Brain, Behavior, and Immunity xxx (2008) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Invited Minireview

Psychological intervention and health outcomes among women treated for breast cancer: A review of stress pathways and biological mediators ☆

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ARTICLE INFO

Article history:
Received 3 June 2008
Received in revised form 22 July 2008
Accepted 8 August 2008
Available online xxxx

Keywords:
Psychosocial intervention
Breast cancer
Stress and psychological adaptation
Neuroendocrine
Immunologic
Health outcomes

ABSTRACT

Breast cancer is a common cancer among American women. The diagnosis, treatment, and the challenges of survivorship all have potential to increase women's levels of distress to levels that might influence their adaptation and possibly the course of their disease. Psychological distress can influence tumor progression via many different pathways (e.g., genetic changes, immune surveillance, pro-angiogenic processes). Psychological intervention has been shown to facilitate psychological adaptation to breast cancer. But can psychological intervention influence cancer relevant biological outcomes among breast cancer survivors? We review the literature on how psychological intervention can influence cancer relevant biological outcomes among breast cancer patients. We limited the present review to randomized controlled trials reported in the past 6 years that tested the effects of psychological intervention on biological dependent variables among patients with non-metastatic breast cancer. There are data to suggest that psychological intervention can influence neuroendocrine (e.g., cortisol) and immune function indicators, especially lymphocyte proliferation and TH1 cytokine production. Future psychological intervention studies should also focus on more newly discovered stress-tumor pathways (e.g., neuroendocrine processes promoting tumor growth and metastasis) and follow larger cohorts of the more vulnerable patients over longer periods to evaluate the biobehavioral mechanisms and lasting effects of these interventions on health and quality of life.

1. Introduction

Breast cancer is the second leading cause of cancer death among women in the USA. In 2007 an estimated 178,480 women were diagnosed with invasive breast cancer and approximately 40,460 died of the disease (American Cancer Society, 2007). With advances in treatment and increased rates of early detection, however, the number of breast cancer survivors is increasing such that at the end of 2004 (the most recent date available) there were 2.4 million breast cancer survivors in the USA (Ries et al., 2007).

Despite the increasing survival rates, however, breast cancer continues to be a stressful experience for those affected (Carver et al., 1993). Breast cancer patients have significant psychosocial concerns and needs, which vary along the disease trajectory (diagnosis, active treatment, survivorship) (e.g., Spencer et al., 1999). Because of this, a recent Institute of Medicine (IOM) report recommended that psychosocial intervention (PI) be incorporated into standard medical care for breast cancer patients at all phases of treatment (Hewitt et al., 2004). A number of research studies have shown that PI can improve psychological functioning among breast cancer patients (e.g., Luebbert et al., 2001; Meyer and Mark, 1995; Trijsburg et al., 1992; Zimmermann et al., 2007). While there is a growing literature documenting the effects of stress on cancer relevant biological processes (Antoni et al., 2006b), less is known about how PI can influence these biological process in breast cancer patients. The purpose of the present manuscript is to review the literature demonstrating PI effects on biological outcomes among breast cancer patients. However, we will first briefly summarize several of the cancer relevant biological processes which may be influenced by stress and thus amenable to stress-modulating PI.

2. Stress influences on cancer relevant biological processes

As illustrated in Fig. 1, psychological distress can negatively influence multiple cancer relevant biological processes. Cancer initiation and progression is a complex process that relies on multiple steps including environmental exposures and behaviors, genetic changes, evasion of apoptosis, proliferation, escape from immune surveillance, vascularization, and metastases. There is emerging

☆ Funded by grants from the National Cancer Institute (KO7 CA107085-01; R01-CA-064710).

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doi:10.1016/j.bbi.2008.08.002

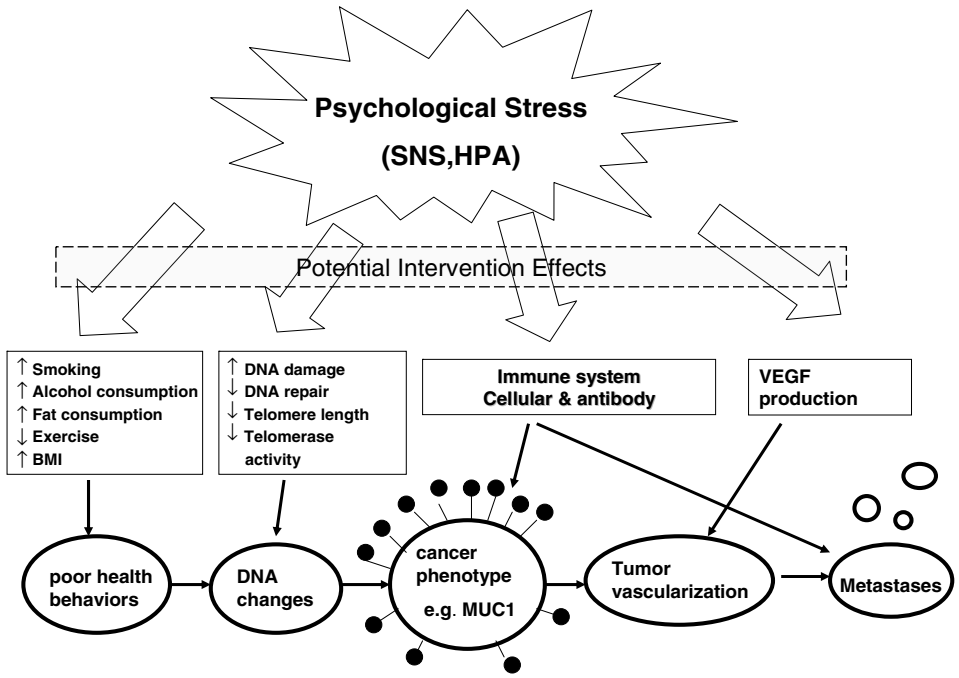

Fig. 1. The development and progression of cancer and how psychological stress and psychological interventions might influence the process. SNS, sympathetic nervous system; HPA, hypothalamus pituitary adrenal axis; BMI, body mass index; VEGF, vascular endothelial growth factor.

evidence that psychosocial stress can influence the course of disease at many points during this process (Antoni et al., 2006b).

Psychological distress is associated with health behaviors that may promote tumor growth and development. Distress states are associated with increased body mass index (BMI) and greater waist circumference (Wing et al., 1991). Increased body weight, especially central adiposity, is associated with increased risk for breast cancer (Connolly et al., 2002). Increased BMI is thought to be due to stress-related increases in consumption of sweet foods and high fat foods (O'Connor et al., 2008), and stress-related decrements in physical activity (e.g., Scully et al., 1998). Stress-related increases in waist circumference are due to the fact that visceral fat is highly vascular so is more accessible to factors in the blood, such as cortisol. Visceral fat also has a high concentration of glucocorticoid receptors. When cortisol binds to these receptors, the lipoprotein lipase (a fat-storing enzyme) gene in adipose tissue is activated and increased visceral fat storage results (Bjorntorp and Rosmond, 1999).

Psychological distress states are also associated with changes in gene function. Psychological stress is associated with increased DNA damage and poorer DNA repair (Flint et al., 2007; Gidron et al., 2006), and DNA repair pathways are important in the etiology of breast cancer. The two known genes associated with increased breast cancer risk, BRCA1 and BRCA2, both code for proteins that are involved in DNA repair pathways (Venkitaraman, 2002). Chronic stress is also associated with shortened telomeres and decreased telomerase activity (Epel et al., 2004), and genetic instability associated with telomere dysfunction (i.e., short telomeres) is an early event in tumorigenesis (Wu et al., 2003).

There is a large literature documenting the effects of psychological distress on immune function (Segerstrom and Miller, 2004). In the past 10 years, it has become clear that human breast cancer is immunogenic (Disis and Lyerly, 2005). The immune system can recognize breast cancer antigens (Disis and Lyerly, 2005) such as HER-2 Neu (Disis et al., 1999) and MUC-1 (Finn et al., 1995), and patients who have immune responses to tumor antigens have better outcomes (von Mensdorff-Pouilly et al., 2000). Tumor eradication may be influenced by many different immune pathways. Antigen presenting cells, such as dendritic cells, natural killer (NK) cells, cytotoxic-T-cells, T regulatory (T regs) cells, and B cells, are all believed to play an important role in the host response against spontaneous tumors (Disis and Lyerly, 2005) and in dealing with metastatic shed of tumor cells (Melief and Kast, 1991). Tumor cells evade detection by the immune system not only because they present antigens that are recognized as "self" by the host, but also by actively secreting immunosuppressive factors (e.g., Transforming Growth factor-beta (TGF-β), interleukin (IL)-10, prostaglandin E2 (PGE2) (Wojtowicz-Praga, 1997).

Elevated levels of psychological distress have been associated with suppressed cellular immune function among breast and ovarian cancer patients. In a study with 116 stage I–III breast cancer patients in the weeks after surgery, increased psychological distress (intrusive thoughts about cancer) were associated with decrements in lymphocyte proliferative response (LPR) to anti-CD3, natural killer cell cytotoxicity (NKCC), and NK cell response to interferon-gamma (IFNγ) (Andersen et al., 1998). In a study of ovarian cancer patients, greater levels of distress were associated with reduced NKCC in peripheral blood and also NKCC in the tumor microenvironment (Lutgendorf et al., 2005). Breast cancer patients have significantly lower NKCC compared to healthy controls, even among stage I–III patients, and NKCC appears to be even lower in stage IV patients (Baxevanis et al., 1993; Konjevic and Spuzic, 1993) and in those with liver metastases (Yamasaki et al., 1993). Among patients with solid tumors, higher NKCC predicted longer survival time without metastases over a 13-year period (Pross and Baines, 1988). *Lower* NKCC also predicted development of distant metastases in patients with head and neck tumors (Schantz and Goepfert, 1987). Thus, psychosocial distress has been associated with decrements in LPR and lower NKCC in cancer patients, including those with breast cancer, and this may in turn predict poorer clinical outcomes.

Psychological stress is thought to exert its influence on the immune system via both behavioral and neuroendocrine pathways. During periods of chronic stress, people are more likely to experi-

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ence poor sleep quality (Hall et al., 1998) and engage in unhealthy coping techniques such as smoking or alcohol consumption (Miller and Cohen, 2001). Biological mediators of the effect of psychological distress on immune function may also include cortisol, catecholamines and neuropeptides (McEwen, 1998). Psychological stress activates the hypothalamic–pituitary–adrenal (HPA) axis, which results in elevated plasma levels of cortisol and over time may lead to cortisol dysregulation. Psychological stress also activates the sympathetic nervous system (SNS), which results in the production of catecholamines. It has long been known that immune system organs are highly innervated by the SNS (Afan et al., 1997; Felten et al., 1985), and that this innervation has functional significance (Maestroni, 2000; Steidl et al., 2004).

Cortisol and catecholamines not only provide an objective indicator of stress-induced HPA and SNS activity, and a means by which stress may impact breast cancer progression via immune modulation, but also a means by which psychological stress may have direct influences on mammary epithelium and tumor vascularization. In vitro studies have shown that elevated levels of glucocorticoids signal a potent survival (anti-apoptosis) pathway in an immortalized human mammary epithelial cell line (Moran et al., 2000). Elevated levels of cortisol associated with social isolation may have a direct role in the etiology of breast cancer among African American women who are at increased risk for triple negative (estrogen reception-negative [ER−], progesterone receptor-negative [PR−] and her2 neu receptor-negative [Her2−]) tumors (McClintock et al., 2005). Also, in a mostly Caucasian sample of women with metastatic breast cancer, flatter daily di-urnal cortisol slopes were associated with greater social isolation on the one hand (Turner-Cobb et al., 2000) and with increased mortality on the other (Sephton et al., 2000), suggesting that social isolation and cortisol dysregulation may relate to shorter survival time once metastatic disease has been diagnosed. Taken together, these studies suggest a role for cortisol in the etiology and course of breast cancer that should be investigated further. It is plausible that PIs capable of improving social support (e.g., supportive group interventions) and modulating cortisol dysregulation (e.g., relaxation training) may thereby contribute to improving disease outcomes. Evidence for the effects of these interventions on psychological indicators such as social support and physiological indicators such a cortisol in breast cancer patients is reviewed in a later section.

Stress-related activation of the SNS in conjunction with the HPA axis may also influence tumor progression. Vascular Endothelial Growth Factor (VEGF), a promoter of tumor angiogenesis, has an important role in the progression of solid tumors (Thaker et al., 2006). In a mouse ovarian cancer model, chronic restraint stress, via β-adrenergic activation, resulted in enhanced production of VEGF, increased vascularization of tumor, and greater tumor burden (Thaker et al., 2006). In human studies with ovarian cancer patients, women with more social support had lower serum levels of VEGF (Lutgendorf et al., 2002). Follow-up in vitro studies showed that norepinephrine (NE) stimulated production of VEGF from an ovarian cancer cell line and these effects were compounded in the presence of cortisol (Lutgendorf, 2003). Similar studies have yet to be done in breast cancer patients though angiogenic blocking agents are becoming an important part of the anti-cancer armamentarium across many cancer types (Hendrix et al., 2003). Given that cortisol dysregulation may predict shorter survival time in breast cancer (Sephton et al., 2000) it would be intriguing to test whether cortisol dysregulation (and SNS activity) relates to VEGF production in this population.

Chronic distress is also associated with immunologic processes that may compromise quality of life and increase the physical side effects breast cancer treatment. Studies show that distress states relate to increased levels of inflammatory cytokines (Bower et al., 2007) and activation of their signaling pathways (Miller et al., 2008). Chronically increased levels of inflammatory cytokines (e.g., IL-1, IL-6, tumor necrosis factor-alpha, (TNF-α)) are released in response to tissue damage that occurs during and after treatment for breast cancer (Collado-Hidalgo et al., 2006). These changes are associated with a constellation of related symptoms which include fatigue, depression, sleep problems, and cognitive dysfunction (Bower et al., 2006; Dantzer, 2001; Miller et al., 2008). This constellation of symptoms is also known as "sickness behavior" (Dantzer, 2001; Kelley et al., 2003) and is thought to reflect the body's attempt to ward off a pathogenic threat, in this case, cancer. Pro inflammatory cytokines may be elevated in breast cancer survivors even 3–5 years after treatment (Bower et al., 2006; Nieboer et al., 2005). The extent to which these inflammatory changes can be modulated by cortisol dysregulation in breast cancer patients is a reasonable question and one that has produced some interesting work in the context of cancer-related fatigue. This work has the potential to make major contributions to understanding how psychosocial and pharmacologic interventions may be used to optimize symptom management during and after treatment for breast cancer. However, the remainder of this review will focus on how PIs modulate distress-associated changes in biological processes that may affect disease course in breast cancer.

3. Psychosocial interventions and biological outcomes in breast cancer patients

We have pointed to evidence that psychological distress, and associated alterations in the HPA axis and SNS, can negatively influence biological processes relevant for breast cancer development and progression. Given that distress states are associated with some of these biological processes, it would follow that PIs that reduce psychological distress could positively influence the development and course of breast cancer.

It has been demonstrated that stress-reducing PIs have the potential to affect health outcomes through neuroimmune mechanisms in different cancers (Antoni et al., 2006d) and other conditions such as HIV infection (Carrico and Antoni, 2008). However, the science demonstrating the effects of PI on biological outcomes among breast cancer survivors is quite limited. A review by Luecken and Compas published nearly 7 years ago (Luecken and Compas, 2002) concluded there is strong evidence that PIs can have positive benefits on psychological adjustment among breast cancer survivors but noted that the evidence supporting the effects of PI on cortisol and immune function was "extremely limited." Is there more evidence now that PIs can modulate biological function among breast cancer patients? In this review, we focus on intervention studies with breast cancer patients that were published in the 6 years since this earlier review (see Table 1). We also include some work published prior to these studies to give a background to the research line.

In 1989, Spiegel et al. published what would become a landmark study showing that women with metastatic breast cancer who participated in an expressive supportive group therapy intervention lived about twice as long as women in the comparison condition (Spiegel et al., 1989). This effect has been partially replicated in a subset of women with estrogen-receptor negative tumors (Spiegel et al., 2007). While some groups attempted to replicate Spiegel's survival findings with only limited success (for a review see Falagas et al., 2007), other teams conducted studies focusing on neuroendocrine and immune mechanisms to explain the putative health effects of PI with breast cancer patients.

Studies conducted prior to 2002 suggested that PIs could influence indices of neuroendocrine and immune function among breast cancer patients; however, these studies were conducted on small samples, lacked sufficient controls, and had short follow-up periods. In general, more recent intervention studies con-

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Table 1
Summary of effects of psychosocial interventions on psychological, neuroendocrine and immune and health variables from randomized controlled trials with breast cancer patients

Study	Intervention Type	Intervention timing	Analyses	Sample (control condition)	Psychological variables	Immune or Neuroendocrine variables	Health Status
Andersen et al. (2004)[a]	24 weeks coping skills training, relaxation training and health education	Immediately after surgery, before adjuvant therapy	Baseline to 4 months post	227 women with stage II/III breast cancer (Assessment only)	↓Anxiety ↑Social support	LPR to ConA No↓ in LPR to PHA	↑Dietary habits ↓Smoking
Andersen et al. (2007)[a]	24 weeks coping skills training, relaxation training and health education	Immediately after surgery, before adjuvant therapy	Baseline, 4 and 12 months post	227 women with stage II/III breast cancer (Assessment only)	↓ Mood disturbance among participants high in cancer-specific stress at baseline.	↑ LPR to PHA	↑Health status ratings
Antoni et al. (2006a,c)[a,b,c]	10 weeks CBSM	<8 weeks after surgery	Baseline to12 months post-surgery	199 women with stages 0–III nonmetastatic breast cancer (1 day seminar)	↓Social disruption ↑Emotional well-being ↑Benefit finding ↑Positive states of mind ↓Thought intrusion ↓Emotional distress ↓Interviewer ratings of anxiety		↑Positive lifestyle change
McGregor et al. (2004)[c]	10 weeks CBSM	<8 weeks after surgery	Pre to 3-months post	34 women with stage I/II breast cancer (Wait-list control)	↑Benefit finding	↑LPR to anti-CD3	
Savard et al. (2005a,b)	8 weeks CBT	Mean 42 months post-diagnosis	Pre to 3, 6, 12 months post	57 women with newly diagnosed breast cancer (Waiting list)	↑Subjective sleep ↓Depression ↓Anxiety ↑Global QOL	↑in vitro IFN-γ & IL-1 β production	
Phillips et al. (in press)[b]	10 weeks CBSM	<8 weeks after surgery	Pre, 6 and 12 months post	128 women with stages 0–III nonmetastatic breast cancer (1 day seminar)	↑Perceived ability to relax	↓Late afternoon serum cortisol	

[a] These papers use the same or a subset of the same sample and intervention. Participants met weekly for 4 months then monthly for 8 months.
[b] These papers use the same or a subset of the same sample and intervention.
[c] These papers use the same intervention but have different samples.

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ducted with breast cancer patients in the last 6 years have utilized larger samples, randomized controlled designs, a minimum of 3 months follow-up, and controls for confounders of immune variables. These studies have been based on interventions using cognitive behavioral therapy (CBT) techniques that target distress such as cognitive behavioral stress management (CBSM) (Antoni et al., 2001); employ a combination of CBT and health education tio facilitate better quality of life (e.g., Andersen et al., 2004); or promote better sleep quality (Savard et al., 2005a). Supportive expressive therapy has also been used in a number of studies with metastatic breast cancer patients, but the studies did not have biological dependent variables so they are not included in the present review. While there are some differences in the CBT interventions included in this review, most included some type of relaxation training, coping skills training, cognitive restructuring, and all provided a supportive group environment.

Cognitive behavioral stress management has been tested in a series of studies with breast cancer patients undergoing active treatment. In one body of work, 199 women with stage 0–III breast cancer who were up to weeks past surgery (but who had not yet initiated adjuvant therapy) were assigned to a 10-week group-based CBSM or a 1-day psycho-educational control group. This intervention combined training in anxiety-reduction techniques such as progressive muscle relaxation (PMR), guided imagery, autogenics, deep breathing and meditation, with cognitive behavioral techniques such as cognitive restructuring, coping skills training and interpersonal skills training (Antoni, 2003). This set of techniques delivered in a group CBSM format was chosen because it had been shown previously to decrease distress, reduce cortisol and catecholamine levels, and improve immune status in other disease conditions (e.g., HIV infection, Carrico and Antoni, 2008). Women assigned to the 10-week CBSM intervention (vs those in a psycho-educational 1-day seminar) showed improvements in psychological adaptation, including decreased cancer-specific intrusive thoughts, general anxiety symptoms, rates of depression, and interpersonal disruption, as well as increases in benefit finding, optimism, positive affect and positive states of mind. Importantly, these effects held up to 12 months later (Antoni et al., 2006a,c). Confidence in using newly learned relaxation skills was found to account for the majority of these effects (Antoni et al., 2006a).

CBSM was also associated with decreases in afternoon serum cortisol at follow-up in a subset of 128 women who provided blood samples, and cortisol reduction paralleled increases in perceived relaxation skills over a similar period (Phillips et al., in press). Ongoing studies are examining CBSM effects on TH1 cytokine production (IFN-γ and IL-2) in parallel with psychological changes at 6–12 month follow-up in this same sub-sample. In a separate set of studies drawn from an earlier and smaller cohort of breast cancer patients who were 4–8 weeks post-surgery, women assigned to CBSM also showed decreased late afternoon serum cortisol levels just after the intervention (Cruess et al., 2000) and increases in LPR to anti-CD3 stimulation at 3-month follow-up (McGregor et al., 2004). The cortisol reductions (Cruess et al., 2000) and increases in LPR (McGregor et al., 2004) were greatest in women with the largest psychological improvements during CBSM. Thus, there is some evidence replicated across cohorts of women with non-metastatic breast cancer, that CBSM can improve psychological adaptation (including distress reduction) in parallel with changes in cortisol and indicators of cellular immune functioning.

Other investigators have tested the effects of combining CBT techniques targeting distress with the provision of health information in 227 stage II and III breast cancer patients (Andersen et al., 2004). As in the case of the CBSM studies just summarized women were recruited after their surgery but before the start of adjuvant therapy. The intervention included training in stress management, positive coping skills, problem solving, improving utilization of social support, improving health behaviors, and various relaxation techniques (PMR and others). Participants also received disease and breast cancer treatment education to improve treatment adherence. Groups met weekly for 4 months then monthly for 8 months. As such this intervention can be viewed as providing a much greater "dose" of intervention than the women received in the CBSM studies just noted.

At the 4-month assessment, women assigned to the intervention had increased LPR to the mitogen Con A, and no change in LPR to PHA, while women in the control group had significant decreases in LPR to both Con A and PHA. Women in the intervention also reported more healthy eating habits (avoiding fat and substituting lower fat foods), reduced smoking rates, and better treatment adherence (Andersen et al., 2004). At the 12-month follow-up health status was measured using Karnofsky Performance Status and physical symptoms/signs documented by chart review and patient interview using a scoring checklist. Intervention participants had improved health at 12 months compared to the comparison group participants. Reductions in distress at the 4-month time point were associated with improved health at 12 months among the intervention participants. In contrast, improvements in LPR at the 4-month time point were not associated with improved health at 12 months (Andersen et al., 2007).

This study joins a small set of work in cancer patients that has established associations between changes in psychological adaptation during an intervention and later health effects (e.g., Fawzy et al., 1993). It remains to be seen whether intervention effects on health will hold over longer periods and whether these effects will be explained by sustained intervention-related relaxation and cognitive coping skills, improvements in social support and emotional expression, and maintenance of positive health behaviors such as dietary changes or adherence to tamoxifen or other long-term regimens. Sustained management of distress levels may also be accompanied by neuroendocrine, immunologic and other tumor related biological processes (e.g., angiogenesis) that may relate more directly to tumor growth and metastasis. It is noteworthy that distress levels reported during treatment for breast cancer are predictive of distress and quality of life as much as 8 years later (Carver et al., 2005). Thus, reducing distress during medical treatment with PI may have long-lasting effects. It is critical for PI studies with early stage cancer patients (including breast cancer) to conduct long-term follow-up of psychological, physiological and physical health indicators (e.g., at least 5 years post-intervention). Retaining the cohorts and securing the funding to conduct these types of studies presents significant challenges but these must be surmounted in order to move the field forward.

Recent work has begun to focus CBT-based interventions on particular symptom challenges faced by women with breast cancer such as sleep disruptions. One study used CBT to treat insomnia among 57 women with insomnia secondary to or exacerbated by breast cancer (Savard et al., 2005a). Women randomized to an 8-week group CBT intervention to treat insomnia (vs, those in a control condition), reported better subjective sleep, lower levels of depression and anxiety, and better global quality of life, immediately after the intervention and at 12-month follow-up. Participants in the intervention also had greater in vitro IFN-γ and IL-1β production immediately after the intervention and greater IFN-γ production at 12-month follow-up (Savard et al., 2005b). This type of symptom-focused study may provide a blueprint for using CBT and other psychological techniques (or using pharmacologic approaches) to address other common symptoms that breast cancer patients must cope with including fatigue, pain, and cognitive difficulties. It is plausible, as well, that interventions that use CBT techniques to teach better stress and sleep management in combination with health behavior education may have the greatest

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impact on psychological adaptation and associated changes in biological processes that could promote optimal health outcomes. The studies covered in this mini-review suggest that CBT-based interventions used in breast cancer patients elicit changes in psychological adaptation that parallel changes in neuroendocrine and cellular immune measures, namely decreases in cortisol, increases in lymphocyte proliferation, and increases in TH1 cytokine production. While it is intriguing that there has been some convergence among the variables that seem to be sensitive to these interventions in breast cancer patients it remains to be seen whether these indicators are at all relevant for maintaining long-term health and promoting quality and length of survival after cancer treatment is completed.

4. Summary and recommendations

In this review, we note that: (1) women with breast cancer report elevated levels of stress during and after treatment, which may result in poorer psychological adaptation; (2) chronic stress and other indicators of poor psychological adaptation are associated with a number of biological variables relevant for breast cancer including BMI and waist circumference, DNA repair and telomerase activity, immune function, and pro-angiogenic processes; and (3) these associations may be mediated through stress-related dysregulation of cortisol production and increases in catecholamines. We posed that if chronic psychological distress is associated with health-relevant behavioral and biological processes in cancer patients, then it is plausible that PIs that reduce psychological distress and promote psychological adaptation could possibly influence health outcomes in breast cancer patients.

Over the past 6 years numerous RCTs have demonstrated the efficacy of PIs for promoting psychological adaptation in persons coping with breast cancer and its treatment. Far more controversial is the question of whether PIs modulate biological functions that can confer physical health benefits for patients with breast cancer. Prior to 2002 this research area had a history plagued by inconsistent findings likely due to the inclusion of underpowered samples made up of patients with different types of cancer (and in fact, different types of breast cancer (e.g., ER−, PR− HER2−), patients differing in stage and treatment; non-standardized interventions; and unreliable outcome assessments. Moreover, many of these studies lacked a clear conceptual model outlining how psychosocial changes achieved during PI are translated into biological changes that are relevant for the clinical course of specific cancers. Hence little progress had been made in identifying the biobehavioral mechanisms underlying the effects that have been observed in intervention studies completed decades ago (Spiegel et al., 1989). Because most of the associations between psychological stress and tumor processes illustrated in Fig. 1 have been identified only recently (e.g., stress effects on VEGF; Lutgendorf, 2003; Thaker et al., 2006) most PI studies published between 2003 and 2008 have focused on a finite set of neuroendocrine and immune effects.

In reviewing reports of randomized controlled trials (RCTs) published in the past 6 years, we found that cognitive behavioral therapy (CBT)-based interventions are associated with decreases in late afternoon cortisol levels in women undergoing treatment for non-metastatic breast cancer (Phillips et al., in press), an effect that replicates similar findings established with a separate cohort sampled at the same point in their medical treatment (Cruess et al., 2000). This is potentially important because flatter di-urnal cortisol slopes (possibly due to higher PM levels) have been associated with decreased survival among women with metastatic breast cancer (Sephton et al., 2000). Whether cortisol dysregulation in early stage breast cancer patients also predicts disease course remains to be seen.

We also found that PIs appeared to modulate some indices of cellular immune function among breast cancer patients, namely lymphocyte proliferative response (LPR) and TH1 cytokine production. The Andersen et al. (2004) intervention, which combined CBT and health behavior information and health behavior change techniques in a group format, was associated with improved LPR to Con A. Similarly, group-based CBSM was associated with increased LPR in response to stimulation with anti-CD3 (the T cell receptor) (McGregor et al., 2004). These increases in LPR could have clinical significance. In a prospective study of 90 breast cancer patients, mitogen stimulated LPR was a good clinical predictor of disease recurrence (Wiltschke et al., 1995). The Savard et al. (2005a,b) study found that a group-based CBT intervention to treat insomnia was associated with increased production of TH1 cytokines in breast cancer patients (Savard et al., 2005b). TH1 cytokines are important for supporting cellular immune processes that are involved in tumor eradication, such as those involving antigen presenting cells, cytotoxic-T-cells, and T regulatory (T regs) cells (Disis and Lyerly, 2005).

Until we are able to understand how specific immune parameters change across the peri-surgical and adjuvant therapy periods in standard breast cancer treatment it will be challenging to interpret and compare changes in immune indicators across PI studies such as the ones presented here. As a first step then, it may be advisable to use growth modeling techniques to document the architecture of immune (and neuroendocrine) changes across the cancer experience by collecting regular samples from the time of diagnosis, pre and post-surgery, and before and after adjuvant therapy. This could lay the groundwork for planning the timing of assessment of biological functioning for future PI studies with breast cancer patients. Another critical "timing" issue will involve dealing with neo-adjuvant therapy clinical protocols where chemotherapy and radiation are administered prior to surgery as well as after.

To address the efficacy of PI for affecting health and survival in breast cancer, longer-term follow-up of patients enrolled in prior RCT studies may be the fastest way to tie biological changes to disease outcomes. This would require funding to track cohorts of women who have completed PI trials and might involve conducting annual assessments of neuroendocrine, immune, and sub-clinical disease activity markers as well as sustained psychological adaptation and clinical health outcomes. It should be stressed, however, that such studies may require much larger sample sizes to detect health effects than were necessary to demonstrate changes in biological parameters reflecting neuroendocrine and immune functioning over the shorter terms represented in the papers reviewed herein. This presents a challenge for the field since the work conducted to date involves samples of breast cancer patients that range from less than 50 to just over 200 women. Pooling samples from different intervention trials presents issues concerning equivalence of sampling populations and sampling methods, medical treatment setting, intervention approaches and delivery methods, and assessments and bioassays used to measure outcome, mediator and control variables.

Alternatively, multi-site prospective trials may be used to generate a large cohort of women who are randomized to a standard PI vs a well-planned control condition, and then followed annually for several years. These studies are challenging as they require long follow-up periods, and careful analysis of intercurrent medical treatments and co-morbidities as well as life stressors and other psychosocial phenomena. It may also be critical in such longer-term follow-up studies to use state-of-the-art multivariate growth analyses to model linear and non-linear changes over time. Given the advances in early detection and adjuvant therapy, it may be difficult for PIs to have health and survival effect sizes large enough to be detectable after the larger effects of medically treating early

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stage breast cancer (with survival rates >90%) are taken into account. Therefore, it may be important to identify subgroups of breast cancer patients who are at heightened risk for poorer health outcomes due to clinico-pathological features of the cancer, family history and genetic characteristics, ethnic minority status, and lower socioeconomic status, to name a few. It may be plausible to demonstrate effects of PIs on health outcomes in these more vulnerable groups.

Because breast cancer is so common (>2 million survivors in 2004), this patient population has been well studied in terms of psychosocial processes that relate to better outcomes (e.g., social support, cancer-specific coping strategies, and optimistic attitude). This information could be used to devise new interventions to embellish the CBT-based approaches that are currently used. While the findings from PIs with breast cancer patients are not totally generalizable to all cancer patients, breast cancer is a good model to study the effects of PI on cancer relevant stress-sensitive biological processes due to the shear number of diagnosed cases to participate in research trials. In keeping with the IOM recommendations (Hewitt et al., 2004), PI should be available to eligible (i.e., stressed) women at all phases of the cancer continuum. While the issues change at different phases (e.g., coping with early-stage vs metastatic disease), women report distress at all phases and intervention could have clinically meaningful psychological as well as biological effects. Many of the measures shown to change during interventions may be relevant to the course of quality of life and health outcomes in women at all stages of the breast cancer continuum and stress-sensitive processes, as noted in Fig. 1, may provide a roadmap for directing our continued efforts. While the clinical relevance of physiological changes in the peripheral blood as well as the tumor environment remains controversial (Antoni et al., 2006b), stress-related immune function indicators and other stress-sensitive cancer relevant biological outcome variables (e.g., angiogenic cytokines; DNA repair and telomerase activity) could be tested in intervention studies as possible pathways by which PIs have their effects on health outcomes, though different biological indicators may be more or less relevant based upon the clinico-pathological features of the disease and its treatment.

To date, there are very few studies relating PIs to changes in health behaviors, sub-clinical disease activity or clinical progression in breast cancer patients at different points during active treatment and survivorship. This greatly precludes our ability to create guidelines for clinical practice and to understand the mechanisms by which these interventions might influence longer-term health and quality of life outcomes in breast cancer patients. These gaps in our knowledge base challenge us to develop and test models that specify how altering stress physiology through PI can influence health outcomes in the large and growing number of individuals affected by this disease.

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