Biomarkers in Breast Cancer Survivors: The Search for Predictors

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To everyone who made this journey so rich and unique...

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Abstract

Receiving a breast cancer (BC) diagnosis generates significant physical and psychological stress that may persist months, years, or even decades beyond treatment completion. Such chronic stress can severely alter the biological systems of BC survivors (BCS). Yet, little is known about the impact and associated variables of these long-term physiological sequelae. Considering that the number of BCS continues to grow each year, it is imperative to assess the extent to which a BC experience impacts human physiological mechanisms by examining the secretion patterns of associated stress- and immune-related biomarkers and by exploring the behavioural, physical, and psychological variables implicated in these dysregulations. Such research is of particular importance in order to guide cancer survivorship care and develop interventions promoting optimal health outcomes in BCS. This research program sought to address this through three inter-related studies.

Study One was a quasi-experimental design study examining both the diurnal and reactive concentration patterns of secretory immunoglobulin A (SIgA) in a sample of women with (n = 22) and without a prior history of BC (n = 26). SIgA concentration patterns were contrasted to concentration patterns of cortisol and salivary alpha-amylase (sAA) in the same individuals (complementary to two previously published studies). Participants supplied saliva samples at five time points on two consecutive typical days (for diurnal data) and at seven time points before, during, and after an acute laboratory stressor (for reactive data). Results reveled no evidence of uncharacteristic SIgA diurnal or reactive concentration patterns, suggesting a normal and well-functioning immunological SIgA system in BCS on average 4.6 years post-diagnosis. Study One acted as a summary article allowing readers to grasp the "big picture" of long-term physiological dysregulations in BCS as a whole.

Building on this, Study Two, which used the same dataset as Study One, aimed to determine whether physical activity (PA) could mitigate the adverse physiological effects of a BC experience in

BCS (n = 25), as indexed by their cortisol concentration patterns. Participants self-reported their PA frequency and engaged in the same cortisol assay protocol reported in Study One. Results indicated no statistically significant differences in diurnal and reactive cortisol patterns between low- and high-PA groups. A trend that PA might not have the same effect on women with and without a history of BC was noted. Important limitations to Study Two included the small sample size and the lack of sensitivity and objectivity of the PA measure.

To address Study Two's limitations and to consider a wider range of modifiable variables that could contribute to the physiological dysregulations observed in BCS, Study Three aimed to assess the predictive value of six behavioural, physical, and psychological variables on the physiological effects of a BC experience, as indexed by cortisol (n = 192) and C-reactive protein (CRP; n = 168) levels over the first 1.5 year post-treatment. CRP, a biomarker that had not been considered so far in this research program, allowed to assess systemic inflammation in BCS post-treatment. Study Three also aimed to describe naturally occurring changes in cortisol and CRP levels and assess whether they changed in tandem. Data were drawn from 201 BCS who provided capillary blood and saliva samples at approximately 3.5 months post-treatment and again 3, 6, 9, and 12 months later. At each time point, participants also completed self-report questionnaires and wore an accelerometer for seven consecutive days. Multilevel modeling analyses revealed no significant change over time for cortisol levels post-treatment and a non-linear trajectory of change for CRP levels which was not predicted by cortisol levels. Associations between cortisol and sedentary time as well as associations between CRP and PA, body mass index, and health- and cancer-related stress were found.

Collectively, these three inter-related studies uniquely add to the literature by describing long-term physiological trajectories of stress- and immune-related biomarkers in BCS. This research program attempts to gain a better understanding of the underlying mechanisms that tie behavioural, physical, and

psychological variables and biomarker secretion to a BC experience. It also offers opportunities to identify women at greater risk of physiological dysregulations following a BC experience. This represents an important step towards the development of tailored interventions targeting specific BCS that most warrant them. With the number of BCS climbing each year, cancer survivorship needs to be a priority in research and efforts to better understand, monitor, and mitigate the physiological consequences of a BC experience are critical.

Table of Content

Overview of Thesis

The following is a scholarly presentation of my doctoral research program. It comprises five chapters, followed by references and appendices. Chapter One of this document provides the background information of my research program and ends with the overarching purpose of the thesis and its specific objectives and hypotheses. Chapter Two, Three, and Four present the three studies included in this research program and the scientific articles that resulted from them. Study One, Two, and Three resulted in one manuscript each, for a total of three scientific articles that have all been published in peer-reviewed journals. Chapter Five collates key findings and highlights the contributions and implications of this research program. Following Chapter Five are the References as well as the Appendices.

List of Abbreviations

ANOVA=Analysis of variance

AUC=area under the curve

BC=Breast cancer

BCS=Breast cancer survivors

CRP=C-reactive protein

HPA= hypothalamic-pituitary-adrenal

sAA=Secretory alpha-amylase

SD=Standard deviation

SIgA=Secretory immunoglobulin A

TSST=Trier social stress test

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CHAPTER ONE

Review of the Literature

Breast Cancer Burden

According to Canadian data, besides non-melanoma skin cancers, breast cancer (BC) is the most common cancer diagnosed in Canadian women. These data provide further evidence for BC burden. Specifically, one in eight women is expected to be diagnosed with BC in their lifetime and one in 33 is expected to die from it. In 2020, approximately 27 400 Canadian women were diagnosed with BC. Fortunately, the mortality rates of BC are the lowest they have been since 1950, with a steady five-year survival rate of 88%. Continued advancements in BC detection and treatment strategies along with the aging and growth of the population have resulted in an ever-increasing number of survivors in the population. It is estimated that more than 157 000 Canadian women are currently living with or survivors of BC.

A diagnosis of BC is an extremely stressful, possibly traumatic, event that poses numerous social, physical, and psychological challenges to the patient and their family (Hauken et al., 2013; Knobf, 2007; Mikal et al., 2020). It encompasses repeated distressing events, including a series of difficult treatment procedures that can give rise to adverse side effects such as pain, cognitive impairment, and fatigue which may impact weight, appetite, and overall quality of life (Abrahams et al., 2018; Carlson et al., 2018; Schreier et al., 2019; Swartzman et al., 2017). Drastic changes in daily routine as well as family and work concerns also often emerge, which further contribute to the emotional distress experienced (Duijts et al., 2014). This is noteworthy given that the stress linked to a BC diagnosis has been repeatedly associated with reduced survival rates, overall quality of life, and medical care satisfaction (Budden et al., 2014; Härtl et al., 2010; Moreno-Smith et al., 2010; Ravindran et al., 2019).

Beyond general agreement that a cancer diagnosis generates significant stress, it is becoming increasingly obvious that the adverse impact of the cancer experience can continue well beyond the end of treatment. Indeed, several cross-sectional and longitudinal studies indicated that the symptom burden linked to cancer survivorship can persist for more than 10 years following treatment completion (Green McDonald et al., 2013; Harrington et al., 2010; Jones et al., 2016). Along with the physical and psychological sequelae, the high and persistent level of stress experienced by women diagnosed with BC (referred to as breast cancer survivors [BCS] in this research program) can negatively impact multiple biological rhythms and processes (McGregor & Antoni, 2009). There is a large body of literature documenting the relationship between a cancer experience and the chronic activation of the stress systems, which over time can lead to long-term abnormalities in stress-related biological mechanisms as indexed by dysregulated biomarkers concentration patterns (Couture-Lalande et al., 2014; Hsiao et al., 2017; Leschak et al., 2020; Wan et al., 2016).

Biomarkers and Cancer Research

It has long been known that chronic stress can severely alter human biological systems in many ways (Huss, 2015). One way to examine the extent to which stress impacts stress-related physiological mechanisms is to examine the secretion patterns of associated biomarkers. Over the last 50 years, the use of the term *biomarker* (or biological marker for long) has drastically increased in the scientific literature. A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an ... intervention" (Biomarker Definitions Working Group, 2001 p. 91). The examination of biomarkers holds many advantages. For instance, their measurement is often easier, quicker, and cheaper compared to other endpoint alternatives because they are present in tissues, blood, and/or body fluids such as urine, stool and sputum (Aronson, 2005). Moreover, biomarkers allow for objective and precise indications of the

medical and physiological state of an individual that are not dependent on self-perceptions (Micheel et al., 2012). Hence, biomarkers have become an integral part of current health research and are now assessed in a wide variety of clinical practices including oncology as well as neurological, immune, and metabolic disorders (Nonaka et al., 2012). In the field of oncology specifically, the collection and analysis of biomarkers play a crucial role in cancer risk appraisal, early detection, diagnosis, and disease management (Miaskowski & Aouizerat, 2012). They are also used to inform the development of certain drugs used for cancer treatment and show significant clinical utility in guiding treatment decisions (Goulart et al., 2007; Harris et al., 2016). Indeed, many researchers have shown that different biomarkers help to predict drug resistance and treatment response in cancer patients (Kelloff et al., 2004; Sawyers, 2008).

Although biomarkers' clinical utility is well established in the field of oncology, the role of biomarkers in assessing the long-term and lasting effects of a cancer experience is a relatively new field of scientific inquiry (Miaskowski & Aouizerat, 2012). Through both humans and animals studies, an increasing number of researchers have worked towards the development and identification of clinically relevant biomarkers that could be used to evaluate the impact of a cancer experience on survivors as indexed by common post-cancer symptoms such as fatigue, sleep problems, and depression (Schmidt et al., 2016; Sharpley et al., 2019; Xiao et al., 2017). Such research efforts are promising as they represent a step towards a better overall understanding of the mechanisms underlying the physiological sequalae that persist well after treatment completion. Findings can also be used to identify survivors at greater risk of poorer quality of life and health outcomes following a cancer experience and to inform the development of more effective post-treatment intervention strategies (Miaskowski & Aouizerat, 2012).

Measurement of Biomarkers in Cancer Survivors.

Studies that aim to measure the extent to which a cancer experience impacts human physiological mechanisms and systems have used two main approaches in order to assess stress-related biomarkers. The approach selected depends on the research question being investigated. The first approach is to measure concentrations at different time points during waking hours and examine the rate at which they vary. This allows to gather precise information about the biomarker fluctuations over time and assess metrics such as circadian rhythm, slope, awakening response, and reactivity (Adam & Kumari, 2009; Ryan et al., 2016). Study One and Study Two of the current research program employed this approach. The second approach involves calculating the absolute concentration of a given biomarker by collecting multiple assays over a 12- or 24-hour period and then compute the area under the curve (AUC). This alternative approach allows to measure the total overall exposure and/or increase of an individual to a given biomarker (Clow, 2004; Ryan et al., 2016). Study Two and Study Three of the current research program applied this approach.

Using these two approaches, two main types of patterns of concentrations can be investigated, namely diurnal and reactive patterns. The assessment of diurnal concentration patterns of a given biomarker involves the collection of biomarker samples without subjecting the individual to any external stressor and physiological systems. On the other hand, the assessment of reactive concentration patterns of a given biomarker allows to measure an individual's response/reactivity to stress and involves the collection of samples when the individual is exposed to a stressor characterized as unpredictable, uncontrollable, and threatening (Kirschbaum & Hellhammer, 1989, 1994; Ryan et al., 2016). In the current research program, Study One and Study Two examined both diurnal and reactive patterns while Study Three focused on diurnal patterns solely.

The overarching objectives of the current research program are to investigate the physiological sequelae experienced by BCS as indexed by the secretion profiles of four key biomarkers, and explore variables associated with these secretion patterns over the survivorship period. Cortisol, alpha-amylase (sAA), secretory immunoglobulin A (SIgA), and C-reactive protein (CRP) are all considered to be reliable and sensitive biomarkers of an individual's biological response to different types of stressors and are hence the focus of the current research program.

Cortisol. The hypothalamic-pituitary-adrenal (HPA) axis is a system that serves to regulate an individual's response to stress by transducing psychological and environmental stressors into physiological reactions that are relevant to health (Adam & Kumari, 2009; Ryan et al., 2016). Cortisol is the downstream hormone of the HPA axis and has become the "gold standard" biomarker to evaluate the responses of the hypothalamic-pituitary-adrenal axis to internal or external stressors (Ali & Nater, 2020; Clow, 2004; D. H. Hellhammer et al., 2009; Mason et al., 1936). The typical diurnal concentration patterns of a healthy and well-functioning HPA axis is characterized by cortisol concentrations that peak 30 to 45 minutes after awakening and gradually decreases throughout the day until its reaches its lowest level around midnight (Clow, 2004; Kirschbaum & Hellhammer, 2000). When a stressor is perceived, the hypothalamus releases a hormone called corticotropin releasing hormone, which in turn prompts the release of adrenocorticotropic hormones by the pituitary gland. The release of adrenocorticotropic hormones then triggers the adrenal glands to produce cortisol (Fulford & Harbuz, 2005; Gunnar & Quevedo, 2007).

Cortisol plays a critical role in regulating bodily functions by initiating a series of metabolic processes such as the suppression of immune function and energy metabolism, which allow the body to reach optimal physical and psychological performance to cope with a stressor (Gatti et al., 2009). When the stressor is removed, the hypothalamus and pituitary glands stop their production and cortisol

typically returns to its baseline levels within 1 or 2 hours after stress cessation (Armario et al., 2004; Hellhammer & Schubert, 2012). There exist no widely accepted thresholds and norms with regard to typical cortisol concentration patterns and the extent of cortisol reactivity increase as numerous methodological and personal factors can impact concentrations (Gatti et al., 2009; Salimetrics, 2011; Yeo et al., 2000). For instance, recent studies suggest that individuals differ in the stressor severity required to provoke peak cortisol reactivity and that factors such as internalizing risks, perception biases, and trait rumination contribute to those individuals differences (Conway et al., 2016; Vrshek-Schallhorn et al., 2018). It is strongly suggested to establish reference range and cut-off points based on the study of a control group in relation to an experimental group (Gatti et al., 2009).

Although the activation of the HPA axis and the release of cortisol are absolutely crucial for healthy living and everyday functioning, too frequent, extreme, and/or chronic activation may result in dysregulation of the HPA axis, which is associated with several adverse health outcomes (Adam & Kumari, 2009; Kirschbaum & Hellhammer, 1994). Dysregulation of the HPA axis present as abnormalities in diurnal and/or reactive cortisol concentration patterns. Atypical cortisol awakening responses, sustained high cortisol concentrations, or flattened cortisol slopes are all indicators of a dysregulated HPA axis functioning (Adam & Kumari, 2009; De Kloet, 2004). Cortisol dysregulations have been observed in response to persistent job strain, school stress, unpleasant noise, and children maltreatment (Alink et al., 2012; Dettweiler et al., 2017; Lefèvre et al., 2017; Rydstedt & Devereux, 2013). Abnormally high cortisol levels have been associated with depression (Barca et al., 2019; Fiksdal et al., 2019; Stetler & Miller, 2011), obesity (Chu et al., 2017; Hewagalamulage et al., 2016), diabetes (Champaneri et al., 2012; Hackett et al., 2016; Joseph & Golden, 2017), and cardiovascular diseases (Iob & Steptoe, 2019; Walker, 2019). Abnormally low cortisol levels have also been linked to adverse health outcomes such as pain, fatigue, high stress sensitivity, and increased risk for developing post-

traumatic stress disorder and fribromyalgia syndrome (Cuneo et al., 2017; Nicolson & Ponnamperuma, 2019; Riva et al., 2010; Sveinsdottir et al., 2016).

A cancer experience, which typically involves being subjected to stress for an extended period of time (i.e., situation of chronic stress), can also lead to dysregulation of the HPA axis. Indeed, several studies have showed that BCS often exhibit flatter diurnal and/or reactive cortisol concentration patterns compared to individuals without a history of cancer (Abercrombie et al., 2004; Bower et al., 2005; Hsiao et al., 2017; McGregor & Antoni, 2009; Schmidt et al., 2016). These dysregulated patterns have been associated with persistent post-treatment symptoms including fatigue, depression, sleep problems, and anxiety (Banasik et al., 2011; Carlson et al., 2007; Cuneo et al., 2017; Giese-Davis et al., 2004).

Secretory Alpha-Amylase. The sympathetic-adrenal-medullary system, a system comprised by the autonomic nervous system, works along with the HPA axis to maintain homeostasis and prepare the body to deal with various stressors (Ali & Nater, 2020; Nater & Rohleder, 2009; Thiel & Dretsh, 2011). Similar to the HPA axis, the autonomic nervous system and the sympathetic-adrenal-medullary system play a crucial role in the biological processes involved in the pathogenesis of stress-related symptoms and diseases. Nonetheless, studies on the effect of stress on the autonomic nervous system and the sympathetic-adrenal-medullary system are limited compared to those examining the HPA axis and cortisol. Typically, sAA concentrations sharply decrease in the first 30 to 60 minutes post-awakening and then steadily increase throughout the day, reaching their highest levels on late afternoon or early evening (Ali & Nater, 2020; Nater et al., 2007). Dysregulation of the sympathetic-adrenal-medullary system, which has been associated with situations of chronic stress, typically presents as a blunted awakening response (i.e., less decline after the awakening peak) and higher sAA levels throughout the day (Nater et al., 2007; Nater & Rohleder, 2009). These blunted sAA patterns have been observed, for

instance, in individuals experiencing burnout (de Vente et al., 2015), war refugees (Thoma et al., 2012), and individuals with tinnitus (Alsalman et al., 2016).

Within the last 15 years, sAA has been widely accepted as a sensitive and non-invasive biomarker for the assessment of stress-related changes in the autonomic nervous system and sympathetic-adrenal-medullary system (Ali & Nater, 2020; Buchanan et al., 2010; Nater & Rohleder, 2009). Previous studies have measured sAA in response to different acute stressors such as writing a test, performing a challenging task, exposure to derogatory comments, social evaluative threat, emotional arousal, and skydiving (Bibbey et al., 2015; Fischer et al., 2017; Y. Liu et al., 2020; Vrijen et al., 2018). Yet, despite increased popularity within the last decade, the number of studies assessing sAA response to acute stressors remain fairly small (Ali & Nater, 2020). Typically, acute stressors induce predictable changes in sAA secretion, that is, a rapid increase within 1 minute followed by a return to baseline within a 20-minute period after exposure to the stressor (Ali & Nater, 2020; Nater & Rohleder, 2009). Given that physiological stress response is complex and multifaced, researchers have highlighted that measuring sAA in tandem with cortisol allows for a significantly more comprehensive evaluation of the stress responses (Ali & Pruessner, 2012; Strahler et al., 2017). As such, Bielajew's group assessed both cortisol and sAA in the same BCS and found a blunted reactive cortisol stress response and a 36% elevated diurnal sAA levels in BCS as compared to women without a history of cancer (Couture-Lalande et al., 2014; Wan et al., 2016). Very few other studies have documented the sAA profile of cancer survivors specifically; additional studies are needed to address this gap in research.

Secretory Immunoglobulin A. Given that the majority (roughly 95%) of infectious agents enter the human body via mucosal surfaces (Castro-Sánchez & Martín-Villa, 2013; Sato & Kiyono, 2012), one of the most important and powerful lines of defense against pathogens is the mucosal immune system (Bishop & Gleeson, 2009; Li et al., 2020). SIgA is the predominant effector of that specific

system and its role is to continually monitor the environment in order to maintain a balance between tolerance to harmless bacteria invasion and immunity to potentially life-threatening invasion (Corthésy, 2013). The mechanisms involved in SIgA's ability to distinguish between the two and prevent massive invasion are highly complex and far from being fully understood (Corthésy, 2013). SIgA acts primarily through receptor blockage and immune exclusion to combat microbial infections and pathogens, alongside with other innate mucosal defense agents such as lactoferrin and lysozyme (Corthésy, 2013). In the last decade, salivary SIgA has been considered the most commonly studied marker of immune competence and has also often been used as a marker of environmental stress (Bellussi et al., 2013; Mantis et al., 2011; Moreira et al., 2013; Trueba et al., 2012). Yet, compared to cortisol, the role of SIgA in stress is under-explored.

Identified patterns of diurnal rhythm of SIgA concentrations are quite inconsistent across studies. Some studies reported that SIgA levels peak in the morning and then progressively declines to a plateau effect by the evening (Dimitriou et al., 2002; Hucklebridge et al., 1998; Li & Gleeson, 2004; Shirakawa et al., 2004); some found a second peak of increase in the afternoon (Bellussi et al., 2013); and some found no evidence of diurnal variation in SIgA levels (Dwyer et al., 2010; Kobayashi et al., 2017). Several factors such as age, sex, diet, fitness level, recent infection, hydration state, and caffeine/ or alcohol ingestion can impact SIgA levels, thereby making it very difficult to establish reference values (Corthésy, 2013; Jafarzadeh et al., 2010; Mantis et al., 2011). Studies that have explored the effects of acute stress on immune system responses have concluded that acute stress is associated with an increase in SIgA levels (Fan et al., 2009; Romero-Martínez et al., 2014; Trueba et al., 2012). This activation in response to stress highlights the immune system’s fundamental ability to protect the body, whereby when the demands of a situation are higher, mucosal defenses are strengthened (Laurent et al., 2015; Segerstrom & Miller, 2004).

Whilst acute stress evokes a rise in SIgA levels, chronic or long-term stress, on the other hand, has been found to have a suppressive effect on SIgA levels (Dhabhar, 2009; Koh & Koh, 2007; Phillips et al., 2006; Walsh et al., 2011). Indeed, a diminished SIgA level was found in long-time neglected toddlers, soldiers, caregiver of a sick/disabled relative, and nurses enduring chronic stress at work (Gallagher et al., 2008; Kvietkauskaite et al., 2014; Shirtcliff et al., 2009; Vermeer et al., 2012). Dysregulated SIgA concentration patterns have been linked to several negative health outcomes. For instance, low SIgA levels have been associated with higher susceptibility to cold, increased risks of infections, depression, and higher cancer incidence and mortality (Ludvigsson et al., 2013, 2016; Oikawa et al., 2015; Phillips, Carroll, Drayson, & Der, 2015; Tsuboi et al., 2008), whereas high levels of SIgA have been linked to inflammatory bowel disease, certain types of kidney diseases, and higher total and cause-specific mortality rates (Brandtzaeg, 2010; Papista et al., 2011; Phillips, Carroll, Drayson, & Batty, 2015).

Certain studies have found a marked decreased in SIgA levels in individuals currently being treated for cancer (Shpitzer et al., 2007; Zhang et al., 2017). Although the reasons for this reduction in SIgA in the presence of tumors is not fully understood, some have suggested that certain immunoglobulin receptors might be inhibited, making it difficult to connect with the correct ligand for SIgA synthesis and secretion (Johansen et al., 2000; Zhang et al., 2017). To our knowledge, very few studies have measured SIgA levels in individuals who completed cancer treatment and are now considered disease-free. Jensen et al. (2008) found a decrease in SIgA levels in BCS following chemotherapy, but levels were returned to baseline at one year post-treatment. Fernández-de-las-Peñas et al. (2012) also assessed SIgA levels in BCS but did not include a control group for comparison; rather, they compared different genotypes amongst BCS.

C-Reactive Protein. CRP, which is secreted by the liver in response to a high level of inflammatory cytokines, also plays an important role in regulating one's ability to fight infections (Black et al., 2004; Izawa et al., 2013; Reeves, 2007). The primary role of CRP is to monitor and recognize pathogens and provide early defense by sending proinflammatory signals leading to the activation of the adaptive immune system (Boras et al., 2014; Du Clos, 2009). Average CRP levels in the general population typically range between 1.4 and 2.9 mg (Riese et al., 2002; Rutter et al., 2013). CRP provides a sensitive marker of systemic inflammatory levels within the human body as infections, trauma, and inflammation all lead to a rapid increase in CRP levels (Sproston & Ashworth, 2018). In some studies, CRP levels have been found to remain unchanged despite important symptoms severity; the mechanism behind this "selective" reactivity remains unclear (Reeves, 2007). Yet, studies found that low CRP levels might not directly reflect an improved health profile per se but might instead indicate a particular, perhaps inherited, physiological status (Kathiresan et al., 2006; Rogowski et al., 2007).

The basic features and rhythm of CRP concentration patterns are not well understood. The few studies that have investigated the circadian rhythms and biological basis of CRP have reported that salivary CRP levels typically peak at awakening and steadily decrease during the daytime (Izawa et al., 2013; Koc et al., 2010; Out et al., 2012). Serum CRP levels (where the highest levels of CRP are typically found), however, are significantly less variable, some studies even suggesting an absence of CRP circadian variability in asymptomatic individuals (Meier-Ewert et al., 2001; Mills et al., 2009). The very low baseline levels of serum CRP and its remarkable time-of-day stability make it a very powerful marker of "acute-phase response" following tissue infection or injury, as well as in response to cytokines within a tumor environment (Asegaonkar et al., 2015).

Evidences on CRP response to acute stress are mixed (Slavish et al., 2015; Steptoe et al., 2007). For instance, Veldhuijzen et al. (2005) and Nijm et al. (2007) found that an induced stress task led to an

increase in CRP levels in individuals with rheumatoid arthritis and with coronary artery disease, respectively, but not in individuals with osteoarthritis or in clinically healthy individuals. Similarly, there was no change in the CRP levels of healthy college students following an acute stress situation (Campisi et al., 2012). The inconsistencies of findings across students have led some researchers to suggest that CRP levels may not be a reliable marker of *acute* stress but may instead better capture responses to *chronic* stress (Campisi et al., 2012; Laurent et al., 2016). In support of this hypothesis, a positive relationship has been observed between chronic stress duration and CRP levels (von Känel et al., 2012). Also, elevated CRP levels have been found in adults who experienced different types of early-life adversity – typically chronic in nature – such as maltreatment, abuse, and bullying (Baldwin et al., 2018; Baumeister et al., 2016; Danese et al., 2011) as well as in individuals who encountered traumatic life events such as terrorism attacks, war, and chronic caregiving and financial stress that can cause enduring stress (Brummett et al., 2013; Canetti et al., 2014; von Känel et al., 2012). Finally, cancer survivors typically have higher CRP levels than individuals without history of cancer (Jones et al., 2007; Thomson et al., 2009).

When the immune system is activated but an immune response is not actually needed (e.g., there is no pathogen to fight) or when the activation of the immune response (i.e., CRP secretion) cannot be turned off, several adverse effects on health may result. For instance, elevated CRP levels, which typically refer to levels above a threshold of 3.0 mg (Kushner et al., 2006; Pearson et al., 2003), have been associated with meningitis (Peltola et al., 2016; Prasad et al., 2005), depression (Köhler-Forsberg et al., 2017), anxiety (Glaus et al., 2018), cancer risks (Frydenberg et al., 2016; Siemes et al., 2006), cardiovascular diseases (Kaur, 2017; Shrivastava et al., 2015), and obesity (Choi et al., 2012). Moreover, high CRP levels have been associated with lower quality of life and higher disability, which has led some to suggest that CRP can be used as an indicator of general health and longevity (Dhamoon et al.,

2017; Kuo et al., 2006). In BCS, lower CRP levels have been linked to reduced morbidity and mortality outcomes (Allin & Nordestgaard, 2011; Basu et al., 2015; Pierce, Ballard-Barbash, et al., 2009; Villasenor et al., 2014), whereby higher CRP levels have been associated with greater post-treatment pain intensity, fatigue, depression, and cancer recurrence (Allin et al., 2010; Han et al., 2011; Pertl et al., 2013; Starkweather et al., 2011).

Predictors of Physiological Dysregulations in BCS

Although the presence of physiological dysregulations following a BC experience is well documented in the literature (Hsiao et al., 2017; Wiley et al., 2017), predictors of these dysregulations have seldom been examined and thus remain largely unknown. Given the known adverse health effects of such dysregulations (as described above), it is critical to examine predictors in order to identify subgroups of women at higher risk and develop interventions to decrease the risk of negative long-term physiological outcomes. Several studies have demonstrated that the general health and quality of life of cancer survivors are impacted by modifiable everyday health behaviours (Lynch et al., 2013; Rock et al., 2012). Therefore, drawing on previous research showing that certain behavioural, physical, and psychological variables are associated with cancer prognosis in terms of cancer recurrence, survival rates, and quality of life (Bloom et al., 2004; Ellsworth et al., 2012; Rozenberg et al., 2007), Study Three of the current research program aimed to assess the predictive value of a wide range of modifiable variables on cortisol and CRP concentration patterns over the first 1.5 year post-treatment among BCS. Candidate predictors were selected based on previous literature suggesting their associations with cortisol and CRP and availability within the existing database. They included sedentary time, physical activity, body mass index, depressive symptoms, perceived general stress, and health- and cancer-related stress.

Candidate Behavioural Predictors of Cortisol and CRP Levels.

Sedentary time. Sedentary time includes activities such as sitting, lying and reclining behaviours requiring minimal energy expenditure (Booth & Lees, 2007; Hartman et al., 2018). Elevated levels of sedentary time can contribute to negative health outcomes among cancer survivors (Campbell et al., 2013; Hartman et al., 2018; Phillips et al., 2016). For instance, sedentary time has been associated with a higher incidence of comorbid conditions, greater fatigue and pain severity, depression, and lower health-related quality of life in BCS (George et al., 2013; Phillips et al., 2016; Trinh et al., 2015). Researchers investigating the association between sedentary time and cortisol levels have found mixed results. For instance, Nabi, Prestin, and So (2016) observed that greater television viewing was linked to lower cortisol levels wherein greater video games playing was linked to higher cortisol levels. Several others have found no association between sedentary time and cortisol levels (Ivarsson et al., 2009; Jackson et al., 2019; Teychenne et al., 2018). In contrast to cortisol, the association between sedentary time and CRP levels has been more consistent, with higher levels of sedentary time being linked to higher CRP levels (Howard et al., 2015; Pierce, Ballard-Barbash, et al., 2009; Pinto Pereira et al., 2012; Stubbs et al., 2015). More sedentary women have also been found to have greater risk of BC as opposed to their less sedentary counterparts (Lynch et al., 2011; Wiseman et al., 2014). Considering that BCS spend the vast majority of their waking hours engaging in sedentary time and generally have higher sedentary time level than individuals without a history of cancer (Kim et al., 2013; Sweegers et al., 2019), it is imperative to establish whether sedentary time predicts cortisol and CRP levels in BCS shortly after treatment completion so as to intervene as soon as possible. Indeed, observing an association would suggest that lifestyle modification interventions targeting sedentary time could be an effective strategy to reduce the adverse physiological effect of BC early on during survivorship.

Physical activity. Several studies have found that sedentary time and physical activity are distinct behaviours with unique and independent metabolic consequences and that one can have elevated levels of sedentary time while also meeting public health recommendation for weekly physical activity (Healy et al., 2008; Panahi & Tremblay, 2018). Regardless of levels of sedentary time, low level of physical activity has adverse consequences on health, whereas engaging in physical activity on a regular basis has been associated with reduced side-effects of treatment, greater quality of life, and lower risk of cancer recurrence and mortality among cancer survivors (Courneya, 2017; Lynch et al., 2011; Schmid & Leitzmann, 2014). Several researchers have found a negative association between physical activity level and CRP levels, both in the general population and in cancer survivors (Costa et al., 2019; Kang et al., 2017; Yu et al., 2009). Yet, the association between physical activity and cortisol levels is not as clear. Some researchers have found a negative relationship between physical activity and cortisol levels (Melin et al., 2014; Rimmele et al., 2009), others have found a positive relationship (Hill et al., 2008; Viru & Viru, 2004), and some have not found any association (Brumby et al., 2013; Jacks et al., 2002). Studies exploring the relationship between physical activity and cortisol and/or CRP levels in BCS specifically have reported similar findings than in the general population, that is, a negative association between physical activity and CRP levels and mixed results for cortisol (Kang et al., 2017; Lambert et al., 2018; Payne et al., 2008; Sabiston et al., 2018). The discrepancy in results for cortisol across studies may partly reflect differences in the type, duration, frequency, and intensity of physical activity analyzed or differences in the samples studied (Gatti & De Palo, 2011; Hill et al., 2008; Rimmele et al., 2007), warranting additional studies using objective measure of physical activity to allow for the assessment of the role of different physical activity parameters (e.g., intensity, duration). Accordingly, Study Three of this research program used accelerometers to measure sedentary time and physical activity levels, thereby allowing for the collection of precise data on movement patterns and how these relate to cortisol

and CRP levels in BCS. The inclusion of both sedentary time and physical activity as candidate predictors permitted the determination of whether an intervention targeting sedentary time and physical activity could be more effective one or the other with regards to promoting optimal physiological outcomes in BCS.

Candidate Physical Predictors of Cortisol and CRP Levels.

Body mass index. Studies assessing the association between cortisol levels and body mass index have yielded mixed results. Some studies found a negative correlation between body mass index and cortisol levels in adults without a history of cancer (Champaneri et al., 2012; Ward et al., 2003), whereas others have found either a positive association (Manenschijn et al., 2011; Stalder et al., 2012) or no association (Odeniyi et al., 2015; Roelfsema et al., 2017). Some researchers have demonstrated that elevated cortisol levels were indeed linked to both highest and lowest levels of body mass index, thereby suggesting that the relationship between cortisol and body mass index is U-shaped (Kumari et al., 2010; Schorr et al., 2015). As for CRP levels, higher body mass index has been consistently associated with higher levels of circulating CRP, implying systemic inflammation in obese individuals (Kao et al., 2009; Piva et al., 2013; Timpson et al., 2011). Studies that have investigated these relationships in BCS specifically found that a body mass index categorized as obese or overweight was associated with flattened cortisol patterns and increased CRP levels (Babaei et al., 2015; Hsiao et al., 2017; Pierce, Neuhouser, et al., 2009; Sabiston et al., 2018). Extending past research, Study Three of this research program assessed the predictive role of body mass index on cortisol and CRP levels over time and determined whether a healthy body mass index after BC treatment could act as a protective agent against the long-term cortisol and CRP dysregulation experienced by BCS.

Candidate Psychological Predictors of Cortisol and CRP Levels.

Depressive symptoms. Several studies have demonstrated that atypically high cortisol levels increase vulnerability to depression and that cortisol levels are significantly increased in individuals with depressive symptoms (Knorr et al., 2010; Penninx et al., 2013; Stetler & Miller, 2011). Indeed, in the general population, it has been suggested that 40 to 60% of individuals experiencing depressive symptoms also exhibit dysregulation in their cortisol concentration patterns (Booij et al., 2015; Keller et al., 2017). Similarly, BCS with a high level of depressive symptoms have also been found to show more abnormality in their cortisol concentration patterns than those with no/low depressive symptoms (Abercrombie et al., 2004; Giese-Davis et al., 2004; Spiegel & Giese-Davis, 2003). Depressive symptoms have been linked to inflammation (Howren et al., 2009; Khandaker et al., 2014; Valkanova et al., 2013). Indeed, higher CRP levels have been repeatedly associated with the development of depressive symptoms in the general population (Köhler-Forsberg et al., 2017; Wium-Andersen et al., 2013). Yet, the few studies investigating the link between CRP levels and depressive symptoms in cancer survivors have yield mixed findings whereby some have found positive associations (Archer et al., 2012; McFarland et al., 2018; Pertl et al., 2013) and other did not find any (Bower et al., 2011; Laird et al., 2011; Orre et al., 2011). It has been suggested that this inconsistency in results might be partly explained by the timing of CRP levels assays (e.g., during treatment vs. after treatment completion) or other factors such as fatigue and perceived stress (Balkwill & Coussens, 2004; Bower et al., 2011; Pertl et al., 2013; Soygur et al., 2007). Given that between 9% to 66% of BCS report experiencing depressive symptoms at some point during their survivorship trajectory (Badger et al., 2004; Maass et al., 2015), the inclusion of depressive symptoms as candidate predictor in the Study Three of this research program was warranted in order to further investigate its association with cortisol and CRP levels in BCS specifically.

Perceived stress. A cancer experience poses numerous social, physical, and psychological challenges that often lead to a significant level of perceived stress by survivors. Even after treatment completion, survivors continue to experience an important level of stress linked to lasting effects of treatment, going back to work, and expectations to return to previous roles and responsibilities (Allen et al., 2008; Bower et al., 2007; Hauken et al., 2013). In the short-term, an elevated level of stress generally leads to increases in cortisol levels (Kirschbaum & Hellhammer, 2000; Sladek et al., 2016; Walvekar et al., 2015). However, when stress is enduring and becomes chronic (like it is the case for BCS), it can result in cortisol levels below normal levels (Fries et al., 2005; Hannibal & Bishop, 2014; Miller et al., 2007). Consistent with these ideas, both elevated and blunted cortisol levels have been reported in BCS (Abercrombie et al., 2004; Bower et al., 2005; Couture-Lalande et al., 2014). Studies have suggested that the prolonged elevated stress levels experienced by BCS during treatment may dampen their stress response system, making some women less responsive over time (Kirschbaum & Hellhammer, 2000; McEwen, 1998). With regards to CRP, higher levels of perceived stress has been repeatedly associated with higher levels of CRP, both in the general population and in cancer survivors (Gouin et al., 2012; Slavish et al., 2015; Villasenor et al., 2014; Wiley et al., 2017). The presence of cancer cells inducing inflammation as well as the chronic stress associated with an experience of cancer may explain observed elevated CRP levels in BCS (Asegaonkar et al., 2015; Seruga et al., 2008). Most studies investigating the associations between perceived stress and cortisol and/or CRP levels in cancer survivors do not distinguish between general perceived stress and perceived stress directly related to one's health and cancer specifically. The chronicity of the stress experienced by BCS after treatment completion can also be explained in part by the cancer-related worries (such as fear of cancer recurrence) that persist well beyond the end of treatment (Deimling et al., 2006; Koch et al., 2013). Assessing both general and context specific stress allows to gain more insight about whether sources of stress and its content (i.e.,

whether stress has the same effect, regardless of the reasons for and sources of it) play a role in these relationships. Accordingly, Study Three of this research program included both perceived general stress and health- and cancer-related stress as two distinct candidate predictors of cortisol and CRP levels in BCS.

Thesis Objectives and Hypotheses

The overarching purposes of the research program were: (1) to expand knowledge on the long-term physiological impact of cancer among BCS by examining four key biomarkers, that is, cortisol, sAA, SIgA, and CRP, and (2) to identify predictors of those enduring physiological dysregulation. Survivorship quality, which implies good health, is the most central outcome of BC and yet, it is one of the least studied and understood aspects of the disease (Parry, 2008). While many researchers and scientists focus on the major challenge of finding a cure for cancer, it is equally important to understand the lasting and enduring challenges faced by cancer survivors and identify variables that could be targeted to reach optimal health outcomes. To this end, in the context of this research program, three inter-related studies were completed.

Chapter Two includes Study One, the findings which have been published in *Contemporary Oncology* (2018). Study One was a quasi-experimental study aimed at examining both the diurnal and reactive concentration profiles of SIgA in BCS (n = 22) and to compare these to women with no history of BC (n = 26). A secondary purpose of the study was to further investigate how SIgA concentration patterns relate and compare to the concentration patterns of cortisol and sAA in the same individuals. Given the well-documented effect of chronic stress on several human biological systems including immune systems, it was expected to find SIgA concentration pattern abnormalities in BCS.

Chapter Three includes Study Two, the findings which have been published in *Complementary Therapies in Medicine* (2018) and presented at the *Canadian Society for Psychomotor Learning and*

Sport Psychology (SCAPPS) Conference (2018). Study Two was a quasi-experimental design that aimed to determine whether physical activity could mitigate the negative physiological effects of a cancer experience in BCS (n = 25), as indexed by their cortisol concentration patterns. Based on the abundance of research linking health benefits and physical activity in cancer survivors (Friedenreich et al., 2020; Irwin et al., 2017), it was hypothesized that BCS who reported engaging in physical activity more frequently would exhibit significantly less abnormalities in their cortisol concentration patterns than those who reported engaging in physical activity less frequently or not at all.

Chapter Four includes Study Three, which partial results have been presented at the *Applied Research for Cancer Control Conference* (2019) and full findings have been published in *Brain, Behavior, & Immunity – Health* (2021). Study Three was a longitudinal cohort study that aimed to assess the predictive value of several behavioural, physical, and psychological variables on the physiological effects of a BC experience, as indexed by cortisol (n = 192) and CRP (n = 168) levels over the first 1.5 year post-treatment. Considering the aforementioned complex nature of the association between chronic stress and cortisol, no directional hypothesis was put forward for cortisol levels but a downward quadratic trend was hypothesized for CRP levels. It was also hypothesized that higher sedentary time and body mass index, lower physical activity, and greater depressive symptoms and stress would predict higher CRP levels in BCS, both at the inter- and intra-individual levels. As for cortisol levels, although significant associations with sedentary time, physical activity, body mass index, depression symptoms, and general and health- and cancer-related stress were expected, no directional hypothesis was put forward given the different plausible associations between chronic stress and cortisol levels.

The final chapter, Chapter Five, summarizes the main findings of the three studies of this research program and contrasts them with findings in the extended literature. The major contributions of each study are discussed along with the main limitations of this research program.

CHAPTER TWO

Study One, Article One

Salivary secretory immunoglobulin A reactivity: A comparison to cortisol and alpha-amylase patterns in the same breast cancer survivors

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Abstract

One way to examine the extent to which the stress associated with a breast cancer experience (BC) impacts stress-related physiological mechanisms is to study the secretion patterns of associated biomarkers. Unlike cortisol and α-amylase (sAA), biomarkers of immune functioning such as secretory immunoglobulin A (SIgA) have rarely been examined in BC survivors. This study had two principal aims: the first was to evaluate the basal secretion profiles of SIgA as well as its response to an acute stressor as a marker of immune health in BC survivors and women with no history of BC, and the second was to determine how SIgA stress-related patterns compare to published cortisol and sAA patterns in the same women. Overall, the findings indicate that BC survivors exhibit a blunted cortisol reaction to an acute stressor, a generally elevated diurnal sAA concentration pattern, and normal SIgA profiles, compared to women with no history of cancer. This study serves as a foundation for future research to elucidate the relationships between BC experience variables, stress biomarkers, and health outcomes in BC survivors.

Introduction

Cancer is the cause of nearly 30% of all deaths in Canada and is quickly becoming a worldwide pandemic [1]. In men, prostate cancer is the leading cancer site, while in women, it is breast cancer (BC), with a lifetime risk of developing it estimated to be one in nine women [1]. The mortality rates of BC in Canada are now the lowest since 1950, with a five-year survival rate of 88% [1]. Continued advances in BC detection and treatment strategies along with the aging and growth of the population have resulted in an ever-increasing number of survivors.

Despite general agreement that a cancer diagnosis generates significant stress due to difficult treatment procedures, drastic changes in daily routine, and family and work concerns [2], what is less obvious is that the cancer experience continues well beyond the end of treatment. In fact, based on several cross-sectional and longitudinal studies, the symptom burden linked to cancer survivorship can persist for more than 10 years following treatment [3]. Unrelenting symptoms can include fatigue, pain, distress, and cognitive impairment [4].

It has long been known that chronic stress can severely alter human biological systems in many ways [5]. The stress associated with the cancer trajectory – from diagnosis to post-treatment – has been shown to suppress or dysregulate innate and adaptive physiological responses [6]. One way to examine the extent to which stress impacts stress-related physiological mechanisms in BC survivors is to evaluate the secretion patterns of associated biomarkers. Several biomarkers are considered to be very reliable and sensitive indicators of an individual's biological response (biochemical, physiological, cellular, or behavioural responses) to different types of stressors [7].

Salivary Cortisol as a Stress Biomarker

The cancer experience has been shown to cause a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, a system that tightly regulates stress responses [8]. Studies have found associations

between HPA dysregulation and mortality and disease severity in BC patients [9]. Cortisol, which is a steroid hormone secreted in response to stress, is often used to assess the activity of the HPA system and has received extensive attention in research on stress physiology. Situations characterised as unpredictable, uncontrollable, and threatening (such as a BC diagnosis) elicit increases in cortisol concentrations [10].

A diurnal cortisol pattern that peaks at awakening and gradually decreases throughout the day is the typical response of a functional HPA axis [11]. Flatter diurnal cortisol patterns, or concentration patterns that remain fairly unchanged throughout the day, occur significantly more often in BC survivors than in healthy individuals [8, 12]. During acute stress situations, cortisol secretion is temporarily increased and concentration levels usually return to normal within one or two hours after stress cessation [13]. While cortisol is essential for regulating bodily functions and responding to environmental challenges [10], sustained high cortisol levels can have damaging effects on the human body and have been associated with depression [14], obesity [15], diabetes [16], and social isolation [17]. Low levels of cortisol, on the other hand, have been linked to pain, fatigue, high stress sensitivity [18], and stress-related disorders such as post-traumatic stress disorder and fibromyalgia syndrome [19].

In our laboratory, we have examined the salivary cortisol diurnal rhythmicity and reactivity in long-term BC survivors compared to women with no history of BC [20]. Although we found no group differences in their diurnal cortisol secretion, the groups showed significant distinctive patterns in response to an acute stressor: the concentrations of cortisol in women with no history of cancer peaked at 10–20 minutes following the stressor whereas the levels in BC survivors remained fairly blunted over the same time course. While our study revealed that both groups appraised psychological stress in an almost identical fashion, survivors demonstrated a considerably diminished physiological response to the acute stressor. Similar findings have also been reported from other laboratories [8, 21, 22].

Salivary α-amylase as a Stress Biomarker

More recently, investigators have been studying salivary α-amylase (sAA), an indicator of sympathetic nervous system (SNS) activity, for its potential as a stress biomarker. To date, a number of studies have suggested that sAA responds to both physical and psychological stress [23, 24]. Its concentrations have been found to be directly related to the subjective stress levels of BC survivors [25]. Distinctly different from that of cortisol, typical sAA concentrations are reduced significantly within 60 minutes after awakening and gradually increase throughout the day, reaching their peak in the late afternoon or evening [24, 26].

Salivary α-amylase levels have also been measured in response to different acute stressors such as writing a test [27] and skydiving [28]. Both studies revealed significant increases in sAA levels the days preceding the expected stressor. Other studies reported that sAA activity was significantly higher in samples collected after subjects were exposed to an acute stressor compared to samples collected at any other time [29]. Furthermore, the total sAA released after exposure to an acute stress has been found to be positively correlated with heart rate, pain intensity, and the total amount of cortisol released [30, 31]. This suggests the coordination between the HPA system and the SNS in their response to acute stress.

Based upon the results of our previous study and findings from other groups of researchers, we reasoned that HPA regulation abnormalities in BC survivors, as interpreted from cortisol patterns, would probably be accompanied by SNS dysregulation [32]. Consequently, we explored the circadian and reactive profiles of sAA in the same groups of participants who showed blunted cortisol patterns in response to acute stress [20]. We found that, while BC survivors had significantly higher diurnal and reactive sAA patterns than women with no history of cancer, the overall pattern was the same in both groups. In other words, the sAA difference in acute stress responses was not related to a specific acute stress response but was instead reflected by a heightened basal level of concentration.

Salivary secretory Immunoglobulin A as a Stress and Immune Biomarker

One of the most important lines of defence against human pathogens is the mucosal immune system [33]. The main immunoglobulin, secretory A (SIgA), is the predominant effector of that specific system and has often been used as a marker of immune competence [33, 34]. Immunoglobulins are antibodies secreted by plasma cells that combine with antigens and direct an immune response against them [35]. Secretory immunoglobulin A is a component of the adaptive immune system and works alongside other innate mucosal defence factors such as α-amylase, lactoferrin, and lysozyme in order to fight surfacing pathogens [33, 36, 37]. Similar to cortisol, SIgA concentration peaks in the morning and then progressively declines to its nadir by the evening [38]. Several other studies have replicated those findings [31, 39, 40].

Components of saliva, including SIgA, are crucial indicators of health. Low levels of salivary SIgA can signal bacterial and viral infections in an individual [41–43]. For instance, patients diagnosed with Acquired Immune Deficiency Syndrome are found to have a significantly lower level of salivary SIgA, resulting in very frequent oral infections [44]. Moreover, an earlier study by Brown *et al.* [45] found that cancer recurrence was associated with elevated SIgA levels, which may indicate a specific secretory response to tumour. They suggested that SIgA could potentially be used to distinguish patients who are at risk of recurrence.

Chronic stress and secretory immunoglobulin A

The relationship between stress, immunity, and environmental influences has long been of interest to researchers who investigate the effects of stress on health [43]. There is widespread agreement that psychological stress increases susceptibility to disease [46–48]. The duration of the stressor seems to play an important role in the immune response to psychological stress [49]. Several studies have reported that chronic or long-term stress has a suppressive effect on immune functioning

and SIgA [6, 50]. For instance, a diminished SIgA level has been found in continually neglected toddlers [51], soldiers [52], and nurses enduring chronic work stress [53]. While this suggests that a long-term cancer experience might suppress immune function, most research on stress responses in BC survivors has been focused on more traditional stress-related biomarkers such as cortisol and sAA.

Acute stress and secretory immunoglobulin A

Very few studies have explored the effects of acute stress on immune system responses. However, the few that have claim an association between acute stress and an increase in immune functioning and SIgA levels [6, 36]. This activation in response to stress highlights the immune system's fundamental ability to protect the body from disease [49]. Elevated SIgA levels were found in soccer coaches during a crucial game [54] and in police officers during a grave accident [55]. Laboratory-induced stress, such as speech and arithmetic tasks, also supports this claim [37, 56].

The Present Study

To our knowledge, no study to date has compared the profiles of several stress biomarkers in the same cancer survivors. Because cortisol and sAA are secreted by different hormonal systems and have unique diurnal secretion patterns [26, 57], the measurement of both biomarkers in tandem following stress induction provides a more comprehensive understanding of different aspects of stress regulation and its mechanisms. Moreover, the significant gap in the literature on SIgA diurnal patterns of concentrations and its response to an acute stressor highlights the need for more research on this under-explored biomarker. The examination of SIgA concentrations in BC survivors not only gives us more information on the activity of their stress systems but also provides a mean of examining their immune function.

To that end, the aim of this current study was to investigate the relationship between SIgA reactivity and the stress biomarkers, cortisol and sAA, in the same individuals; the latter findings have

been published [20, 32]. The first objective was to examine the basal secretion profiles of SIgA as well as its response to an acute stressor in BC survivors, and to compare these to women with no history of BC. The second objective was to determine the association between SIgA diurnal and reactive concentration patterns in BC survivors and how these relate to their cortisol and sAA patterns. We hypothesised the following: First, that the stress associated with a BC experience would result in abnormalities in SIgA diurnal concentration patterns. Second, based on previous literature highlighting the link between the HPA axis and immunocompetence [38, 58], we further hypothesised that BC survivors and women with no history of cancer would exhibit differences in their SIgA response to the Trier Social Stress Test (TSST), a widely-used stress-inducing laboratory protocol, (see Methods section for further description). Third, we also examined whether medical factors related to BC such as cancer stage, time since diagnosis, and treatment regimen had any impact on the SIgA response observed in survivors.

Material and Methods

Participants

Via printed advertisements and cancer support groups, a total of 48 women were recruited: 22 women BC survivors and 26 women with no history of cancer. Table 1 characterizes the participants by age, ethnicity, level of education, and family income. The medical characteristics of the BC survivors are shown in Table 2. Please note that Table 1 and Table 2 are also reported in [20] and in [32], as they depict the same group of individuals.

The eligibility inclusion criteria for BC survivors included: a) a diagnosis of BC at least one year prior, b) completion/cessation of all cancer-related treatments at least six months earlier, and c) the ability to provide informed consent. Individuals with: a) history of other cancers (except non-invasive skin cancer and cervical cancer), b) substance abuse problems, or c) any major disabling conditions interfering with their quality of life (for example, psychiatric disorders) were excluded from the present

study. Women who were breast feeding, pregnant, taking any medication that could alter hormonal secretion (e.g. hydrocortisone, hypnotics, benzodiazepines), or had bleeding gums were also excluded. The women in the control arm had to meet the following criteria: a) completion of routine mammography screening with negative results, b) no history of cancer, as well as the exclusion criteria listed in c) above.

Prior to inclusion in the study, written informed consent was obtained from all participants. Participants received $50 as travel compensation and a chance to win a $250 prize. The study was approved by the University of Ottawa Ethics Review Board and was conducted at Dr. Bielajew's Laboratory at the University of Ottawa.

Measures of Stress

Salivary secretory immunoglobulin A

Extraction of SIgA from saliva was carried out using a commercially available highly-sensitive enzyme-linked immunosorbent assay (ELISA). The assay kits and the protocol were obtained from Salimetrics, State College, PA, USA [59].

Trier Social Stress Test

The Trier Social Stress Test (TSST) has become the gold standard for evaluating acute stress response in the laboratory setting [60, 61]. Its effects on biomarker concentration patterns, including cortisol, sAA, and SIgA, have been shown in past research [56, 62, 63]. The TSST protocol we used had two major components: 1) a mock interview during which participants had to give a five-minute free speech to a panel of three confederate evaluators acting as a hiring committee, and 2) a five-minute arithmetic task which required that the participants count down from 1022 by increments of 13 as quickly as possible [64].

Visual Analog Scale

The Visual Analog Scale (VAS) is a bipolar line quantifying a specific characteristic across a continuum [65]. In this context, it was used to measure participants' subjective stress response before, during, and after the TSST. Participants were asked to mark a spot on the line that indicated their subjective stress appraisal. Based on the statement "I feel stressed", participants estimated their perceived stress between 0 (not at all) to 100 (very much). Their score was based on the distance between the left end of the line and the appraisal mark.

Questionnaires

Participants were asked to complete a series of questionnaires in order to assess their socio-demographic characteristics and stress perception. The package included: a) socio-demographic questionnaire requesting information about participants' general life history, health history (for BC survivors, this included questions related to their BC history), and life habits; b) the Daily Stress Inventory, a 58-item questionnaire inquiring about recent (past 24 h) stressful events and their intensity [66]; c) the Perceived Stress Scale of 14 items measuring subjective appraisals of stressful situations in the past month [67]; and d) the Life Experiences Survey, a questionnaire used to record the frequency and impact of life events, both positive and negative, that occurred in the past year [68].

Procedure

Eligible participants were asked to attend two laboratory visits at the University of [location withheld for blinded review]. In order to promote neutrality in the results and also to control for potential confounding variables such as practice and expectation effects, participants were only told that the aim of the study was to examine the effect of stress. The other details of the experiment remained unknown to them.

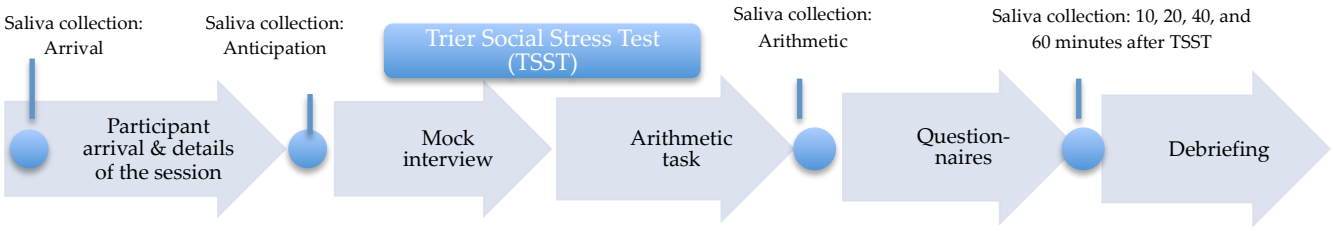
The first meeting, which lasted about 30 minutes, served to obtain informed consent and to teach participants the correct method of collecting saliva samples at home for the purpose of the diurnal

analyses. They were asked to: 1) rinse their mouth 10 minutes before collection (as a way to avoid sample dilution), 2) place the salivette directly under their tongue for a full three minutes, 3) avoid touching the salivette with their fingers, and 4) store the salivettes in the supplied containers in the refrigerator until delivery to the lab. We also asked participants to avoid smoking and drinking alcohol for 24 h before sample collection and ingesting caffeine products and exercising for an hour prior to collection. Participants were then given a home kit of pre-labelled salivettes. They were required to collect a total of five saliva samples at home on each of two consecutive days at the following times: upon waking, 30 min after waking, at 1200 h, 1600 h, and 2100 h. In the event that participants did not have access to a refrigerator to store their salivettes until delivery to the laboratory, we provided them with an insulated lunch bag and ice packs.

The second laboratory visit was the stress induction portion of the study (the TSST), which lasted about two hours; it was scheduled within seven days following the first visit. In the laboratory, seven saliva samples were collected. Figure 1 is a schematic representation of the procedure of the laboratory session. The first one, labelled "arrival", was retrieved as soon as the participant entered the laboratory. They were then taken into the testing room where a mock panel of committee members explained the TSST instructions. The first task of the TSST involved the preparation and delivery of a five-minute speech about the reasons why they believe they are the most suitable candidate for the mock job position. The second task, the arithmetic task, followed immediately after. The saliva sample collected between the speech preparation and the speech delivery was labelled "anticipation" and the one upon completion of the arithmetic task, "arithmetic". At each time-point that a saliva sample was collected, participants had to rate their subjective stress level on the VAS. Upon completion of the TSST, participants were asked to relax in a room for one hour and complete a series of questionnaires measuring their perceived stress, anxiety, and fear of recurrence. Four additional saliva samples were

collected at 10, 20, 40, and 60 minutes during this phase. Finally, participants were debriefed and the true aim of the study was explained to them. Each saliva sample was divided into three aliquots immediately after collection and then transferred to separate Eppendorf tubes, in order to avoid multiple freezing and thawing cycles. To foster optimal stability of the samples, they were stored at –80°C until processed [69]. Cortisol was analysed first, followed by sAA, and finally SIgA.

Figure 1. Schematic representation of the laboratory session procedure.



Results

Participants Characteristics

Participant demographics and characteristics are depicted in Table 1 (also depicted in [20] and [32]). In short, the study had a total of 48 participants, which included 22 BC survivors and 26 women with no history of BC. Both groups had an average age in the late 50s (t-test group difference $p = 0.488$; note that BC survivors tend to be older women and thus the age range of our sample would be truncated by definition), a similar number of women with postmenopausal status (χ^2 group difference $p = 0.147$), and about 90% of each group self-identified as White. To our knowledge, aside from a few cases of hypertension, diabetes, and osteoarthritis, no serious or untreated medical conditions were present in participants. The medical characteristics of the BC survivors are shown in Table 2 (also see [20] and [32]). Their mean age at diagnosis was 54 ±9 years (SD), and they were all recruited about five years after their diagnosis. The majority of the participants identified with stage 1 BC. Almost half of the

participants underwent a lumpectomy procedure. All participants went through chemotherapy, radiation, hormone therapy, and/ or surgery; most received a combination of these treatments. Two participants suffered a recurrence of BC and were therefore excluded from the study.

Table 1. Demographic characteristics of participants

	Participants	
Demographic Characteristics	**Breast Cancer Survivor (*N*=22)**	**Healthy women (*N*=26)**
Age (years): Mean [SD] (Range)	58.9 [10.1] (39-81)	57.4 [11] (41-73)
	No. of Participants (%)	**No. of Participants (%)**
Ethnicity		
White	20 (90.9)	23 (88.5)
Black	-	1 (3.8)
Asian	-	2 (7.7)
First Nations	2 (9.1)	-
Highest level of education (%)		
High school	6 (27.3)	9 (34.6)
College	4 (18.2)	4 (15.4)
Bachelor's degree	11 (50.0)	7 (26.9)
Graduate degree	1 (4.5)	6 (23.0)
Family income (CDN) *		
Under $40,000	3 (15)	5 (20.8)
$40,000 to $79,999	10 (50)	10 (41.7)
$80,000 to $119,999	5 (25)	5 (20.8)
$120,000 and over	2 (10)	4 (16.7)

*Breast cancer survivor group (*N*=20); Control group (*N*=24)

Table 2. Medical characteristics of the breast cancer survivors.

Medical Characteristics	**Breast cancer survivors (*N*=22)**
Mean age (years) of diagnosis (SD)	54.1 (8.7)
Mean time (years) since diagnosis (SD)	4.6 (3)
Stage of breast cancer	**No. of Participants (%)**
0	4 (18.2)
1	10 (45.5)
2	5 (22.7)
3	3 (13.6)
Type of surgery	
Unilateral mastectomy	6 (27.3)
Bilateral mastectomy	7 (31.8)
Lumpectomy	9 (40.9)
Treatment *	
Chemotherapy	10 (45.5)
Hormone therapy	14 (63.6)
Radiation therapy	14 (63.6)
Breast cancer recurrence	
None	20 (83.3)
One recurrence	1 (4.2)
Two recurrence	1 (4.2)

* Almost all participants received a combination of treatments

Data Analysis

We eliminated from our data analysis participants who had more than two missing saliva samples (out of 10) for their diurnal data and more than three missing samples (out of seven) for their reactive data. Based on those criteria, four participants associated with the diurnal data and 10 associated with the reactive data had to be excluded. Diurnal analyses were therefore performed on 44 participants, and reactive analyses were performed on 38 participants. The single missing value was replaced using the EM algorithm in SPSS. Standard data and cleaning procedures were applied to the data before analysis including tests of normality and skewness; no transformations were required. All analyses were conducted using SPSS (v23).

A series of mixed-design analysis of variance (ANOVA) were conducted to determine group differences in SIgA diurnal and reactive concentrations patterns. Bonferroni corrections were used to control for multiple comparisons. Violation of the assumption of sphericity, as indicated by a significant Mauchly's Test of Sphericity value, was offset by the Huynh–Feldt correction procedure, which adjusts the degrees of freedom [70].

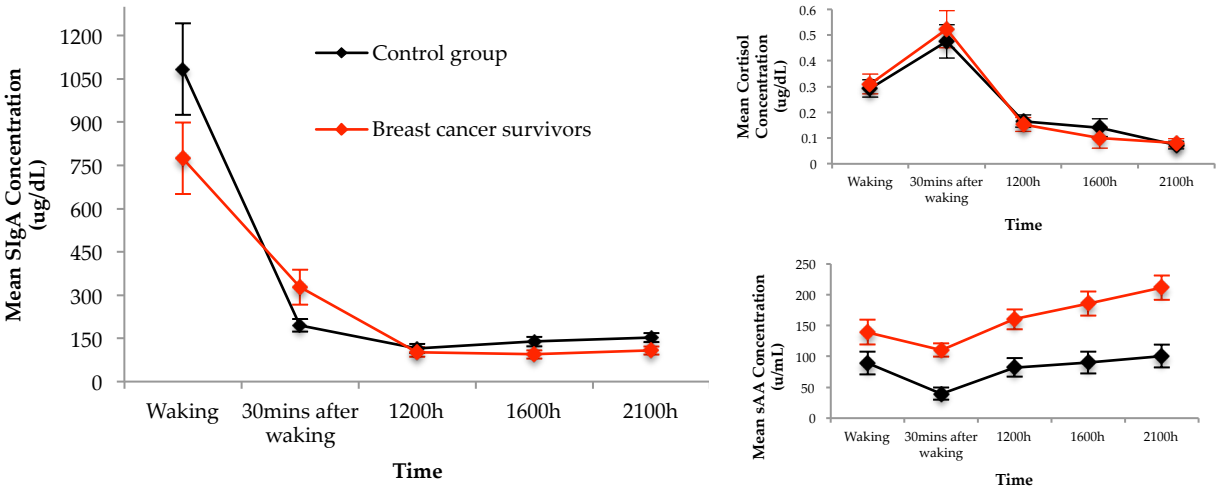
Diurnal Secretory Immunoglobulin A

A 2 × 5 mixed design ANOVA was used to examine differences in mean SIgA concentrations collected at five time points over two consecutive days. The analyses were performed on the two-day average of the concentrations. The between-subject factor was group (BC survivors or women with no history of BC) and the within-subject factor was time (waking, 30 min after waking, at 1200 h, 1600 h, and 2100 h).

Figure 2A shows the plot if the diurnal SIgA concentrations. The inset graphs on the upper right side are the cortisol (Fig. 2B) and the sAA (Fig. 2C) data in the same subjects for comparison purposes [20, 32]. Overall, both groups demonstrated similar diurnal SIgA patterns, with the highest

concentration upon waking followed by a decrease to its nadir by 2100 h. The statistical results revealed a significant main effect of time ($F(1.15, 48.43) = 60.40$, $p < 0.001$, $\eta^2 = 0.59$), no group effect ($F(1, 42) = 1.22$, $p = 0.275$, $\eta^2 = 0.03$), and a marginally significant group x time interaction ($F(1.15, 48.43) = 3.71$, $p = 0.054$, $\eta^2 = 0.08$). Overall, BC survivors showed consistently elevated sAA values (Fig. 2C), but otherwise basal values of cortisol and SIgA were comparable to those of women with no history of cancer.

Figure 2. Mean diurnal SIgA concentrations over two consecutive days. Inset graphs include published diurnal cortisol and sAA for the same sample (Couture-Lalande et al., 2014; Wan et al., 2016). Error bars represent standard error of the mean.

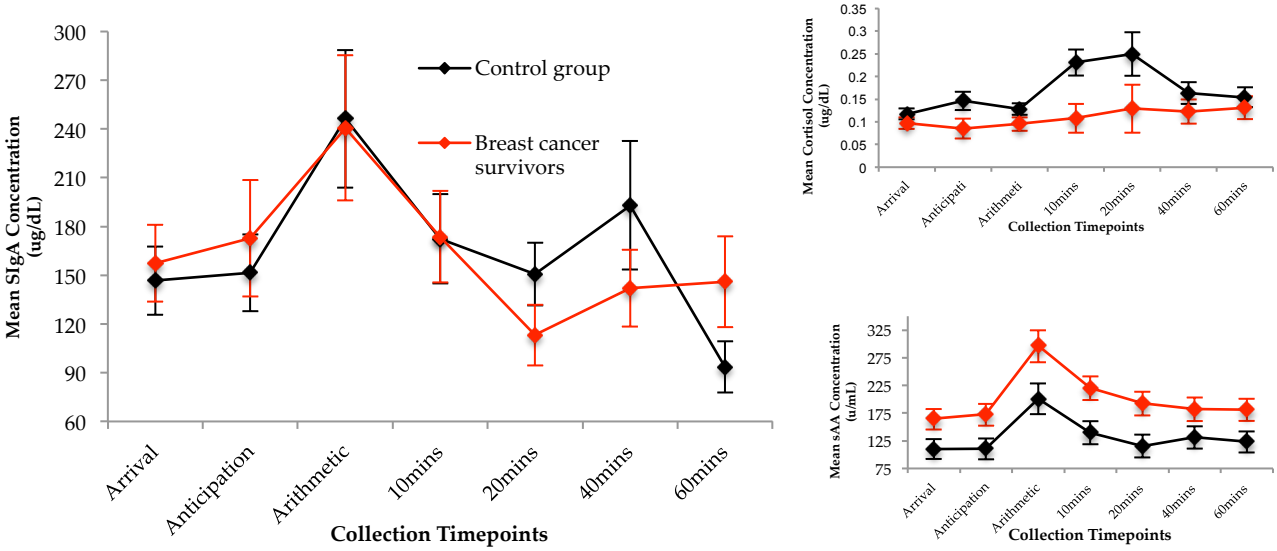


Secretory immunoglobulin A in Response to Acute Stress

Figure 3A illustrates the profile of SIgA concentration patterns in response to an acute stressor, i.e. the TSST. The inset graphs represent the cortisol (Fig. 3B) and sAA (Fig. 3C) data for the same subjects for comparison purposes [20, 32]. A 2 × 7 mixed-design ANOVA was used to examine group and time differences in mean SIgA concentrations. The between-subject factor was group (BC survivors or healthy women), and the within-subject factor was time (arrival, anticipation, arithmetic, and 10 min, 20 min, 40 min, and 60 min after the TSST).

Both groups displayed a similar biphasic pattern with the first SIgA increase at arithmetic and the second increase at 40 minutes after the completion of the TSST. The analysis demonstrated a significant main effect of time ($F = 8.60$, $p < 0.001$, $\eta^2 = 0.193$) and no group ($F = 0.001$, p $p = 0.971$, $\eta^2 = 0.000$) or group x time interaction ($F = 1.65$, $p = 0.175$, $\eta^2 = 0.044$). Across biomarkers, significant interactions were only found in cortisol concentrations in response to an acute stressor (Fig. 3B); the group differences observed in the sAA data (Fig. 3C) match their baseline rates (Fig. 2C) and therefore are not related to the stress exposure.

Figure 3. Mean acute SIgA concentrations. Inset graphs include published diurnal cortisol and sAA for the same sample (Couture-Lalande et al., 2014; Wan et al., 2016). Error bars represent standard error of the mean.



Secretory Immunoglobulin A Reactivity Profiles and Medical Characteristics

Additional correlational analyses were performed in order to evaluate the relationship between BC characteristics such as the number of years since diagnosis, cancer stage, and type of treatment (chemotherapy or no chemotherapy), and the SIgA profile observed during the TSST. None of these analyses indicated any group differences based on medical variables. Furthermore, both groups showed the same degree of stress, as indicated by their VAS ratings, throughout the TSST [20].

Discussion

Secretory Immunoglobulin A Findings

The goal of the current study was to complement the findings on the concentration patterns of cortisol and sAA in BC survivors by exploring the diurnal and reactive profiles of an immune biomarker, i.e. SIgA, in the same participants. We reasoned that the HPA and SNS dysregulation found in BC survivors, as interpreted from cortisol and sAA patterns, respectively, might also be accompanied by abnormal SIgA concentrations, a biomarker of immunocompetence. However, our data showed no evidence of uncharacteristic SIgA basal or reactive secretion patterns, suggesting a normal and well-functioning immunological SIgA system.

Several studies have suggested an association between cancer experience and immune impairment [71–73], hence the reason why we selected SIgA as the candidate biomarker to evaluate immunocompetence in BC survivors. To our knowledge, only one study has measured salivary SIgA in women after the end of treatment for BC. Jensen *et al.* [73] surveyed a group of women diagnosed with BC prior to treatment, during treatment, and six and 12 months after treatment. Their results indicated a significant decrease in SIgA in response to and following chemotherapy; the levels had normalised one year after treatment. They suggested that BC treatment depressed the SIgA producing plasma cells or inhibited the immunoglobulin transport mechanism in the salivary gland cells. As far as we know, the very few other studies that have used SIgA as a biomarker of immune function in a cancer population have investigated SIgA levels in relation to disease progression and/or prognosis and have not looked at BC specifically [33, 74, 75].

Using biomarkers other than SIgA, other studies have also reported immune deficiency in cancer patients. For example, Campbell *et al.* [76] studied patients undergoing definitive surgery for BC and found a clear deficit in cytokine production, suggesting a general immune dysfunction in BC patients. They also noted that larger tumours were associated with more depressed levels of T cell responses.

A recent study by Verma *et al.* [71] found that antibody levels never returned to their pre-cancer levels and that all types of lymphocytes significantly dropped after BC treatment. Similarly, Standish *et al.* [72] reported an important reduction in the numbers and functions of cells from both the adaptive and innate immune system following cancer treatment. Although these studies represent a significant contribution to the literature of cancer and immune impairment, none of them examined immunological dysfunction in long-term survivors of cancer (more than one year after treatment).

There are a few potential explanations for the fact that the SIgA concentration pattern of our BC survivor group did not differ from that of women with no history of cancer. First, low levels of SIgA are typically associated with the occurrence of different clinical diseases and infections [77–79]. Despite being survivors of BC, women in our study were perfectly healthy; they did not suffer from any post-cancer medical conditions (at least at the time of the saliva collection). Second, this similarity in the SIgA concentration patterns of our two groups may be due to recovery function of the immune system in BC survivors [80]. Studies have shown that cancer patients typically exhibit functional immune response abnormalities up to 12 months after treatment, with the percentage of patients with entirely intact immune responses increasing gradually with time [73, 81]. Because the saliva samples of our participants were collected on average 4.6 years after diagnosis, it is reasonable that the negative impact of the cancer experience on individuals' immunity may have normalised over time. Third, SIgA only makes up for a small proportion of all salivary immune ingredients and antibacterial proteins, including immunoglobulin and non-immunoglobulin [33]. Although salivary SIgA is defined as the primary means of assessing the body's "first line of defence" and is the most prolific antibody in saliva [33, 82], perhaps the measurement of other immunoglobulins such as immunoglobulin G or M or non-immunoglobulins such as lysozyme would have revealed more about the immune status of our participants.

Cortisol, Alpha-Amylase, and Secretory Immunoglobulin A Findings

Taken together, the SIgA findings reported here, complemented by the cortisol and sAA findings in the same individuals [20, 32] suggest three main conclusions. Breast cancer survivors, roughly five years after diagnosis: 1) exhibit a dysregulated HPA system, as indexed by a blunted cortisol pattern when confronted with an acute stressor, but otherwise had normal basal rhythms of the hormone; 2) displayed a dysregulated SNS on their elevated diurnal sAA concentration patterns, which was sustained in the face of an acute stressor; and 3) did not show mucosal immunity dysregulation, as demonstrated by their normal basal and reactive SIgA profiles.

Being diagnosed with cancer involves multiple complex and repeated stressful events over the course of diagnosis, treatment, and survivorship trajectory [83]. Our observation of a disruption of biological systems might, at least in part, be the result of these repeated "hits" of excessive stress that accompany a BC diagnosis and its aftermath [84]. Since the stress systems play a central role in the coordination and regulation of multiple system responses such as behavioural, physiological, and metabolic responses [85, 86], it is not surprising that HPA axis and SNS abnormalities have been associated with several negative outcomes such as depression, diabetes, post-traumatic stress disorder, metabolic dysfunction, hypertension, anxiety disorders, and cardiovascular diseases [87–90]. McGirr *et al.* [91] even found a relationship between dysregulated HPA axis and SNS and higher risk for suicide. Gaining a better understanding of how these abnormalities in stress systems lead to increased risks for various medical conditions is therefore primordial for the prevention and protection of vulnerable populations such as BC survivors.

The biological dysregulations found in our studies clearly indicate that BC survivors could benefit from additional follow-up care and post-treatment surveillance. Medical practices promoting regular and consistent monitoring for the late effects of cancer by physicians should be implemented in

cancer care routine. The elaboration of health promotion and lifestyle intervention strategies aiming to optimise health after cancer should be a basic consideration and achieved based on the recommendations of the many studies that have identified factors associated with psychological and physical health in cancer survivors. For instance, interventions promoting social support, purpose in life, self-acceptance, and expressive activities have been shown to maximise survivors' health outcomes [92, 93]. Indeed, many studies have suggested that psychological interventions following cancer treatment reduce the stress associated with the cancer survivorship trajectory, decrease the risk of recurrence, and enhance positive coping, quality of life, and physiological responses, such as those studied in the current study [12, 94, 95]. It would therefore be beneficial to consider the incorporation of such services into standard medical care for cancer survivors.

With the number of cancer survivors climbing each year, efforts to better understand, monitor, and mitigate the physiological consequences of a cancer experience is critical. This study is the first to describe long-term trajectories of cancer-related stress in BC survivors by examining SIgA levels specifically and comparing them to cortisol and sAA levels in the same women. The present work allows us to further elucidate the physiological sequelae of a cancer experience on the human stress systems and has important clinical significance as it represents a step forward towards the development of specific guidelines and practical recommendations for optimal cancer survivorship care plan. Moreover, as some studies found that being a survivor of cancer may divert attention away from other health conditions, thereby leading to delayed healthcare [96], it is even more important to educate people and raise awareness in public health organisations about the adverse long-term effects of a cancer experience.

Limitations and Future Directions

First, the sample size in our study is small, albeit comparable to that observed in other published

reports of this nature [72, 75, 97]; these study protocols are quite demanding, making recruitment very challenging. Second, while we did compare our clinical results to that of a disease-free sample, it would have been useful to have had information on the baseline status of the biomarkers we examined in our studies. Third, it would be ideal to include the measurement of other immunoglobulin levels in order to allow for a broader assessment of BC survivors' immune functioning. Because of: a) SIgA under-investigation in the BC survivor population, b) its critical role in immune function, and c) its direct impact on many anti-inflammatory and immunological responses, its assessment appeared to be the most pertinent biomarker of stress and immunity to examination in this study, given our limited resources. Finally, the reliance on convenience sampling may undermine the ability to extend our findings to the BC survivor population as a whole.

This study prompts several future research directions and objectives. With all the notable evidence derived from cancer survivorship research on the long-term adverse effects of a cancer experience, it is essential now that cancer research not solely focus on curing the underlying disease but also simultaneously strive towards finding interventions with minimal toxicity but optimal effectiveness, in order to limit the undesirable post-treatment outcomes. Future studies should not only investigate biomarkers and their underlying mechanisms but should also explore ways and methods of reversing these biological dysfunctions caused by the cancer experience. Furthermore, because most of the cancer survivorship research to date has employed cross-sectional cohorts, longitudinal studies examining the trajectories of the physiological and biological consequences of the cancer experience over time are essential to evaluate decrements in survivor functioning. Finally, it is crucial for future cancer survivorship studies to consider including immune biomarkers such as SIgA more often in their design because components of the innate mucosal system are vital in the body's defence against pathogens.

Conclusions

There are still many gaps in the literature that need to be addressed in order to gain a better overall understanding of the consequences of a BC experience on an individual's stress-related physiological functioning. Our results indicate certain abnormalities in biological systems following a cancer experience and emphasise the need for continued research in this ever-growing cancer survivor population. They further suggest that our ongoing healthcare and support services be re-evaluated in order to ameliorate the late and long-term effects of a cancer experience. Since the population of cancer survivors continues to grow each year, cancer survivorship needs to be a research priority in order to keep up with their needs.

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CHAPTER THREE

Study Two, Article One

Aerobic physical activity and salivary cortisol levels among women with a history of breast cancer

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Abstract

Background: Physical activity (PA) helps reduce cancer-related symptoms and improves overall functioning for women with and without a history of breast cancer (BC). Few researchers have examined the associations between PA and physiological stress measures. The aim of this study was to determine whether aerobic PA was associated with diurnal and reactive cortisol patterns, and whether these associations differed for women with and without a history of BC.

Methods: Participants were 25 women with a history of BC and 23 women without a history of BC who self- reported aerobic PA frequency. To assess diurnal cortisol patterns, participants provided five saliva samples collected on two consecutive days at the following times: upon awakening, 30 min after waking, 12 PM, 4 PM, and 9 PM. To measure reactive cortisol patterns, participants provided seven saliva samples collected before, during, and after doing the Trier Social Stress Test.

Results: Cortisol patterns differed statistically based on women's cancer history, whereby women without a history of BC had significantly higher overall cortisol reactivity to an acute stressor, and a marginally significant (p=.05) cancer experience by aerobic PA interaction was observed when analyzing diurnal cortisol data.

Conclusions: Findings suggest that PA may not have the same effect on women with and without a history of BC.

Introduction

In recent decades, there has been a surge in the number of studies focusing on identifying the benefits of physical activity (PA) for women diagnosed with breast cancer (BC).[1–3] There is now robust evidence showing that PA can decrease cancer-related fatigue, improve overall physical functioning, and reduce the risk of cancer recurrence in this population.[4–11] There is also evidence showing that PA can improve mood and reduce stress, anxiety, and depression in women diagnosed with BC.[12–15] In light of this body of literature, PA is now recognized as being safe and beneficial for women with a history of BC, and thus should be widely promoted.[1,16–19] Notwithstanding the evidence that PA confers numerous health benefits for women diagnosed with BC, much of the evidence linking PA to psychological health benefits is based on data collected via questionnaires assessing psychological health outcomes. As a result, whereas the positive effect of PA on self- reported mood and stress are well established,[13,20,21] the effects of PA on physiological measures of stress are still unclear. Some investigators have started to explore the association between PA and biomarkers in people diagnosed with cancer.[22] Cortisol is one biomarker that plays an essential role in energy metabolism, information processing, and stress responsiveness. It is commonly used to assess the activity of the hypothalamic-pituitary-adrenal (HPA) axis, a system that tightly regulates the stress response.[23,24] In the single study that examined the effect of PA on cortisol secretion among women receiving treatment for BC (n = 20), no significant relationship between PA and cortisol was found other than a trend toward lower cortisol levels in the PA intervention group.[25] However, it is not possible to render a conclusion about the relationship between PA and cortisol in women who have completed treatment for BC based on this study.

The importance of studying whether PA can have a normalizing effect on the cortisol secretion patterns among women once treatment for BC has ended is highlighted by findings showing that these

women typically exhibit a flatter cortisol pattern in response to an acute stressor compared to women with no history of cancer.[26–28] An abnormal cortisol concentration pattern in response to acute stress situations can lead to various negative health consequences because cortisol is essential for regulating bodily functions and responding to environmental challenges.[23] Indeed, persistent low cortisol levels have been linked to pain, fatigue, high-stress sensitivity,[29] and increased vulnerability to stress-related bodily disorders.[30,31] Moreover, mortality, disease severity, and several other negative health outcomes such as obesity,[32] depression,[33] and diabetes[34] have been associated with general dysregulation of the HPA axis (i.e., atypical cortisol concentration patterns).[35,36]

As several studies have reported that abnormalities in the cortisol secretion patterns of women treated for BC[26–28,35,37–39] and given evidence of the benefits of PA on the overall health-related outcomes for women diagnosed with BC,[1,3] it is important to investigate whether PA plays a protective role in the cortisol dysregulation found in women with a history of BC. In doing so, it is valuable to compare whether the role is comparable to that of women without a history of BC. Previous studies with adults without a history of cancer and with athletes both indicate that PA influences the functioning of the HPA axis and regulates cortisol secretion,[40,41] whereby PA generates an almost immediate HPA response by activating and stimulating cortisol releases. The long-term effect of PA on cortisol patterns, however, remains un- investigated in these populations (as well as in women with a history of BC). The purpose of the present study was to extend this research and evaluate the association between aerobic PA and cortisol patterns among women with a history of BC who were, on average, 6.5 years post-adjuvant treatment as well as with women without a history of BC. The specific objectives were twofold: (1) assess whether aerobic PA was associated with diurnal and reactive cortisol patterns, and (2) determine whether the association between aerobic PA and cortisol patterns differed between women

with and without a history of BC. It was hypothesized that women with a history of BC who reported engaging in aerobic PA more frequently at the time of testing (moderate/high-PA group) would exhibit significantly less abnormalities in their cortisol patterns than those who reported engaging in aerobic PA less frequently or not at all (no/low-PA group). Given the exploratory nature of the second aim, no hypothesis regarding whether a cancer experience moderated the association between aerobic PA and cortisol patterns was proposed.

Methods

Participants

Women with and without a history of BC were recruited through printed advertisements and cancer support groups. To be eligible for this study, women with a history of BC had to meet the following criteria: (a) have been diagnosed with stage 0-III BC, (b) be more than 6 months post-adjuvant treatment (i.e., surgery, chemotherapy, and/or radiation therapy) for BC, and (c) be able to read and speak English. Women without a history of BC had to meet the following criteria: (a) have completed a routine mammography screening with negative results, (b) have no history of other types of cancer (except non-invasive skin cancer and cervical cancer), and (c) be able to read and speak English. Women were not eligible if they: (a) had a substance abuse problem, (b) were suffering from a major disabling conditions interfering with their quality of life and level of functioning (e.g., psychiatric disorders), and/or (c) were breastfeeding, pregnant, or taking any medication that could alter hormonal secretion (e.g., hydrocortisone, hypnotics, benzodiazepines).

Procedures

The study protocol was approved by the University of Ottawa's Research Ethics Review Board. All participants provided written in- formed consent prior to data collection, received financial compensation for travel ($50 CAD), and were entered in a raffle to win one of four $250 CAD gift

certificates. Once eligibility was confirmed over the phone, women were scheduled to attend two laboratory visits at the University of Ottawa Stress, Immunocompetence, and Health Laboratory. The first visit lasted approximately 30 min and served to obtain informed consent, provide instructions on the collection of saliva samples, and supply participants with labeled salivettes. Participants were asked to collect five saliva samples on two consecutive days at the following times: at awakening, 30 min after waking, 12 PM, 4 PM, and 9 PM. Commensurate with recommended protocols,[42] participants were instructed to rinse their mouth 10 min before saliva collection in order to avoid sample dilution, to place the salivette directly under their tongue for 3 min, and to store the salivettes in the refrigerator until delivery to the laboratory for the second visit (approximately 1 week after their first visit). Further, participants were asked to refrain from smoking and drinking alcohol 24 h prior to saliva collection, as well as avoid caffeine products and exercising 1h before saliva collection. Upon arrival at the Laboratory, the saliva samples were transferred to Eppendorf tubes and stored in a freezer at −80 °C until processed for cortisol.

The second visit lasted approximately 2h and served to assess participants' reactive cortisol responses. During this visit, participants were subjected to the Trier Social Stress Test (TSST; see description below)[43] at which time seven saliva samples were collected. The first sample was collected upon arrival at the laboratory ("arrival" sample), the second and third during the TSST (i.e., "anticipation" sample which occurred between the speech preparation and the speech delivery; "arithmetic" sample which occurred upon completion of the arithmetic task). After completing the TSST, participants were taken to a quiet room for 1 h to complete a questionnaire assessing sociodemographic characteristics and aerobic PA. Four additional saliva samples were collected during this time: 10, 20, 40, and 60min after the TSST. Second visits were conducted between 3 PM and 5 PM in order to coincide with the time at which cortisol levels are near their lowest and most stable daytime

values.[44]

Measures

Cortisol Levels

Cortisol was assessed using commercially available highly-sensitive enzyme-linked immunosorbent assay (ELISA). The assay kits and the protocols was provided by Salimetrics, State College, PA, USA.[42] For diurnal cortisol, cortisol concentrations were assessed on two consecutive days and the means of each of the five time points were subsequently computed for each participant. For reactive cortisol, cortisol concentrations were assessed before, during, and after the TSST as described previously. The TSST is a two-task protocol that has been designed to induce a physiological stress response.[45,46] A detailed overview of the TSST protocol has previously been published.[43] Briefly, the task consists of a 5-min mock interview and a 5-min arithmetic subtraction task in front of three confederate evaluator judges. Participants were told that the session would be video-taped for later review. The TSST has successfully been shown to induce subjective stress, cardiovascular changes, and endocrine responses.[45,46]

Aerobic PA

A single item was used to assess participants' engagement in aerobic PA. Participants reported how often they participated in cardiovascular activities per week. Cardiovascular activity was described to participants as any exercise, regardless of its intensity, that raises heart rate. Response options were: once per week or less, 2–3 times per week, 4–5 times per week, and 6–7 times per week, and more than 7 times per week. Responses were then dichotomized into 'no/low PA' and 'moderate/ high PA' levels based upon two different methods. For the first dichotomization (PA1), participants who reported engaging in aerobic PA once per week or less were placed in the 'no/low PA' group and all other participants in the 'moderate/high PA' group. For the second dichotomization (PA2), participants who

reported engaging in aerobic PA three times per week or less were placed in the 'no/low PA' group and other participants in the 'moderate/high PA' group. We divided PA frequency both ways to determine if the groups would be distinguished by difference in PA frequency, i.e., none or almost none vs. irregular PA (PA1) and none, almost none, or irregular vs. regular PA (PA2). The sample sizes were insufficient to analyze the data based on a tertiary scheme reflecting low, moderate, and high PA frequencies.

Data Preparation and Analyses

Data Preparation

Once collected from participants, the saliva samples were transferred to Eppendorf tubes and stored in a −80 °C freezer; they were processed in duplicate within 3 months at the University of Ottawa Stress, Immunocompetence, and Health Laboratory using commercially available highly-sensitive enzyme linked immunosorbent assay kits and the protocol designed by Salimetrics, State College, PA, USA. For diurnal cortisol, the means and standard deviations were computed for samples taken at the same time across both days, yielding five scores in mol/L per participant, which were then used to determine the area under the curve to increase (AUCi) using trapezoidal integration methods[47] to represent participants' overall daily cortisol secretion level. For reactive cortisol, the seven saliva samples collected during the TSST protocol were used to compute the AUCi representing participants' individual overall cortisol response to stress.

Data were screened for missing responses, which amounted to less than 5% overall and were typically due to insufficient saliva amounts. The expectation-maximization (EM) algorithm was used to impute missing values when participants had no more than two missing data points (out of 10) for diurnal cortisol and no more than three (out of seven) for reactive cortisol; otherwise data of those participants missing more values were excluded from the current analyses. Based on these criteria, the data associated with seven participants were eliminated, leaving a total of 48 participants. Data were

also screened for outliers and tested for assumptions of homogeneity of variance, sphericity, and normality.[48]

Statistical Analysis

Data analyses were performed using SPSS version 21.0.[49] Two-way analysis of variance (ANOVA) and mixed-design ANOVA were used to evaluate diurnal and reactive cortisol patterns. Two-way ANOVAs were first computed to examine between-group differences in cortisol pat- terns based on cancer experience (no history vs. history of BC) and aerobic PA (no/low vs. moderate/high PA group); the total cortisol AUCi score served as the dependent variable. Second, three-way mixed- design ANOVAs were performed to gain more insight into the pattern of diurnal and reactive cortisol concentrations. The between-subjects or randomized group factors were cancer experience (history vs. no his- tory of BC) and aerobic PA (no/low vs. moderate/high PA group) and the within-subjects or repeated factor was time (diurnal – at awakening, 30 min after awakening, 12 PM, 4 PM, and 9 PM; reactive –arrival, anticipation, arithmetic, 10, 20, 40, and 60 min after the TSST). All analyses were conducted separately for the PA1 and PA2 dichotomization schemes. Factors such as age, socioeconomic status, and time since diagnosis were considered as potential covariates; however, none of them were significantly correlated with cortisol levels and were therefore not retained for analyses of covariance.

Results

Participants Characteristics

The demographic characteristics of the 48 participants included in the current study are depicted in Table 1. The participants were, on average, 57.9 years of age at study inception. Most were married (56.3%), self-identified as White (91.7%), consumed less than one alcoholic beverage per day (91.6%), and did not smoke (95.8%). Also, 44% were retired and most (58.3%) had an annual family income

below $80,000 CAD. There was no statistically significant group (cancer experience and PA frequency) difference on these demographic characteristics based on parametric (ANOVA) and non-parametric (chi- square) analyses. In the group consisting of women with a history of BC, the average age at diagnosis was 52.8 years (*SD* = 9.36; range= 32–76) and the average time since diagnosis was 6.5 years (*SD* = 3.34; range = 0.5–40). Most (64.0%) were diagnosed with stage 0 or I BC and underwent some combination of treatment, including lumpectomy (40.0%), chemotherapy (44.0%), radiation (60.0%), and hormone therapy (60.0%).

Table I. Characteristics of participants.

Demographic characteristics	Participants	
	Women with a history of breast cancer (*N*=25)	Women without a history of breast cancer (*N*=23)
Age [mean years [SD] (Range)]	59.5 [10.1] (39.0-81.0)	56.3 [11.3] (29.0-73.0)
Ethnicity [*n* White (%)]	23 (92.0)	21 (91.3)
Relationship status [*n* (%)]		
Single	2 (8.0)	2 (8.7)
Common law	3 (12.0)	1 (4.3)
Married	14 (56.0)	13 (56.5)
Divorced/separated	4 (16.0)	5 (21.7)
Widowed	2 (8.0)	2 (8.7)
Highest level of education attained [*n* (%)]		
High school	6 (24.0)	7 (30.4)
College	5 (20.0)	3 (13.0)
Bachelor's degree	12 (48.0)	7 (30.4)
Graduate degree	2 (8.0)	6 (26.1)
Work status [*n* (%)]		
Blue collar	0	1 (4.3)
White collar	11 (44.0)	6 (26.1)
Self-employed	1 (4.0)	3 (13.0)
Medical leave of absence	3 (12.0)	1 (4.3)
Retired	9 (36.0)	12 (52.2)
Family income (CAD) [*n* (%)]		
< $40,000	4 (17.4)	4 (18.2)
$40,000 to $79,999	10 (43.5)	10 (45.5)
$80,000 to $119,999	6 (26.1)	4 (18.2)
≥ $120,000	3 (13.0)	4 (18.2)
Aerobic physical activity per week [*n* (%)]		
≤ 1 time	6 (24.0)	5 (21.7)
2 to 3 times	9 (36.0)	12 (52.2)
4 to 5 times	6 (24.0)	6 (26.1)
6 to 7 times	4 (16.0)	0
> 7 times	0	0

Diurnal Cortisol

The analytical sample comprised of 19 women with a history of BC and 23 women without a history of BC. Fig. 1 provides plots of the data showing the relationship between aerobic PA frequency, cancer experience, and diurnal cortisol AUCi. Using the PA1 cutoff (Fig. 1, left), a two-way ANOVA yielded no significant main effect for cancer experience [$F(1,38) = 1.65$, $p = .206$, $\eta^2 = .04$] or aerobic PA [$F(1,38) = 2.11$, $p = .15$, $\eta^2 = .05$], nor a significant interaction be- tween cancer experience and aerobic PA [$F(1, 38)=1.40$, $p =.25$, $\eta^2 = .04$]. Using the PA2 cutoff (Fig. 1, right), a two-way ANOVA yielded no significant main effect for cancer experience [$F(1,38) = 0.02$, $p = .88$, $\eta^2 = .001$] or aerobic PA [$F(1,38) = 1.32$, $p = .26$, $\eta^2 = .03$], nor a significant interaction between cancer experience and aerobic PA [$F(1,38) = 0.99$, $p = .33$, $\eta^2 = .03$].

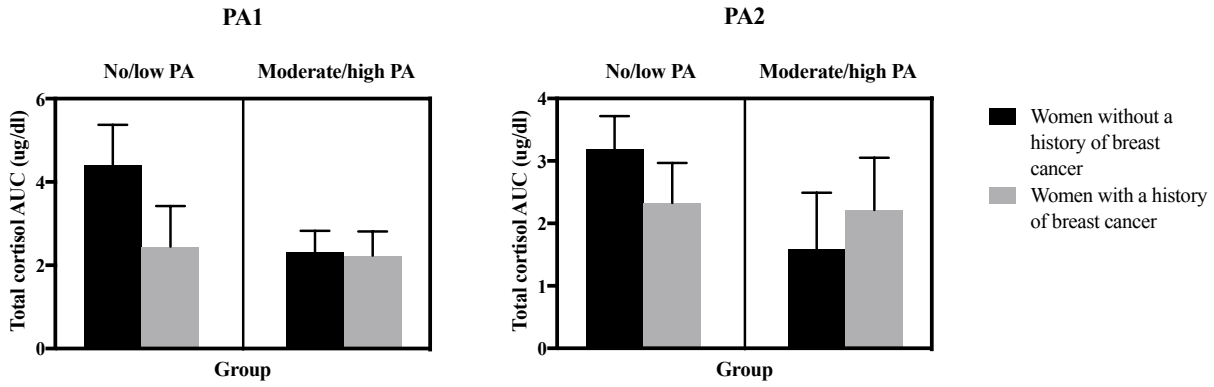

Figure 1. Average diurnal cortisol AUCi scores for participants by cancer experience and aerobic PA frequency. On the left side (PA1), no/low PA plots participation in PA ≤ one time per week and moderate/high PA participation in PA ≥ two times per week. On the right side (PA2), no/low PA indicates participation in PA ≤ three times per week and moderate/high PA participation in PA ≥ four times per week.

Fig. 2 displays the plots of the diurnal cortisol fluctuation pattern across five time points by cancer experience and aerobic PA frequency. Using the PA1 cutoff (Fig. 2, left), a mixed-design ANOVA yielded a significant main effect for time [$F(1.99,75.71) = 33.74$, $p < .001$, $\eta^2 = .47$], with the pattern suggesting typical diurnal cortisol fluctuation. No significant main effects were found for cancer

experience [$F(1,38) = 0.17$, $p = .68$, $\eta^2 = .004$] or aerobic PA1 [$F(1,38) = 0.47$, p = .50, $\eta^2 = .01$]. In addition, no significant interactions were observed [cancer experience × time: $\eta^2 = .02$; aerobic PA1 × time: $\eta^2 = .01$; cancer experience × time × aerobic (1.99,75.71) = 0.50, $p = .61$, $\eta^2 = .01$]; cancer experience × aerobic PA1: F(1,38) = 0.33 $p = .57$, $\eta^2 = .01$], indicating that the differences across time points were similar for participants with and without a history of BC who reported no/low and moderate/high PA.

Using the PA2 cutoff (Fig. 2, right), a mixed-design ANOVA yielded a significant main effect of time [$F(2.03,77.02) = 42.22$, $p < .001$, $\eta^2 = .53$] and no significant main effect for cancer experience [$F(1,38) = 0.62$, $p = .44$, $\eta^2 = .02$] or aerobic PA2 [$F(1,38) = 1.53$, $p = .22$, $\eta^2 = .04$]. A cancer experience × aerobic PA2 interaction effect was observed to approach significance [$F(1,38) = 4.05$, $p = .05$, $\eta^2 = .10$] due to group differences in the awakening and 30 min later response that was lower in women without a history of BC relative to those with a history of BC. No other significant interaction effects were observed [cancer experience × time: $F(2.03,77.02) = 1.25$, $p = .29$, $\eta^2 = .03$; aerobic PA2 × time: $F(2.03,77.02) = 0.12$, $p = .89$, $\eta^2 = .003$; cancer experience × time × aerobic PA2: $F(2.03,77.02) = 2.39$, $p = .10$, $\eta^2 = .06$].

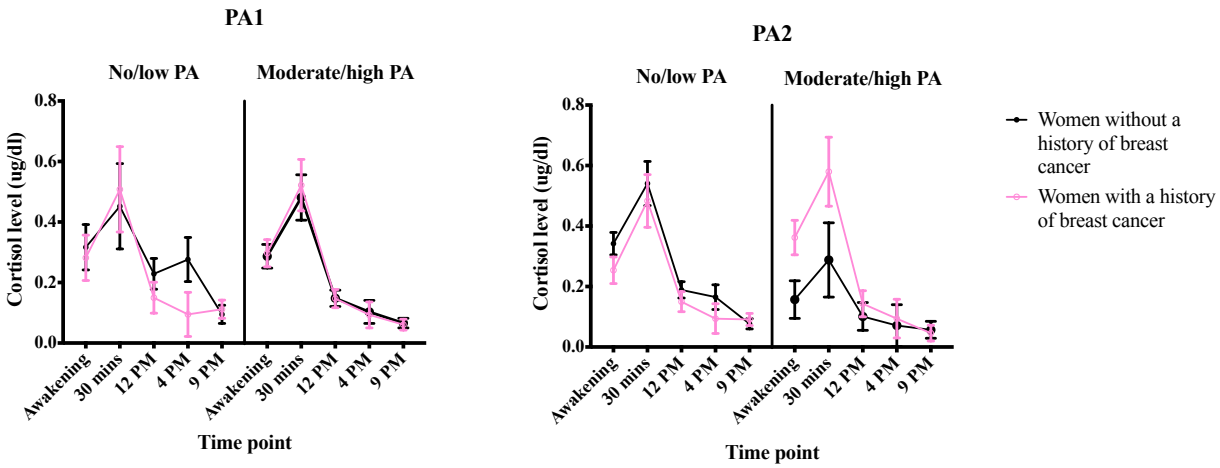

Figure 2. Diurnal cortisol profiles of participants with and without a history of BC by aerobic PA frequency. On the left side (PA1), no/low PA plots participation in PA ≤ one time per week and moderate/high PA participation in PA ≥ two times per week. On the right side (PA2), no/low PA reflects participation in PA ≤ three times per week and moderate/high PA participation in PA ≥ four times per week.

Reactive Cortisol

Fig. 3 provides plots of the data showing the relationship between aerobic PA frequency, cancer experience, and reactive cortisol AUCi. The analytical sample comprised 21 women with a history of BC and 22 women with no history of BC. Using the PA1 cutoff (Fig. 3, left), a two- way ANOVA yielded a significant main effect of cancer experience [$F(1, 39) = 4.22$, $p = .05$, $\eta^2 = .10$], whereby women without a history of BC had a significantly higher cortisol AUCi ($M = 1.61$, $SD = 0.22$) than women with a history of BC ($M = 1.01$, $SD = 0.19$), a non-significant main effect for aerobic PA1 [$F(1,39) = 0.56$, $p = .50$, $\eta^2 = .01$], and a non-significant interaction effect between cancer experience and aerobic PA1 [$F(1,39) = 0.35$, $p = .56$, $\eta^2 = .01$]. Using the PA2 cutoff (Fig. 3, right), a two-way ANOVA yielded no significant main effect of cancer experience [$F(1,39) = 2.08$, $p = .16$, $\eta^2 = .05$] or aerobic PA2 [$F(1,39) = 0.05$, $p = .83$, $\eta^2 = .001$], nor a significant interaction between cancer experience and aerobic PA2 [$F(1,39) = 0.92$, $p = .34$, $\eta^2 = .02$].

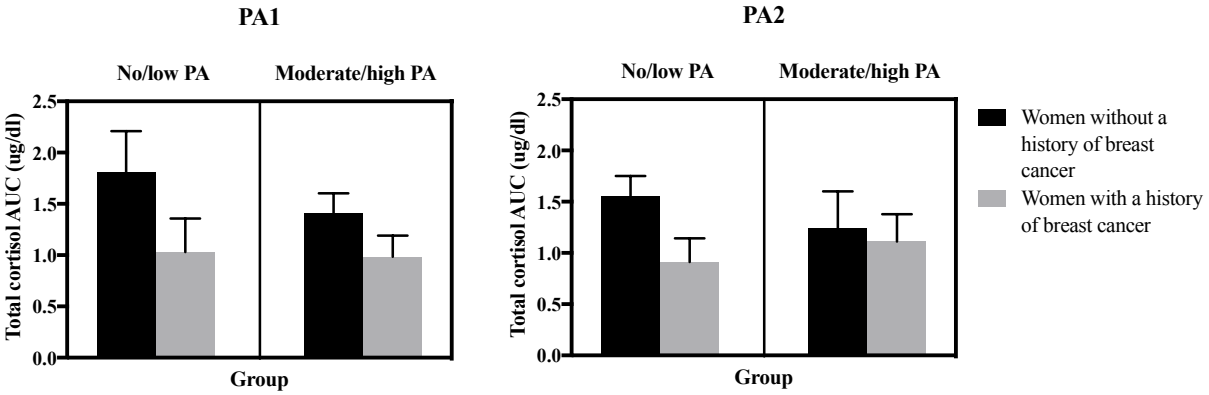

Figure 3. Average reactive cortisol AUCi scores for participants by cancer experience and aerobic PA frequency. On the left side (PA1), no/low PA shows participation in PA ≤ one time per week and moderate/high PA participation in PA ≥ two times per week. On the right side (PA2), no/low PA shows participation in PA ≤ three times per week and moderate/high PA participation in PA ≥ four times per week.

Fig. 4 displays the plots of the reactive cortisol pattern across seven time points during an acute stress situation by cancer experience and aerobic PA frequency. Using the PA1 cutoff (Fig. 4, left), a mixed-design ANOVA yielded a significant main effect for time [$F(2.76,107.79) = 3.56$, $p = .02$, $\eta^2 = .08$], supporting an expected difference in cortisol levels in response to an acute stressor. A significant main effect was found for cancer experience indicating that women without a history of BC had a significantly higher mean cortisol levels ($M = 0.19$, $SD = 0.02$) than women with a history of BC ($M = 0.12$, $SD = 0.02$). No significant main effect was found for aerobic PA1 [$F(1,39) = .86$, $p = .36$, $\eta^2 = .02$] and no significant interaction effects were observed [cancer experience × time: $F(2.76,107.79) = 2.37$, $p = .08$, $\eta^2 = .06$; aerobic PA1 × time: $F(1.99, 107.79) = 0.79$, $p = .49$, $\eta^2 = .02$; cancer experience × time × aerobic PA1: $F(2.76, 107.79) = 0.97$, $p = .41$, $\eta^2 = .02$]; cancer experience × aerobic PA1 [$F(1,39) = .447$, $p = .51$, $\eta^2 = .01$], indicating that the differences across time points were similar for participants with and without a history of BC who reported no/low and moderate/high PA.

Using the PA2 cutoff (Fig. 4, right), a mixed-design ANOVA yielded a significant effect for time [$F(2.89,112.64) = 3.12$, $p = .03$, $\eta^2 = .07$]. No significant main effects were found for cancer experience

[$F(1,39) = 2.65$, $p = .11$, $\eta^2 = .06$] or aerobic PA2 [$F(1,39) = 0.04$, $p = .84$, $\eta^2 = .001$]. In addition, no significant interaction effects were observed [cancer experience × time: $F(2.89,112.64) = 0.75$, $p = .52$, $\eta^2 = .02$; aerobic PA2 × time: $F(2.89, 112.64) = 0.26$, $p = .85$, $\eta^2 = .01$; cancer experience × time × aerobic PA2: $F(2.89, 112.64) = 1.66$, $p = .18$, $\eta^2 = .04$]; cancer experience × aerobic PA2: $F(1,39) = .71$, $p = .40$, $\eta^2 = .02$], indicating that the differences across time points were similar for participants with and without a history of BC who reported no/low or moderate/high PA.

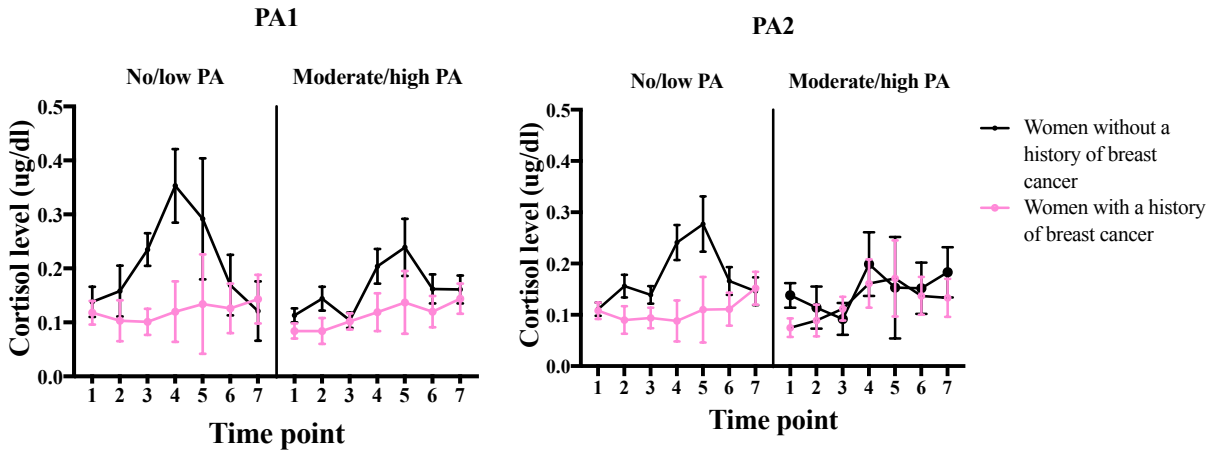

Figure 4. Reactive cortisol profiles of participants with and without a history of cancer by aerobic PA frequency. On the left side (PA1), no/low PA shows participation in PA ≤ one time per week and moderate/high PA participation in PA ≥ two times per week. On the right side (PA2), no/low PA reflects participation in PA ≤ three times per week and moderate/high PA participation in PA ≥ four times per week.
**1 = upon arrival; 2 = anticipation; 3 = arithmetic; 4 = 10 minutes after the Trier Social Stress Test (TSST); 5 = 20 minutes after the TSST; 6 = 40 minutes after the TSST; 7 = 60 minutes after the TSST*

Discussion

The specific objectives of the present study were to assess whether aerobic PA is associated with diurnal and reactive cortisol patterns, and whether the association between aerobic PA and cortisol patterns differed between women with and without a history of BC. In regards to our first objective, our hypothesis that women who engaged in aerobic PA more frequently (moderate/high PA group) would exhibit significantly less abnormalities in their cortisol patterns than those who engaged in aerobic PA less frequently or not at all (no/low PA group) was not supported as diurnal and reactive cortisol patterns

did not differ statistically across aerobic PA groups. In regards to our second objective, a marginally significant (p = .05) cancer experience by aerobic PA interaction was observed when analyzing diurnal cortisol data suggesting that women without a history of BC who engaged in aerobic PA more frequently (moderate/high PA group) had a lower cortisol level at awakening and 30 min after awakening than women with a history of BC. Moreover, the association between aerobic PA and reactive cortisol patterns appeared to differ statistically based on women's cancer experience (i.e., history vs. no history of BC) when using the PA1 cutoff, whereby women without a history of BC had a significantly higher overall cortisol reactivity to an acute stressor (both in terms of AUCi and time point fluctuations) than women with a history of BC.

Others have also failed to detect a significant association between PA and cortisol patterns, regardless of history of cancer.[25,50] For example, similar to our findings, Payne et al.[25] did not find differences in diurnal cortisol levels between women in an exercise group comprised of home-based walking compared to women in a usual care group during hormonal treatment for BC. Yet, the authors did observe a downward trend for women in the exercise group compared to the usual care group, suggesting that women exposed to the exercise intervention (n = 10) had lower overall cortisol levels than women in the usual care group (n = 10). Nevertheless, the current evidence does not allow for conclusive inferences in favor of an association between PA and cortisol among women with a history of BC. It is possible that other factors or comorbid conditions may confound the association between PA and cortisol. First, cancer is often comorbid with several medication conditions that may impair cortisol regulation,[32–34] thus decreasing the effect of PA on cortisol regulation especially in those who experience severe medical conditions. Second, recent findings suggest that poor sleep may have powerful effects on the immune function and that it is a risk factor for impaired cortisol regulation.[51,52] Accordingly, as insomnia is common among women with a history of BC,[53,54] inflammatory responses

to sleep deprivation may represent one mechanism affecting the association between PA and cortisol. Third, the biological mechanisms underlying the observed association between PA and cortisol in the general population are unclear.[40,41] It may be that alterations in hormonal responses caused by BC treatment compromise the beneficial effect of PA on cortisol among women with a history of BC. Thus, further research should include the simultaneous inclusion of a number of covariates known to be related to both PA and cortisol regulation.

It is important to note that our study, similar to others,[40] falls short of measuring PA parameters that may be implicated in the PA-cortisol association. Indeed, our PA measure was intended to provide an index of the total frequency of cardiovascular activities that raises a person's heart rate, but it lacks sensitivity to test whether intensity (e.g., light, moderate, vs. vigorous), duration (e.g., shorter long and continuous vs. short intervals), type (e.g., aerobic vs. anaerobic), context (e.g., indoors vs. outdoors or individual vs. group-based), and/or time of day moderates the association between PA and cortisol among women. For in- stance, many studies have suggested that increases in circulating cortisol levels are relatively proportional to PA intensity whereby a minimum intensity (i.e., threshold) is required in order to provoke a HPA response.[55–57] As the PA variable in our study was self-reported, we had no way to precisely measure whether PA intensity went above thresholds required to influence inflammatory responses. Moreover, other behavioural variables such sleep, sedentary time, fitness status, and food/beverage intake that may alter cortisol responses to PA[58–61] were also not considered (either due to limitations in sample size or because data were not collected). Future studies with direct assessments of PA (e.g., actigraphy) and more detailed PA questionnaires are needed, as well as better control for PA parameters and behavioural factors that could influence the association between PA and cortisol before firm conclusions can be made. Nevertheless, the effect sizes (based on the partial eta^2 values) in this study suggest that there is an association between aerobic PA frequency and cortisol patterns among

women, which is critical as cortisol dysregulation is central to the etiology of several chronic conditions[23,30,31] and it would be valuable to determine which specific aspects of PA can be promoted to prevent this dysregulation. Over the years, researchers and statisticians have high- lighted the importance of the use of effect sizes and explained why reporting p-values alone might not be enough in order to truly under- stand the results of a study.[62–66] Unlike p-values, effect sizes are not impacted by sample size and offer readers a quantitative index of the magnitude of the difference between groups. In the context of this study, consideration of the effect sizes in tandem with p-values give primordial interpretive information about the results that are not con- founded with sample size. For that reason, we cannot discount the possibility that PA may still represent a protective factor for cortisol regulation and with a larger sample size, significant results might have emerged.[67]

Additionally, our results provide some evidence that aerobic PA may relate to cortisol patterns among women without a history of BC (Figs. 1 and 3). Albeit not statistically significant, the mean cortisol levels (diurnal and reactive) of women with a history of BC appear to remain fairly unchanged regardless of PA status (no/low vs. moderate/ high PA group), whereas the mean cortisol levels of women without a history of BC who were included in the moderate/high PA group had lower levels than other women without a history of BC who were included in the no/low PA group. Although we hypothesized that more frequent engagement in aerobic PA may help to counter the negative physiological effect of a BC experience and that post-cancer cortisol dysregulation may be exacerbated by a lack of aerobic PA, collectively, our findings suggest that PA may not have the same effect on women with and without a cancer experience. Speculatively, fear of cancer recurrence, depression, overall stress, and fatigue which are common among women with a history of BC, might play a role in this relation- ship.[68,69] It seems necessary to further examine these mechanisms in larger samples as researchers have linked mortality rates of women with BC to the extent to which diurnal cortisol profiles

deviate from the 'normal' pattern of cortisol secretion, thereby making cortisol dysregulation an important prognostic indicator of BC.[36,70] Indeed, whereas studies show that adults diagnosed with cancer who engage in PA regularly have lower risk of cancer recurrence,[2,7] this type of investigation may help shed light on one of the potential mechanisms through which PA exerts its effect.

Strengths and Limitations

There are several limitations to this study. For instance, the small sample size significantly reduced the statistical power of the analyses and may explain our failure to obtain statistical significance. The self- report aerobic PA measure did not allow for the consideration of other factors such as duration and intensity that could influence the relationship between aerobic PA and cortisol. It is also important to consider that the prolonged duration of time since the BC treatment of our participants prevents generalization of our findings to women more recently diagnosed and treated for BC; thus findings are limited to long- term survivors.

This study has significant strengths as well. First, it is the first to examine the association between aerobic PA and cortisol patterns (diurnal and reactive) in women with and without a history of BC. Whereas in the current literature researchers have compared cortisol patterns between women with and without a history of BC,[26–28] very few have considered the role of PA.[40,41] Second, despite the recognition that diurnal and reactive cortisol are distinct,[23] few researchers have assessed both in relation to PA in the same participants in order to establish whether the relationship between PA and cortisol patterns is different for diurnal and reactive patterns. Third, the TSST was used to induce stress responses in participants; this protocol has repeatedly shown to yield sufficient HPA activity,[43,45,46] thereby allowing reliable and valid assessment of the cortisol reactivity profiles to be obtained from participants.

Conclusions

Although it is not possible to draw firm conclusions about the association between PA and cortisol patterns in women with and without a history of BC, examination of effect sizes indicates some relationship will require larger sample sizes to be explored more fully. Approximately 70% of women with a history of BC exhibit some dysregulation in their cortisol profile;[36,71] it is therefore crucial to further investigate modifiable lifestyle factors such as PA that could be used to counterbalance the negative physiological effects of BC. Encouraging women to engage in aerobic PA regularly may not only be effective in reducing subjective stress as shown in past studies,[13,14,21] but may also be used as a way to minimize physiological stress response dysregulation. Clearly, studies with larger sample sizes are warranted that include additional, more detailed self-report measures as well as direct assessments of PA in order to capture context, type, and intensity of PA and any covariates (e.g., behavioural factors, physical factors).

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CHAPTER FOUR

Study Three, Article One

Behavioural, physical, and psychological predictors of cortisol and C-reactive protein in breast cancer survivors: A longitudinal study

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Abstract

***Background*:** Breast cancer survivors (BCS) can exhibit a dysregulation of cortisol and elevated C-reactive protein (CRP) levels post-treatment, which increase the risk of diverse health outcomes. Certain behavioural, physical, and psychological variables may help to predict cortisol and CRP levels post-treatment. The aims of this study were to: (1) describe naturally occurring changes in absolute diurnal cortisol and CRP levels over a period of 1.5 years post-treatment among BCS, (2) assess if absolute diurnal cortisol and CRP levels change in tandem, and (3) assess behavioural, physical, and psychological variables as predictors of absolute diurnal cortisol levels and CRP levels.

***Methods*:** Capillary blood and saliva samples were collected from 201 BCS, on average, 3.5 months post-treatment (T1) and again 3, 6, 9, and 12 months later (T2-T5). At each time point, five saliva samples were collected on two nonconsecutive days: at awakening, 30 min after awakening, 2:00 pm, 4:00 pm, and at bedtime. At each time point, participants also completed self-report questionnaires and wore an accelerometer for seven consecutive days. Data were analyzed using multilevel modeling.

***Results*:** Absolute diurnal cortisol levels did not change significantly over time. CRP levels decreased across time points (B_{linear}=-0.31, p=.01), though the rate of decrease slowed over time ($B_{quadratic}$=0.05, p=.03). Generally, greater sedentary time predicted higher overall absolute diurnal cortisol levels (B<0.01, p=.01); whereas higher physical activity (B=-0.004, p<.01), lower body mass index (B=0.10, p<.01), and lower health- and cancer-related stress (B=0.24, p=.04) predicted lower overall CRP levels. Also, lower absolute diurnal cortisol levels were evident when participants engaged in more sedentary time, as compared to their own average sedentary time (B=-0.01, p<.01).

Conclusions: Results offer insight into the nature of change in diurnal cortisol and CRP among BCS from treatment completion onwards and offer clinical implications. Helping BCS manage their weight, reduce stress, increase physical activity participation, and decrease sedentary time as soon as possible after treatment may help to reduce physiological dysregulations, thereby lowering the risk of adverse health outcomes in this population. Further research investigating specific intervention parameters such as type, context, frequency, and intensity are warranted for the development of the most optimal interventions.

Behavioural, physical, and psychological predictors of cortisol and C-reactive protein in breast cancer survivors: A longitudinal study

1. Introduction

Experiencing stress due to cancer and its treatment can negatively influence people's psychological and physical health (Selye, 2013). For example, long-term prolonged stress can lead to depression and serious health risks such as obesity and heart diseases in non-clinical (da Estrela et al., 2020; Miller & Blackwell, 2006) and clinical populations (Coughlin, 2011; Maass et al., 2015). In response to stressful life events (e.g., cancer diagnosis), the human body releases stress hormones like adrenaline and cortisol. In the short-term, these hormones are helpful because they can increase a person's ability to respond to a stressor, while they generally return to normal levels once the stressful situation has passed (Slavish et al., 2015). However, in the long-term, when stress is chronic, the body's production of stress hormones becomes dysregulated, thereby impeding a return to normal (McEwen, 1998; Miller et al., 2007). Over time, these hormones can lead to changes in physiology and cause serious health problems (McEwen, 1998, 2008; Selye, 2013). For instance, chronic stress may lead to either elevated or below normal cortisol levels and both types of dysregulations can have important negative effects on health (Herriot et al., 2020; McEwen, 2008; Miller et al., 2007). Dysregulation of cortisol levels may in turn prompt an increase in circulating C-reactive protein (CRP) levels, a marker of systemic inflammation (Gouin et al., 2012; Rueggeberg et al., 2012; Slavish et al., 2015). These physiological dysregulations have been linked to several negative health outcomes such as increased disability and reduced longevity (Reza et al., 2014; Schrepf et al., 2013; Sharpley et al., 2019).

Although there are data showing that breast cancer survivors (BCS) feel stressed (Allen et al., 2008) and exhibit dysregulated cortisol levels and elevated CRP levels post-treatment (Hsiao et al., 2017; Wiley et al., 2017), studies are needed to explore the long-term effects of chronic stress on cortisol and CRP levels once treatment ends. Findings suggest that dysregulated cortisol and elevated CRP levels in BCS tend to normalize and have a trend towards recovery with the passage of time followed the end of treatment (Couture-Lalande et al., 2014; Hsiao et al., 2017; Villasenor et al., 2014; Wiley et al., 2017; Zeitzer et al., 2016). Though these existing studies are informative, little is known about *how* cortisol and CRP levels change over time post-treatment. Studies assessing trajectory of changes and predictive variables are needed to gain a better understanding of the long-term physiological outcomes of an experience of breast cancer, and identify women at greater risk of dysregulations. Physiological disturbances are concerning in BCS, given that cortisol and CRP can exert downstream implications on general health and play an essential role in a person's ability to regulate stress and fight infections and injuries (Asegaonkar et al., 2015; Miller et al., 2007).

The Role of Behavioural and Psychological variables in the Physiological outcomes of BCS

Andersen's biobehavioural model (1994) suggests that a diagnosis of cancer and its treatments generate a significant level of stress and alter quality of life thereby leading to behavioural and psychological responses, which in turn influence physiological processes. More specifically, the model proposes that the stress caused by a cancer experience increases engagement in poor health behaviours such as unhealthy diet and drug use (e.g., alcohol, nicotine), and reduce initiation of positive health behaviours such as physical activity (PA). This can in turn produce changes in survivors' physiology (Andersen et al., 1994). Since the development of the model, accumulating evidence has supported a general conclusion that

various behavioural, physical, and psychological variables might predict the physiological outcomes of cancer survivors (Hsiao et al., 2017; Villasenor et al., 2014). Examining predictors of cortisol and CRP levels in BCS guides the development of targeted health interventions.

Our team previously examined socio-demographic, health-, and cancer-related predictors of absolute diurnal cortisol and CRP levels in BCS (Lambert et al., 2020). Results showed that: (1) absolute diurnal cortisol and CRP levels fluctuate over time, (2) older age and post-menopausal status are associated with higher absolute diurnal cortisol and CRP levels, (3) more advanced cancer stages and chemotherapy exposure are associated with lower absolute diurnal cortisol levels, and (4) being overweight/obese is associated with higher CRP levels. Although these findings help to identify women who may be at greater risk of post-treatment physiological dysregulations, these factors are largely non-modifiable. Examining *contributing* and *modifiable* factors is still needed to help select appropriate intervention strategies to promote optimal health outcomes. Moreover, although our extant work has used the conventional approach to examining predictors in a longitudinal design is to employ analytical techniques that treat clustering that occurs because repeated observations are nested within participants as nuisance (e.g., repeated and mixed analyses of variance), multilevel modeling (MLM; Sherry & MacKinnon, 2013) may provide a more sohisticated approach. MLM views such clustering as a feature of the data and one that is of substantive interest. Additionally. MLM allows researchers to consider continuous candidate predictors (rather than categorical) and intra- and inter-individual component in the associations between predictors and physiological outcomes, whereas conventional approaches focus on the inter-individual component solely. Consideration of both intra- and inter-individual level association is necessary as observing an inter-individual level association does not guarantee a similar intra-individual level association and vice versa, and associations at both

levels have different implications for the design of interventions (Hox, 2010). Specifically, intra-individual level associations help to identify which factors have the potential to elicit individual change (and thus the most effective elements worth targeting in interventions), whereas inter-individual level associations help to identify who is at greater risk. Thus, using MLM to examine *contributing* and *modifiable* factors associated with cortisol and CRP levels would help not only to remedy limitations of analytical approaches, such as those employed by Lambert et al. (2020; i.e., repeated and mixed analyses of variance), but help to identify *who* would most likely benefit from interventions, along with *what* should be addressed in those interventions.

In another study (Sabiston et al., 2018a), our team found that: (1) BCS have lower CRP levels when they are more active (as compared to their average PA level), and (2) BCS who generally engage in more PA have lower average CRP levels as compared to BCS who generally engage in less PA. We consider these results important for two reasons. From a practical standpoint, they suggest that PA interventions might help mitigate adverse physiological dysregulations post-treatment. From a research standpoint, they imply that these variables should be included in future analyses to account for their association with CRP levels when examining other predictive factors such as psychological health. Moreover, given the importance and prevalence of dysregulated cortisol levels post-treatment for cancer, the assessment of these associations with cortisol levels would also be warranted.

The Current Study

In order to extend current knowledge on cortisol and CRP levels among BCS (Hsiao et al., 2017; Lambert et al., 2020; Sabiston et al., 2018a; Villasenor et al., 2014), the first objective of this study was to explore how absolute diurnal cortisol and CRP levels change over the first 1.5 year post-treatment using a multilevel modeling approach. Based on previous findings

(Rutter et al., 2013), it was hypothesized that changes in CRP levels over time would be best described by a quadratic trend whereby a sharp decrease would be initially observed followed by a deceleration in decrease to a slow return to normative values. Given the different plausible associations between chronic stress and cortisol levels (Bower et al., 2005; Hsiao et al., 2017), no specific hypothesis was put forward for direction and form of change for absolute diurnal cortisol levels. Additionally, given that studies suggest that dysregulated cortisol levels might prompt the release of inflammatory markers such as CRP (Black, 2003; Slavish et al., 2015), the second objective of this study was to assess whether changes in CRP levels were predicted by initial and/or concurrent absolute diurnal cortisol levels. It was hypothesized that changes in CRP levels would be predicted by changes in cortisol levels.

Finally, in line with Andersen's (1994) biobehavioural model that highlights the importance of behavioural and psychological factors for health outcomes among cancer survivors, the third objective of this study was to identify modifiable time-varying variables that account for intra- and inter-individual differences in initial absolute diurnal cortisol and CRP levels (i.e., intercepts) as well as rate of change (i.e., slopes) in BCS over the first 1.5 year post-treatment. Variables included as candidate predictors were: sedentary time (ST), depressive symptoms, perceived general stress, and perceived health- and cancer-related stress. Moderate-to-vigorous intensity PA (MVPA) and body mass index (BMI) were also included as candidate predictors considering the associations observed in our previous work (Lambert et al., 2020; Sabiston et al., 2018a) and to account for their variance in the estimated models. Consistent with findings in non-clinical population (Colbert et al., 2004; Howard et al., 2015; Kao et al., 2009; Shimanoe et al., 2014; Valkanova et al., 2013), it was hypothesized that higher ST and greater depressive symptoms and stress (general and health- and cancer-related) would predict higher

CRP levels in BCS, both at the inter- and intra-individual levels. As for cortisol levels, although significant associations with ST, depression symptoms, and general and health- and cancer-related stress were expected, no directional hypothesis was put forward given the different patterns of findings in the literature (Miller et al., 2007).

2. Methods

2.1. Participants and Procedures

Data analyzed for this study were drawn from a longitudinal study that aimed to examine BCS' lifestyle behaviours and their associations with physical and psychological health outcomes (Sabiston et al., 2018b). Briefly, participants were recruited through advertisements, word of mouth, and referrals from oncologists in different medical clinics and hospitals across Montreal, Quebec. Inclusion criteria were: (a) be at least 18 years of age, (b) have a previous diagnosis of stage I-III breast cancer, (c) be 0-20 weeks post-primary treatment (i.e., chemotherapy, radiotherapy, surgery), (d) be able and willing to provide informed consent, and (e) be able to read and speak English or French. Exclusion criteria were: (a) had received a previous diagnosis of cancer, and/or (b) have suffered from a health condition that may prevent PA.

The study protocol was approved by University and hospital research ethics committees. Once eligibility was confirmed, at approximately 3.5 months post-treatment (T1) and every 3 months thereafter (T2-T5), participants completed a self-report questionnaire package (to measure BMI, depressive symptoms, and stress levels) and wore an accelerometer for seven consecutive days (to measure ST and MVPA). At all time points (T1-T5), they were also asked to collect five saliva samples on two nonconsecutive days at awakening, 30 min after awakening, 2:00 pm, 4:00 pm, and at bedtime (to measure absolute diurnal cortisol levels) and provide a

drop of capillary blood (to measure CRP levels). Participants were asked not to brush their teeth and engage in PA during the 30 min prior to the saliva collection. Saliva and blood samples were stored in participants' refrigerator and returned to the laboratory within 7 days in a biosafety bag. Once at the laboratory, samples were stored at − 80° Fahrenheit until analysis.

2.2. Measures

2.2.1. Cortisol

Cortisol assays were analyzed in duplicate at the University of University of Trier, Germany, using a time-resolved fluorescence immunoassay with a cortisol–biotin conjugate as a tracer (Kirschbaum & Hellhammer, 2000). Areas under the curve with respect to ground (AUCg) cortisol levels were calculated for each of the two nonconsecutive days using the trapezoidal method. The mean AUCg for both days was computed for T1–T5 to provide a single summary represent absolute diurnal cortisol levels (Pruessner et al., 2003).

2.2.2. CRP

At T1-T5, a capillary whole blood drop was collected from participants' index or middle finger using a single-use lancet. Blood drops were collected on a Whatman protein saver card (VWR International, QC). All samples were analyzed at the Laboratory for Human Biological Research at Northwestern University using a high-sensitive enzyme immunoassay protocol (McDade, 2007).

2.2.3. ST and MVPA

At T1-T5, participants wore a GT3X accelerometer (Actigraph, Pensacola, Florida) on their hip during waking hours (except for periods of bathing/showering or other water activities) for 7 consecutive days. Accelerometer data were downloaded in 60-sec epochs and daily min of ST (<100 counts•min^{-1}) and MVPA (≥1952 counts•minute^{-1}) were calculated using established

cut-points (Freedson et al., 1998) while controlling for the number of days and hours the accelerometer was worn. Daily ST and MVPA min were summed across the 7-day period to obtain total weekly ST and MVPA min. Accelerometer data were included in the analysis if there were no extreme counts (>20,000) and if participants wore the device for at least 4 days for a minimum of 600 min per day (Troiano et al., 2008).

2.2.4. BMI

At T1-T5, participants self-reported their weight and height, and BMI was calculated as weight in kilograms divided by height in meters squared.

2.2.5. Depressive Symptoms

At T1-T5, participants completed a self-reported questionnaire package including the 10-item version of the Centre for Epidemiological Studies Depression Scale (CES-D; Andresen et al., 1994). The CES-D inquires about the frequency to which 10 symptoms were experienced during the past week (7 days) using a scale ranging from 0 (*rarely* or *none of the time*; <1 day) to 3 (*all the time*; 5-7 days). After reverse scoring positively worded items, average scores were computed, whereby higher scores represent greater frequency of depressive symptoms.

2.2.6. Perceived General Stress and Health- and Cancer-related Stress

At T1-T5, participants completed the Perceived Stress Scale (PSS; Cohen & Williamson, 1988) and the revised 5-item Assessment of Survivors Concerns (ASC) scale (Gotay & Pagano, 2007). The PSS is a general measure of perceived stress and includes 10 items measuring participants' perception of how uncontrollable, unpredictable, and overwhelming their life had been over the last month on a scale ranging from 1 (*never*) to 5 (*very often*). The ASC scale comprises two subscales, namely a general health worry subscale (includes fear of dying and health status in general) and a cancer worry subscale (includes fear about future tests, new

cancer, and recurrence), with responses ranging from 1 (*not at all*) to 4 (*very much*). After reverse scoring negatively worded items for the PSS, average scores for PSS and the ASC scale were computed, where higher scores indicate greater general stress and greater health- and cancer-related stress, respectively.

2.3. Data Preparation and Analyses

Data were analyzed using SPSS (version 26; IBM Corp, Armonk, NY, USA). The level of statistical significance was set to $p<.05$. All data handling described below were performed in line with strategies advised by Bauer and Curran (2016). Prior to the main analyses (i.e., multilevel modeling), data were examined for accuracy of entry, patterns of missing data, potential outliers, and model assumptions. Because one of the important advantages of multilevel modeling is that it allows for the analysis of incomplete repeated measures data without restrictive assumptions on the covariance matrix, all Level-1 variables with at least one available time point were included in the analyses and missing data were not replaced.

For the main analyses, a series of longitudinal multilevel models which had a multilevel structure with five repeated measures nested within participants were estimated using Restricted Maximum Likelihood (REML) estimation with absolute diurnal cortisol and CRP levels as outcomes. These analyses were conducted through a stepwise model building approach. As multilevel models work by assuming that participants' data over time are correlated with each other, the first step was then to specify the covariance structure. Two plausible structures, i.e., heterogeneous first order autoregressive structure and unstructured covariance structure, were tested. To identify which structure provided the best model fit, models were compared using Aikaike's Information Criterion (AIC) and Schwartz's Bayesian Information Criteria (BIC) values.

Next, separate unconditional multilevel growth models were estimated to assess the optimal nature and shape of change in absolute diurnal cortisol and CRP levels over time (objective 1). This was done by including a *time* and *time* by *time* variable to model the linear and non-linear effect of time, respectively, as compared to a model without a time variable (i.e., a model assuming no change). Models assuming no change, linear change, and non-linear (quadratic) change were compared using AIC and BIC values. Second, to examine whether change in absolute diurnal cortisol levels predicted change in CRP levels (objective 2), a conditional model with CRP as the outcome variable and absolute diurnal cortisol as unique Level-1 predictor was estimated. Given that Level-1 predictors can contain both intra- and inter-individual variability, grand-mean and group-mean (also called person-mean) centered values were computed for absolute diurnal cortisol levels to allow for the disaggregation of intra- and inter-individual effects of absolute diurnal cortisol on CRP levels (Bauer & Curran, 2016; Curran & Bauer, 2011). No other predictor was included in this model. Finally, in order to assess if behavioural, physical, and psychological variables predict absolute diurnal cortisol and CRP levels (objective 3), an individual model for each candidate predictor (i.e., ST, MVPA, BMI, depressive symptoms, perceived general stress, and cancer-related stress) was estimated, for a total of 12 models (six with absolute diurnal cortisol levels as the outcome variable and six with CRP levels as the outcome variable). All predictors were time-varying and therefore included as Level-1 variables. Additionally, each Level-1 predictor was decomposed by calculating grand-mean and group-mean centered variables (Curran & Bauer, 2011). Because it was assumed that not all participants had the same levels at T1 or rate of change over time, models with fixed effects only and models with both fixed and random effects were tested and compared. General conclusions remained unchanged when candidate predictors were allowed to vary across persons

(i.e., when random effects were included) and when they were not (i.e., when only fixed effects were included). However, including random effects led to worse model fit, and the variance around the slopes were not significant, suggesting the rate of change was not different across persons. They were therefore excluded from the analyses. The retained conditional multilevel growth model for each candidate predictor was re-tested with potential confounding variables available within the database measured at T1 (i.e., age, education, cancer stage, medication use, time since diagnosis, hormonal treatment, smoking status). The general conclusions drawn from the adjusted models did not differ from the unadjusted models; therefore, only results from the unadjusted models are presented for parsimony.

3. Results

3.1. Participants Characteristics

Socio-demographic and cancer-related characteristics for the analytical samples (cortisol, *n*=192; CRP, *n*=168) are depicted in Table 1. Participants were, on average, 55 years old, self-identified as White (>85%), were post-menopausal (>64%), and married or living with a spouse (>63%). Most of them were diagnosed with stage I or II breast cancer (>81%) and received chemotherapy as part of their treatment regiment (>64%).

3.2 Summary of Main Results

Overall, results indicated that absolute diurnal cortisol levels did not significantly change over time post-treatment, but that CRP levels significantly decreased over time, albeit in a non-linear fashion and these changes were not predicted by initial levels and change in absolute diurnal cortisol levels. In the prediction of absolute diurnal cortisol levels, increases in participants' ST level (relative to their own average levels) were associated with a reduction of absolute diurnal cortisol levels (intra-individual level association), while having higher overall

ST (relative to others) was associated with higher overall absolute diurnal cortisol levels (inter-individual association). In addition, engaging in more PA, having a lower BMI, and reporting lower health- and cancer-related stress (relative to others) was associated with lower overall CRP levels (inter-individual level associations).

Table 1. Characteristics of participants included in the analyses

Demographic characteristics	**Cortisol** (*n*=192)	**C-reactive protein** (*n*=168)
Age [mean years [SD] (range)]	55.1 [11.0] (28.0-79.0)	55.2 [11.0] (28.0-79.0)
Ethnicity [*n* White (%)]	163 (84.9)	144 (85.7)
Relationship status [*n* (%)]		
Single, divorced/separated, or widowed	68 (35.4)	61 (36.4)
Married or living with a life partner	124 (64.6)	107 (63.7)
Highest level of education attained [*n* (%)]		
College, technical degree or below	95 (49.5)	81 (48.2)
University undergraduate degree or above	97 (50.5)	87 (51.8)
Household income ($CAD) [median]	70,000	70,000
Time since diagnosis [mean months [SD] (range)]	10.6 [3.4] (2.0-20.0)	10.5 [3.5] (2.0-20.0)
Received chemotherapy [*n* (%)]	123 (64.1)	109 (64.9)
Post-menopausal [*n* (%)]	126 (65.6)	109 (64.9)
Cancer stage [*n* (%)]		
I	79 (41.4)	67 (39.9)
II	76 (39.6)	70 (41.7)
III	37 (19.3)	31 (18.5)
Predictors [grand mean [SD] (range)]		
Weekly sedentary time (minutes)	4215.8 [680.4] (1984.8-6096.0)	4312.8 [690.9] (1984.8-6096.0)
Weekly MVPA time (minutes)	103.0 [81.9] (0.0-526.0)	102.7 [80.5] (0.0-459.3)
Body mass index	26.0 [5.3] (17.4-50.2)	26.3 [5.4] (17.4-50.1)
Depressive symptoms	1.7 [0.5] (1.0-3.7)	1.7 [0.5] (1.0-3.7)
General stress	2.5 [0.6] (1.0-4.6)	2.6 [0.6] (1.0-4.2)
Health- and cancer-related stress	2.5 [0.8] (1.0-4.0)	2.6 [0.8] (1.0-4.0)

Note. *MVPA* = moderate-to-vigorous intensity physical activity

3.3. Objective 1: How do absolute diurnal cortisol and CRP levels change over time post-treatment?

A heterogeneous first order autoregressive structure minimized AIC and BIC values and was therefore retained both for cortisol and CRP levels models. This structure assumes homogeneous variances and correlations that decline exponentially with distance. In this case, this means that the variability in a measurement (e.g., cortisol), is constant regardless of which time point it was measured at. It also means that two measurements that are adjacent in time are

most highly correlated and that as measurements get further and further apart, they are less and less correlated. Using a heterogeneous first order autoregressive structure, a model assuming no change over time was retained for absolute diurnal cortisol levels based on AIC and BIC values. In this retained model, the fixed estimate indicated that there was a significant mean intercept (B=10.90, standard error [SE]=0.12, p<.01), indicating that average level of absolute diurnal cortisol was significantly different from zero; however, the model implies that levels remain stable over time (B=0.05, SE=0.04, p=.17). For CRP, a model assuming non-linear (i.e., quadratic) change was retained. In this retained model, the fixed estimates indicated that there was a significant mean intercept (B=1.45, SE=0.14, p<.01), indicating that average level of CRP was significantly different from zero. It also implied that CRP levels changed over time in a curvilinear way, whereby levels decreased over time but more sharply initially (B_{linear}=-0.31, SE=0.11, p=.01; $B_{quadratic}$=0.05, SE=0.02, p=.03). Table 2 provides scores for absolute diurnal cortisol and CRP levels over the five time points.

Table 2. Means and standard deviations of cortisol and CRP levels over the five time points[1]

Time point	Cortisol (nmol/Lxh)	C-reactive protein (mg/L)
T1: 3.5 months post-treatment [mean [SD] (range)]	10.78 [1.78] (7-16)	1.43 [1.67] (0-8)
T2: 6.5 months post-treatment [mean [SD] (range)]	11.27 [2.47] (5-18)	1.21 [1.38] (0-8)
T3: 9.5 months post-treatment [mean [SD] (range)]	11.07 [2.14] (6-16)	1.08 [1.28] (0-9)
T4: 12.5 months post-treatment [mean [SD] (range)]	10.55 [2.12] (5-15)	1.13 [1.35] (0-9)
T5: 15.5 months post-treatment [mean [SD] (range)]	11.29 [2.25] (5-18)	1.16 [1.61] (0-10)

3.4. Objective 2: Is change in CRP levels predicted by initial levels or change in absolute diurnal cortisol levels?

Results indicated no association between absolute diurnal cortisol and CRP levels both at the inter- (B=0.07, SE=0.05, p=.15) and intra-individual level (B=-0.05, SE=0.06, p=.39). This

[1] Values are different than the ones reported in Lambert et al. (2020) given the larger sample of the current study.

means that differences in levels of absolute diurnal cortisol *between* participants' did not account for the changes in CRP levels over time, and that differences *within* participants' levels of absolute diurnal cortisol over time did not explain the decreases in CRP levels, respectively.

3.5. Objective 3: What variables predict absolute diurnal cortisol and CRP levels?

The results of the conditional multilevel growth models are presented in Table 3. When comparing the conditional multilevel growth models with the unconditional multilevel models, the conditional multilevel models with statistically significant predictors resulted in a reduction in AIC and BIC values, indicating better fit. This implies that the addition of these predictors helped to explain significant individual differences in absolute diurnal cortisol and CRP levels.

3.5.1. Predicting Absolute Diurnal Cortisol levels

Results showed that ST, both at the inter- (B<0.01, SE<0.01, p=.01) and intra-individual level (B=-0.01, SE=0.01, p<.01), was significantly associated with absolute diurnal cortisol levels. The significant inter-individual level association indicates that participants who generally reported higher ST (as compared to others) had overall higher levels of absolute diurnal cortisol. The significant intra-individual level association, on the other hand, indicates that participants had lower absolute diurnal cortisol levels when they engaged in more ST than (as compared to their own average across time points). MVPA, BMI, depressive symptoms and perceived general and health- and cancer-related stress were not significantly associated with absolute diurnal cortisol levels, either at the inter- or intra-individual levels (Bs≤ 0.24, SEs≥0.33, ps≥.18).

3.5.2. Predicting CRP levels

Results indicated an inter-individual level association between CRP levels and MVPA (B=-0.004, SE<0.01, p<.01), BMI (B=0.10, SE=0.01, p<.01), and health- and cancer-related stress (B=0.240, SE=0.12, p=.04). These results mean that participants who generally engaged in

more MVPA, had a lower BMI, and reported lower health- and cancer-related stress (as compared to others), had overall lower CRP levels. There was no intra-individual level association between CRP levels and MVPA, BMI, and health- and cancer-related stress. Similarly, there was no inter- and intra-individual level associations between CRP levels and ST, depressive symptoms, and perceived general stress (*B*s≤0.20, SEs≥0.24, *p*s≥.14).

Table 3. Fixed effect results of multilevel modeling analyses testing time-varying predictors of absolute diurnal cortisol and CRP levels in BCS.

	Absolute diurnal cortisol levels			**CRP levels**		
	B	**SEs**	***p*s**	***B***	**SEs**	***p*s**
Sedentary time						
Intercept	10.881	0.118	<.01*	1.457	0.142	<.01*
Time	-	-	-	-0.316	0.115	<.01*
Time squared	-	-	-	0.056	0.025	.03*
Inter-individual effect	<0.001	<0.001	.01*	<0.001	<0.001	.62
Intra-individual effect	-0.001	<0.001	<.01*	-0.001	<0.001	.81
MVPA						
Intercept	10.875	0.119	<.01*	1.455	0.139	<.01*
Time	-	-	-	-0.302	0.114	<.01*
Time squared	-	-	-	0.051	0.025	.04*
Inter-individual effect	0.001	0.002	.41	-0.004	0.001	<.01*
Intra-individual effect	-0.002	0.002	.42	0.002	0.001	.14
Body mass index						
Intercept	10.845	0.119	<.01*	1.406	0.139	<.01*
Time	-	-	-	-0.303	0.117	.01*
Time squared	-	-	-	0.055	0.026	.03*
Inter-individual effect	0.010	0.022	.67	0.096	0.014	<.01*
Intra-individual effect	0.091	0.068	.18	-0.049	0.043	.26
Depressive symptoms						
Intercept	10.863	0.120	<.01*	1.451	0.142	<.01*
Time	-	-	-	-0.300	0.115	.01*
Time squared	-	-	-	0.0527	0.025	.04*
Inter-individual effect	0.240	0.277	.39	0.195	0.202	.34
Intra-individual effect	-0.360	0.331	.28	-0.146	0.239	.54
Perceived general stress						
Intercept	10.850	0.120	<.01*	1.455	0.143	<.01*
Time	-	-	-	-0.313	0.116	.01*
Time squared	-	-	-	0.0548	0.025	.03*
Inter-individual effect	0.189	0.120	.47	-0.067	0.189	.72
Intra-individual effect	-0.273	0.316	.39	0.195	0.222	.38
Health- and cancer-related stress						
Intercept	10.883	0.120	<.01*	1.460	0.141	<.01*
Time	-	-	-	-0.304	0.115	.01*
Time squared	-	-	-	0.053	0.025	.04*
Inter-individual effect	-0.206	0.167	.22	0.240	0.118	.04*

Intra-individual effect	0.127	0.208	.54	-0.120	0.152	.43

Notes. *MVPA* = moderate-to-vigorous intensity physical activity. *B* = estimate; *SE* = standard error. Separate models were tested for each variable to conserve statistical power. Parameters are unstandardized coefficients.
*$p<.05$

4. Discussion

The objectives of this study were to (1) describe BCS' absolute diurnal cortisol and CRP level patterns over the first 1.5 year post-treatment, (2) assess whether change in CRP levels was predicted by initial levels and/or rate of change in absolute diurnal cortisol levels, and (3) present the associations between absolute diurnal cortisol and CRP levels and a wide range of modifiable behavioural, physical, and psychological variables. ST, depressive symptoms, perceived general stress, and health- and cancer-related stress were considered as candidate predictors of absolute diurnal cortisol and CRP levels. Based on previously published findings by our team (Lambert et al., 2020; Sabiston et al., 2018a), MVPA and BMI were also included to take their variance into consideration in our models. Results indicated that absolute diurnal cortisol levels did not significantly change over time post-treatment, but that CRP levels significantly decreased over time, albeit in a non-linear fashion and these were not predicted by initial levels and change in absolute diurnal cortisol levels. In the prediction of absolute diurnal cortisol levels, increases in participants' ST level (relative to their own average levels) were associated with a reduction of absolute diurnal cortisol levels (intra-individual level association), while having higher overall ST (relative to others) was associated with higher overall absolute diurnal cortisol levels (inter-individual association). In addition, engaging in more PA, having a lower BMI, and reporting lower health- and cancer-related stress (relative to others) was associated with lower overall CRP levels (inter-individual level associations).

Very few studies have assessed the nature and shape of change in absolute diurnal cortisol and CRP levels over time in cancer survivors post-treatment. Hsiao et al. (2017) found

that diurnal cortisol levels fluctuated over time post-treatment in BCS, whereby diurnal patterns changed from a flatter to a steeper slope, suggesting a trend towards recovery. These changes were not observed in this study. Indeed, in contrast to the hypothesis, absolute diurnal cortisol levels did not significantly fluctuate from approximately 3.5 to 15.5 months post-treatment. Given that some studies observed no diurnal cortisol level dysregulation post-treatment in BCS when compared to women with no history of cancer (Couture-Lalande et al., 2014; Zeitzer et al., 2016), it is possible that participants in this study also did not exhibit cortisol dysregulation in the first place, thus explaining the absence of return-to-recovery evidence. Villasenor et al. (2014) reported that CRP levels decreased over time in BCS. Consistent with these findings, the results support this trend and provide further insight into the nature of change from treatment completion onwards. Whilst Villasenor et al. (2014) showed that CRP levels return to normal ranges following cancer treatment, they could not assess whether levels changed in a linear or non-linear fashion due to the design of their study. In this study, with five assessments spanning a 15.5-month period, results show that CRP levels decreased in a non-linear, quadratic pattern. CRP levels have been identified as a very sensitive marker of tumor growth and metastasis (Mantovani et al., 2008; Seruga et al., 2008; Villasenor et al., 2014). The rapid initial decrease in CRP levels observed post-treatment completion could thus imply that the cessation of treatment coincided with tumor deletion. Additionally, treatment completion also typically corresponds to a time when BCS return to usual activities and experience improvements in quality of life, vitality, and treatment-related stress (Connerty & Knott, 2013; Costanzo et al., 2007), all of which could contribute to the rapid initial decrease in CRP levels. The slow-down in decrease over time can be explained by factors such as stress with regard to going back to work and expectations to return to previous roles and responsibilities, fatigue, as well as hormonal

disruption following treatment (Allen et al., 2008; Bower et al., 2007). Further research is needed to gain a better understanding of the underlying mechanisms and factors involved in cortisol and CRP level fluctuations post-treatment for breast cancer.

No evidence of intra- or inter-individual level associations between absolute diurnal cortisol and CRP levels was found in this study. Chronic exposure to elevated levels of cortisol (as it might be the case in situation of long-term stress such as an experience of cancer) may weaken the sensitivity of immune cell receptors and make them non-responsive to cortisol-mediated signaling, thereby interfering with the transduction of the typical physiological effects of cortisol on CRP and immune functions (Miller et al., 2008; Rueggeberg et al., 2012). Additional research is needed to gain further insight into the cortisol-CRP relationship reported in other studies and examine whether other variables may influence the relationship (Sharpley et al., 2019).

It is widely known that high ST is associated with important health risks, both physical and psychological (Allen et al., 2019; Biswas et al., 2015; Zhai et al., 2015). Among BCS, elevated ST has been associated with a higher incidence of comorbid conditions, greater fatigue and pain severity, depression, and lower health-related quality of life (George et al., 2013; Phillips et al., 2016; Trinh et al., 2015). Studies investigating the association between ST and cortisol levels have found mixed results (Nabi et al., 2016; Jackson et al., 2019; Teychenne et al., 2018). In this study, participants who reported higher ST (relative to others) had higher absolute diurnal cortisol levels (i.e., inter-individual level association). This finding could be partly explained by the fact that sedentary individuals typically report greater fatigue, lower energy levels, and poorer mental health than active individuals (Ellingson et al., 2014; Sanchez-Villegas et al., 2008). In turn, fatigue and mental health difficulties (e.g., depression) have been associated

with increased cortisol levels in BCS (Hsiao et al., 2012; Schmidt et al., 2016). In addition, results of this study show that, fluctuations in ST within participants is associated with absolute diurnal cortisol levels. Specifically, results suggest that increases in participants' ST levels (as compared to their own average) was associated with lower absolute diurnal cortisol levels (i.e., intra-individual association). Whilst this intra-individual level association is in the opposite direction than the inter-individual association, it supports the notion that observing an inter-individual level association does not guarantee a similar intra-individual level association and vice versa (Hox, 2010), and underscores the value of using analytical approaches that can consider both intra- and inter-individual level associations (e.g., MLM). To explain the inverse association, researchers may want to consider the type of ST activity. It is possible that participants may have engaged in lower-arousal ST activities (such as reading and napping vs. higher-arousal ST acitivities such as watching a scary movie and playing video games) on those particular days. However, data on type of ST activity were not collected. Considering that BCS spend most of their waking hours engaging in ST and generally have higher ST than individuals without a history of cancer (Kim et al., 2013; Sweegers et al., 2019), it is imperative to establish whether ST plays a role in the physiological outcomes of BCS post-treatment, and if so, which type of ST activities. Moreover, based on the inter-individual results in this study, interventions targeting BCS with high ST levels could be an effective strategy to promote optimal health outcomes in BCS. Additional studies to confirm these associations are however warranted.

Lower MVPA, higher BMI, and greater health- and cancer-related stress were associated with higher CRP levels in general based on observed inter-individual level associations. Together, these variables are known to contribute to poorer general health outcomes, including increased morbidity and all-cause mortality (Bauman et al., 2017; Strohacker et al., 2013),

thereby providing an explanation for their associations with elevated CRP levels. These findings are in line with several studies conducted in the general population (Colbert et al., 2004; Costa et al., 2019; Timpson et al., 2011) as well as in BCS (Asegaonkar et al., 2015; Babaei et al., 2015). They also confirm inter-individual associations observed by our team between CRP levels, MVPA and BMI using conventional analyses (Lambert et al., 2020), and thus echo ours and others previous recommendations to implement of weight management and PA interventions to decrease inflammatory levels and promote optimal health post-treatment among BCS (Ballard-Barbash et al., 2012; Fairey et al., 2005; Sabiston et al., 2018a). In addition though, the inter-individual level associations between health- and cancer-related stress and CRP levels underline that other factors, not previously examined, may help to explain why some BCS report more physiological dysregulation than others – i.e., those with higher stress levels. These novel results suggest that lowering health- and cancer-related stress in BCS may further help to enhance BCS' health post-treatment. Indeed, they add that helping BCS effectively manage stress may improve the efficacy of weight management and PA interventions.

Depressive symptoms and perceived general stress were not associated with absolute diurnal cortisol and CRP levels in this sample of BCS. These findings are dissimilar to those of McFarland et al. (2018) and Ricci el al. (2018) who found positive associations between these psychological variables and CRP levels in cancer survivors. Speculatively, the lack of association in this study may be explained by participants' relatively low reporting of depressive symptoms and general stress, as well as the limited variability in those variables. Alternatively, it may be explained by the timing of the assessments in this study. Some have suggested that depressive symptoms and stress experienced by cancer survivors might be *outcomes* of inflammatory pathway activation rather than *predictors* (Lee et al., 2004; Miller et al., 2008).

Accordingly, CRP levels during treatment could predict later depressive symptoms and stress post-treatment (T1-T5). Additional longitudinal studies covering both treatment and post-treatment phases with larger samples reporting varying levels of depressive symptoms and stress are warranted to further assess the nature, timing, and direction of these relationships. Nevertheless, continued monitoring, prevention and treatment of depressive symptoms and stress remains of crucial clinical relevance given their high prevalence in BCS (Badger et al., 2004; Groarke et al., 2013; Stanton, 2006) and because these psychological states may impair PA/ST behaviour post-treatment (Spector et al., 2013; Ventura et al., 2013), which was found to be predictors of cortisol and CRP levels in this study.

4.2. Strengths & Limitations

The repeated measurement of a wide range of behavioural, physical, and psychological predictors in BCS constitutes an important contribution to the cancer survivorship literature. The inclusion of six distinct modifiable candidate predictors into our models allows for a powerful approach to gaining of greater understanding of the influence of general lifestyle habits and psychological health on outcomes of cancer survivors. Very few studies have included such frequent data collections and focused on the early post-treatment phase of cancer survivorship and the current study addresses this gap in the literature (Allen et al., 2008; Roundtree et al., 2011; Stanton, 2012). Extending from the results from our previous work (Lambert et al., 2020; Sabiston et al., 2018a), the analytical techniques employed overcome some of the limitations in the current literature by examining both intra- (within) and inter- (between) individual level associations and trends. The objective and precise assessment of both ST and PA, as well as the relatively large sample size, are other strengths of the study. Nonetheless, this study also has limitations. First, although self-report is appropriate to assess depressive symptoms and different

types of perceived stress (Gotay & Pagano, 2007; Roberti et al., 2006; Vodermaier et al., 2014), some bias may have affected the results (due to socially desirable responding, for instance). A second limitation is that participants volunteered to take part in this study, with the majority of them being White, on average 55 years of age, post-menopausal, well-educated, and diagnosed with early-stage breast cancer, thereby limiting the ability to generalize the findings to all BCS. Finally, this study is non-experimental and therefore inferences of causality and direction of effects cannot be made.

5. Conclusion

Given that cancer survivors with persistent post-treatment physiological dysregulations have elevated risk of adverse health outcomes (Reza et al., 2014; Schrepf et al., 2013; Sharpley et al., 2019), studies aiming to identify cancer survivors at greater risk of such dysregulations are of high priority. This study provides evidence that lifestyle modification interventions (including weight management, stress reduction, and activity level strategies) might be effective, non-pharmaceutical strategies to promote physiological health in BCS. Data on ST and PA parameters such as frequency (e.g., everyday for shorter periods of time vs. only twice a week but for longer periods of time), intensity (e.g., high intensity interval training vs. moderate intensity continuous exercise), type (e.g., strength training vs. aerobic training; video games vs. watching television vs. reading), context (e.g., indoors vs. outdoors or individual vs. group-based), and time of the day should be collected in future studies to enable the development of the most optimal and beneficial interventions.

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CHAPTER FIVE

General Discussion

Although cancer survivors may be cancer-free after treatment completion, they may continue to experience lingering problems that can significantly impair their quality of life. Gaining more knowledge on the persisting physiological problems BCS experience and identifying variables that could be targeted in interventions to improve health outcomes in BCS are critical to inform development of optimal survivorship care plans. The three inter-related studies of the current research program addressed knowledge gaps in the literature to advance current knowledge on the late and long-term physiological impact of a BC experience and inform practice. The main findings can be summarized as follows. First, contrary to Study One's hypothesis, we found no difference in the SIgA concentration patterns of BCS compared to those of women with no history of BC, though differences were observed in their cortisol and sAA concentration patterns. Second, in line with Study Two's and Three's hypotheses, 4 out of 6 behavioural, physical, and psychological variables examined (i.e., physical activity level, sedentary time, body mass index, and health- and cancer-related stress) were associated with physiological dysregulations in BCS. In the following sections, we discuss these main findings along with other key findings within two main sections about: (a) the physiological dysregulations observed in BCS post-treatment, and (b) the predictors of observed physiological dysregulations. We also contrast and compare our findings to the extended literature and highlighted their contributions while noting limitations. It is important to note that, while we acknowledge that cortisol and sAA were not directly examined in Study One and that their respective findings were previously published elsewhere, we still believe they are an integral part of this research program. As such, all findings reported in the article associated with Study One will be included in the general discussion below.

Physiological Dysregulations observed in BCS post-treatment

Results from the current research program point to physiological dysregulations that can occur in BCS post-treatment. As highlighted in Study One (Lambert et al., 2018), compared to women with no history of cancer, BCS displayed blunted cortisol reactivity in response to an acute stress situation (as also reported in Couture-Lalande et al., 2014) as well as an elevated diurnal sAA profile (as also reported in Wan et al., 2016). Whilst evidences of this blunted reactive cortisol profile was captured through examination of patterns of fluctuations over time (specific time points of measurements) in Study One, evidence of it using the absolute amount of cortisol increase in response to stress (as indexed by areas under the curve to increase) were demonstrated in Study Two. Together, these findings indicate that, although BCS may subjectively appraise stress similar to women without a history of cancer, their physiological reaction to stress may differ. These results are in line with studies reporting dysregulated cortisol patterns in BCS (Bower et al., 2005; Hsiao et al., 2017). To our knowledge, other than the data reported in Study One, no study in the literature has compared sAA concentration patterns in cancer survivors and individuals with no history of cancer. Both the HPA (cortisol) and the SAM axis (sAA) are crucial in maintaining homeostasis and prepare the body to effectively respond to stressors and abnormalities in the functioning of those systems are associated with several adverse health outcomes (Fulford & Harbuz, 2005; Piazza et al., 2010). Therefore, findings highlighted in Study One and Study Two suggest that post-treatment surveillance and targeted follow-up care might play an important role in the longevity of the BCS population. Additionally, given that cortisol and sAA are markers of different hormonal systems and highlight different components of stress regulation, their assessment in tandem appears to be a promising approach for a more comprehensive understanding of stress responses in BCS (Nater, 2018). Indeed, many have suggested that an imbalance of the two systems (rather than the

dysregulation of one system solely) might trigger a wide range of adverse health outcomes (Ali & Pruessner, 2012; Booij et al., 2015).

Results of Study One revealed no evidence of uncharacteristic SIgA diurnal or reactive concentration patterns, suggesting a normal and well-functioning immunological SIgA system in the sampled BCS who were on average 4.6 years post-diagnosis. Several studies have suggested immune impairment following a cancer experience (Standish et al., 2008; Verma et al., 2016), yet very few have used SIgA as indicator of immune function. The two studies that did, reported depressed SIgA levels in cancer survivors (Jensen et al., 2008; Sun et al., 2016). However, dissimilar to our study, participants of those studies were either patients currently receiving treatment (for types of cancer other than BC) or BCS who completed treatment within the last year as opposed to several years prior. The timing of biomarker assays in relation to treatment might therefore explain incongruence in findings. Indeed, in line with our results, Jensen et al. (2008) suggested that SIgA levels normalized approximately one year after treatment completion, which our findings seem to support. Given the crucial role of SIgA in maintaining a balance between tolerance to harmless bacteria invasion and immunity to potentially life-threatening infections or pathogens (Bishop & Gleeson, 2009; Li et al., 2020), the findings of Study One, along with those of Jensen et al. (2008), are meaningful as they represent a positive and hopeful outlook of cancer survivorship and suggest a prospective immune recovery in long-term BCS.

In Study Three, we found that absolute diurnal cortisol levels did not significantly change from approximately 3.5 to 15.5 months post-treatment. Given the complex nature of the relationship between a cancer experience and cortisol, it is difficult to make firm conclusions about the expected and desired direction of the effect. Dissimilar to results of our study, Hsiao et al. (2017) reported that cortisol levels fluctuated significantly during the first year after treatment, whereby BCS who had dysregulated diurnal cortisol patterns (flatter slopes) tended to recover towards normal diurnal patterns (steeper slopes) over

time. Some studies, however, found no diurnal cortisol level dysregulations post-treatment in BCS (Couture-Lalande et al., 2014; Zeitzer et al., 2016). It is therefore possible that our participants in Study Three did not exhibit cortisol dysregulations in the first place, thus explaining the absence of return-to-recovery evidence (i.e., absence of significant changes over time). It is also possible that post-treatment cortisol patterns were too complex (e.g., higher degree polynomials than those tested) to be captured using multilevel modeling. Although mathematically sophisticated and increasingly popular for analyzing data with repeated measurements, only linear and quadratic forms of changes were estimated in Study Three given that non-linear models are highly complex to interpret and understand. Therefore, cortisol change patterns may reflect other polynomial forms of change (e.g., cubic), as repeated downward cortisol trends due to brief reduction in overall stress exposure, tumor deletion, and changes in physiological processes (Asegaonkar et al., 2015; Kober et al., 2018; Miller et al., 2007) might be followed by upward trends due to late-appearing treatment side effects such as fatigue, insomnia, and pain, return to work and daily responsibilities, and reduction in social support (Allen et al., 2008; Bower et al., 2005, 2007). Finally, the sample of women in Study Three were relatively physically active, and given the positive effect of physical activity on cortisol reported in the literature (Anderson & Wideman, 2017; Payne et al., 2008), the sampled women may be less likely to experience physiological dysregulations following a BC experience and generally have physiological outcomes different than BCS who are less physically active. Nevertheless, the results pertaining to cortisol patterns reported in Study Three exemplify the highly complex nature of the relationship between diurnal cortisol and a cancer experience and indicate that much remains to be known as to which women may be at risk for post-treatment cortisol dysregulations. Future studies estimating polynomial forms of changes and including variables that could contribute to cortisol levels in BCS (e.g., social support, fatigue, stress expose) are warranted.

Additionally, Study Three revealed that CRP levels decreased over time in a non-linear fashion in BCS following treatment completion – a finding consistent with other studies that reported a CRP return to baseline (normalization) over time in BCS post-treatment (Villasenor et al., 2014; Wiley et al., 2017). Nonetheless, to our knowledge, our study was the first to provide insight on the trajectory of changes of CRP (linear vs. non-linear) as past studies used designs that did not permit the assessment of non-linear trends over time. Given that CRP level has been repeatedly identified as a non-specific sensitive indicator of advanced cancer stage, tumor size, and general cancer prognostic (Allin & Nordestgaard, 2011; Wiley et al., 2017), decreases in CRP following treatment completion, such as what we found in Study Three, appear coherent and logical. Such finding is encouraging because it is indicator of a reduced systemic inflammatory state in BCS and normative regulation of CRP is associated with better overall health outcomes (Frydenberg et al., 2016; Kaur, 2017; Xiao et al., 2017).

Finally, results of Study Three also showed that changes in CRP levels were not predicted by initial levels and/or changes in cortisol levels in BCS, that is, that fluctuations in cortisol levels did not prompt an increase in circulating CRP levels. This finding does not support findings of other studies suggesting that cortisol and CRP operate in tandem and that a dysregulated HPA system might trigger impaired activity in immune cells resulting in an increase in CRP/inflammation (Herriot et al., 2017; Johnson et al., 2013; Slavish et al., 2015). Yet, to our knowledge, Study Three is the first study to investigate the cortisol-CRP interaction in cancer survivors specifically. Additional studies on the covariation of cortisol and CRP levels in BCS are warranted given that research has repeatedly shown that the HPA axis and inflammatory systems need to be inherently intertwined in a reciprocal manner for optimal health outcomes (Pace et al., 2009; Suarez et al., 2015).

Predictors of Cortisol and CRP levels in BCS

Whilst Study One and Three helped to provide a comprehensive picture of BCS' physiological functioning and advanced knowledge on *if* and *how* specific biomarker dysregulations occur, Study Two and Three offered insight on variables associated with observed levels and dysregulations. Results of Study Two and Three revealed no significant association between both self-reported and objectively-measured physical activity level and cortisol levels. Such findings are consistent with the few studies in BCS which found no evidence of a physical activity effect on their cortisol levels (Ligibel et al., 2009; Payne et al., 2008). Yet, in the general population, the relationship between cortisol and physical activity remains unclear as no association as well as both positive and negative associations have been reported (Brumby et al., 2013; Hill et al., 2008; Melin et al., 2014). Different biomarkers (e.g., types [serum vs. salivary], assay procedures) and physical activity parameters (e.g., intensity, context, types) might play a role in these inconsistencies. Whilst physical activity level was not identified as a significant predictor of cortisol levels in Study Three, sedentary time was significantly associated with cortisol levels both at the intra- and inter-individual levels, meaning that variability in sedentary time levels relative to others as well as relative to one's own average related to cortisol. Similar to the association between cortisol and physical activity, the association between cortisol and sedentary time has also been found to be inconsistent in the literature, perhaps also due to a wide range of sedentary time parameters such as types of activities and patterns (Benatti & Ried-Larsen, 2015; Mansoubi et al., 2015). Collectively, these findings highlights that physical activity and sedentary time are indeed two distinct constructs, with different physiological outcomes in BCS and that one is not equal the inverse of the other (van der Ploeg & Hillsdon, 2017).

In Study Three, we also found that higher physical activity level was associated with lower overall CRP levels. In the literature, physical activity has been repeatedly associated with reduced stress and inflammation in BCS (Meneses-Echávez et al., 2016; Pierce et al., 2009; Sabiston et al., 2018).

Indeed, many have suggested that the wide range of health benefits of physical activity (both in the general population and in cancer survivors) can be partly explained by its capacity to decrease chronic low-grade inflammation within the body (Löf et al., 2012; Meneses-Echávez et al., 2016). Findings of Study Three also revealed positive associations between body mass index and lower health- and cancer-related stress and overall CRP levels (relative to others; inter-individual level associations). These findings are also in line with reported evidence in both the general population and in BCS specifically (Babaei et al., 2015; Gouin et al., 2012; Timpson et al., 2011; Wiley et al., 2017). The high volume of pro-inflammatory agents secreted by adipose tissue along with the stress-inflammatory mechanisms involved in higher perceived-stress situations likely explain these associations. The high CRP levels found in Study Three might reflect higher systemic chronic inflammatory status in BCS who feel more stressed regarding their health and have a higher body mass index (Goldberg & Schwertfeger, 2010; Liu et al., 2017).

Study Two and Three of this research program addressed limitation in the current cancer survivorship literature by examining the role of *modifiable* variables that could be directly targeted in interventions to improve physiological outcomes in BCS. The vast majority of previous studies have focused on demographic or cancer-related variables (e.g., age, menopausal status, type of treatment, cancer stage, time since diagnosis), that is, variables that cannot be readily modified by interventions (Hsiao et al., 2017; Lambert et al., 2020; Wiley et al., 2017). Whilst findings of those studies are informative and help gain a greater understanding of the factors that may potentiate or hinder adverse physiological outcomes in BCS post-treatment (thus identify women at greater risks), they are limited in terms of the insight they offer for the development of specific intervention strategies. Assessing a wide range of candidate predictors and their associations with two distinct biomarkers in the same BCS, collectively, Study Two and Three's findings indicate that cancer survivorship care plans including

strategies to (a) increase activity level (increase physical activity; decrease sedentary time), (b) encourage healthy dietary habits and general health awareness (to promote lower body mass index), and (c) develop stress-related coping abilities could lead to better physiological outcomes in BCS post-treatment. This is in line with the wide range of studies suggesting that modifiable health behaviours play a crucial role in the general health, prognosis, and quality of life of cancer survivors (Bloom et al., 2004; Ellsworth et al., 2012; Lynch et al., 2013).

Study Two and Three of this research program adds to existing research efforts aimed at generating knowledge that can inform the design and development of cancer survivorship plans by identifying variables associated with optimal outcomes post-treatment (Aaronson et al., 2014; Recklitis & Syrjala, 2017; Stanton, 2012). Collectively, findings indicate that plans integrating behavioural and lifestyle interventions aiming to promote physical activity, sleep quality, healthy eating, weight control, body image, and reduce sedentary time, alcohol consumption, smoking, fear of cancer recurrence, post-traumatic stress symptoms, and feelings of social isolation. Although in recent years workshops, peer support groups, and counseling/psychotherapy have become increasing available for cancer survivors (Akers et al., 2021; Bluethmann et al., 2015; Mohamed, 2018; Ochoa et al., 2017), no intervention has been designed specifically to respond to the long-term physiological dysregulations observed post-treatment (such as those reported in Study One and Two). Results of Study Two and Three could serve as the foundation for the elaboration of intervention strategies aiming to optimize physiological health after cancer. Continued efforts are needed to better understand cancer survivors' needs and assess the direct efficacy of such interventions.

Strengths and Contributions

With the number of cancer survivors climbing each year, cancer survivorship needs to be a priority in research and efforts to better understand, monitor, and mitigate the physiological

consequences of a cancer experience are critical. Collectively, this program of research uniquely adds to the literature by providing critical information about the enduring physiological effects of an experience of BC and helps shape new research questions and directions for the development of post-treatment interventions.

The purpose of Study One was to compare the cortisol, sAA, and SIgA secretion patterns of BCS with those of women without history of cancer in order to better describe the extend of the physiological dysregulations observed in BCS. The assessment of multiple biomarkers and secretion patterns (diurnal and reactive) over several time points in the same group of BCS is something that, to our knowledge, had not been done before. The article associated with Study One serves to describe BC survivors' physiological profile pertaining to three distinct biomarkers within a single study. Whist the assessment of cortisol and sAA levels in BCS has been done in the past (although very limited for sAA), the assessment of SIgA levels represented an important contribution to the BC survivorship literature as only one study to date has examined this specific biomarker in a BCS population (Jensen et al., 2008). Including SIgA assessment in such research allows to gain more insight on the long-term impact of a cancer experience regarding immune functions. Study One provided a foundation for the subsequent studies of this research program and highlighted the necessity to investigate variables associated with these dysregulations in order to inform post-treatment intervention strategies and promote optimal health outcomes in this population. Study One further highlighted BCS' needs for and the importance of post-treatment monitoring through specific surveillance programs, which would allow to identify and potentially treat any complications and long-term effects of care (Tralongo et al., 2017).

The main contributions of Study Two and Study Three of this research program include the identification of variables that are associated with cortisol and/or CRP levels and could be readily

targeted for optimal post-treatment outcomes. Study Two is of high relevance given that we are not aware that any other study has investigated the role of PA on cortisol levels in women with a history of cancer and controls within a single study and considered both diurnal and reactive concentration patterns over several time points. Similarly, Study Three makes important contributions to the field given that no other study has examined multiple predictors of two different biomarkers in the same cancer survivors. Together, not only do these studies represent a step forward towards the identification of variables that could either potentiate or hinder positive physiological outcomes after BC treatment but they also have the potential to inform the development of new and more effective intervention strategies targeting specific variables. Findings highlight that BCS should be encouraged to adopt certain lifestyle and behavioural regimen following treatment completion. The findings may also help to gain a better understanding of the potential biological mechanisms behind the physiological dysregulations observed in BCS. The longitudinal design of Study Three allowed for the description of natural trends of cortisol and CRP levels over time after an experience of BC. Moreover, multilevel modeling enabled for both between- and within-person analysis, thereby offering a unique survivor-centered perspective that allowed to evaluate the potential impact of relevant variables unique to each individual (e.g., sedentary time and physical activity levels, psychological health). Study Three's results further underscore the value of using analytical approaches that can consider both intra- and inter-individual level associations as an association at an inter-individual level does not guarantee an association at an intra-individual level and vice versa.

The assessment of sedentary time and physical activity simultaneously in Study Three contributed to the notion that these concepts are two distinct behaviours with unique and independent physiological consequences and addressed the limitation of several studies that equate a lack of physical activity as equivalence to sedentary time. Further, as it has been shown that self-reported

measures of sedentary time and physical activity are prone to errors such as misinterpretation and misclassification as well as over- and under-reporting (Altschuler et al., 2009; Sallis & Saelens, 2000), the use of accelerometers to objectively monitor sedentary time and physical activity in Study Three is another strength of this research program. Finally, Study Three significant adds to the current literature as it addressed early post-treatment phase of cancer survivorship, which has been understudied (Stanton, 2012; Trinh et al., 2015).

Limitations

Although the three studies comprising this research program make a number of contributions to the cancer survivorship literature, there are some limitations. First, given that all biomarkers were assessed post-treatment, there is no way of knowing if, for instance, physiological dysregulations were present before treatment/diagnosis and were associated with cancer development in the first place. The inclusion of a group of women with no history of cancer in Study One and Two served as a way to counterbalance this limitation. Nonetheless, Study Three did not include a control group, precluding analysis of possible similarities or differences in results for women with and without a history of cancer. Another limitation is that certain variables examined were assessed using self-reported measurements (i.e., physical activity in Study Two; depression symptoms and stress levels in Study Three) rather than objective measures or structured clinical diagnostic assessment; this may have introduced bias due to social desirability and recall inaccuracy for instance, which may have affected the results. It is also important to consider that findings of Study Two and Three regarding associated predictors of cortisol and CRP levels do not imply that intervention strategies targeting these specific variables will be effective in promoting better physiological outcomes in BCS. Instead, they suggest that trials assessing the direct effect on an intervention on BCS' physiological functioning are warranted. Finally, as with most studies conducted with cancer survivors, the three studies of this

research program are limited by their small sample size (for Study One and Two), convenience samples, and overrepresentation of self-identified White participants. More heterogeneous samples may have led to different results. Limitations specific to each particular study are described within relevant chapters of this dissertation (i.e., Chapter Two, Chapter Three, and Chapter Four).

Conclusion

Studies presented in this dissertation offered insights on the long-term physiological sequalae experienced by BCS and examined variables associated with these dysregulations. Together, these three studies help to raise awareness and educate people about the fact that cancer survivors continue to face significant challenges after treatment completion and that, as BC survival rates increase, new challenges emerge (Harrington et al., 2010). Results may help facilitate a better understanding for clinicians and caretakers when providing post-treatment care to cancer survivors and promote effective responses to their needs. Predictors identified in this research program are all readily modifiable, thereby making the results of these studies useful not only to identify BCS at higher risks of exhibiting psychological dysregulations post-treatment and those in greater need of close monitoring and interventions if/when resources are limited but also serve as an important impetus for the development of individualized cancer care plans to prevent physiological dysregulations post-treatment.

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Appendix A

TSST protocol and script for Study One and Two

Before the participant arrives

Room preparation:

- *There will be three confederates acting as committee members. Each committee member will have a seat behind a table, a pen, and a notepad.*
- *A video camera will be set up and plugged in, but it will not be recording.*
- *A stopwatch for Confederate A to time the tasks*

Confederates

*During the experimental procedure**, confederates will be asked to not give any emotional or verbal feedback to the participant. Respond in a neutral manner, polite (but stern) manner. Do not harass or anger the participant.** Only one confederate (A) will be asking questions, and will be introduced as the interviewer sent on behalf of the Hudson's Bay Company to conduct the interviews. The second and third confederates (B & C) will be introduced as individuals who have been trained to monitor nonverbal behaviour during the task. Confederates will be encouraged to take notes on the participant's performance as if were a real interview.*

Experimenter will bring the participant into the room and introduce the participant to the confederates approximately 15 minutes after the participant's arrival. After the introduction and brief explanation, experimenter will bring participant back to the other room to prepare her speech (5 minutes).

What to do if...

- The participant tries to shake the committee members hands --> Please stay where you are.
- The participant asks if we have any questions (and used up 5 minutes) --> No, we will be moving onto the next task.
- The participant says that they do not want to continue --> **Do not force them to continue**. Ask if they would like to try the second task (arithmetic), if so introduce the second task as you normally would: "For your second task,..." If they say no say: "that is ok (with no emotion). That will be all."

First task: Mock Job Interview

After the participant re-enters the experimental room, one of the confederates will pretend to turn on the video camera. Confederate A will let the participant know that she may begin her speech.

If participant's speech is less than 5 minutes:
Confederate A: You still have some time left. Please continue!

If participant finishes before 5 minutes a second time:
Pause briefly (~20 seconds) and proceed with asking prepared questions to fill up the 5 minutes:

- What are your personal strengths and weaknesses?
- Have you had any conflicts with a previous team member or colleague? How did you handle it?
- Where do you see yourself in 5 years?
- What is the most difficult task that you have had to deal with at a previous job?
- What are three traits that you consider to be important in the position you are applying for?
- What makes you better than other applicants for the same position?

Once 5 minutes is over:
Confederate A will give the instructions to the second task.

Second task: Arithmetic task

Confederate A: That's fine, thank you. For the second task please serially subtract 13 from 1022, as fast and accurately as possible. If you make a mistake, you will need to restart the task from the beginning. Do you have any questions?

If participant says yes: *Confederate A will answer the question.*

If the participant does not know what it is meant by a serial subtraction, Confederate A, please define it as counting down by a certain number. For example, to serially subtract 2 from 12, means to start at 12 and to continuously subtract 2 from the answer, so 12, 10, 8, 6, and so on.

If participant says "no": Confederate A: You may begin.

If participant makes a mistake: That is incorrect, please start again from 1022.

After 5 minutes: Confederate A: That will be all. We're done, please return to the other room.

Appendix B

Visual Analog Scales (VAS) for Study One

Below the example, please draw a vertical line on the horizontal line to indicate your feelings

Example:

I feel happy.

I feel anxious.

Not at all Very Much

I feel stressed.

Not at all Very Much

Appendix C

Socio-demographic Questionnaire for Study One and Two

The following question involves gathering information with respect to your socio-demographic background. For each question, please circle the appropriate answer.

General history

sd1. What is your ethnic background?
1. White/Caucasian
2. Black (e.g. Haitian, African, Jamaican, Somali)
3. Asian (e.g. Chinese, East Indian, Japanese, Vietnamese)
4. Latino or Hispanic
5. Pacific Islander
6. Middle Eastern
7. Native Canadian/First Nations/Métis
8. Other. Specify: _____

sd2. How old are you? _____

sd3. What is your relationship status?
1. Single
2. Dating
3. Common Law
4. Married/Civil Union
5. Separated/Divorced
6. Widowed

sd4. If you are in a relationship, how long have you been with your partner (months and/or years)?

_____

sd5. What level of education have you completed?
1. Elementary School
2. High School
3. College
4. Bachelor's Degree
5. Master's Degree

6. Doctoral Degree

sd6. What is your current work status?
1. Blue collar (construction, factory worker, manual work, etc.)
2. White collar (administrator, lawyer, director, office work, sales, etc.)
3. Business owner or self-worker
4. Unemployed
5. Student
6. Stay at home
7. Medical leave of absence
8. Retired
9. Other

sd6a. If so, what was your employment before? _____
sd6b. How long have you been on a medical leave of absence? _____
sd6c. If so, what was your employment before? _____
sd6d. Please specify: _____

sd7. What is your current annual family income?
1. Under $20, 000
2. $20, 000 – $39, 999
3. $40, 000 - $59, 999
4. $60, 000 – $79, 999
5. $80, 000 – $99, 999
6. $100, 000 – $119, 999
7. $120, 000 – $139, 999
8. $140, 000 – $159, 999
9. $160, 000 – $179, 999
10. $180, 000 – $199, 999
11. $200, 000 and above

Breast cancer history

The breast cancer history section is divided in two sections. The first one pertains to an initial breast cancer diagnosis and its treatment, the second section pertains to a recurrence in breast cancer (if this applies) and its treatment.

Initial breast cancer:

sd8. When were you diagnosed with your initial breast cancer? _____/_____ Month Year

sd9. How old were you when you were diagnosed? _____

sd10. What stage of breast cancer were you diagnosed with?
1. Stage 0 (very early or "in situ")
2. Stage I (localized, no spreading)
3. Stage II (some localized spreading into lymph nodes)
4. Stage III (some localized spreading into lymph nodes)
5. Stage IV (metastases, where the cancer has spread to other parts of the body)
6. Not sure

We would like to know more about the treatment you received for your initial breast cancer diagnosis.

sd11. What type of surgery did you have?
1. Unilateral mastectomy
2. Bilateral mastectomy
3. Lumpectomy on one breast
4. Lumpectomy on both breasts
5. Surgery

sd12. Did you receive chemotherapy?
1. Yes
2. No, but I will (please go directly to question no. 13)
3. No, and I will not (please go directly to question no. 13)

What type of chemotherapy did you receive?

sd12a. I received neoadjuvant chemotherapy only (given before surgery to shrink the size of a tumor)
1. Yes
2. No

sd12b. I received adjuvant chemotherapy only (given after surgery to reduce the risk of recurrence)
1. Yes
2. No

sd12c. I received palliative chemotherapy (used to control the cancer in settings in which the cancer has spread beyond the breast and localized lymph nodes)
1. Yes

2. No

What chemotherapy regimen did you receive?

sd12d. Frequency (e.g. once every three weeks): _____

sd12e. Duration (e.g. 5 months): _____

sd13. Did you receive hormone therapy (or are you still receiving hormone therapy)?
1. Yes
2. No, but I will (please go directly to question no. 14)
3. No, and I will not (please go directly to question no. 14)

Sd13a. What type of hormone therapy did you receive (i.e. Tamoxifen)? _____

Sd13b. How long did you receive hormone therapy for (or how long have you been receiving hormone therapy)? _____

sd14. Did you receive radiation therapy?
1. Yes
2. No, but I will (please go directly to question no. 15)
3. No, and I will not (please go directly to question no. 15)

sd14a. If yes, how many sessions in total did you have? _____

sd15. Have you had breast reconstruction surgery or are you planning on having this surgery?
1. Yes, I have had breast reconstruction surgery
2. Yes, I plan on having breast reconstruction surgery
3. No, I have not, and do not plan on having breast reconstruction surgery

sd16. Have you experienced a recurrence in breast cancer?
1. Yes
2. No (Please go directly to question no. 26)

Recurrence in breast cancer

sd17. When did your recurrence occur? _____/_____ Month Year

sd18. How old were you when you were diagnosed with your recurrence? _____

sd19. What stage of breast cancer were you diagnosed with for this cancer?
1. Stage 0 (very early or "in situ")
2. Stage I (localized, no spreading)
3. Stage II (some localized spreading into lymph nodes)
4. Stage III (some localized spreading into lymph nodes)
5. Stage IV (metastases, where the cancer has spread to other parts of the body)
6. Not sure

sd20. What type of surgery did you have?
1. Unilateral mastectomy
2. Bilateral mastectomy
3. Lumpectomy on one breast
4. Lumpectomy on both breasts
5. Surgery

sd21. Did you receive chemotherapy?
1. Yes
2. No (please go directly to question no. 22)
3. No, and I will not (please go directly to question no. 22)

What type of chemotherapy did you receive? (Please select all the ones that apply)

sd21a. I received neoadjuvant chemotherapy only (given before surgery to shrink the size of a tumor)
1. Yes
2. No

sd21b. I received adjuvant chemotherapy only (given after surgery to reduce the risk of recurrence)
1. Yes
2. No

sd21c. I received palliative chemotherapy (used to control the cancer in settings in which the cancer has spread beyond the breast and localized lymph nodes)
1. Yes
2. No

sd22. Did you receive hormone therapy (or are you still receiving hormone therapy)?
1. Yes
2. No, but I will (please go directly to question no. 23)

3. No, and I will not (please go directly to question no. 23)

sd22a. What type of hormone therapy did you receive (i.e. Tamoxifen)? _____

sd22b. How long did you receive hormone therapy for (or how long have you been receiving hormone therapy)? _____

sd23. Did you receive radiation therapy?
1. Yes
2. No, but I will (please go directly to question no. 24)
3. No, and I will not (please go directly to question no. 24)

sd23a. If yes, how many sessions in total did you have? _____

sd24. Have you had breast reconstruction surgery or are you planning on having this surgery?
1. Yes, I have had breast reconstruction surgery
2. Yes, I plan on having breast reconstruction surgery
3. No, I have not, and do not plan on having breast reconstruction surgery

sd25. Have you experienced a recurrence in breast cancer?
1. Yes (Please complete the "recurrence in breast cancer" section)
2. No (Please skip to the "other health history" section)

Other health history

sd26. Have you been diagnosed with another cancer (of any type) after being diagnosed with breast cancer (apart from breast cancer recurrence)?
1. Yes
2. No (if no, please go directly to question no. 27)

sd26a. What kind of cancer were you diagnosed with? _____

sd26b. When were you diagnosed? _____

sd26c. How was it treated? Please indicate whether you had surgery, chemotherapy, hormone therapy, radiation therapy, or another treatment: _____

sd27. Have you ever had a chronic medical condition other than breast cancer (e.g. diabetes, high blood pressure, multiple sclerosis, etc.)?
1. Yes. Please specify: _____
2. No (if no, please go to question no. 28)

sd27a. How much do you worry about this (these) medical condition(s)?
1. Not at all
2. A little bit
3. A lot
4. All the time

sd27b. Does (Do) this (these) medical condition(s) interfere with your daily activities?
1. Not at all
2. A little bit
3. A lot
4. All the time

The following questions refer to your parenting history; if you do not have any children, please go directly to question no. 32

Habits

sd33. Do you take any prescribed medication? If so, please list the name(s) and dose(s):
_____
_____

sd34. Please indicate the average amount of alcoholic beverages you consume per day.
1. 0-1
2. 2-3
3. 4-5
4. 6-7 5. 8 +

sd35. Please indicate the average amount of caffeinated beverages you consume per day.
1. 0-1
2. 2-3
3. 4-5
4. 6-7
5. 8 +

sd36. Do you smoke cigarettes?

1. Yes
2. No (if no, please go directly to question no. 38)

sd37. If so, please indicate the average amount of cigarettes you smoke per day?

1. Half a pack or less
2. 1 pack
3. 1 1⁄2 pack
4. 2 packs or more

sd38. How often do you brush your teeth?

1. Two times or more per day
2. One time per day
3. One time every two days
4. Less than one time every two days

sd39. When you brush your teeth, is there blood in your saliva?

1. Always
2. Often
3. Sometimes
4. Never

sd40. When was your last visit to the dentist?

1. Within the last 6 months
2. Within the last year
3. Within the last 18 months
4. Within the last 24 months
5. More than 24 months ago

sd41. How often do you do cardiovascular exercise?

1. Once a week or less
2. Two to three times a week
3. Four to five times a week
4. Six to seven times a week
5. More than seven times a week

Appendix D

Home-based saliva collection instructions

LIST OF THINGS TO AVOID

1. Avoid alcohol consumption **24 hours before** sample collection.

2. Do not eat a major meal **within 60 minutes** of sample collection.

3. Avoid dairy products, foods high in sugar and/or acidity (e.g., candy, soda, oranges, etc.), caffeinated products (e.g., chocolate, coffee, tea, energy drinks), and non-prescription medication **1 hour before** sample collection.

4. Avoid exercising/workingout/training and brushing your teeth 1 hour before sample collection.

LIST OF THINGS TO DO

1. **Rinse your mouth** with water to remove food residue before sample collection (**for afternoon samples only**) and to swallow to increase saliva production.

2. **Wait at least 10 minutes** after rinsing before you collect saliva samples.

3. Put the swab directly under your tongue and leave it there for **three minutes**. When the time is up put the swab back into its appropriate tube, **avoid using your fingers**.

Detailed instructions for saliva sample collection

*****Please DO NOT drink alcohol on the day/night before or on your second lab visit*****

1. On each night before the collection (2 consecutive nights and lab day), please place the collection tubes by your bedside.

2. Please avoid alcohol consumption the day/night before the collection days because alcohol interferes with the stress hormones found in saliva.

3. On each day, please avoid eating, drinking, and brushing your teeth until **both** morning samples are collected (i.e., waking and 30 minutes after waking), as well as one hour before afternoon samples (i.e., 12:00pm, 4:00pm, and 9:00pm).

4. Please keep the saliva samples **refrigerated** until your second lab visit.

5. Fill out the corresponding page in the recording book after each saliva collection.

Specific instructions

MORNING SAMPLES: Waking, 30 minutes after waking

1. Immediately after you wake up, take the tube labeled as *waking* and put the synthetic swab in that tube under your tongue for 3 minutes. **Please stay in bed during the 3 minutes**.

2. Do not eat, drink, smoke, or brush your teeth **until** you have collected the *30 minutes after waking* sample.

3. Refrigerate all saliva samples after collection and fill out recording book.

AFTERNOON SAMPLES: 12:00pm, 4:00pm, 9:00pm

1. Avoid eating and drinking **1 hour** before the scheduled collection time. Please especially avoid the following foods/drinks 1 hour before the collection: non-prescription medication, caffeine (e.g., coffee, tea, chocolate, energy drinks), dairy products, chips, and chewing gum.

2. Avoid exercise and brushing your teeth 1 hour before the scheduled collection time.

3. Rinse your mouth 10 minutes before the scheduled collection time.

4. Place the swab under your tongue for 3 minutes, then place it back into the appropriate tube without touching the swab with your fingers.

5. Refrigerate all saliva samples immediately after collection and fill out recording book.

Appendix E

Baseline Questionnaire for Study Three

Background & Demographics

The following information will only be asked of you once. Please report as accurately as possible.

Date (day/month/year): _____

Personal Information

1. Identification number (provided by researcher): _____

2. Date of birth (day/month /year) _____

3. People living in Canada come from many different cultural and racial backgrounds. Are you (check all that apply):

☐… White?
☐… Chinese?
☐… South Asian (e.g., East Indian, Pakistani, Sri Lankan)?
☐… Black?
☐… Filipino?
☐… Latin American?
☐… Southeast Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese)?
☐… Arab?
☐… West Asian (e.g., Afghan, Iranian)?
☐… Japanese?
☐… Korean?
☐…Other – Specify _____

4. What language you speak most often at home?

☐ English	☐ Portuguese
☐ French	☐ Punjabi
☐ Arabic	☐ Spanish
☐ Chinese	☐ Tagalog (Pilipino)
☐ Cree	☐ Ukrainian
☐ German	☐ Vietnamese
☐ Greek	☐ Persian
☐ Dutch	☐ Hindi

☐ Hunagrian
☐ Italian
☐ Korean
☐ Russian
☐ Tamil
☐ Other, specify____

5. What is your highest level of education?

☐ Did not complete high school
☐ High school diploma
☐ Some post-secondary, but did not complete diploma or degree
☐ College or technical diploma or certificate (CEGEP, community college)
☐ University undergraduate degree
☐ Post-graduate degree

6. What is your best estimate of the total income, before taxes and deductions, of all household members from all sources in the past 12 months?

$ ☐☐☐☐☐☐☐

7. How many members of the household contribute to the total income? ☐☐

8. How many individuals live in the home? ☐☐

   a. How many individuals are less than 12 years of age? ☐☐
   b. How many individuals are 13 to 18 years of age? ☐☐
   c. How many individuals are 19 to 30 years of age? ☐☐
   d. How many individuals are 31 to 64 years of age? ☐☐
   e. How many individuals are 65 years of age and older? ☐☐

9. What is your marital status?

☐ Single
☐ Married or living with a life partner
☐ Separated
☐ Divorced
☐ Widowed

10. Which of the following describes you :

☐ I have no children

OR, I have :

☐ Daughter(s) ⇒ How many daughters? |_|_|
☐ Step-Daughter(s) ⇒ How many step-daughters? |_|_|

- ☐ Son(s) ⇒ How many sons? |_|_|
- ☐ Step-son(s) ⇒ How many daughters? |_|_|
- ☐ Grand-Daughter(s) ⇒ How many grand-daughters? |_|_|
- ☐ Grand-son(s) ⇒ How many grand-sons? |_|_|

Breast Cancer Information

1. What was the date of your most recent diagnosis for breast cancer? _____

2. What stage of breast cancer were you diagnosed with?

   - ☐ Stage 0
   - ☐ Stage I
   - ☐ Stage II
   - ☐ Stage III
   - ☐ Stage IV

3. Indicate which medical treatments have you received for breast cancer and the date of the last treatment, if applicable

Treatment	**Received?**	**Date of last surgery/treatment (day/month/year)**
Lymph or axillary node dissection	☐ Yes ☐ No	_____
Lumpectomy	☐ Yes ☐ No	_____
Single Mastectomy	☐ Yes ☐ No	_____
Double Mastectomy	☐ Yes ☐ No	_____
Reconstructive surgery	☐ Yes ☐ No	_____
Chemotherapy	☐ Yes ☐ No	_____
Radiotherapy	☐ Yes ☐ No	_____
Hormonal therapy	☐ Yes ☐ No	_____
Other Specify:		_____

4. Please describe:

a. The type of chemotherapy you were prescribed: _____

_____

b. The location of radiation you received: _____

_____

c. The hormones you have been prescribed: _____

_____

5. What was your usual weight, in pounds, before breast cancer diagnosis? _____lbs

6. Describe your adult weight status before breast cancer diagnosis:

☐ Very steady adult weight (little to no weight losses or gains per year)
☐ Fairly steady adult weight (weight changed by less than 2 pounds per year)
☐ Fairly unstable adult weight (weight changed by 2 to 5 pounds per year)
☐ Very unstable adult weight (weight changed by more than 5 pounds per year)

7. What is your height, in feet and inches? _____ft, _____in.

8. Are you:

☐ Pre-menopausal
☐ Going through menopause
☐ Post-menopausal

Appendix F

Psychological Measures for Study Three

Center for Epidemiologic Studies Short Depression Scale (CES-D)

Below is a list of some of the ways you may have felt or behaved.

Please indicate how often you have felt this way during the past week by checking the appropriate box for each question.

	Rarely of non of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of the time (3-4 days)	All of the time (5-7 days)
1. I was bothered by things that usually don't bother me.				
2. I had trouble keeping my mind on what I was doing.				
3. I felt depressed.				
4. I felt like everything I did was an effort.				
5. I felt hopeful about the future.				
6. I felt fearful.				
7. My sleep was restless.				
8. I was happy.				
9. I felt lonely.				
10. I could not "get going".				

Perceived Stress Scale (PSS)

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate by circling how often you felt or thought a certain way.

0 = Never 1 = Almost never 2 = Sometimes 3 = Fairly often 4 = Very often

1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Assessment of Survivors Concerns - Revised 5-item Scale

Item	I worry about...				
1	future diagnostic tests	1	2	3	4
2	another type of cancer	1	2	3	4
3	my cancer coming back	1	2	3	4
4	dying	1	2	3	4
5	my health	1	2	3	4

1 = Not at all; 2 = A little bit; 3 = Somewhat; 4 = Very much