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STRESS MANAGEMENT INTERVENTIONS TO FACILITATE PSYCHOLOGICAL ADAPTATION AND OPTIMAL HEALTH OUTCOMES IN CANCER PATIENTS AND SURVIVORS

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ABSTRACT:

Cancer diagnosis and treatment constitute profoundly stressful experiences involving unique and common challenges that generate uncertainty, fear, and emotional distress. Individuals with cancer must cope with multiple stressors, from the point of diagnosis through surgical and adjuvant treatments and into survivorship, that require substantial psychological and physiological adaptation. This can take a toll on quality of life and well-being and may also promote cellular and molecular changes that can exacerbate physical symptoms and facilitate tumor growth and metastasis, thereby contributing to negative long-term health outcomes. Since modifying responses tostressors might improve psychological and physiological adaptation, quality of life, and clinical health outcomes, several randomized controlled trials have tested interventions that aim to facilitate stress management. We review evidence for the effects of stress management interventions on psychological and physiological adaptation and health outcomes in cancer patients and survivors and summarize emerging research in the field to address unanswered questions.

Keywords: Cancer-Related Stressors, Psychological Adaptation, Physiological Adaptation, Cognitive Behavioral Therapy, Stress Management Intervention, Cancer Health Outcomes.

INTRODUCTION:

Stressors and Challenges among Cancer Patients and Survivors:

Receiving a cancer diagnosis is a profoundly stressful experience involving unique and common challenges that often introduces uncertainty, fear, and emotional distress (Singer 2018, Stanton 2006). Patients are tasked with understanding new information and making important and often complex treatment decisions. These treatment decisions occur while experiencing significant disruptions to patients' daily lives and the social/occupational roles that often define their identity (Henoch & Danielson 2009). A diagnosis of cancer also frequently brings salient awareness of one's own mortality and vulnerability

and a degree of uncertainty that can further exacerbate negative emotional reactions (Lee & Loiselle 2012). Most cancers require intervention; however, the specific therapy or therapies and duration of treatment can vary greatly across cancer types and stages (Am. Cancer Soc. 2020a). Common targeted cancer treatments that remove or destroy malignant tissue include surgery to excise a tumor and radiation to ablate DNA in cancer cells. Common systemic therapies (i.e., treatments that target cancer cells throughout the entire body) include chemotherapy to kill rapidly growing and dividing cancer cells, hormone therapy to modify hormones like estrogen or androgens that fuel growth in specific types of cancer cells, and immunotherapy to enable a person's own immune system to identify and attack cancer cells. Collectively, these treatments can create short- and long-term side effects and toxicities that persist well beyond treatment.

Cancer treatments can be classified into different categories based on the goal or intention of the treatment. 1 Primary treatment refers to the first or main treatment used to eliminate or reduce traceable cancer. Adjuvant therapy is additional treatment given after primary treatment to eliminate any remaining cancer cells using either systemic or nonsystemic therapies. Neoadjuvant therapy is treatment that occurs prior to initial treatment (most typically surgery) to facilitate the primary treatment or make it more effective. Palliative treatment or treatment with palliative intent is the use of any therapy with the goal of improving quality of life (QoL; i.e., social, functional, emotional, physical functioning) and reducing the physical burden of cancer by relieving treatment side effects or symptoms related to the cancer itself. Palliative treatment can be applied to patients with any stage of cancer experiencing symptom burden; however, it is often the focal treatment for those with metastatic cancer that has spread to other parts of the body from where it originated.

METHODOLOGY:

Challenges and Opportunities:

An individual's response to treatment with respect to both its effectiveness and its side effects is highly variable. Symptomatic side effects or toxicities, such as pain, nausea, fatigue, and neuropathy, can significantly reduce the tolerability of cancer treatments (a patient's capacity to adhere to therapy) and therefore have a negative impact on QoL and psychosocial adjustment (Basch et al. 2009, Pearman et al. 2018). Cancer treatment and related disability also have a negative impact on an individual's finances as a result of the direct and indirect costs of treatment. This economic challenge, known as financial toxicity, is highly prevalent

among individuals with cancer (Carrera et al. 2018, Lentz et al. 2019) and further compromises QoL. Patients who are more recently diagnosed and those who receive adjuvant therapies are more likely to experience financial toxicity (Chino et al. 2017). Similar to other toxicities, financial toxicity reduces the tolerability of cancer treatments and has a deleterious impact on QoL and psychosocial adaptation (Carrera et al. 2018, Lentz et al. 2019). It can also result in material consequences like reduced income, increased debt, depletion of savings, and bankruptcy (Lentz et al. 2019).

Advances in cancer prevention, screening, and treatment have led to a significant increase in the number of individuals who live beyond a cancer diagnosis and the completion of curative-intent treatment (Miller et al. 2019). Although many individuals recover from the decrements in QoL that they experience during cancer treatment after treatment completion, these effects may persist long-term in some individuals or emerge for the first time months or even years later (known as late effects; Am. Soc. Clin. Oncol. 2019). The most common symptoms individuals experience are pain, fatigue, and impairments in physical functioning; however, sexual and urinary/bowel dysfunction, cognitive impairment, and sleep disturbance are also frequently reported (Kent et al. 2015, Stanton et al. 2015, Stein et al. 2008). Receiving cancer treatment can also increase the risk for subsequent cancers (known as second primary cancers), and toxicities can adversely impact the cardiovascular and reproductive systems (Demoor-Goldschmidt & de Vathaire 2019, Ganz 2001). As a result, individuals previously treated for cancer often undergo long-term surveillance by both specialists and primary care providers in order to mitigate these risks (Wilbur 2015).

In contrast to treatment with curative intent, treatment for incurable advanced or metastatic cancer is often not circumscribed to a definitive period and does not include a post–treatment completion phase as with curative-intent treatment (Am. Cancer Soc. 2020b). Furthermore, treatment plans and their intent (e.g., palliation versus life-prolonging) must be tailored to an individual's treatment response. Due to the nature of the advanced disease, these patients experience a high degree of uncertainty and anxiety tied to multiple repeated diagnostic procedures as care teams must continuously evaluate how their cancer is responding to treatment and whether their treatment plan needs to be changed (Bauml et al. 2016, Dunn et al. 2017). Accordingly, patients may experience significant treatment-related burnout and cumulative effects of cancer treatment on symptomatic side effects and toxicities, which underlines

the importance of patient-centered care and ongoing discussion with care providers regarding the goals of care and the possible benefits and side effects of cancer treatments (Langbaum & Smith 2019).

IMPLICATIONS FOR THE FUTURE OF PSYCHOLOGY:

Psychological Adaptation: Cancer-Related Distress:

Given the stressors and challenges associated with diagnosis and treatment, it is not surprising that cancer can take a significant toll on emotional well-being and require sustained psychological adaptation. Anxiety and depressed mood are two of the most common emotional reactions among individuals who are undergoing cancer treatment (Jacobsen & Andrykowski 2015) or have completed treatment (Stanton et al. 2015). About 30–40% of individuals with cancer meet diagnostic criteria for anxiety and other mood disorders (Mitchell et al. 2011); however, subclinical elevations in symptoms and other forms of cancer-related distress still negatively impact QoL and should be addressed. As expected, disease severity, premorbid psychological functioning, access to care, and functional limitations typically exacerbate negative emotional reactions and compromise psychosocial adjustment following the diagnosis and treatment of cancer. Further, fear of cancer progression or recurrence is one of the most frequent and persistent concerns individuals experience following a cancer diagnosis (Koch et al. 2013, Simard et al. 2013). Anxiety in anticipation of cancer-related surveillance scans (referred to as scanxiety) is also common during and following treatment (Bui et al. 2021, Custers et al. 2021). Fear of cancer progression or recurrence and scanxiety are distressing and are associated with significantly worse QoL (Bui et al. 2021, Koch et al. 2013, Simard et al. 2013). Furthermore, uncertainty about the future and concern for close others are two supportive care needs that individuals often report have not been adequately addressed by their care team (Armes et al. 2009, Harrison et al. 2009).

Psychological Adaptation: Resilience:

Despite the considerable impact of cancer on psychological adaptation, individuals often demonstrate resilience. Facing cancer can lead to opportunities for positive change as individuals engage in efforts to find meaning in their experience (Algoe & Stanton 2009, Park et al. 2008, Stanton et al. 2006). Positive changes, such as enhanced life appreciation, improved social relationships, and a deepened sense of self and meaning that individuals attribute to stressful life experiences like cancer, have been referred to as benefit finding, post-traumatic growth, and personal growth (Helgeson et al. 2006, Tedeschi &

Calhoun 2004). Most individuals who have completed cancer treatment report experiencing some level of post-traumatic growth in response to their cancer diagnosis and treatment (Jim & Jacobsen 2008, Stanton et al. 2006), which is generally associated with better psychological adaptation, including lower anxiety and depressive symptoms as well as better QoL and increases in optimism, hope, and positive affect (Algoe & Stanton 2009, Casellas-Grau et al. 2017, Rajandram et al. 2011, Stanton et al. 2006). Individuals with advanced or metastatic cancer also cite finding meaning at the end of life as important and perceive positive consequences as a result of their experience (Moreno & Stanton 2013). Importantly, the commonly used term "post-traumatic growth" is paradoxical in this context, given that advanced cancer often has an uneven course, which is not circumscribed to a definitive period with a beginning and an end as is more likely for illnesses treated with curative intent. Personal growth in the context of advanced cancer is positively associated with both distress, including depressive symptoms and cancer-specific intrusive thoughts and avoidance, and positive well-being, including optimism, positive affect, and acceptance (Moreno & Stanton 2013). This co-occurrence of personal growth with both cancer-related distress and positive well-being suggests that personal growth in this unique context is characterized by perceived positive consequences in the face of considerable demands, which may be reflected by greater negative and positive markers of psychological adaptation.

RESULTS AND DISCUSSION:

Psychological Stress and Neuroendocrine-Mediated Changes in Immune Activation and Regulation in Cancer:

Much work in the past 30 years has related stress processes to changes in immune system activity and regulation in cancer patients (Antoni & Dhabhar 2019). Much of the earlier work focused on associations of negative affect and depressive symptoms with in-vitro cellular immune function indicators such as lymphocyte proliferative responses (LPR), T-lymphocyte helper-type 1 (Th1) cytokine [interleukin-2 (IL-2) and interferon-gamma (IFN-γ)] production, and natural killer cell cytotoxicity (NKCC) in breast cancer patients (Andersen et al. 1998, Levy et al. 1987). More recently attention has turned to relating stress factors to indicators of systemic inflammation such as circulating interleukin-1-beta (IL-1β), IL-6 and tumor necrosis factor-alpha (TNF-α), and upregulated immune cell (leukocyte) gene expression for these proinflammatory cytokines and others. For instance, among breast cancer patients undergoing primary treatment,

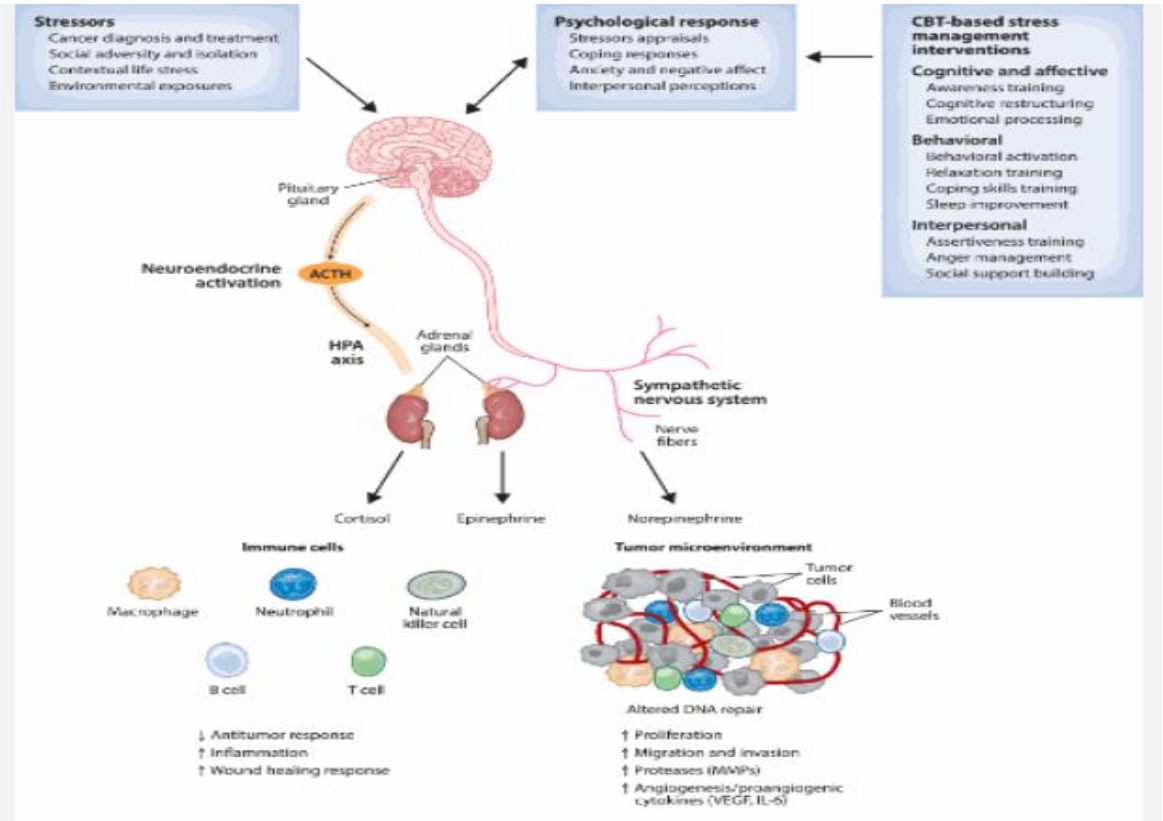
greater depressive symptoms, negative affect, cancer-specific distress, and low social support have been related to greater serum IL-1β, IL-6, TNF-α, IL-1 receptor antagonist (IL-1RA), and TNF receptor II (TNF-RII) levels (Blomberg et al. 2009, Bouchard et al. 2016, Bower et al. 2011); greater s100A8/A9 levels (Taub et al. 2019); greater leukocyte nuclear NFκB DNA binding (Diaz et al. 2021); and greater leukocyte IL1A, IL1B, IL6, and TNFA gene expression as well as increased expression of several chemokine, COX2 (prostaglandin-E, or PGE), and prometastatic (e.g., MMP-9) genes (Antoni et al. 2012, Jutagir et al. 2017). With growing interest in the effects of stress factors on transcriptional (gene expression) changes in cancer and immune cells, molecular work has related stress-related variables to a comprehensive gene expression profile termed the conserved transcriptional response to adversity (CTRA) (Slavich & Cole 2013). The CTRA pattern describes the impact of stress responses to threats on immune system components originally developed to optimize survival. Accordingly, immune responses to threatening stressors were initially designed to optimize innate immunity (inflammatory reactions) against bacterial infections due to physical attack by directing energy away from antiviral (interferon-mediated) and antibody [immunoglobulin (Ig)-making] immune system components. This CTRA pattern is believed to have been conserved as a response to modern-day psychosocial stressors (Fredrickson et al. 2013, Slavich & Cole 2013). Using a CTRA index based on 51 inflammatory (e.g., greater proinflammatory cytokines, chemokines, and COX2), antiviral (e.g., lower IFN type I and type II), and antibody (e.g., lower Ig) genes, researchers have related greater leukocyte CTRA expression to psychosocial adversity conditions such as greater negative affect, depressive symptoms, and lower socioeconomic status (SES) (Cohen et al. 2012, Knight et al. 2016) in cancer patients.

Psychological and Physiological Adaptation and Clinical Course of Cancer:

There is growing evidence that adverse psychosocial factors (depression, distress, low social support, low SES) are associated with shorter survival time for a wide number of different cancers (Chida et al. 2008). For instance, greater depressive symptoms predict shorter overall survival in patients treated for nonmetastatic (Antoni et al. 2017) and metastatic (Giese-Davis et al. 2011) breast cancer and in patients with RCC (Cohen et al. 2012). Lower SES predicts shorter leukemia-free survival (Knight et al. 2016), and lower social support predicts shorter survival in patients with ovarian cancer (Lutgendorf et al. 2012). As noted previously, there are

several comprehensive reviews of the neuroendocrine pathways underlying physiological stress responses and their associations with important biological processes that promote disease progression (Antoni & Dhabhar 2019, Antoni et al. 2006b, Chang et al. 2022, Eckerling et al. 2021). This literature provides a rationale for investigating the effects of stress management interventions (SMIs) to optimize health in cancer patients through their role in modulating biobehavioral processes. Figure 1 summarizes our contemporary understanding of a biobehavioral model for the role of stressors, psychological responses, and neuroendocrine activity on peripheral tissue (immune and cancer cells) and the putative role of cognitive behavioral therapy (CBT)-based SMIs in modulating these processes in cancer patients

Figure: Biobehavioral model for stressors, psychological responses, neuroendocrine activity, and impact on peripheral tissue in cancer and their interactions with cognitive behavioral therapy (CBT)-based stress management interventions. Abbreviations: ACTH, adrenocorticotrophic hormone; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; MMP, matrix metalloprotease; VEGF, vascular endothelial growth factor.



Cognitive Behavioral Stress Management Effects on Psychological Adaptation in Cancer Patients and Survivors:

As per Cole SW, Nagaraja AS, Lutgendorf SK, Green PA, Sood AK. 2015 Cognitive behavioral stress management (CBSM) is a 10-week CBT-based SMI that incorporates cognitive, behavioral, and interpersonal skills training and relaxation training through in-session didactic and role-playing activities as well as homework and daily practice to help improve QoL and reduce symptoms (Antoni 2003a, Penedo et al. 2008). This protocol integrates core CBT principles and practices such as cognitive restructuring (identifying and disputing irrational or maladaptive thoughts), behavioral activation (engagement in pleasant experiences, social activity, or experiences of mastery), and relaxation training like diaphragmatic breathing, progressive muscle relaxation, and meditation/imagery. Example CBSM intervention topics include introducing stress awareness and physical responses, stress awareness and the appraisal process, automatic thoughts and cognitive distortions, cognitive restructuring and rational thought replacement, coping strategies, social support, anger management, and assertiveness training. Research demonstrates that CBSM confers numerous effects on psychological adaptation in cancer survivors, including improved overall QoL and social support, increased positive affect, benefit finding, and relaxation and coping skills as well as reduced depressive symptoms, anxiety, and emotional distress (Addison et al. 2022; Antoni et al. 2006a,c, 2009; Penedo et al. 2004, 2006; Tang et al. 2020).

Effects of Psychological Intervention on Long-Term Clinical Outcomes in Cancer Survivors: Initial Studies:

The question of whether psychosocial interventions can improve long-term clinical outcomes in cancer patients has been of longstanding interest and a source of controversy in the field since the report by Spiegel et al. (1989) that metastatic breast cancer patients randomized to a 12-month group-based SET intervention appeared to live twice as long (~36 months) as those assigned to treatment as usual (~18 months). This report was a major driver of RCTs over the next 30 years testing a variety of different psychosocial interventions for survival effects. Efforts to replicate these effects in metastatic breast cancer patients have been unsuccessful to date in larger samples using the same SET intervention protocol (Goodwin et al. 2001, Spiegel et al. 2007), though subgroups of patients with a poorer prognosis (those with estrogen receptor–negative disease) have shown

improved survival with SET (Spiegel et al. 2007). However, other trials testing CBT-based and SET-based interventions in patients with metastatic breast cancer have also failed to show effects on overall survival (Kissane et al. 2007). In one of the first trials to report the effects of a CBT-based SMI on psychological, biological, and health outcome parameters, Fawzy and colleagues observed among 66 patients with malignant melanoma that those assigned to a 6-week group intervention showed improved coping and mood (Fawzy et al. 1990a), increases in NKCC (Fawzy et al. 1990b), and longer survival and lower odds of recurrence over a 6-year follow-up (Fawzy et al. 1993), but these effects on survival were no longer significant at 10 years (Fawzy et al. 2003). Unfortunately, it does not appear that this group reported associations between intervention-related biological changes and long-term clinical outcomes.

Meta-Analyses of Effects of Stress Management Interventions on Long-Term Survival in Cancer:

As per Collins LM, Murphy SA, Strecher V. 2007 looking across the entire psycho-oncology literature, several reviews reported primary or secondary analyses of RCTs for which follow-up data on clinical endpoints were available for periods ranging from 1 to 15 years. Efforts to summarize this literature have appeared in multiple qualitative and quantitative reviews (and at least 8 meta-analyses) in the past 10 years (Antoni 2013, Eckerling et al. 2021, Mirosevic et al. 2019, Oh et al. 2016). A meta-analysis of 15 RCTs completed prior to 2015 and meeting Cochrane criteria for methodological quality involved nearly 3,000 cancer patients (Oh et al. 2016). Results indicated no overall survival benefits of a variety of psychosocial interventions; however, interventions delivered early in disease (in 6 trials with 1,448 patients with nonmetastatic disease) showed a 41% reduced risk of cancer mortality (Oh et al. 2016). Since the time of this meta-analysis, other major reviews and meta-analyses have generally supported the notion that SMIs may show significant effects on overall survival in cancer patients (Eckerling et al. 2021, Mirosevic et al. 2019). These later reviews are based on trials published up to 2017, include patients with multiple cancer types and disease stages, and focus on interventions of various theoretical orientations (e.g., CBT, SET) and delivery formats (individual, group). One recent review focused on 22 studies reporting long-term effects of what were referred to as stress-reducing interventions among patients with nonmetastatic breast cancer (N = 5), metastatic breast cancer (N = 7), malignant melanoma (N = 2), and several other cancer types (N = 8) including lymphoma; esophageal, lung, and gastrointestinal cancer; and

samples of mixed cancer types (Eckerling et al. 2021). These trials were quite heterogeneous regarding sample size (N = 60–303), cancer type and stage, treatment orientation, individual versus group delivery format, duration, and timing within the cancer care continuum. Eckerling et al. (2021) noted that of the 22 studies examined, 8 reported a significant survival effect. Among breast cancer patients, the two trials showing survival benefits for patients with nonmetastatic disease were CBT-based group SMIs with 11-year follow-up periods (Andersen et al. 2008, Stagl et al. 2015b), and the one showing survival benefits for metastatic breast cancer was group SET with a 10-year follow-up (Spiegel et al. 1989). Among interventions for malignant melanoma, CBT-based SMIs showed survival effects in one trial over a 6-year follow-up (Fawzy et al. 1993) but not in another trial with a 4- to 6-year follow-up (Boesen et al. 2011).

Role of Central Nervous System Processes in Research on Stress Management Interventions:

First, we lack an understanding of the brain activities related to stress processing in cancer patients that could inform development of more precise SMI approaches. Reviews of the brain imaging literature have identified some key cortical and subcortical regions whose activity relates to individual differences in depressive symptoms, anxiety, and distress levels in cancer patients; these reviews have proposed the interoceptive network as a key network that should be included in future studies investigating brain-mediated biobehavioral processes in cancer (e.g., Reis et al. 2020). Greater distress/negative affect has been associated with less activity in cortical and subcortical regions that are important to stressor processing, including the anterior insula, thalamus, hypothalamus, ventromedial prefrontal cortex (PFC), and lateral PFC (Reis et al. 2020). To the extent that activity in the PFC and other regions is critical for optimal stress processing and stress management, this work suggests objective neural indicators that may be useful in future SMI research with cancer patients (Reis et al. 2020).

Methodologic Challenges Going Forward:

As per Cruess DG, Antoni MH, McGregor BA, Kilbourn KM, Boyers AE et al. 2000 Multiple challenges remain in SMI research in cancer populations. Importantly, progress needs to be made in developing systems, methods, and incentives to identify and engage underrepresented populations, many of whom face extensive barriers to accessing health care, let alone research trials. These include individuals who are medically vulnerable, such as those who are older, are obese, or have significant comorbidities as well as individuals who are minoritized because of race, ethnicity, sexual orientation, gender

identity, and so on. As described above, technology and cultural adaptation are two possible approaches to improving the reach of SMIs to diverse populations. Relatedly, more research is needed to optimize not only the timing of intervention (i.e., before, during, and after cancer treatment) but also the length, frequency, and delivery of intervention contact. Best practices for recruitment and retention of cancer patients and survivors in SMI research are also largely understudied. Importantly, innovative trial designs, such as just-in-time adaptive intervention (JITAI), multiphase optimization strategy (MOST), and sequential multiple assignment randomized trial (SMART) (Collins et al. 2007, Klasnja et al. 2015), as well as advancements in measurement and assessment such as computer adaptive tests (CATs) and ecological momentary assessments (EMAs), have the potential to generate novel findings that inform future SMI research.

FUTURE ISSUES AND CONCLUSION:

As per Custers JAE, Davis L, Messiou C, Prins JB, van der Graaf WTA. 2021With growing evidence for the efficacy of SMIs in cancer patients, future research questions will need to ask which, when, where, and for whom these interventions might be used optimally in clinical oncology settings (Antoni & Dhabhar 2019). The "which" question asks, among all of the psychological intervention approaches, which ones produce the largest effects on psychological and physiological adaptation and clinical health outcomes in cancer patients. Based upon recent meta-analyses, it appears that CBT-based SMI approaches are particularly effective, but more so in patients with earlier, nonmetastatic disease, in particular breast cancer (Mirosevic et al. 2019). While there is growing evidence that these interventions can create changes in stress-related biobehavioral processes for periods up to 12 months in patients with early-stage nonmetastatic disease, it remains to be determined whether they are able to modulate these biobehavioral processes in patients with advanced cancers. Similarly, there are two SMI trials that have shown effects on long-term recurrence and survival in early-stage patients receiving intervention in the postsurgical period (Andersen et al. 2008, Stagl et al. 2015a). Given the established effects of surgery on stress-related biological processes, the peri-surgical period may be an important point to explore in further SMI trials with cancer patients (Eckerling et al. 2021). As per Demoor-Goldschmidt C, de Vathaire F. 2019 this could include recruiting patients just after biopsy-confirmed diagnosis, randomizing them to study conditions either prior to neoadjuvant therapy (which precedes surgery) or just prior to surgery (a period of heightened anxiety and stress)

to test intervention effects on biobehavioral processes pre-/post-surgery, or recruiting patients after surgery and testing effects pre/post adjuvant therapy to see if early inoculation has lasting effects.

Issues that should be considered in future research include:

1. Increasing the inclusiveness and diversity of cancer populations studied in SMI research and development;

2. Examining the effects of SMIs on most vulnerable groups of patients and survivors (e.g., individuals who are obese, older, have cardiometabolic or other comorbidities);

3. Understanding the role of psychosocial and physiological adaptation processes in advanced cancers and developing novel SMIs to optimize quality of life and health outcomes.

4 Understanding how SMIs affect central nervous system (CNS) processes, neuroendocrine mediators, and changes in peripheral physiology, multiple microbiomes (e.g., gut-brain axis), and carcinogenic processes.

5. Examining how stress processes modulate the cancer–aging bidirectional loop and designing SMIs to slow cancer-accelerated aging from mind to cells;

6. Blending SMIs with health promotion interventions (physical activity, diet/nutrition, medication management) and pharmacologic interventions (β-blockers) in phased care during cancer treatment.

7. Developing and testing evidence-based SMIs that are specifically designed to be integrated before (prehab) and during cancer treatment.

8. Identifying determinants of risk in order to stratify cancer patients and survivors by risk profile to personalize/individualize care (consistent with the precision medicine movement);

9. Leveraging technology (electronic health records, virtual reality, gamification) to identify cancer patients and survivors and effectively deploy SMIs; and

10. Optimizing research–private sector partnerships to implement SMIs into cancer centers as exemplars of sustainable health care.

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