93%) and the intervention group demonstrated greater t-cell proliferative responses to the mitogens ConA and PHA. Patients in the intervention also had greater reductions in anxiety, improvements in social support, and better health behaviors such as sleep and diet.

Similarly, a recent study reported a sample of 76 patients who were randomly assigned to a body-mind-spirit group, supportive-expressive therapy or a social support self-help group [68]. This type of study pitting various psychosocial interventions against one another creates a very hard test of specificity, as it is quite difficult to demonstrate the superiority of one group over another. Nonetheless, the authours found that only the body-mind-spirit group showed reductions in total salivary cortisol after 8-months, and higher social support was related to lower cortisol concentrations. Participants in the body-mind-spirit group also had decreases in health concerns, fewer negative emotions and felt more positive support than the other two groups.

To summarize, then, this body of work has demonstrated the potential for psychosocial interventions to affect a wide array of outcomes such as increasing NK cell cytotoxicity and decreasing salivary cortisol levels. Research in this area has focused mostly on immune and cortisol outcomes, and mostly on women with breast cancer. The potential significance of these changes will be addressed in the following section.

ENDOCRINE/IMMUNE MEASURES AND DISEASE PROGRESSION/SURVIVAL

Much of the motivation behind investigating the neuroendocrine and immune impacts of psychosocial interventions in the previous section is based on the assumption that the intermediary outcome measures used are meaningful. Hence, the studies reviewed document associations between manipulating psychosocial factors and consequent changes in immune and endocrine measures. However, whether or not these outcomes have much or anything to do with disease processes has not been well explored. This question can be addressed by looking at both the animal and human research into the psychobiology of cancer, which has been reviewed by a number of investigators [9,10,13,14,22-24,80,81].

Researchers have looked at several potential pathways between immune and endocrine function, some of which can be altered by psychosocial factors, and disease progression in both humans and animals. Simply speaking, at least five interacting systems are involved in these relationships: 1) psychological factors (i.e. stress; depression); 2) CNS factors including HPA and SNS reactivity and regulation; 3) endocrine factors, including HPG reactivity of estrogens and testosterone and circadian rhythms of melatonin; 4) immune factors including immunosurveillance; and 5) tumour-related factors in the tumour microenvironment itself, including processes such as angiogenesis and programmed cell death (apoptosis). These systems clearly interact, so breaking them down into separate categories is an artificial heuristic that may help with understanding, but it is quickly obvious that they interact with one another in a myriad of ways. The first factor, psychological processes, has been addressed in earlier sections; the remainder of this section will selectively look at interactions between the other systems and disease progression.

HPA Axis

A growing body of research has investigated the stress-related concept of allostatic load, and a large body of evidence has associated excessive release of cortisol with suppression of the immune system (for reviews see [11,82,83]). Cortisol is largely responsible for the downregulation of immune function as a result of stress. Its hypersecretion also results in depressed mood [84,85]. Cortisol levels are typically highest in the morning, and decrease during the day, resulting in the downward sloping profile characteristic of most healthy individuals. However, cortisol levels have been reported to be elevated and overall diurnal profiles flatter in breast cancer patients compared to control women [86-88]. This supportive data stems primarily from women with metastatic, rather than earlier stage, cancers. For example, abnormal patterns of cortisol secretion have been reported in up to 75% of a sample of metastatic breast and ovarian cancer patients [89]. Further, the slope of the rate of change of cortisol levels measured four times a day for three consecutive days was associated with survival time in a group of 104 women with metastatic breast cancer. Those women who displayed less variation in salivary cortisol levels, expressed as a flatter slope and indicating a lack of normal diurnal cortisol variation, experienced earlier mortality over a 7-year follow-up period [15].

When these patients were split at the median cortisol slope for descriptive purposes, 77% of those with flat rhythms had died after surviving an average of 3.2 years. In contrast, 60% of the patients with relatively steep rhythms had died, with an average survival of 4.5 years. Hence, the women with steeper slopes survived more than 1 year longer on average. This relationship held even when other prognostic medical variables were taken into account, such as markers of disease status (e.g. location of metastases, estrogen receptor status), medical treatment (e.g. chemotherapy drugs) and psychosocial variables (e.g. stress levels and marital satisfaction) [15]. The authors speculate that these abnormal circadian rhythms of cortisol secretion represent compromised HPA axis functioning, which may be responsible for earlier mortality. Indeed other studies have reported circadian abnormalities in the secretion of 12 hormones in women at high risk for developing occurrences of breast cancer [90], as well as associations with later stages of cancer development and other prognostic indicators such as poorer performance status and more metastatic involvement [89,91]. In addition to affecting hormones, potentially through cell receptors and cell signalling pathways, excess cortisol may directly facilitate tumour growth through metabolic pathways, such that normal cells in which cortisol inhibits glucose uptake may become resistant to this effect when they mutate into cancer cells. Hence, glucocorticoids may suppress energy uptake in healthy cells but facilitate the ability of cancer cells to preferentially utilize energy, providing a metabolic advantage [92].

HPA axis dysregulation also has direct effects on immune function, both in terms of cellular and innate immunity. Immune defences against tumours are very complicated and include specific mechanisms such as tumour cell targeting by cytotoxic and helper T-cells and B-cell mediated cell lysis, and also natural immunity channels including cell death through NK cells, macrophages and ganulocytes. Abnormal cortisol rhythms were associated with reduced NK cell number and cytotoxicity in women with metastatic breast cancer [15], and decreased NK activity has been associated with tumour progression in animals [81] and humans [93]. Hence, excess cortisol in the blood stream of cancer patients due to allostatic load and HPA axis dysregulation can affect both numbers and activity levels of lymphocytes, macrophages and granulocytes [10].

SNS Factors

There is preliminary evidence suggesting that autonomic control may sometimes be impaired among BC patients [94]. Women at high familiar risk for breast cancer showed a greater catecholamine response to laboratory stressors than healthy women with normal risk levels [95], and they also had higher urinary levels of epinephrine (EP) during the work day [96]. During sleep there is usually a reduction of sympathetic nervous system (SNS) activity and an increase in parasympathetic (PNS) function, but the quality of sleep contributes to these autonomic changes. Deep-wave sleep is characterized by markedly reduced SNS activity, in that both norepinephrine (NE) and EP levels decline [97]. Hence, sleep quality can impact production of SNS catecholamines, or vice versa (higher SNS arousal can negatively impact sleep quality). If SNS activity is not reduced sufficiently during sleep, other systems may also suffer dysregulation. Hence, sleep is an important variable in maintaining SNS regulation and potentially contributing to cancer outcomes as well.

Influences of stress-related SNS products on *in vivo* tumour growth is illustrated by a wealth of studies demonstrating the negative effects of various types of stressors on tumour growth and metastasis in animal models. Typically animals may be injected with tumour cell lines, subjected to stress, and tumour growth quantified. For example, immobilization stress led to increased incidence of tumours and more growth in rats injected with the carcinogen diethylnitrosamine [98]. Other physical, social and psychological stressors including swimming stress, surgical stress, social confrontation and hypothermia all lead to increased lung metastasis from injected breast cancer cell lines [81,99,100]. In a chemical model simulating stressor effects, animals were subjected to elevated levels of injected β-adrageneric agonists, which simulate the effect of SNS activation, on tumour growth. Several animal studies have found β-adrageneric agonists cause increases in lung and mammary tumour metastases [101]. Conversely, pre-treatment of animals with β-adrageneric antagonists to block SNS activity also blocked effects of behavioural stress on lung tumour metastases previously observed [102]. There is also evidence that stress in animals may compromise mechanisms of DNA repair [10], thought to be important for recovery of cells from DNA damage due environmental or therapeutic exposure to radiation. Hence, products of the SNS elevated during the stress response or when circadian systems are dysregulated have direct facilitative effects on tumour growth and metastasis. The molecular basis for this effect is not fully understood but being actively researched.

Hormonal Factors

Estrogen (E)

Endocrine factors altered through stress and other psychological processes are extremely important for cancer development and progression, particularly in the case of cancers such as breast and prostate. Researchers have reported circadian abnormalities in the secretion of 12 hormones in women at high risk for developing occurrences of breast cancer [103] , as well as associations with later stages of cancer development and other prognostic indicators such as poorer performance status and more metastatic involvement [89,91]. Although estrogen is essential for normal mammary development and ductal growth, it also plays a role in the development and progression of breast cancer, and increased exposure to estrogens and increases in estrogen receptor expression in mammary epithelial cells increases risk. Primary risk factors for breast cancer include measures of lifelong E exposure, such as early menarche, fewer or no children, later age of parity, later menopause and obesity (for a review see Velie, 2005) [104]. Typically, women are tested at the time of diagnosis for E receptors and tumours with a high concentration of E receptors are referred to as positive (ER-positive) whereas those with a low or non-existent concentration of receptors are negative (ER-negative). Generally, ER-positive tumours respond best to hormonal treatments like Tamoxifen, which preferentially bind to ERs on breast cancer cells, taking the place of the naturally occurring estrogen and inhibiting the expression of estrogen-regulated genes that would normally induce cell proliferation [105].

Estrogen biosynthesis is catalyzed by the aromatase enzyme (aromatase cytochrome P450), which converts androgens to estrogens through the process of aromatization. Aromatase levels increase with age and BMI. The increase with rising BMI is thought to be

due to tumour-adipocyte interactions [106]. Adipocytes are endocrine cells making up the bulk of the human breast (epithelial cells account for only 10% of the volume), and their numbers increase with increasing body weight and fat concentrations. They secrete various cytokines, polypeptide and hormone-like molecules, such as TNF-alpha and IL-6, which stimulate the production of aromatase [106]. Hence, more aromatase available for conversion of T to E may account for higher levels of E in obese women, as aromatase (and not T) is usually the rate-limiting factor.

Recall also that psychosocial interventions have been observed to alter levels of these aromatase-producing cytokines [78] which may result in less aromatase and subsequent less conversion of T to E in women with breast cancer participating in these interventions. No studies to their awareness have directly measured E level changes as a result of participation in psychosocial interventions. However it is well known that IL-6, TNF-alpha and other proinflammatory cytokines are elevated during periods of stress, and also in depression [107]. The cytokine pattern of depression is in fact very similar to that of cancer, leading researchers to suggest a high degree of similarity between the pathobiochemistry and immunology of cancer, cancer pain and depression [108]. Cancer treatment incorporating immune therapy with IL-2 and/or IFN-alpha is associated with depressive symptoms in a large proportion of patients [109,110]. This effect seems to be mediated by the activation of the cytokine network, including IL-6 [111], which is also elevated in depressed patients [112-114]. It makes sense, then, that if levels of pro-inflammatory cytokines can be decreased through the treatment of stress and depression, this may also affect levels of bioavailable E, especially in obese women, which is important for the development and progression of many breast cancers.

Testosterone

There is an interesting controversy around the role of testosterone in the development and progression of prostate cancer. Although the common assumption is that testosterone (T) plays a role in prostate cancer development due to the observation that castration (either surgical or biochemical) is an effective treatment for prostate cancer disease [115,116], a review of 34 studies investigating T levels in individuals newly diagnosed with prostate cancer compared to those without is inconclusive. That is, there is no clear-cut evidence that men who get prostate cancer have higher circulating levels of testosterone than those free of the disease [116]. This non-association between T levels and prostate cancer incidence has been shown in clinical trials of T supplementation, in longitudinal population-based studies, and in men who receive exogenous T treatment for hypogonadism. These findings have lead researchers to propose an indirect link between T and prostate cancer, perhaps through the acquisition of multiple non-specific sexually-transmitted diseases (STDs) caused by higher levels of sexual activity in men with higher T in their youth. This may promote transformation of prostate cells and damage to Leydig cells in the testis, which may contribute to the pathogenesis of prostate cancer, but not be observed as higher T levels around the time of diagnosis [116].

Not all researchers agree, as another meta-analysis found a 2.34 fold increase in the risk of prostate cancer in men in the highest quartile of T production, but they also found the same level of risk associated with higher serum IGF-1, and conversely, higher levels of sex hormone-binding globulin were associated with lower risk. Estrogens and DHT did not seem

to play a role in prostate cancer risk [117]. The question of whether T levels can be altered through stress or psychosocial interventions is open. It is well known that T can affect mood states, and in aging there is a moderate decline of total T and a more significant decline of bioavailable T [118]. Elderly men who are most depressed also have the lowest T values, and T replacement in men with low T levels often results in improved mood. Indeed, even in hypogonadal men with clinical depression, T administration in some cases alleviated the depression [118]. Whether treatment of depression through psychosocial interventions may influence T production (and potentially prostate cancer progression) is not known, but one study did find that a combination treatment of diet, stress reduction, meditation and yoga resulted in arrest or regression, in some cases, of prostate-specific antigen (PSA) levels, the primary marker of disease activity in prostate cancer [119]. The mechanism for any such action is currently unknown.

Melatonin

The pineal hormone melatonin has been implicated in the treatment of many types of cancers and other diseases [120,121]. Proposed mechanisms of action include its effects as a free radical scavenger, an antioxidant, as well as an immunomodulatory agent and through the promotion of apoptosis of cancer cells in animal and human models [122]. In both *in vitro* and *in vivo* investigations, melatonin protected healthy cells from radiation-induced and chemotherapeutic drug-induced toxicity [123,124]. In humans, a series of clinical trials using melatonin in conjunction with standard treatment found superior survival response in patients with advanced cancer receiving adjuvant melatonin therapy [125], and higher tolerance of standard chemotherapy regimes [125,126]. A review of the animal and human literature concluded that converging evidence supports large transnational research-based clinical trials of melatonin therapy for a wide variety of cancers [122]. For years reports have indicated that women with breast cancer have suppressed or absent nocturnal melatonin peaks [127]. Epidemiological studies have also shown increased risk of breast cancer in women who work night shifts [128,129]. One biologically plausible explanation for this association is that these women have blunted melatonin secretion rhythms, and lack the nocturnal melatonin peak that is associated with normal sleep cycles.

We have evaluated the associations between sleep, stress, urinary melatonin and catecholamines in women recovering from breast cancer and matched healthy controls, and found higher levels of depressive symptoms, anxiety, fatigue, confusion, cardiopulmonary symptoms of stress and sleep disturbance in breast cancer patients than the comparison women; however, despite these disturbances there were no group differences on any of the biomarkers, including salivary cortisol, urinary catecholamines and melatonin, with the exception of higher dopamine levels in the control participants [130]. The women with breast cancer in their group were diagnosed with stages I-III breast cancer, primarily stage II, with no metastatic spread. This may account for the failure to find differences in any of the endocrine measures. However, the issue of the potential role of melatonin in disease development, circadian rhythm dysregulations and mood and stress remains a promising area of research [91,122].

Immune Factors

Cell-mediated immunity is the most studied outcome area in the intervention studies reviewed above, but the question arises as to the importance of the measures shown to be responsive to psychosocial interventions – most commonly increases in the number of lymphocytes, including NK cells, [64,67,72,73] NK cell cytotoxicity [72] and cytokine production [69,77].

Even though NK cells have been the target outcome measure in a number of psychosocial intervention trials and some changes have been observed, they have rarely been correlated with disease outcome (i.e. Fawzy et al, 1991 [72]). Many authours are skeptical of a role for immune factors in cancer progression (e.g. [23], including mainstream cancer biologists). Points raised by Garssen and Goodkin [23] against an important role of immune factors in cancer development include observations that: 1) spontaneously arising cancers in mice (in contrast to those induced by experimental methods) provoke little or no immune response; 2) tumour cells can easily mutate and avoid being targeted by cytotoxic T cells by constantly changing their antigens; 3) tumour cells can directly suppress the efficacy of various immune cells; and 4) due to the fast proliferation of some tumour cells the immune response is not capable of limiting their growth.

However, decreased NK activity has been associated with tumour progression in some studies of animals [81] and humans [93] and abnormal cortisol rhythms were associated with reduced NK cell number and cytotoxicity in women with metastatic breast cancer [15]. A persuasive argument has been made by Ben-Eliyahu for a role of cell-mediated immunity in the promotion of metastatic spread [81]. He speculates that the postoperative period when immunosupression occurs as a result of the surgical assault is a vulnerable period, in that dislodged tumour cells are most likely to travel through the bloodstream and metastasize to other parts of the body, if not controlled through immunomodulatory mechanisms. Mechanisms thought to be important for this process include cell-mediated immunity (CMI) though cytotoxic T lymphocytes, NK cells, NKT cells, tissue macrophages, dendritic cells and helper T cells. Research has shown that cell-mediated immunosuppression following surgery or stress coincides with periods of compromised resistance to metastasis of a cancer cell line known to be NK-sensitive [131]

Hence Ben-Eliyahu (2003) [81] makes an argument for the role of surgery in promoting metastatic spread through suppression of CMI based on the following points: 1) In human models, general anaesthesia has been shown to suppress aspects of human CMI, such as NK activity and helper T-cell ratios, but local or regional anaesthesia is not immunosuppressive. When given in conjunction, local anaesthesia blunts the SNS and HPA reactivity to surgery and attenuates the degree of immunosuppression. In animals local anaesthesia when added to general, results in less suppression of CMI and less metastatic spread; 2) Blood transfusions suppress CMI (decreased NKCC and T-cell blastogenesis) and are also associated with poorer prognosis, independent of other complications and risk factors; 3) In the past, colorectal cancer was treated with two successive surgeries; when these were reduced to one, lower rates of metastatic spread and better survival was seen, in both humans and animal models; 4) minimally invasive surgeries are less immunosuppressive and also reduce the promotion of metastatic spread, in both animals and humans. Hence, an argument can be made for an important role of CMI in preventing metastatic spread after surgery, but little is known about

what specific level of various immune cells or function is required to prevent such spread. It may also be the case that beyond the post-surgical period immune factors are relatively *un-important* in the progression of tumour growth, which is supported by angiogenesis and the failure of apoptosis.

Growth Factors and Angiogenesis

Effects of stress on the tumour microenvironment including effects on the growth of a blood supply to tumours have been investigated quite extensively in recent years. Associations between elevated stress, lower social support and elevated levels of IL-6, a proinflammatory cytokine, and vascular endothelial growth factor (VEG-F), both promoters of angiogenesis in the tumour site, have been documented in ovarian cancer patients as well as *in vitro* cell cultures [13,132-134]. Immobilization stress increased tumour burden and enhanced angiogenesis and production of VEG-F within the tumour cell – angiogenesis is critical for tumour mass to increase beyond a certain size as the tumour cannot nourish itself without this development of its own blood supply. VEG-F also stimulates endothelial cell migration and proliferation and interferes with the development of T cells and the functional maturation of dendritic cells, which suggests additional negative effects on anti-tumour immune responses [10].

There are also effects of stress on viral oncogenesis, with many studies demonstrating accelerated growth of virally-induced tumours in animals who have been subjected to stressors [10]. Antoni et al [10] reviewed the neuroendocrine influences on various virally-related tumours and drew associations between HPA dysregulations and liver as well as cervical and head and neck cancers caused in part by Hepatitis B and C and human papilomavirus (HPV) viral exposure. They also drew associations between ANS reactivity and leukemia/lymphoma and Kaposi sarcomas cased in part by T-cell lymphotropic virus and Kaposi sarcoma-associated herpes virus, respectively [10], based on a review of primarily *in vitro* studies.

In summary, there are many potential avenues that stress and other psychological factors can “get in the body” and affect a whole host of processes important in cancer development and progression. Although the role of immunosurveillance is not a promising area of study for many cancer biologists, it may play an important role in prevention of metastatic spread of cancer cells following surgery. Other substances such as elevated epinephrine and cortisol may be cancer-promoting through several different mechanisms such as suppression of CMI. Elevated estrogens as a result of stress may also play a role in the pathogenesis of breast cancer, and testosterone may be important indirectly for its ability to aromatize to estrogens which can feed breast cancer cells, or by directly impacting prostate cancer development.

OTHER ISSUES FOR INTERVENTION RESEARCH

Timing of Interventions

Little research has been done to investigate the importance of the timing of psychosocial intervention delivery, but there is reason to believe that the impact may be different depending on where in the process of diagnosis, treatment and recovery interventions are applied. Keeping in mind the research on the effects of surgery on CMI, it seems that post-surgery might be an opportune time to apply psychosocial interventions likely to enhance cellular immunity. Levels of distress are also high at this time, as evidenced not only by large surveys of distress levels [78,125], but also by studies of anxiety around the time of biopsy [136,137]. Women assessed at that time, both pre- and post-biopsy also showed changes in immune function. Lymphocytes at pre biopsy showed a lower expression of NFkB and Ap-1, transcription factors that regulate lymphocyte function, compared to post-biopsy. At post biopsy NFkB activity increased threefold and AP-1 activity nearly doubled. Post biopsy, the transcription factors were similar to those of the healthy controls [137]. In another similar study, women undergoing breast biopsy (later confirmed either malignant or benign) and a control group were assessed on levels of T-lymphocytes, NK cells, helper lymphocytes, cytotoxic lymphocytes, circulating monocytes and cytokines [136]. NK cell activity was reduced pre-biopsy and remained so for 3 months after results for the benign group of women. NK cell activity remained reduced for the women in the malignant group. IFN-γ was reduced in the malignant and nonmalignant groups pre and post biopsy but returned to normal levels for both groups at 3 months. This data illustrates that the time around biopsy and initial surgery is not only stressful, but also may be a time of biological vulnerability.

Only one study we are aware of investigated the effects of delayed versus early psychosocial interventions for women with early stage breast cancer [138], but they did not assess any immune or endocrine markers. All participants had received surgery no longer than 4 months prior to study participation. Participants were randomized to 1 of 4 conditions: early or late start and experiential existential group psychotherapy or a support group. Groups were closed and limited to 6-10 women. Thirty-three women were assigned to the early start: 19 in psychotherapy and 14 in social support, and 34 women were assigned to the delayed start condition: 16 in psychotherapy and18 in social support. In both interventions, women met for 2.5 hours for 12 weeks and included follow up groups at 1 and 2 months post-completion. Women who were assigned to the late intervention appeared more distressed at follow up than did the early starters, after controlling for baseline differences. Overall there were improvements in distress, body image, social interaction, and recreational activities.

Hence it may be possible, through carefully choosing the timing of interventions, to maximize the effects of psychosocial treatments to have the most beneficial effects on both reduction of psychological symptoms, and biological processes potentially important for disease course. Whether concomitant changes occurred in important parameters related to CMI as a result of these interventions, either soon after surgery or later, remains to be investigated in further research.

Type and Stage of Cancer

The issue of the importance of the specific type of cancer for determining psychological and biological responses to interventions has been addressed only infrequently in the psychosocial literature, but it is likely quite a critical point, as the pathophysiology of cancers varies greatly. Unfortunately, most of the research in these areas has been conducted on breast cancer populations, and most in early stage women after treatment. Hence it is difficult to directly compare effects of interventions on different types of cancer patients at a variety of stages of disease progression.

However, in one review on the etiology and progression of cancer in relation to psychosocial characteristics, effects were compared among different types and stages of cancers. The proportion of studies that found a link between psychosocial factors and disease progression was 73% in breast cancer, 75% in malignant melanoma, 67% in haematological malignancies, and an astounding 100% in lung cancers [30]. This is interesting as some researchers have suggested that psychosocial factors are more likely to be important in diseases with more favourable prognoses, where the tumour burden is perhaps less and more amenable to respond to changes in immune and endocrine function caused by psychosocial interventions [50]. The result that all studies included in this review found an association between lung cancer incidence and psychosocial factors can partly be explained by the behaviour of smoking, as not all studies controlled for the correlation between depression and smoking. Looking just at those that did statistically control for smoking, two-thirds failed to find a relationship between depression and lung cancer initiation, but one-third still upheld the relationship. However, if smoking is controlled for, there appears to be no stronger association between psychosocial factors and disease initiation in lung cancer than other commonly studied types. The authors of this review conclude that there is little convincing evidence that psychosocial factors are more important in the initiation of some types of cancers more than others.

Another perspective on this issue is put forth by Antoni et al [24], who suggest that virally-mediated tumours are likely to be more responsive to psychosocial influences than solid epithelial tumours. This is based on their work in HIV and AIDS-related conditions where they have shown significant effects of cognitive-behavioral stress management on numbers and function of important T-cell subtypes and NK cells. They speculate that cervical cancer, a causal factor of which is HPV infection, may be more responsive to psychosocial interventions than solid tumours with different pathogenesis such as breast cancers. This possibility has not yet been tested empirically.

The impact of the stage of tumour development on the effect that psychosocial interventions can have on disease progression has also been considered in the literature, but not extensively evaluated. The literature in the area of breast cancer is the only area extensive enough within which to directly address this question. In one review, 64% of 14 studies looking at nonmetastatic breast cancer found relationships between psychosocial factors and disease initiation or progression, and this was even higher in metastatic breast cancer at 83% [30]. However, some reviewers have concluded that interventions for treating cancer patients might best be applied to earlier-stage diseases, in the hopes of intervening earlier in the disease process before the tumour burden becomes overwhelming [50]. This issue awaits resolution with further research.

Health Behaviours

Included in the biopsychosocial model of disease etiology and progression are other factors with potential to influence disease outcomes, including health behaviours such as sleep, exercise, and diet. There is evidence linking each of these to cancer initiation and progression. In terms of sleep, in the general North American population 1/3 of adults experience intermittent insomnia, and 10% suffer chronic insomnia [139,140]. The prevalence of chronic insomnia is much higher in cancer, with anywhere from 30-50% of patients reporting sleep difficulties [141,142] that often persist well into the post-treatment period. In metastatic breast cancer patients, 63% reported serious sleeping problems [143]. Individuals with insomnia have been characterized by increases SNS activity, increased 24-hour metabolic rate, and elevated cortisol and NE. A general state of physiological hyperarousal is considered to be symptomatic of these poor sleepers, and insufficient sleep duration has recently been shown to be associated with all-cause mortality [144]. Hence, it is very important to consider the effects of sleep quality on disease outcome, and the impact improving sleep during psychosocial interventions such as stress reduction could have on overall outcomes.

Exercise has emerged in the literature of late as a risk factor for both cancer incidence and progression [145,146]. Recent epidemiological research analyzed the relation between physical activity and breast cancer incidence between 1990 and 2002 among 90,509 French women between 40 and 65 years of age [147]. A linear decrease in risk of breast cancer was observed with increasing amounts of moderate and vigorous recreational activities. Compared with women who reported no recreational activities, those with more than five weekly hours of vigorous exercise had a relative risk of 0.62 (CI=0.49-0.78). This decrease was still observed among women who were overweight, had no children, had a family history of breast cancer, or used hormone replacement therapy [147]. After diagnosis, exercise rehabilitation programs have been successful in improving quality of life and reducing all-cause mortality [148,149], and recent observational evidence suggests that moderate levels of physical activity may reduce the risk of death from breast cancer after diagnosis [150]. This study was based on responses from 2987 nurses in the Nurses' Health Study who were diagnosed with stage I, II, or III breast cancer. Women who engaged in higher levels of physical activity (the equivalent of walking at average pace of 2 to 2.9 mph for 1 hour, 3 times/week, at minimum) were less likely to die from breast cancer than those who exercised less. The benefit of physical activity was particularly apparent among women with hormone-responsive tumours (ER positive). This is the opposite of the recent study of supportive-expressive therapy which found effects only for women who were ER negative [62]. The potential interactions between ER status and psychosocial interventions have yet to be investigated in great detail.

Another study examined colorectal cancer death rates and exercise, and found similar results: Increasing levels of exercise after diagnosis of nonmetastatic colorectal cancer reduced cancer-specific mortality ($p = .008$) and overall mortality ($p = .003$) [151]. In this case, prediagnosis physical activity was not predictive of mortality. Women who increased their activity (when comparing prediagnosis to postdiagnosis values) had a hazard ratio of 0.48 for colorectal cancer deaths and a hazard ratio of 0.51 for any-cause death, compared with those with no change in activity. Hence, there is little question that physical activity can

be an important factor in improving disease outcomes, and changes in this variable associated with decreased depression and stress should be addressed in future research.

Finally, diet is known as one of the most important risk factors for the development of a host of cancers, and thought to account for about 30-35% of overall risk [25]. In general, plant-based diets high in fruits and vegetables and low in red meat and saturated fats are considered to be the healthiest in terms of avoiding or recovering from cancer. Specifically, according to Key et al., (2004) [152] fruits and vegetables probably reduce the risk for cancers of the oral cavity, oesophagus, stomach and colorectum; preserved meat and red meat probably increase the risk for colorectal cancer; salt preserved foods and high salt intake probably increase the risk for stomach cancer; and very hot drinks and foods probably increase the risk for cancers of the oral cavity, pharynx and oesophagus.

Recommendations regarding diet in several other reviews are similar, but focussing more on the role of obesity and alcohol consumption. Indeed, as reviewed previously, obesity increases breast cancer risk in postmenopausal women by around 30%, probably by increasing serum concentrations of estradiol. Moderate alcohol intake increases breast cancer risk by about 7% per alcoholic drink per day, perhaps also by increasing estrogen levels. Populations with high fat intake generally have higher rates of breast cancer, but studies of individual women have not confirmed an association of high fat diets with breast cancer risk. Speculation is that nutrition might affect breast cancer risk by altering levels of growth factors such as insulin-like growth factor (IGF)-I [153].

In colorectal and other gastric cancers, consumption of fruits and vegetables appeared to have a modest role in prevention [154]. In contrast, the roles of alcohol consumption and overweight on risk of gastrointestinal cancer are more clear and similar to breast cancer: overweight and obesity are important risk factors for adenocarcinoma (but not squamous carcinoma) of the esophagus and colorectal cancer (particularly in men). Alcohol consumption is a risk factor for squamous carcinoma (but not adenocarcinoma) of the esophagus, gastric cancer and colorectal cancer [154].

One research group wished to investigate the interactions among diet, exercise and markers of prostate cancer risk including measures of insulin, free T, E, and IGF as well as sex hormone-binding globulin (SHBG), a positive prognostic marker [155]. They found that in men who undertook a low-fat diet and/or exercise program all these factors changed in the predicted directions, and these changes impacted prostate cancer cell lines in vitro to reduce cell growth and induce apoptosis (programmed cell death), primarily through increasing tumour cell p53 proteins [155]. This is a compelling example of the potential for dietary factors to directly affect processes known to be important for cancer development and progression.

In summary, it is possible that psychosocial interventions that often include discussion of health behaviours and extol the virtues of taking control of lifestyle factors may also result in changes in these important behaviours, not to mention stopping smoking, which accounts for about 30% of the risk for all cancers combined. Stress reduction interventions often report better sleep in participants [156], which may be a pathway though which changes in immune and endocrine function are mediated. Some interventions explicitly recommend or include exercise, and the literature on specific exercise effects in cancer patients is growing, although it was not reviewed in this paper [145,146].

CONCLUSION

In conclusion, this chapter has addressed associations between psychosocial variables and both disease initiation and progression, showing that the evidence is strongest for a role of social support, emotional repression, hopelessness and depression as potentially important factors in disease progression. As well, the evidence that psychosocial interventions can effect survival was reviewed, with the conclusion that there may be effects, but if so they are quite weak. The literature on the effects of psychosocial interventions on immune and endocrine outcomes was reviewed in greater detail, with the conclusion that a wide variety of psychosocial programs may effect aspects of cell-mediated immunity and stress hormone production. Potential mechanisms of action between immune and endocrine variables and cancer progression were summarized, including HPA and SNS mechanisms, the role of various hormones, immunosuppression and other mechanisms such as HPA promotion of angiogenesis and virally-induced tumour growth. All pathways show some promise but perhaps the most hope for future research finding links between psychosocial interventions and important factors in disease pathogenesis lies with the effect of stress on the regulation of circadian rhythms, growth factors such as VEG-F, and hormones such as melatonin, although very little research has been conducted in these areas to date. Finally, specific factors such as the timing of interventions, the types of cancers targeted and the stage of disease progression are important to consider, as are other factors that may affect outcomes such as sleep, exercise, diet and smoking. Application of a comprehensive biopsychosocial model of disease progression will help to guide future research efforts.

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ANS	autonomic nervous system
AP-1	activator protein 1
BDI	Beck Depression Inventory
BEST	breast expressive-supportive therapy
BMI	body mass index
CD3, CD4, CD8	specific t-cell cluster of differentiation
CES-D	Center for Epidemiological Studies-Depression
CI	confidence interval
CMI	cell mediated immunity
CNS	central nervous system
Con-A	canavalin A
CRF	corticotrophin-releasing factor
DHEAS	dehydroepiandosterone sulphate
EORTC-QLQ-30	European Organization for the Treatment of Cancer-Quality of Life Questionnaire-30
E	estrogen
EP	epinephrine
ER	estrogen receptor

FACT-B	Functional Assessment of Cancer Therapy-Breast
HADS	Hospital Anxiety and Depression Scale
HA	hazard ratio
HPA	hypothalamic-pituitary-adrenal
HPG	hypothalamic-pituitary-gonadal
HPV	human papillomavirus
HRT	hormone replacement therapy
IES	Impact of Events Scale
IFN-γ	Interferon-gamma
IgA	immunoglobulin-A
IGF	insulin-like growth factor
IgG	immunoglobulin-G
LGL	large granular lymphocyte
IgM	immunoglobulin-M
IL-1α	interluekin-1 alpha
IL-1β	interleukin-1 beta
IL-2	interleukin 2
IL-4	interleukin 4
IL-10	interleukin 10
MAC	Mental Adjustment to Cancer
MLR	mixed lymphocyte responsiveness
MMPI	Minnesota Multiphasic Personality Inventory
NK cells	natural killer cells
NE	norepinephrine
NFkB	Nuclear Factor kappa B
PBL	peripheral blood lymphocytes
PHA	phytohemagglutinin
PNE	psychoneuroendocrine
PNI	psychoneuroimmune
PNS	parasympathetic nervous system
POMS	Profile of Mood States
PSA	prostate-specific antigen
PSS	Perceived Stress Scale
RCT	randomized controlled trial
SEGT	supportive expressive group therapy
SHBG	sex hormone-binding growth factor
SIgA	salivary immunoglobulin A
SNS	sympathetic nervous system
SOSI	Symptoms of Stress Inventory
STAI	State-Trait Anxiety Inventory
STD	sexually transmitted disease
T	testosterone
VEG-F	vascular endothelial growth factor
WBC	white blood cell

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REFERENCES

[1] Temoshok, L. Personality, coping style, emotion and cancer: towards an integrative model. *Cancer Surv*, 1987, 6(3), 545-567.

[2] Greer, S; Watson, M. Towards a psychobiological model of cancer: psychological considerations. *Soc Sci Med*, 1985, 20(8), 773-777.

[3] Chen, E; Hanson, MD; Paterson, LQ; Griffin, MJ; Walker, HA; Miller, GE. Socioeconomic status and inflammatory processes in childhood asthma: the role of psychological stress. *J Allergy Clin Immunol*, 2006, 117(5), 1014-1020.

[4] Cohen S, Doyle WJ, Skoner DP. Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosom Med*, 1999, 61(2), 175-180.

[5] Daruna, JD. *Introduction to psychoneuroimmonology*. London, UK, Elsevier Academic Press, 2004.

[6] Miller, GE; Cohen, S; Ritchey, AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychol*, 2002, 21(6), 531-541.

[7] Rozlog, LA; Kiecolt-Glaser, JK; Marucha, PT; Sheridan, JF; Glaser, R. Stress and immunity: implications for viral disease and wound healing. *J Periodontol*, 1999, 70(7), 786-792.

[8] Segerstrom, SC; Miller, GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull*, 2004, 130(4), 601-630.

[9] Spiegel, D; Giese-Davis, J. Depression and cancer: mechanisms and disease progression. *Biol Psychiatry*, 2003, 54(3), 269-282.

[10] Antoni, MH; Lutgendorf, SK; Cole, SW; Dhabhar, FS; Sephton, SE; McDonald, PG; Stefanek, M; Sood, AK. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nat Rev Cancer*, 2006, 6(3), 240-248.

[11] Andersen, BL; Kiecolt-Glaser, JK; Glaser, R. A biobehavioral model of cancer stress and disease course. *Am Psychol*, 1994, 49(5), 389-404.

[12] Cameron, LD; Leventhal, H. *The self-regulation of health and behavior*. New York, Routledge, 2003.

[13] Lutgendorf, SK; Costanzo, ES. Psychoneuroimmunology and health psychology: an integrative model. *Brain Behav Immun*, 2003, 17(4), 225-232.

[14] Sephton, S; Spiegel, D. Circadian disruption in cancer: A neuroendocrine-immune pathway from stress to disease? *Brain, Behavior, & Immunity*, 2003, 17(5), 321-328.

[15] Sephton, SE; Sapolsky, RM; Kraemer, HC; Spiegel, D. Diurnal cortisol rhythm as a predictor of breast cancer survival. *Journal of the National Cancer Institute*, 2000, 92(12), 944-1000.

[16] Spiegel, D; Sephton, SE. Psychoneuroimmune and endocrine pathways in cancer. effects of stress and support. [Review] [184 refs]. *Seminars in Clinical Neuropsychiatry*, 6(4), 252-65, 2001.

[17] Classen, C; Koopman, C; Hales, R; Spiegel, D. Acute stress disorder as a predictor of posttraumatic stress symptoms. *Am J Psychiatry*, 1998, 155(5), 620-624.

[18] Newell, SA; Sanson-Fisher, RW; Savolainen, NJ. Systematic review of psychological therapies for cancer patients: overview and recommendations for future research. *J Natl Cancer Inst*, 2002, 94(8), 558-584.

[19] Ross, L; Boesen, EH; Dalton, SO; Johansen, C. Mind and cancer: does psychosocial intervention improve survival and psychological well-being? [Review] [69 refs]. *European Journal of Cancer*, 38(11), 1447-57, 2002.

[20] Meyer, TJ; Mark, MM. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. *Health Psychol*, 1995, 14(2), 101-108.

[21] Smedslund, G; Ringdal, GI. Meta-analysis of the effects of psychosocial interventions on survival time in cancer patients. *J Psychosom Res*, 2004, 57(2), 123-131.

[22] van der Pompe, G; Antoni, M; Visser, A; Garssen, B. Adjustment to breast cancer: the psychobiological effects of psychosocial interventions. [Review] [77 refs]. *Patient Education & Counseling*, 28(2), 209-19, 1996.

[23] Garssen, B; Goodkin, K. On the role of immunological factors as mediators between psychosocial factors and cancer progression. *Psychiatry Res*, 1999, 85(1), 51-61.

[24] Antoni, MH. Psychoneuroendocrinology and psychoneuroimmunology of cancer: Plausible mechanisms worth pursuing? *Brain Behav Immun* 2003, 17 Suppl 1:S84-S91.

[25] Dollinger, M; Resenbaum, EH; Cable, G. *Everyone's Guide to Cancer Therapy: How Cancer is Diagnosed*, Treated, and Managed Day to Day. ed 3, Kansas City, Andrews McMeel Publishing, 1997.

[26] Butow, PN; Hiller, JE; Price, MA; Thackway, SV; Kricker, A; Tennant, CC. Epidemiological evidence for a relationship between life events, coping style, and personality factors in the development of breast cancer. *J Psychosom Res*, 2000, 49(3), 169-181.

[27] Price, MA; Tennant, CC; Butow, PN; Smith, RC; Kennedy, SJ; Kossoff, MB; Dunn, SM. The role of psychosocial factors in the development of breast carcinoma: Part II. Life event stressors, social support, defense style, and emotional control and their interactions. *Cancer*, 91(4), 686-97, 2001.

[28] Dalton, SO; Boesen, EH; Ross, L; Schapiro, IR; Johansen, C. Mind and cancer. Do psychological factors cause cancer? *Eur J Cancer*, 2002, 38(10), 1313-1323.

[29] Edelman, S; Kidman, A. Mind and cancer: Is there a relationship? A review of evidence. *Australian Psycologist*, 1997, 32(2), 79-85.

[30] Garssen, B. Psychological factors and cancer development: evidence after 30 years of research. [Review] [81 refs]. *Clinical Psychology Review*, 24(3), 315-38, 2004.

[31] Geyer, S. The role of social and psychosocial factors in the development and course of cancer. *Wien Klin Wochenschr*, 2000, 112(23), 986-994.

[32] McGee, R; Williams, S; Elwood, M. Are life events related to the onset of breast cancer. *Psychol Med*, 1996, 26(3), 441-447.
[33] McKenna, MC; Zevon, MA; Corn, B; Rounds, J. Psychosocial factors and the development of breast cancer: a meta-analysis. *Health Psychol*, 1999, 18(5), 520-531.
[34] Duijts, SF; Zeegers, MP; Borne, BV. The association between stressful life events and breast cancer risk: a meta-analysis. *Int J Cancer*, 2003, 107(6), 1023-1029.
[35] Kroenke, CH; Hankinson, SE; Schernhammer, ES; Colditz, GA; Kawachi, I; Holmes, MD. Caregiving stress, endogenous sex steroid hormone levels, and breast cancer incidence. *Am J Epidemiol*, 2004, 159(11), 1019-1027.
[36] Helgesson, O; Cabrera, C; Lapidus, L; Bengtsson, C; Lissner, L. Self-reported stress levels predict subsequent breast cancer in a cohort of Swedish women. *Eur J Cancer Prev*, 2003, 12(5), 377-381.
[37] Nielsen, NR; Zhang, ZF; Kristensen, TS; Netterstrom, B; Schnohr, P; Gronbaek, M. Self reported stress and risk of breast cancer: prospective cohort study. *BMJ*, 2005, 331(7516), 548.
[38] Petticrew, M; Fraser, J; Regan, MF. Adverse life-events and risk of breast caner: A meta-analysis. *British Journal of Health Psychology*, 1999, 4, 1-17.
[39] Jones, DR; Goldblatt, PO; Leon, DA. Bereavement and cancer: some data on deaths of spouses from the longitudinal study of Office of Population Censuses and Surveys. *Br Med J (Clin Res Ed)* 1984, 289(6443), 461-464.
[40] Kvikstad, A; Vatten, LJ; Tretli, S; Kvinnsland, S. Death of a husband or marital divorce related to risk of breast cancer in middle-aged women. A nested case-control study among Norwegian women born 1935-1954. *Eur J Cancer*, 1994, 30A(4), 473-477.
[41] Kvikstad, A; Vatten, LJ. Risk and prognosis of cancer in middle-aged women who have experienced the death of a child. *Int J Cancer*, 1996, 67(2), 165-169.
[42] Levav, I; Kohn, R; Iscovich, J; Abramson, JH; Tsai, WY; Vigdorovich, D. Cancer incidence and survival following bereavement. *Am J Public Health*, 2000, 90(10), 1601-1607.
[43] Schernhammer, ES; Hankinson, SE; Rosner, B; Kroenke, CH; Willett, WC; Colditz, GA; Kawachi, I. Job stress and breast cancer risk: the nurses' health study. *Am J Epidemiol*, 2004, 160(11), 1079-1086.
[44] Bleiker, EM; van der Ploeg, HM. Psychosocial factors in the etiology of breast cancer: review of a popular link. *Patient Educ Couns*, 1999, 37(3), 201-214.
[45] Reynolds, P; Kaplan, GA. Social connections and risk for cancer: prospective evidence from the Alameda County Study. *Behav Med*, 1990, 16(3), 101-110.
[46] Kroenke, CH; Bennett, GG; Fuchs, C; Giovannucci, E; Kawachi, I; Schernhammer, E; Holmes, MD; Kubzansky, LD. Depressive symptoms and prospective incidence of colorectal cancer in women. *Am J Epidemiol*, 2005, 162(9), 839-848.
[47] Shaffer, JW; Graves, PL; Swank, RT; Pearson, TA. Clustering of personality traits in youth and the subsequent development of cancer among physicians. *J Behav Med*, 1987, 10(5), 441-447.
[48] Bleiker, EM; van der Ploeg, HM; Hendriks, JH; Ader, HJ. Personality factors and breast cancer development: a prospective longitudinal study. *J Natl Cancer Inst*, 1996, 88(20), 1478-1482.

[49] Petticrew, M; Bell, R; Hunter, D. Influence of psychological coping on survival and recurrence in people with cancer: systematic review. *BMJ*, 2002, 325(7372), 1066.

[50] Cwikel, JG; Behar, LC; Zabora, JR. Psychosocial factors that affect the survival of adult cancer patients: A review of research. *Journal of Psychosocial Oncology*, 1997, 15(3/4), 1-34.

[51] Fox, BH. The role of psychological factors in cancer incidence and prognosis. *Oncology (Williston Park)*, 1995, 9(3), 245-253.

[52] Forsen, A. Psychosocial stress as a risk for breast cancer. *Psychother Psychosom* 1991, 55(2-4), 176-185.

[53] Martikainen, P; Valkonen, T. Mortality after the death of a spouse: rates and causes of death in a large Finnish cohort. *Am J Public Health*, 1996, 86(8), 1087-1093.

[54] Jones, DR; Goldblatt, PO. Cancer mortality following widow(er)hood: Some further results from the office of population censuses and surveys longitudinal study. *Stress Medicine*, 1986, 2, 129-229.

[55] Maunsell E, Brisson J, Deschenes L. Social support and survival among women with breast cancer. *Cancer* 1995, 76(4), 631-637.

[56] Reynolds, P; Boyd, PT; Blacklow, RS; Jackson, JS; Greenberg, RS; Austin, DF; Chen, VW; Edwards, BK. The relationship between social ties and survival among black and white breast cancer patients. National Cancer Institute Black/White Cancer Survival Study Group. *Cancer Epidemiol Biomarkers Prev*, 1994, 3(3), 253-259.

[57] Kroenke, CH; Kubzansky, LD; Schernhammer, ES; Holmes, MD; Kawachi, I. Social networks, social support, and survival after breast cancer diagnosis. *J Clin Oncol*, 2006, 24(7), 1105-1111.

[58] Brown, KW; Levy, AR; Rosberger, Z; Edgar, L. Psychological distress and cancer survival: a follow-up 10 years after diagnosis. *Psychosom Med*, 2003, 65(4), 636-643.

[59] Spiegel, D; Classen, C. *Group psychotherapy for cancer patients: A research-based handbook of psycosocial care*. New York, Basic Books, 2000.

[60] Spiegel, D; Bloom, JR; Kraemer, HC; Gottheil, E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet*, 1989, 2(8668), 888-891.

[61] Goodwin, PJ; Leszcz, M; Ennis, M; Koopmans, J; Vincent, L; Guther, H; Drysdale, E; Hundleby, M; Chochinov, HM; Navarro, M; Speca, M; Hunter, J. The effect of group psychosocial support on survival in metastatic breast cancer. *N Engl J Med*, 2001, 345(24), 1719-1726.

[62] Spiegel, D; Butler, LD; Giese-Davis, J; Koopman, C; Miller, E; DiMiceli, S; Classen, C; Fobair, P; Carlson, RW; Kraemer, H. Effects of Supportive-Expressive Group Therapy on Survival of Patients with Metastatic Breast Cancer: A Randomized Clinical Intervention Trial. *Breast Cancer Res Treat*, 2006, 100(Supplement 1), S240.

[63] Gruber, BL; Hersh, SP; Hall, NR; Waletzky, LR; Kunz, JF; Carpenter, JK; Kverno, KS; Weiss, SM. Immunological responses of breast cancer patients to behavioral interventions. *Biofeedback Self Regul*, 1993, 18(1), 1-22.

[64] Andersen, BL; Farrar, WB; Golden-Kreutz, DM; Glaser, R; Emery, CF; Crespin, TR; Shapiro, CL; Carson, WE, III. Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial. *J Clin Oncol*, 2004, 22(17), 3570-3580.

[65] Grossarth-Maticek, R; Eysenck, HJ. Length of survival and lymphocyte percentage in women with mammary cancer as a function of psychotherapy. *Psychol Rep*, 1989, 65(1), 315-321.

[66] Richardson, MA; Post-White, J; Grimm, EA; Moye, LA; Singletary, SE; Justice, B. Coping, life attitudes, and immune responses to imagery and group support after breast cancer treatment. *Altern Ther Health Med*, 1997, 3(5), 62-70.

[67] van der Pompe, G; Duivenvoorden, HJ; Antoni, MH; Visser, A; Heijnen, CJ. Effectiveness of a short-term group psychotherapy program on endocrine and immune function in breast cancer patients: An exploratory study. *J Psychosom Res*, 1997, 42(5), 453-466.

[68] Chan, CL; Ho, RT; Lee, PW; Cheng, JY; Leung, PP; Foo, W; Chow, LW; Sham, JS; Spiegel, D. A randomized controlled trial of psychosocial interventions using the psychophysiological framework for Chinese breast cancer patients. *J Psychosoc Oncol*, 2006, 24(1), 3-26.

[69] Larson, MR; Duberstein, PR; Talbot, NL; Caldwell, C; Moynihan, JA. A presurgical psychosocial intervention for breast cancer patients. psychological distress and the immune response. *J Psychosom Res*, 2000, 48(2), 187-194.

[70] Cruess, DG; Antoni, MH; McGregor, BA; Kilbourn, KM; Boyers, AE; Alferi, SM; Carver, CS; Kumar, M. Cognitive-behavioral stress management reduces serum cortisol by enhancing benefit finding among women being treated for early stage breast cancer. *Psychosom Med*, 2000, 62(3), 304-308.

[71] Hidderley, M; Holt, M. A pilot randomized trial assessing the effects of autogenic training in early stage cancer patients in relation to psychological status and immune system responses. *European Journal of Oncology Nursing*, 2004, 8(1), 61-65.

[72] Fawzy, FI; Kemeny, ME; Fawzy, NW; Elashoff, R; Morton, D; Cousins, N; Fahey, JL. A structured psychiatric intervention for cancer patients. II. Changes over time in immunological measures. *Arch Gen Psychiatry*, 1990, 47(8), 729-735.

[73] Schedlowski, M; Jung, C; Schimanski, G; Tewes, U; Schmoll, H. Effects of behavioral interventions on plasma cortisol and lymphocytes in breast cancer patients: An exploratory study. *Psychooncology*, 1994, 3, 181-187.

[74] Lekander, M; Furst, CJ; Rotstein, S; Hursti, TJ; Fredrikson, M. Immune effects of relaxation during chemotherapy for ovarian cancer. *Psychother Psychosom*, 1997, 66(4), 185-191.

[75] de Vries, MJ; Schilder, JN; Mulder, CL; Vrancken, AM; Remie, M; Garssen, B. Phase II study of psychotherapeutic intervention in advanced cancer. *Psychooncology*, 1997, 6(2), 129-137.

[76] Burns, SJ; Harbuz, MS; Hucklebridge, F; Bunt, L. A pilot study into the therapeutic effects of music therapy at a cancer help center. *Altern Ther Health Med*, 2001, 7(1), 48-56.

[77] Carlson, LE; Speca, M; Patel, KD; Goodey, E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. *Psychosom Med*, 2003, 65(4), 571-581.

[78] Carlson, LE; Speca, M; Patel, KD; Goodey, E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol,

dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. *Psychoneuroendocrinology*, 2004, 29(4), 448-474.

[79] Cruess, DG; Antoni, M; Kumar, M; McGregor, BA; Alferi, SM; Boyers, AE; Carver, CS; Kilshourn, L. Effects of stress management on testosterone levels in women with early stage breast cancer. *International Journal of Behavioral Medicine*, 2001, 8, 194-207.

[80] Bovbjerg, DH. Conditioning, cancer, and immune regulation. *Brain Behav Immun*, 2003, 17 Suppl 1, S58-S61.

[81] Ben-Eliyahu, S. The promotion of tumor metastasis by surgery and stress: immunological basis and implications for psychoneuroimmunology. *Brain Behav Immun*, 2003, 17 Suppl 1:S27-S36.

[82] Spiegel, D; Sephton, SE; Terr, AI; Stites, DP. Effects of psychosocial treatment in prolonging cancer survival may be mediated by neuroimmune pathways. *Ann N Y Acad Sci*, 1998, 840(674), 683.

[83] Cohen, S; Williamson, GM. Stress and infectious disease in humans. *Psychol Bull*, 1991, 109(1), 5-24.

[84] Sikes, CRA; Lasley, BJ. Cognitive sequelae of hypothalamic-pituitary-adrenal (HPA) dysregulation in depression. *Biological Psychiatry*, 1989, 25, 148A-149A.

[85] Wolkowitz, OM. Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. *Psychoneuroendocrinology*, 1994, 3(19), 233-255.

[86] Abercrombie, HC; Giese-Davis, J; Sephton, S; Epel, ES; Turner-Cobb, JM; Spiegel, D. Flattened cortisol rhythms in metastatic breast cancer patients. P*sychoneuroendocrinology*, 2004, 29(8), 1082-1092.

[87] van der Pompe, G; Antoni, MH; Heijnen, CJ. Elevated basal cortisol levels and attenuated ACTH and cortisol responses to a behavioral challenge in women with metastatic breast cancer. *Psychoneuroendocrinology*, 1996, 21(4), 361-374.

[88] Porter, LS; Mishel, M; Neelon, V; Belyea, M; Pisano, E; Soo, MS. Cortisol levels and responses to mammography screening in breast cancer survivors: a pilot study. *Psychosom Med*, 2003, 65(5), 842-848.

[89] Touitou, Y; Bogdan, A; Levi, F; Benavides, M; Auzeby, A. Disruption of the circadian patterns of serum cortisol in breast and ovarian cancer patients: relationships with tumour marker antigens. *British Journal of Cancer*, 74(8), 1248-52, 1996.

[90] Ticher, A; Haus, E; Ron, IG; Sackett-Lundeen, L; Ashkenazi, IE. The pattern of hormonal circadian time structure (acrophase) as an assessor of breast-cancer risk. *International Journal of Cancer*, 1996, 65(5), 591-593.

[91] Mormont, MC; Levi, F. Circadian-system alterations during cancer processes: a review. *Int J Cancer*, 1997, 70(2), 241-247.

[92] Turner-Cobb, J; Sephton, SE; Spiegel, D. Psychosocial effects on immune function and disease progression in cancer:human studies., in: Ader R, Pelten D, Cohen N, (eds), *Psychoneuroimmunology.* San Diego, Academin Press, 2001, pp 565-582.

[93] Levy, SM; Herberman, RB; Lippman, M; D'Angelo, T; Lee, J. Immunological and psychosocial predictors of disease recurrence in patients with early-stage breast cancer. *Behav Med*, 1991, 17(2), 67-75.

[94] Bettermann, H; Kroz, M; Girke, M; Heckmann, C. Heart rate dynamics and cardiorespiratory coordination in diabetic and breast cancer patients. *Clin Physiol*, 2001, 21(4), 411-420.

[95] Gold, SM; Zakowski, SG; Valdimarsdottir, HB; Bovbjerg, DH. Stronger endocrine responses after brief psychological stress in women at familial risk of breast cancer. *Psychoneuroendocrinology*, 2003, 28(4), 584-593.

[96] James, GD; Berge-Landry, HH; Valdimarsdottir, HB; Montgomery, GH; Bovbjerg, DH. Urinary catecholamine levels in daily life are elevated in women at familial risk of breast cancer. *Psychoneuroendocrinology*, 2004, 29(7), 831-838.

[97] Linsell, CR; Lightman, SL; Mullen, PE; Brown, MJ; Causon, RC. Circadian rhythms of epinephrine and norepinephrine in man. *J Clin Endocrinol Metab*, 1985, 60(6), 1210-1215.

[98] Laconi, E; Tomasi, C; Curreli, F; Diana, S; Laconi, S; Serra, G; Collu, M; Pani, P. Early exposure to restraint stress enhances chemical carcinogenesis in rat liver. *Cancer Lett*, 2000, 161(2), 215-220.

[99] Ben-Eliyahu, S; Shakhar, G; Page, GG; Stefanski, V; Shakhar, K. Suppression of NK cell activity and of resistance to metastasis by stress: a role for adrenal catecholamines and beta-adrenoceptors. *Neuroimmunomodulation*, 2000, 8(3), 154-164.

[100] Page, GG; Ben-Eliyahu, S. A role for NK cells in greater susceptibility of young rats to metastatic formation. *Dev Comp Immunol*, 1999, 23(1), 87-96.

[101] Ben-Eliyahu, S; Yirmiya, R; Liebeskind, JC; Taylor, AN; Gale, RP. Stress increases metastatic spread of a mammary tumor in rats: evidence for mediation by the immune system. *Brain, Behavior, & Immunity*, 1991, 5(2), 193-205.

[102] Melamed, R; Rosenne, E; Shakhar, K; Schwartz, Y; Abudarham, N; Ben-Eliyahu, S. Marginating pulmonary-NK activity and resistance to experimental tumor metastasis: suppression by surgery and the prophylactic use of a beta-adrenergic antagonist and a prostaglandin synthesis inhibitor. *Brain Behav Immun*, 2005, 19(2), 114-126.

[103] Ticher, A; Haus, E; Ron, IG; Sackett-Lundeen, L; Ashkenazi, IE. The pattern of hormonal circadian time structure (acrophase) as an assessor of breast-cancer risk. *International Journal of Cancer*, 1996, 65(5), 591-593.

[104] Velie, EM; Nechuta, S; Osuch, JR. Lifetime reproductive and anthropometric risk factors for breast cancer in postmenopausal women. *Breast Dis*, 2005, 24:17-35.

[105] Jaiyesimi, IA; Buzdar, AU; Decker, DA; Hortobagyi, GN. Use of tamoxifen for breast cancer: twenty-eight years later. *J Clin Oncol*, 1995, 13(2), 513-529.

[106] Lorincz, AM; Sukumar, S. Molecular links between obesity and breast cancer. *Endocr Relat Cancer*, 2006, 13(2), 279-292.

[107] Reiche, EM; Morimoto, HK; Nunes, SM. Stress and depression-induced immune dysfunction: implications for the development and progression of cancer. *Int Rev Psychiatry*, 2005, 17(6), 515-527.

[108] Holden, RJ; Pakula, IS; Mooney, PA. An immunological model connecting the pathogenesis of stress, depression and carcinoma. *Med Hypotheses*, 1998, 51(4), 309-314.

[109] Hauser, P; Soler, R; Reed, S; Kane, R; Gulati, M; Khosla, J; Kling, MA; Valentine, AD; Meyers, CA. Prophylactic treatment of depression induced by interferon-alpha. *Psychosomatics*, 2000, 41(5), 439-441.

[110] Capuron, L; Ravaud, A; Dantzer, R. Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon alfa-2b therapy. *J Clin Oncol*, 2000, 18(10), 2143-2151.

[111] Tilg, H; Atkins, MB; Dinarello, CA; Mier, JW. Induction of circulating interleukin 10 by interleukin 1 and interleukin 2, but not interleukin 6 immunotherapy. *Cytokine*, 1995, 7(7), 734-739.

[112] Maes, M; Bosmans, E; De, JR; Kenis, G; Vandoolaeghe, E; Neels, H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine*, 1997, 9(11), 853-858.

[113] Seidel, A; Arolt, V; Hunstiger, M; Rink, L; Behnisch, A; Kirchner, H. Cytokine production and serum proteins in depression. *Scand J Immunol*, 1995, 41(6), 534-538.

[114] Sluzewska, A; Rybakowski, J; Bosmans, E; Sobieska, M; Berghmans, R; Maes, M; Wiktorowicz, K. Indicators of immune activation in major depression. *Psychiatry Res*, 1996, 64(3), 161-167.

[115] Morgentaler, A. Testosterone replacement therapy and prostate risks: where's the beef? *Can J Urol*, 2006, 13 Suppl 1:40-43.

[116] Slater, S; Oliver, RT. Testosterone: its role in development of prostate cancer and potential risk from use as hormone replacement therapy. *Drugs Aging*, 2000, 17(6), 431-439.

[117] Shaneyfelt, T; Husein, R; Bubley, G; Mantzoros, CS. Hormonal predictors of prostate cancer: a meta-analysis. *J Clin Oncol*, 2000, 18(4), 847-853.

[118] Margolese, HC. The male menopause and mood: testosterone decline and depression in the aging male--is there a link? *J Geriatr Psychiatry Neurol*, 2000, 13(2), 93-101.

[119] Saxe, GA; Hebert, JR; Carmody, JF; Kabat-Zinn, J; Rosenzweig, PH; Jarzobski, D; Reed, GW; Blute, RD. Can diet in conjunction with stress reduction affect the rate of increase in prostate specific antigen after biochemical recurrence of prostate cancer? *J Urol*, 2001, 166(6), 2202-2207.

[120] Saez, MC; Barriga, C; Garcia, JJ; Rodriguez, AB; Masot, J; Duran, E; Ortega, E. Melatonin increases the survival time of animals with untreated mammary tumours: neuroendocrine stabilization. *Mol Cell Biochem*, 2005, 278(1-2), 15-20.

[121] Bubenik, GA; Blask, DE; Brown, GM; Maestroni, GJ; Pang, SF; Reiter, RJ; Viswanathan, M; Zisapel, N. Prospects of the clinical utilization of melatonin. *Biol Signals Recept*, 1998, 7(4), 195-219.

[122] Vijayalaxmi, Thomas CR, Jr., Reiter, RJ; Herman, TS. Melatonin: from basic research to cancer treatment clinics. *J Clin Oncol*, 2002, 20(10), 2575-2601.

[123] Vijayalaxmi, Meltz ML; Reiter, RJ; Herman, TS. Melatonin and protection from genetic damage in blood and bone marrow: whole-body irradiation studies in mice. *Journal of Pineal Research*, 1999, 27(4), 221-225.

[124] Vijayalaxmi, Reiter RJ; Meltz, ML; Herman, TS. Melatonin: possible mechanisms involved in its 'radioprotective' effect. *Mutation Research*, 1998, 404(1-2), 187-189.

[125] Lissoni, P; Barni, S; Mandala, M; Ardizzoia, A; Paolorossi, F; Vaghi, M; Longarini, R; Malugani, F; Tancini, G. Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. *Eur J Cancer*, 1999, 35(12), 1688-1692.

[126] Lissoni, P; Cazzaniga, M; Tancini, G; Scardino, E; Musci, R; Barni, S; Maffezzini, M; Meroni, T; Rocco, F; Conti, A; Maestroni, G. Reversal of clinical resistance to LHRH analogue in metastatic prostate cancer by the pineal hormone melatonin: efficacy of LHRH analogue plus melatonin in patients progressing on LHRH analogue alone. *Eur Urol*, 1997, 31(2), 178-181.

[127] Tamarkin, L; Danforth, D; Lichter, A; DeMoss, E; Cohen, M; Chabner, B; Lippman, M. Decreased nocturnal plasma melatonin peak in patients with estrogen receptor positive breast cancer. *Science*, 1982, 216(4549), 1003-1005.

[128] Schernhammer, ES; Laden, F; Speizer, FE; Willett, WC; Hunter, DJ; Kawachi, I; Colditz, GA. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst*, 2001, 93(20), 1563-1568.

[129] Davis, S; Mirick, DK; Stevens, RG. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst*, 2001, 93(20), 1557-1562.

[130] Carlson, LE; Campbell, TS; Garland, SG; Grossman, P. Associations among salivary cortisol, melatonin, catecholamines, sleep quality and stress in women with breast cancer and healthy controls. *J Behav Med*., In press.

[131] Ben-Eliyahu, S; Page, GG; Yirmiya, R; Shakhar, G. Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity. *Int J Cancer*, 1999, 80(6), 880-888.

[132] Costanzo, ES; Lutgendorf, SK; Sood, AK; Anderson, B; Sorosky, J; Lubaroff, DM. Psychosocial factors and interleukin-6 among women with advanced ovarian cancer. *Cancer*, 2005, 104(2), 305-313.

[133] Thaker, PH; Han, LY; Kamat, AA; Arevalo, JM; Takahashi, R; Lu, C; Jennings, NB; rmaiz-Pena, G; Bankson, JA; Ravoori, M; Merritt, WM; Lin, YG; Mangala, LS; Kim, TJ; Coleman, RL; Landen, CN; Li, Y; Felix, E; Sanguino, AM; Newman, RA; Lloyd, M; Gershenson, DM; Kundra, V; Lopez-Berestein, G; Lutgendorf, SK; Cole, SW; Sood, AK. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med* 2006, 12(8), 939-944.

[134] Lutgendorf, SK; Logan, H; Costanzo, E; Lubaroff, D. Effects of acute stress, relaxation, and a neurogenic inflammatory stimulus on interleukin-6 in humans. *Brain Behav Immun*, 2004, 18(1), 55-64.

[135] Zabora, J; BrintzenhofeSzoc, K; Curbow, B; Hooker, C; Piantadosi, S. The prevalence of psychological distress by cancer site. *Psycho-Oncology*, 10(1), 19-28, 2001, -Feb.

[136] Witek-Janusek, L; Gabram, S; Mathews, HL. Psychologic stress, reduced NK cell activity, and cytokine dysregulation in women experiencing diagnostic breast biopsy. *Psychoneuroendocrinology*, 2006.

[137] Nagabhushan, M; Mathews, HL; Witek-Janusek, L. Aberrant nuclear expression of AP-1 and NFkappaB in lymphocytes of women stressed by the experience of breast biopsy. *Brain Behav Immun*, 2001, 15(1), 78-84.

[138] Vos, PJ; Visser, AP; Garssen, B; Duivenvoorden, HJ, de Haes HC. Effects of delayed psychosocial interventions versus early psychosocial interventions for women with early stage breast cancer. *Patient Educ Couns*, 2006, 60(2), 212-219.

[139] Hossain, JL; Shapiro, CM. The prevalence, cost implications, and management of sleep disorders: an overview. *Sleep Breath*, 2002, 6(2), 85-102.

[140] Kushida, CA; Nichols, DA; Simon, RD; Young, T; Grauke, JH; Britzmann, JB; Hyde, PR; Dement, WC. Symptom-Based Prevalence of Sleep Disorders in an Adult Primary Care Population. *Sleep Breath*, 2000, 4(1), 9-14.

[141] Savard, J; Simard, S; Blanchet, J; Ivers, H; Morin, CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. *Sleep* 2001, 24(5), 583-590.

[142] Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001, 19(3), 895-908.

[143] Koopman C, Butler LD, Classen C, Giese-Davis J, Morrow GR, Westendorf J, Banerjee T, Spiegel D. Traumatic stress symptoms among women with recently diagnosed primary breast cancer. *J Trauma Stress* 2002, 15(4), 277-287.

[144] Kripke, DF; Garfinkel, L; Wingard, DL; Klauber, MR; Marler, MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry*, 2002, 59(2), 131-136.

[145] Courneya, KS. Exercise in cancer survivors: an overview of research. *Med Sci Sports Exerc*, 2006, 35, 1846-1852.

[146] Courneya, KS. Exercise interventions during cancer treatment: biopsychosocial outcomes. *Exerc Sport Sci Rev*, 2001, 29(2), 60-64.

[147] Tehard, B; Friedenreich, CM; Oppert, JM; Clavel-Chapelon, F. Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. *Cancer Epidemiol Biomarkers Prev*, 2006, 15(1), 57-64.

[148] Farrell, SW; Braun, L; Barlow, CE; Cheng, YJ; Blair, SN. The relation of body mass index, cardiorespiratory fitness, and all-cause mortality in women. *Obes Res*, 2002, 10(6), 417-423.

[149] McNeely, ML; Campbell, KL; Rowe, BH; Klassen, TP; Mackey, JR; Courneya, KS. Effects of exercise on breast cancer patients and survivors. a systematic review and meta-analysis. *CMAJ*, 2006, 175(1), 34-41.

[150] Holmes, MD; Chen, WY; Feskanich, D; Kroenke, CH; Colditz, GA. Physical activity and survival after breast cancer diagnosis. *JAMA*, 2005, 293(20), 2479-2486.

[151] Meyerhardt, JA; Giovannucci, EL; Holmes, MD; Chan, AT; Chan, JA; Colditz, GA; Fuchs, CS. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol*, 2006, 24(22), 3527-3534.

[152] Key, TJ; Schatzkin, A; Willett, WC; Allen, NE; Spencer, EA; Travis, RC. Diet, nutrition and the prevention of cancer. *Public Health Nutr*, 2004, 7(1A), 187-200.

[153] Key, TJ; Allen, NE; Spencer, EA; Travis, RC. Nutrition and breast cancer. *Breast*, 2003, 12(6), 412-416.

[154] van den Brandt, PA; Goldbohm, RA. Nutrition in the prevention of gastrointestinal cancer. *Best Pract Res Clin Gastroenterol*, 2006, 20(3), 589-603.

[155] Barnard, RJ; Aronson, WJ. Preclinical models relevant to diet, exercise, and cancer risk. *Recent Results Cancer Res*, 2005, 166, 47-61.

[156] Carlson, LE; Garland, SN. Impact of mindfulness-based stress reduction (MBSR) on sleep, mood, stress and fatigue symptoms in cancer outpatients. *International Journal of Behavioral Medicine*, 2005, 12(4), 278-285.