EFFECTS OF AN 8-WEEK SWEDISH MASSAGE PROGRAM ON QUALITY OF LIFE, SLEEP, STRESS, FATIGUE, CORTISOL, C-REACTIVE PROTEIN AND CYTOKINES IN BREAST CANCER SURVIVORS

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ABSTRACT

Background: Many women who have received treatment for breast cancer have a high risk of developing late side effects or persistent cancer-related symptoms (CRS). Although massage therapy (MT) showed to provide positive results in the management of CRS, only a few studies have been conducted to examine persistent CRS in breast cancer survivors (BCS). Additionally, more robust examinations of the biological effects of most integrative therapies, including MT, remains needed. **Objective**: To investigate the effects of an 8-week Swedish massage program on quality of life (QoL), sleep, stress, fatigue, cortisol, c-reactive protein (CRP) and pro-inflammatory cytokines in BCS. **Methodology**: Females over 18 years who were diagnosed with breast cancer - stages I to III and have completed the treatment in the last six months were recruited. Participants underwent a one-hour session of MT once a week. Subjects were assessed for QoL, fatigue, stress, sleep and inflammatory markers before the beginning of the study (baseline), every two weeks during intervention period (assessment 1 and 2) and one week after the program (endpoint). The Functional Assessment of Cancer Therapy Fatigue was chosen to measure QoL and fatigue, and the Perceived Stress Scale was used to measure stress. Circadian sleep-wake rhythms were measured noninvasively through Actigraphy. Saliva was collected to detect the following markers: cortisol, CRP, IL-1β, IL-6, TNF-α and IFN-γ. Oximetry, heart rate and blood pressure were measured pre and post every MT session. **Results**: A total of 24 participants completed the study. The average age of participants was 56.9 (±9.3). QoL improvements were significantly associated with time after cancer treatment completion and cancer stage. Changes in fatigue scores were significantly associated with sleep aids in use and comorbidities. Stress levels significantly improved at endpoint in comparison to baseline, regardless of any covariates tested. Wake after sleep onset showed improvement at endpoint. Sleep onset latency improvement was only significant for Stage III patients. Sleep duration did not show any significant improvement. Subjects showed superior sleep efficiency at the end of the program, however, changes did not attain statistical significance. Overall, all the biomarkers decreased at endpoint in comparison to baseline; however, only cortisol, IL-1β and TNF-α reached significant changes, with IL-1β showing important associations with cancer stage and hormone therapy. Heart rate and oxygen levels improved right after sessions, and blood pressure slightly increased. **Conclusion**: This study reveals evidence of a positive effect of MT in QoL, fatigue, stress, some sleep parameters, oxygen levels, heart rate, cortisol, IL-1β and TNF-α.

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DEDICATION

I would like to dedicate this thesis to my parents, Solange and Emiliano, and to my sister Georgina. To my parents, whose bravery, patience and unrelenting support have enlightened my soul and inspired me to chase my dreams. Your unmeasurable love is what has made me who I am. Finally, to my sister, for being my biggest cheerleader, and most of all, for your care and wisdom words regardless of how hard life got. Thank you for teaching me so many lessons.

TABLE OF CONTENTS

PERMISSION TO USE i

DISCLAIMER i

ABSTRACT ii

ACKNOWLEDGEMENTS iii

DEDICATION iv

TABLE OF CONTENTS v

LIST OF TABLES xii

LIST OF FIGURES xv

LIST OF ABBREVIATIONS xvii

CHAPTER 1: INTRODUCTION 1

1.1 General Introduction 1

1.2 Defining the Problem 2

1.3 Research Purpose 4

1.4 Research Questions 4

1.5 Hypothesis 5

1.6 Background 5

1.6.1 Breast Cancer in Canada 5

1.6.2 Breast Cancer in Saskatchewan 6

1.6.3 Survivorship and Persistent Cancer-Related Symptoms 6

1.6.4 Massage Therapy and Breast Cancer Survivors 7

1.7 Summary of Chapter One 8

CHAPTER 2: LITERATURE REVIEW 9

2.1 General Scope of Literature Review 9

2.2 An Overview on Breast Cancer 9

2.3 Breast Cancer Survivorship 11

2.4 Symptom Burden in Cancer Survivor 12

2.4.1 Symptoms Clustering 13

2.4.2 Quality of Life 14

2.4.3 Fatigue 16

2.4.4 Stress 17

2.4.5 Sleep problems 19

2.5 Biological and Genetic Mechanisms of Cancer-Related Symptoms 20

2.6 Factors Influencing the Persistence and Severity of Cancer-Related Symptoms 22

2.7 Cancer-Related Symptoms Management 25

2.7.2 Allopathic Approach 25

2.7.3 Integrative Medicine Approach 25

2.8 An Introduction to Massage Therapy 27

2.8.1 Swedish Massage 28

2.8.2 Biological Underpinnings and Effects of Massage Therapy 29

2.9 Bio-Behavioral Research in Integrative Oncology 30

2.10 Barriers in the Use and Implementation of Integrative Medicine 31

2.11 Summary of Chapter Two 33

CHAPTER 3: METHODS 35

3.1 Overview 35

3.2 Study Design 35

3.3 Justification of using pre/post-test quasi-experimental design 35

3.4 Philosophical underpinnings 36

3.5 Theoretical Framework 37

3.6 Research Location 38

3.7 Research Ethics 38

3.7.1 Behavioural and Biomedical Research Ethics Board Approval 38

3.8 Participants & Sample Size 39

3.8.1 Inclusion and Exclusion Criteria 39

3.8.2 Power Analysis 40

3.8.3 Subjects 40

3.8.4 Dropouts 41

3.8.5 Recruitment 42

3.9 Methods and Outcome Measures 42

3.9.1 Quality of Life 42

3.9.2 Fatigue 43

3.9.3 Stress 43

3.9.4 Sleep 43

3.9.5 Biomarkers 45

3.9.6 Physiological Parameters 45

3.9.7 Clinical and Demographic Data 46

3.10 Intervention Protocol 46

3.11 Data Collection 48

3.11.1 Piloting Saliva Collection Scheme 48

3.11.2 Saliva Collection 48

3.11.3 Compliance 51

3.11.4 Study Assessments 52

3.12 Laboratory Analysis 53

3.12.1 Saliva Sample Preparation 53

3.12.2 Saliva Sample Analysis 53

3.13 Statistical Analysis 55

3.13.1 Descriptive Statistics 55

3.13.2 Inferential Statistics 56

3.14 Quality Assurance 60

3.15 Knowledge Translation 60

3.16 Summary of Chapter Three 61

CHAPTER 4: RESULTS 63

4.1 Overview 63

4.2 Characteristics of the Participant 63

4.3 Changes in QoL, Fatigue, Stress and Sleep 65

4.3.1 Quality of life 65

4.3.2 Fatigue 76

4.3.3 Stress 84

4.3.4 Sleep Duration 88

4.3.5 Sleep Efficiency 92

4.3.6 Sleep Onset Latency 95

4.3.7 WASO 102

4.3.8 Summary of Findings from Research Question One 106

4.4 Changes in Inflammatory Markers 107

4.4.1 Cortisol 107

4.4.2 CRP 109

4.4.3 IL-1β 110

4.4.4 IL-6 119

4.4.5 TNF-α 121

4.4.6 IFN-γ 127

4.4.7 Summary of Findings from Research Question Two 128

4.5 Changes in Physiological Parameters 129

4.5.1 Blood Pressure Changes Following MT Session 129

4.5.2 Oximetry Changes Following MT Session 129

4.5.3 Heart Rate Changes Following MT Session 131

4.5.4 Summary of Findings from Research Question Three 131

4.6 Correlations Between Inflammatory Markers and PRO 131

4.6.1 Inflammatory Markers, Sleep and Patient-Reported Outcomes 131

4.6.2 Sleep and Patient-Reported Outcomes 133

4.6.3 Inflammatory Markers 135

4.6.4 Summary of Findings from Research Question Four 136

4.7 Effect Sizes 136

4.8 Summary of Results 137

CHAPTER 5: DISCUSSION AND CONCLUSION 138

5.1 Discussion of the results 138

5.1.1 Changes in QoL, Fatigue, Stress and Sleep 138

5.1.1.1 QoL 138

5.1.1.2 Fatigue 141

5.1.1.3 Stress 144

5.1.1.4 Sleep 145

5.1.2 Changes in Inflammatory Markers 149

5.1.2.1 Cortisol 150

5.1.2.2 CRP 153

5.1.2.3 Cytokines 155

5.1.3 Physiological Parameters 159

5.1.3.1 Blood Pressure Changes Following MT Session 159

5.1.3.2 Heart Rate Changes Following MT session 160

5.1.3.3 Oximetry Changes Following MT session 161

5.1.4 Correlations Between Outcomes 162

5.2 Strengths and Limitations of the study 171

5.2.1 Strengths 171

5.2.3 Limitations 172

5.3 Implications on Clinical Practice 174

5.4 Research Contributions Summary 175

5.5 Recommendations 176

5.6 Future Research Directions 177

5.7 Conclusion 179

REFERENCES 181

APPENDICES 246

Appendix A – Permission to Reproduce 246

Appendix B - Certificate of Approval Behavioral Research Ethics Board 247

Appendix C - Consent Form 250

Appendix D - Material for Recruitment 258

Appendix E - Functional Assessment of Cancer Therapy Version B (Fact-B) 261

Appendix F - Functional Assessment of Cancer Therapy Fatigue (Fact-F) 264

Appendix G - Perceived Stress Scale (PSS) 265

Appendix H - Sleep Diary 266

Appendix I - Clinical and Demographic Questionnaire 267

Appendix J - Swedish Massage Therapy Protocol 270

Appendix L - Instructions on Collecting Saliva Samples 275

Appendix M - Saliva Collection Sheet 276

Appendix N - Bulk Messaging Communication Platform 277

Appendix O - Template of the 96-well Plate Used for Saliva Analysis 278

Appendix P - Tables of Descriptive Statistics at All Time-points 279

LIST OF TABLES

Table 4.1.	Descriptive statistics of the clinical-demographic variables of a sample of BCS, Saskatoon (n=24).	63
Table 4.2.	Type II tests of Fixed Effects Results for QoL Model 1 (n=24).	67
Table 4.3.	Estimates of Fixed Effects Results for QoL Model 1 (n=24).	67
Table 4.4.	Mean Difference of QoL scores for each group of Months after Treatment between Timepoints (n=24).	69
Table 4.5.	Mean Difference of QoL scores at each Timepoint for each level of Months After Treatment (n=24).	70
Table 4.6.	Type II tests of Fixed Effects Results for QoL Model 2 (n=24).	70
Table 4.7.	Estimates of Fixed Effects Results for QoL Model 2 (n=24).	71
Table 4.8.	Mean Difference of QoL scores for each group of Cancer Stage between Timepoints.	72
Table 4.9.	Mean Difference of QoL at each Timepoint for each level of the Cancer Stage.	73
Table 4.10.	Type II tests of Fixed Effects Results for fatigue Model 1 (n=24).	77
Table 4.11.	Estimates of Fixed Effects Results for fatigue Model 1 (n=24).	77
Table 4.12.	Mean Difference of fatigue scores for each group of Sleep Aids between Timepoints.	78
Table 4.13.	Mean Difference of fatigue scores at each Timepoint for each level of Sleep Aids.	79
Table 4.14.	Type II tests of Fixed Effects Results for fatigue Model 2 (n=24).	79
Table 4.15.	Estimates of Fixed Effects Results for fatigue Model 2 (n=24).	80
Table 4.16.	Mean Difference of fatigue scores for each group of Comorbidities between Timepoints (n=24).	81
Table 4.17.	Mean Difference of fatigue scores at each Timepoint for each level of Comorbidities (n=24).	82
Table 4.18.	Type II tests of Fixed Effects Results for stress (n=24).	85
Table 4.19.	Estimates of Fixed Effects Results for stress (n=24).	86
Table 4.20.	Type II tests of Fixed Effects Results for SD (n=24).	89

Table 4.21.	Estimates of Fixed Effects Results for SD model (n=24).	90
Table 4.22.	Type II tests of Fixed Effects Results for SOL (n=24).	97
Table 4.23.	Estimates of Fixed Effects Results for SOL (n=24).	97
Table 4.24.	Mean Difference of SOL for each group of Cancer Stage between Timepoints (n=24).	99
Table 4.25.	Mean Difference of SOL at each Timepoint for each level of Cancer Stage (n=24).	100
Table 4.26.	Type II tests of Fixed Effects Results for QoL Model 2 (n=24).	103
Table 4.27.	Estimates of Fixed Effects Results for WASO (n=24).	104
Table 4.28.	Type II tests of Fixed Effects Results for cortisol (n=24).	108
Table 4.29.	Estimates of Fixed Effects Results for cortisol (n=24).	108
Table 4.30.	Type II tests of Fixed Effects Results for IL-β (n=24).	111
Table 4.31.	Estimates of Fixed Effects Results for IL-β Model 1 (n=24).	112
Table 4.32.	Mean Difference of IL-β levels for each group of Cancer Stage between Timepoints (n=24).	114
Table 4.33.	Mean Difference of IL-β levels at each Timepoint for each level of the Cancer Stage (n=24).	115
Table 4.34.	Type II tests of Fixed Effects Results for IL-β Model 2 (n=24).	115
Table 4.35.	Estimates of Fixed Effects Results for IL-β Model 2 (n=24).	116
Table 4.36.	Mean Difference of IL-β levels for each group of Hormone Therapy between Timepoints (n=24).	118
Table 4.37.	Mean Difference of IL-β levels at each Timepoint for each level of the Hormone Therapy (n=24).	118
Table 4.38.	Type II tests of Fixed Effects Results for TNF-α Model 1 (n=24).	122
Table 4.39.	Estimates of Fixed Effects Results for TNF-α Model 1 (n=24).	122
Table 4.40.	Type II tests of Fixed Effects Results for TNF-α Model 2 (n=24).	123
Table 4.41.	Estimates of Fixed Effects Results for TNF-α Model 2 (n=24).	124
Table 4.42.	Type II tests of Fixed Effects Results for TNF-α Model 3 (n=24).	125
Table 4.43.	Estimates of Fixed Effects Results for TNF-α Model 3 (n=24).	126
Table 4.44.	Median SBP pre and post MT sessions (n=24).	130

Table 4.45.	Median DBP pre and post MT sessions (n=24).	130
Table 4.46.	Statistically significant correlations between inflammatory markers and sleep parameters using Spearman's rho (n=24).	133
Table 4.47.	Statistically significant correlations between patient-reported outcomes using Spearman's rho (n=24).	134
Table 4.48.	Statistically significant correlations between inflammatory markers using Spearman's rho (n=24).	135
Table 4.49.	Effect sizes from the 8-week MT intervention (n=24).	137
Table 5.1.	Principal action of selected biomarkers(n=24).	150

LIST OF FIGURES

Figure 2.1.	Cancer stages. Retrieved from Canadian Cancer Society.	10
Figure 2.2.	QoL model for BCS (Ferrel, 1996, adapted by Chopra, 2012).	15
Figure 3.1.	Flowchart of the study participants during data collection.	41
Figure 3.2.	Actigraph Basic Motionlogger®, Ambulatory Monitoring Inc.	44
Figure 3.3.	Saliva Collection Kit.	49
Figure 3.4.	Scheme summarizing the measurements according to the study phases.	52
Figure 3.5.	Saliva samples collected from study participants showing the differences in sample quality.	53
Figure 4.1.	Changes in QoL scores at each timepoint (n=24).	41
Figure 4.2.	Changes in QoL scores by each independent variable (n=24).	75
Figure 4.3.	Changes in fatigue scores at each timepoint (n=24).	76
Figure 4.4.	Changes in fatigue scores by each independent variable (n=24).	83
Figure 4.5.	Changes in stress scores at each timepoint (n=24).	85
Figure 4.6.	Changes in stress scores by each independent variable (n=24).	87
Figure 4.7.	Changes in SD (minutes) at each timepoint (n=24).	89
Figure 4.8.	Changes in SD (minutes) by each independent variable (n=24).	91
Figure 4.9.	Changes in SE (%) at each timepoint (n=24).	93
Figure 4.10.	Changes in SE (minutes) by each independent variable (n=24).	94
Figure 4.11.	Changes in SOL (minutes) at each timepoint (n=24).	96
Figure 4.12.	Changes in SOL (minutes) by each independent variable (n=24).	101
Figure 4.13.	Changes in WASO (minutes) at each timepoint (n=24).	103
Figure 4.14.	Changes in WASO (minutes) by each independent variable (n=24).	105
Figure 4.15.	Changes in cortisol levels at each timepoint (n=24).	107
Figure 4.16.	Changes in CRP levels at each timepoint (n=24).	110
Figure 4.17.	Changes in IL-1β levels at each timepoint (n=24).	111
Figure 4.18.	Changes in IL-1β levels by cancer stage (n=24).	113
Figure 4.19.	Changes in IL-1β levels by hormone therapy (n=24).	117
Figure 4.20.	Changes in IL-6 levels at each timepoint (n=24).	120
Figure 4.21.	Changes in TNF-α levels at each timepoint (n=24).	121

Figure 4.22. Changes in TNF-α levels by age (n=24). 123
Figure 4.23. Changes in TNF-α levels by cancer stage (n=24). 125
Figure 4.24. Changes in TNF-α levels by treatment classification (n=24). 127
Figure 4.25. Changes in IFN-γ levels at each time-point (n=24). 128

LIST OF ABBREVIATIONS

ANS:	Autonomic Nervous Systems
BC:	Breast Cancer
BCS:	Breast Cancer Survivors
CRF:	Cancer-Related Fatigue
CRP:	C-Reactive Protein
CRS:	Cancer-Related Symptoms
FACT-B:	Functional Assessment of Cancer Therapy - Breast Cancer
FACT-F:	Functional Assessment of Cancer Therapy - Fatigue
IFN-γ:	Interferon Gamma
IL-1β:	Interleukin-1 beta
IL-6:	Interleukin 6
IM:	Integrative Medicine
ITT:	Intention To Treat
LMM:	Linear Mixed Models
MT:	Massage Therapy
NCCN:	National Comprehensive Cancer Network
PNI:	Psychoneuroimmunology
PRO:	Patient-Reported Outcome
PSS:	Perceived Stress Scale
QoL:	Quality of Life
RM-ANOVA:	Repeated Measures Analysis of Variance
RT:	Room Temperature
SCC:	Saskatoon Cancer Center
SD:	Sleep Duration
SE:	Sleep Efficiency
SNS:	Sympathetic Nervous System
SOL:	Sleep Onset Latency
TNF-α:	Tumor Necrosis Factor Alpha
WASO:	Wake After Sleep Onset

CHAPTER 1

INTRODUCTION

1.1 General Introduction

Breast tumors are the most feared type of tumor among women. Besides the stigma around breast cancer (BC), breast tumors affect a main symbol of femininity and can compromise not only the patients' physical condition, but also their mental health, as they can affect their self-perceived image (da Silva & Riul, 2011; Fiorentino, Rissling, Liu, & Ancoli-Israel, 2011). As a result of the increased number of cancer survivors, one of the most significant challenges in oncology today is how to best care for these individuals after treatment. Besides the immediate treatment-related symptoms, cancer and its treatment can cause persistent disruptions for years after cure (Brem & Kumar, 2011; Dupont, Bower, Stanton, & Ganz, 2014; Stanton, Rowland, & Ganz, 2015).

Breast Cancer Survivors (BCS) are at risk of developing persistent cancer-related symptoms (CRS) either during the immediate or long-term period after treatment (Brem & Kumar, 2011). Persistent CRS might lead to premature mortality and morbidity and compromise patient's QoL (Brem & Kumar, 2011). The term "persistent CRS" refers to persistent or long-term CRS that last for a number of weeks, months, or even years after the completion of cancer treatment. Most BCS experience prolonged CRS, followed by a period of symptoms resolution until they return to full normal activity. Hence, these individuals may be said to be experiencing persistent CRS (Billhult, Bergbom, & Stener-Victorin, 2007; Billhult, Stener-Victorin, & Bergbom, 2007; Hernandez-Reif et al., 2005; Pruthi, Degnim, Bauer, DePompolo, & Nayar, 2009).

Persistent CRS can be divided as psychological and physiologic effects. The psychological symptoms might include fatigue, fear, loss of self-esteem, sleep problems, anxiety, psychological stress and depression. The physiological symptoms might include hair loss, lymphedema, pain, numbness, cognitive impairment, weight gain, spontaneous menopause,

peripheral neuropathy and reduced libido (Brem & Kumar, 2011; Penttinen et al., 2014; Stanton et al., 2005).

Among these symptoms, fatigue, pain, psychological stress and sleep problems are recognized as the most prevalent CRS (Campos, Hassan, Riechelmann, & Del Giglio, 2011; Couzi, Helzlsouer, & Fetting, 1995; Davidson, MacLean, Brundage, & Schulze, 2002; Lindley, Vasa, Sawyer, & Winer, 1998; Miaskowski et al., 2010). They can significantly impair the quality of life (QoL) of patients for many years, even after the treatment (Campos et al., 2011; Gordon & Siminoff, 2010; Lee et al., 2013; Miaskowski et al., 2010; Penttinen et al., 2014). In this context, the length and quality of survival have become an important endpoint. In order to assist BC patients that completed their treatment to achieve the best survival outcomes, the CRS screening and management need to be closely investigated (Brem & Kumar, 2011; Lopez, Williams, & Larkin, 2015).

Besides the negative impact of these symptoms on patients' QoL, they also play an immunosuppressive effect by changing levels of biological markers such as cytokines, cortisol and α-amylase (Pagel, & Pandi-Perumal, 2007; Illi et al., 2012; Miaskowski et al., 2010; Miller, Cohen, & Ritchey, 2002; Moreno-Smith, Lutgendorf, & Sood, 2010; Reyes-Gibby et al., 2008). For instance, sleep problems and fatigue have been linked to increased function of pro-inflammatory cytokines, such as interleukin-1, tumor necrosis factor-α and interleukin-6 (Illi et al., 2012; Lyon, Mccain, Pickler, Munro, & Elswick, 2011; Miaskowski et al., 2010; Reyes-Gibby et al., 2008) Similarly, psychological stress episodes activate the hypothalamic-pituitary-axis, which releases cortisol in order to regulate inflammation (Dantzer, 1997; Dantzer, Meagher, & Cleeland, 2012).

1.2 Defining the Problem

An essential part of any cancer survivorship care plan is providing effective interventions to manage long-term CRS, such as pain, fatigue, sleep problems, depression, among others (Oeffinger et al., 2014). Even though researchers have begun to document the issues faced during the transition period - from active treatment to survivorship, many questions remain.

The literature highlights many advantages in the use of integrative therapies, including massage therapy (MT) by BC patients. However, this link is virtually unexplored in BCS

(Barnes, Bloom, & Nahin, 2008; Billhult, Lindholm, Gunnarsson, & Stener-Victorin, 2009; Drackley et al., 2012; Kashani, Babaee, Bahrami, & Valiani, 2012; Krohn et al., 2011; Pruthi et al., 2009). Previous studies found that MT was effective in reducing fatigue, pain, anxiety, tension, and creating a general feeling of wellness in different groups of cancer patients, including breast cancer (Barnes et al., 2008; Billhult et al., 2009; Cassileth & Vickers, 2004; Drackley et al., 2012; Kashani et al., 2012; Krohn et al., 2011; Pruthi et al., 2009). Some studies, however, have presented controversial evidence, supporting the necessity for conducting more studies on this topic (Fernández-Lao et al., 2012; Jane, Wilkie, Gallucci, Beaton, & Huang, 2009; Sturgeon, Wetta-Hall, Hart, Good, & Dakhil, 2009).

Although MT studies have been done before, these studies present a considered number of limitations (Billhult et al., 2009; Billhult, Stener-Victorin, et al., 2007; Drackley et al., 2012; Fernández-Lao et al., 2012; Field, Hernandez-Reif, Diego, Schanberg, & Kuhn, 2005; Hodgson & Lafferty, 2012; Krohn et al., 2011; Listing et al., 2009; Sturgeon et al., 2009). Certainly, all the gaps and limitations found in the current literature open wide possibilities for scientific exploration but are also preventing us to properly use these findings in clinical practice. Some of these limitations, are: (i) the massage protocols are not clearly detailed; (ii) the training of massage therapists is not usually indicated, which is an essential step to be taken since therapists must be all equally instructed to homogeneously deliver the study's massage protocol among the subjects; (iii) many studies have examined CRS during the treatment, but far less research has been conducted to examine persistent CRS in BCS shortly after the completion of treatment; (iv) the biological effects of MT in BCS remains a largely unanswered question (Chang, Mu, Jou, Wong, & Chen, 2013; Patterson, Wan, & Sidani, 2013), (v) the few studies that have explored the biological effects of massage have not taken into account the circadian rhythm of the biological markers investigated (Billhult et al., 2009; Billhult, Bergbom, et al., 2007; Drackley et al., 2012; Fernández-Lao et al., 2012; Field et al., 2005; Krohn et al., 2011; Listing et al., 2010, 2009; Sturgeon et al., 2009).

In fact, a systematic review performed in 2017 concluded that there is high certainty of a net benefit of MT only in managing mood disturbance in BCS. There is not enough evidence up to date to conclude that the net benefit of MT is substantial to treat other persistent CRS (Greenlee et al., 2017). Overall, the quantity and quality of preliminary evidence is not sufficient to build trustworthy clinical practice guidelines for MT use. Additional research is needed to

unveil which type of MT is most effective for which specific purpose so that tailored recommendations can be made to target individual interests of the patients. There is an emerging need to establish optimal type-specific norms for integrative therapies use among different cancer survivors' populations.

Biobehavioral studies that encompass the interactions of the numerous biological pathways with patient-reported outcomes (PRO) have not been formally investigated in the context of MT. The justification for and validation of massage benefits to BCS population is in part dependent upon identification of the functional pathways governing the healing process during the transition period. In this context, novel and further studies become increasingly important and needed in moving forward the evidence-based medicine in the context of integrative oncology.

1.3 Research Purpose

The overall purpose of this study was to explore the effects of an 8-week Swedish massage program on QoL, fatigue, stress, sleep, cortisol, c-reactive protein (CRP), interleukin-1 beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) and interferon gama (IFN-γ), heart rate, oximetry, blood pressure pre and post the intervention.

1.4 Research Questions

This study was specifically designed to answer the following research questions:

i. Are there any changes in QoL, fatigue, stress and sleep parameters in BCS submitted to an 8-week Swedish massage program?

ii. Are there any changes in inflammatory markers (cortisol, CRP, IL-1β, IL-6, tumor TNF-α and IFN-γ) in BCS submitted to an 8-week Swedish massage program?

iii. What are the immediate changes in blood pressure, heart rate and oximetry following Swedish MT in BCS?

iv. Are there any correlations between the levels of inflammatory markers and stress, QoL, fatigue and sleep efficiency?

1.5 Hypothesis

Our hypothesis is that, compared to baseline, recently treated breast-cancer survivors undergoing an 8-week protocol of Swedish massage will experience:

i. An improvement in QoL, stress, fatigue and sleep parameters.
ii. Decreased levels of cortisol, CRP, IL-1β, IL-6, TNF-α and IFN-γ.
iii. Decreased levels of blood pressure and heart rate and increased levels of SpO_2.
iv. Positive correlations between fatigue, stress and the inflammatory markers and negative correlations between QoL, sleep efficiency and the inflammatory markers.

1.6 Background

1.6.1 Breast Cancer in Canada

Lung and bronchus, colorectal, breast and prostate cancer are the most common types of cancer in Canada (Canadian Cancer Statistics, 2019; Brenner et al., 2020). According to the Canadian Cancer Statistics, a total of 220,400 new cancers are likely to be diagnosed in Canada in 2019. On average, about 1 in 2 Canadians will develop cancer in their lifetimes, and 1 in 8 females are expected to be diagnosed with breast cancer in their lifetime (Canadian Cancer Statistics, 2019).

Compared to 2017 statistics, several new patterns have emerged in Canada's cancer statistics. Notably, female breast cancer death rates have decreased an estimated 48% since they peaked in 1986 (Canadian Cancer Statistics, 2019). In 2020, pancreatic cancer is expected to be the third leading cause of cancer death in Canada surpassing breast cancer (Brenner et al., 2020). Breast cancer is expected to surpass colorectal cancer and become the second most commonly diagnosed type of cancer in 2019 (Brenner et al., 2020).

Most women diagnosed with breast cancer in Canada (40%) are between 30 and 59 years old. (Canadian Cancer Statistics, 2019). According to a special report released in 2018 by the Canadian Cancer Society Statistics, most of female breast cancers (around 80%) are diagnosed at an early stage (stage I or II) (Canadian Cancer Statistics, 2019).

1.6.2 Breast Cancer in Saskatchewan

BC rates have a similar trend between provinces and territories in Canada, ranging from 117 per 100,000 in New Brunswick to 132 per 100,000 in Ontario. Among women, BC is the most diagnosed type of cancer with 740 cases estimated for 2020. Out of these 740 new cases, 170 deaths are expected for the same period, yielding approximately 560 new BCS (Brenner et al., 2020). In Saskatchewan, most women diagnosed with BC were between the age of 55 to 59 and 65 to 69 (Brenner et al., 2020).

In Saskatchewan, most patients who develop the disease are diagnosed at stage I (47.4%), followed by stage II (34.1%) and Stage III (11.1%) (Canadian Cancer Statistics, 2019). Most patients diagnosed with stage I BC in Saskatchewan are between 60 and 69 years old (Canadian Cancer Statistics, 2019).

1.6.3 Survivorship and Persistent Cancer-Related Symptoms

After several decades of basic, epidemiologic and clinical research, we have learned much about the survivorship aspects of BC and are increasingly paying attention to the long-term and persistent effects of BC treatment (Ganz & Goodwin, 2015).

Although the benefits of current therapeutic strategies are well established, it is well known that many women who have received treatment for BC have a high risk of developing long-term side effects. These long-term disruptions are side effects that occur months or years after cancer treatment and are called persistent CRS (Bower, 2008; Bower et al., 2006, 2000; Dupont et al., 2014; Stanton et al., 2015).

Persistent CRS might lead to premature mortality and morbidity and compromise patient's QoL (Brem & Kumar, 2011). Indeed, the majority of women who experienced cancer do not return to their pre-treatment functional status and QoL (Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007; Henselmans et al., 2010; Lyons, Svensborn, Kornblith, & Hegel, 2015). Long-term CRS can be divided into two categories: *(i) Psychophysiological*: emotional difficulties, loss of self-esteem, fear of recurrence, fatigue, sleep problems, anxiety, cognitive impairment, psychological stress and depression and *(ii) Physiological*: long-term postoperative problems, heart problems (especially those in use of specific drugs such as trastuzumab),

hypertension, lung problems, endocrine problems (affecting menopause and infertility, for instance), bone, joint, and soft tissue problems, hair loss, lymphedema, pain, numbness, weight gain, spontaneous menopause, peripheral neuropathy and reduced libido (Brem & Kumar, 2011; Penttinen et al., 2014; Stanton et al., 2005).

The actual trajectory of CRS after treatment is not known – i.e. if they become weaker or stronger post-treatment. It is well known, however, that after completion of treatment, persistent CRS are reported by all-types of cancer population (Dupont et al., 2014; Kim, Barsevick, Tulman, & McDermott, 2008; Morrow, 2007). Evaluating and treating persistent CRS is an important part of survivorship care. However, there has been a paucity of studies identifying the occurrence of symptom clusters in breast cancer (BC) patients across different points in the post-treatment trajectory (Bodai & Tuso, 2015; Eccles, Grimshaw, Campbell, & Ramsay, 2003; Mazor et al., 2018).

1.6.4 Massage Therapy and Breast Cancer Survivors

The literature highlights the value of several integrative therapies in improving CRS in BC patients (Bernstein & Grasso, 2001; Kang, McArdle, & Suh, 2014; Patterson et al., 2013). Particularly regarding MT, several studies found that this therapy exerts hypoalgesic effects, along with reduction of fatigue, anxiety and tension in different groups of cancer patients (Billhult et al., 2009; Cassileth & Vickers, 2004; Drackley et al., 2012; Fellowes, Barnes, & Wilkinson, 2004; Kashani et al., 2012; Krohn et al., 2011; Pruthi et al., 2009). MT has also shown positive effects within the immune system as changes on several biological markers has been identified, including Th1 molecules (IL-1, IFN- γ) (Cantarero-Villanueva et al., 2011), Th2 (IL-4, IL-10) (Green et al., 2010), cortisol (Cantarero-Villanueva et al., 2011; Fernández-Lao et al., 2012) and CRP (Sheikhsaraf, Peeri, Azarbayjani, & Agha-Alinejad, 2016) in both cancer and non-cancer settings.

It is important to highlight that even though some studies have postulated inconsistencies in their results regarding MT effects (Fernández-Lao et al., 2012; Jane et al., 2011, 2009; Sturgeon et al., 2009), MT has been notably chosen by cancer patients as a non-pharmacological option in reducing CRS. Cancer patients have been using MT in both hospital settings and private clinics, as well as during different phases of the condition and by those undergoing different

treatment types. For example, MT has been used to target not only the side effects of chemotherapy and radiotherapy, but also to help patients following mastectomy. A study that assessed the effect of having MT sessions incorporated into a breast surgical hospital practice after mastectomy, found that postoperative pain, stress, and muscle tension decreased, along with an increase in relaxation (Drackley et al., 2012). However, the definition of 'dose' or more precise recommendations has never been formally conceptualized for MT in the context of BCS population or cancer patients in treatment (Ali, Kahn, Rosenberger, & Perlman, 2012).

As more BCS and care providers seek non-pharmacological modalities for CRS management, it is possible that MT and other myofascial techniques may relieve CRS, however, only a few studies have previously investigated this hypothesis in BCS. Practice guidelines are still needed to inform clinicians and patients about effective and efficient use of MT.

1.7 Summary of Chapter One

The mortality rate and the incidence rate for all cancers combined have been decreasing in Canada. Additionally, the survival rates have been also improving, which has implications for health policy and resource planning. Hence, efforts to support people living with and beyond cancer are of utmost importance.

Fatigue, stress and sleep problem are among the most reported CRS by BCS. These symptoms can last up to 10 years after the treatment placing a great impact on patients' QoL. The majority of BCS use at least one modality of integrative therapy to manage long-term CRS, prevent toxicities, and improve QoL. Women with BC are among the highest users of these therapies.

MT has been used by cancer patients during and beyond cancer treatment to mainly manage fatigue, pain, mood disturbances and to reduce stress and anxiety. However, like other IT, further rigorous trials investigation on MT are still required so this therapy can be recommended as an evidence-based supportive care option for BCS.

CHAPTER 2

LITERATURE REVIEW

2.1 General Scope of Literature Review

The overall aim of this literature review is to describe the occurrence, correlates, and impact of fatigue, stress and sleep problems experienced by BCS on QoL. The biological and genetic mechanisms of these symptoms are also described. The definition of MT, its biological underpinnings, and the effects of MT in cancer patients and survivors were also reviewed. Literature providing explanations on the factors influencing the use of integrative oncology therapies by BCS are also summarized.

2.2 An Overview on Breast Cancer

BC is a result of an abnormal and malignant grow in the cells of the breast. The human breast is a modified, specialized apocrine gland that contains hormonally responsive and hormonally unresponsive tissue elements. Since BC is a hormone-dependent disease, post-menopausal women have lower risk of developing the disease due to the decline in oestrogens production and particularly progestins after menopause (Hunt, 2008; Jacobs & Finlayson, 2011; Peters & Visscher, 1998).

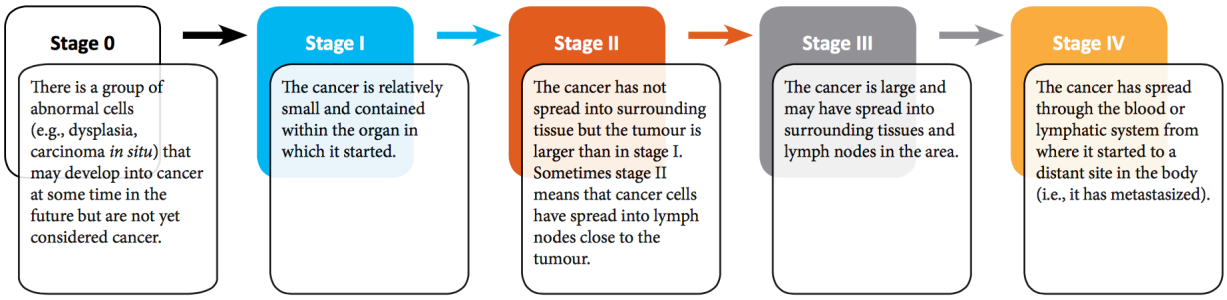
Other risk factors for BC that are beyond patient's control are family history (i.e. BRCA 1, BRCA 2), race, gender (i.e. women have increased risk in comparison to men), and medical history. On the other hand, manageable risk factors related to the patient's life-style are weight, diet, physical activity, exogenous hormones (i.e. oral contraceptives and post-menopausal hormone replacement therapy), smoking, stress levels and alcohol consumption (Hunt, 2008; Jacobs & Finlayson, 2011; Peters & Visscher, 1998). A few studies have also highlighted the socioeconomic disparities in BC incidence and mortality. Higher socioeconomic status has been linked to higher odds but inferior case fatality (Hu et al., 2019; Lundqvist, Andersson, Ahlberg, Nilbert, & Gerdtham, 2016).

Treatment for BC include surgery, chemotherapy, hormonal therapy, and radiotherapy. Recently, phytochemicals have been also tested in BC therapy (Akhtar Siddiqui et al., 2015; Kapinova et al., 2019; Sun, Zhang, Zheng, & Feng, 2019). The choice of treatment depends on many factors including the type and stage of the disease (Hunt, 2008).

Types of BC include ductal carcinoma in situ, invasive ductal carcinoma, inflammatory BC, and metastatic BC. Staging is a method of describing or categorizing a cancer based on how much the disease has spread in the body and where it is at the time of the diagnosis. This is also called extent of cancer. Accurate identification of the cancer stage can lead to appropriate interventions in therapy and during survivorship phase. Cancer staging helps us in understanding how the cancer will behave and ultimately, how patients will do during and after treatment (Hunt, 2008). Figure 2.1 summarizes the stages according to the according to the Canadian Cancer Society (Canadian Cancer Statistics, 2019).

Figure 2.1.

Cancer stages. (Used with permission from Canadian Cancer Society, 2019 – Appendix A).



A more sophisticated way of classifying breast tumors is the staging system proposed by the American Joint Committee on Cancer (AJCC) (Giuliano et al., 2017). This system is the most often used for BC tumors and utilizes in part the TNM scoring system: **T**umor size, **L**ymph **N**odes affected and presence of **M**etastases. The latest version of AJCC incorporated important changes in the staging system such as important biologic factors (i.e. tumor grade, proliferation rate, estrogen and progesterone receptor expression, human epidermal growth factor 2 (HER2) expression, and gene expression prognostic panels) (Giuliano et al., 2017).

2.3 Breast Cancer Survivorship

Due to advances in detection and treatment, millions of cancer survivors are alive today, and the numbers are growing. Cancer survival has increased in Canada since 1990, when the five-year net survival was only 55%, but the last Canadian Cancer Statistics released in 2019 estimates a 63% of survival rate for all cancers combined. Cancer survival generally decreased with advancing age and females show higher net survival rates compared to males (Canadian Cancer Statistics, 2019).

Particularly for breast cancer in Canada, predicted net survival is 97% 1 year after the diagnosis, which decreases to 92% 3 years after the diagnosis reaching the lowest survival rate of 82% 10 years after diagnosis (Canadian Cancer Statistics, 2019). Although the prognosis and survival rates vary widely by the type and stage of cancer, breast cancers and blood-related cancers have the highest survival rates (Rubin, Constine, Marks, & Okunieff, 2008). Additionally, a literature review showed an association between race and BC survival. This same study revealed that a more efficient early detection approach needs to be developed for African-American women and lower income women (Campbell, 2002).

There are many definitions of cancer survivor, however, the most widely used is the one by the National Cancer Institutes from the United States that states that says:

> An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted and are therefore included in this definition (National Cancer Institute, 2019).

Therefore, cancer survivorship is seen as a process that begins at the moment of diagnosis and continues through the balance of life (Marzorati, Riva, & Pravettoni, 2017). A clinical criterion used to classify cancer survivorship is based on cancer-specific survival rates, which refers to cancer patients who did not die from cancer during a certain period after the diagnosis. The most common used period of time is 5 years. Hence, when all signs and symptoms of cancer have disappeared, a patient can be classified in complete remission. If this patient remains in complete remission for 5 years or more, it may indicate that the patient is cured (Denlinger et al., 2014).

A widely used guideline created by the Institute of Medicine and the National Research Council helps patients and health professionals in understanding the essential components of

survivorship care. In 2005, in a report entitled, "From Cancer Patient to Cancer Survivor: Lost in Transition" the following components of survivorship care were presented:

> (1) Prevention of new and recurrent cancers and other late effects; (2) Surveillance for cancer spread, recurrence, or second cancers; (3) Assessment of late psychosocial and medical effects; (4) Intervention for consequences of cancer and treatment (eg, medical problems, symptoms, psychologic distress, financial and social concerns); (5) Coordination of care between primary care providers and specialists to ensure that all of the survivor's health needs are met (Hewitt, Greenfield, & Stovall, 2005).

Cancer survivors experience significant morbidity associated with their disease and treatment regimens, which can be severe, debilitating, and sometimes permanent. A study found that cancer survivors who reported untreated stress showed a poorer performance in complying with surveillance screenings and are less likely to exercise and quit smoking (Carmack, Basen-Engquist, & Gritz, 2011; Denlinger et al., 2014). Many CRS, both physical and/or psychosocial and can be improved through modifying behavioral and psychosocial risk factors. Cancer spread, recurrence, or second cancers are only a few aspects to be accounted in surveillance screenings. Accounting for psychosocial aspects in cancer survivorship care is essential to prevent adverse late outcomes such as psychological and behavioral CRS.

2.4 Symptom Burden in Cancer Survivors

Due to the high number of survivors, especially in North America, more attention has been paid to the persistent adverse effects associated with cancer treatment. Patients who have survived cancer are at risk of developing a range of CRS soon after treatment completion, which can last for short or long-term periods (Brem & Kumar, 2011). Findings from several studies suggest that symptom burden and residual symptoms remain high in cancer survivors, both at early and late cancer survivorship phases (Shi et al., 2011). In a study with 558 survivors (at 6 to 8 months post- diagnosis) of breast, colorectal, gynecologic, lung, or prostate cancer reported an average of 9.2 symptoms (Deshields, Potter, Olsen, Liu, & Dye, 2011).

The first 12 months after treatment had been identified to be the most stressful (Hewitt et al., 2005), however, symptom burden and the occurrence of CRS can vary throughout different phases of survivorship. According to the "seasons of survivorship" theory, once treatment is

completed, survivors go through four cancer survivorship phases: acute, transitional, extended, permanent, and chronic. *Acute phase* refers to the moment of diagnosis until the end of treatment. *Transitional phase* starts at the end of the treatment and goes until months after. *Permanent phase* refers to the period when months have passed since cancer treatment ended. *Chronic phase* refers to a period when there is very low chance that the cancer is going to reoccur. Therefore, the needs of BCS and CRS occurrence can change in each one of these phases (Miller, Merry, & Miller, 2008).

Multiple persistent CRS impair patient's function and QoL and its severity varies depending on the presence of physical and psychological co-morbidities (Gilbertson-White et al., 2019; Shi et al., 2011). Several factors can predict the development of CRS and determine who will experience worse symptom burden. These factors include clinical factors (i.e. type of cancer and treatment (Deshields et al., 2011); social factors (i.e. socioeconomic status and social support) (Kroenke et al., 2013; Sullivan et al., 2016); psychosocial factors (i.e. optimism and psychological stress) (Ho, Fong, & Cheung, 2014); biological factors, (i.e. genetic and inflammatory markers activity) (Aouizerat et al., 2009; Fogelman et al., 2017; Koleck & Conley, 2016; Miaskowski et al., 2017; Oliveira et al., 2014; Reyes-Gibby et al., 2008; Wang et al., 2010).

2.4.1 Symptoms Clustering

Findings suggest that persistent CRS might occur together, influencing one another as a cluster of symptoms, in both patients and BCS (Cleeland, 2007; Cleeland et al., 2013; Dantzer et al., 2012; Dodd, Miaskowski, & Paul, 2001; Dodd, Miaskowski, & Lee, 2004). These symptoms are known to act additively and synergistically (Agasi-Idenburg, Thong, Punt, Stuiver, & Aaronson, 2017; Cleeland, 2007; Cleeland et al., 2013; Dantzer et al., 2012; Dodd et al., 2004; Dodd et al., 2001; Kim, Barsevick, Fang, & Miaskowski, 2012; Miaskowski, Dodd, & Lee, 2004; Nho, Kim, Park, & Kweon, 2018; Reich et al., 2017). It is believed that their co-occurrence is linked to a common underlying inflammatory, neuroendocrine and immunologic etiology (Cleeland, 2007; Dodd et al., 2004; Moreno-Smith et al., 2010).

Fatigue, pain, psychological stress and sleep problems are among the most commonly reported CRS by BCS (Campos et al., 2011; Couzi et al., 1995; Davidson et al., 2002; Lindley et

al., 1998; Miaskowski et al., 2010), with co-occurring symptoms such as nausea/vomiting, peripheral neuropathy, dyspnoea, appetite loss, constipation, anxiety, depression, breast-area discomfort/symptoms and arm/axilla symptoms (Brem & Kumar, 2011; Kim, Lee, & Lee, 2012; Nho et al., 2018; Penttinen et al., 2014; Reich et al., 2017; Stanton et al., 2015). These symptoms group together creating different clusters, such as: *psychological cluster*, representing the inter-relationships among anxiety and depression; *general cluster,* characterizing the inter-relationships among appetite loss, fatigue, insomnia and dyspnoea; *physical cluster*, indicating the inter-relationships among arm symptom, breast symptom, pain and systemic therapy side effects; and *gastrointestinal cluster,* signifying the inter-relationships among nausea/vomiting and constipation symptoms (Nho et al., 2018).

Either as a cluster or as an isolated complaint, CRS can significantly impair the patient's QoL for many years after the treatment (Campos et al., 2011; Gordon & Siminoff, 2010a; M. C. Lee et al., 2013; Miaskowski et al., 2010; Penttinen et al., 2014). Therefore, in order to assist BCS to achieve the best outcomes post-treatment, screening for CRS and management need to be closely investigated (Brem & Kumar, 2011; Lopes-Junior et al., 2019; Lopez et al., 2015). Careful screening and observations of the emotional, social, and medical issues are essential to a favorable prognosis, remission and positive survivorship experience.

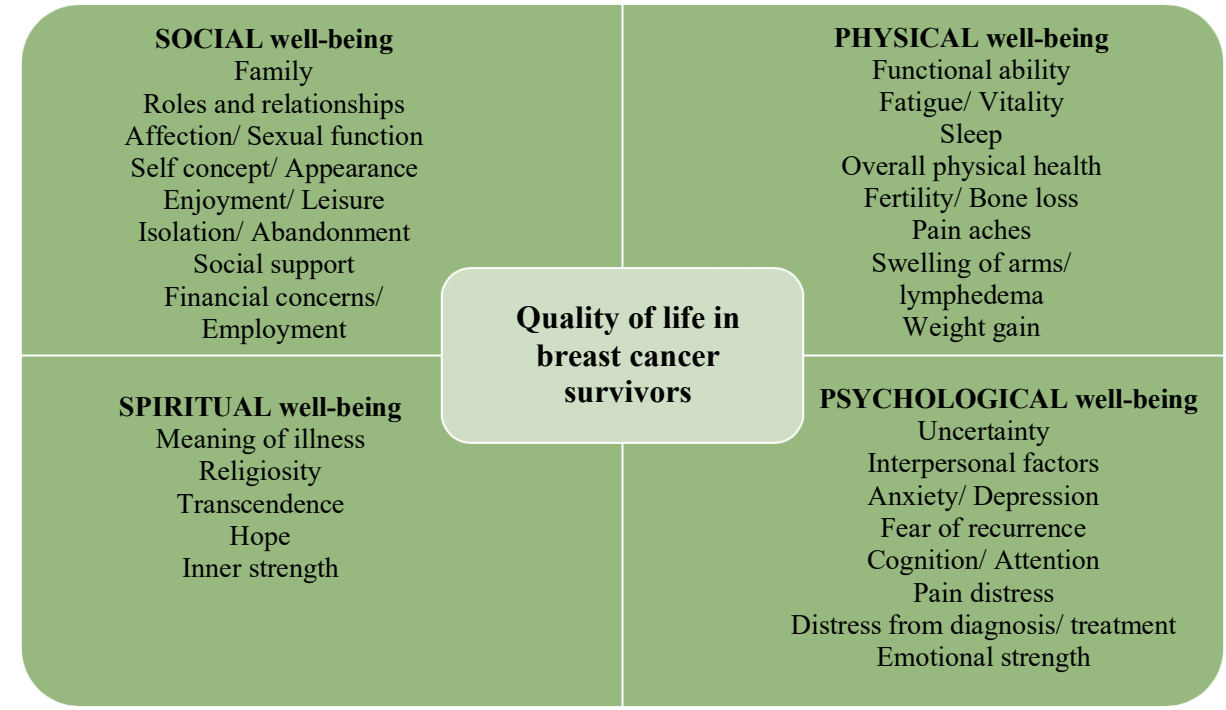
2.4.2 Quality of Life

Many aspects have been shown to affect cancer survivors' QoL, including multiple persistent CRS (Campos et al., 2011; Deshields, Potter, Olsen, & Liu, 2014; Gordon & Siminoff, 2010; Lee et al., 2013; Miaskowski et al., 2010; Penttinen et al., 2014). Results from several studies suggest that QoL negatively correlates with symptom burden and multiple persistent CRS after treatment (Campos et al., 2011; Deshields et al., 2014; Gordon & Siminoff, 2010a; M. C. Lee et al., 2013; Miaskowski et al., 2010; Penttinen et al., 2014). In metastatic breast cancer patients positive relationships were found between QoL and the survival duration of cancer patients and prognosis (Montazeri, 2008, 2009).

The aspects influencing QoL in BCS are listed in the conceptual model created by Ferrel and colleagues (Ferrell et al., 1996) that encompasses four primary domains of well-being that influences QoL in BCS (Figure 2.2) (Chopra & Kamal, 2012).

Figure 2.2.

QoL model for BCS (Ferrel, 1996, adapted by Chopra, 2012).



The idea of psychological, social, physical, and spiritual domains affecting QoL proposed by the model described in Figure 2.2 is in agreement with recent studies being done. A literature review showed that psychological factors (i.e. stress, optimism, resilience) were found to predict QoL and overall survival in breast cancer patients (Montazeri, 2008; Zhang et al., 2017). In addition, a large population-based study that aimed to determine the prognostic value of baseline health-related QoL for survival, found that in breast cancer patients, the following health-related QoL factors were predictive for survival: physical functioning, emotional functioning, global health status, and nausea and vomiting (Quinten et al., 2014).

Additionally, studies have also shown negative correlations between QoL and persistent CRS, such as sleep problems, fatigue and stress in several types of cancer (Bower et al., 2000; Charalambous & Kouta, 2016; Dreidi & Hamdan-Mansour, 2016; Gedaly-Duff, Lee, Nail, Nicholson, & Johnson, 2006; Kim, Kim, Lim, & Kim, 2018; Li, Otomaru, & Taniguchi, 2017; Nunes et al., 2017). For instance, in children and adolescents with cancer, a study showed that general fatigue and relationship distress were significant predictors of QoL (Pan, Wu, & Wen,

2017). Similarly, sleep problems, fatigue and stress might result in poor QoL in adults with breast cancer and BCS (Bower et al., 2000; Huang et al., 2010; Tsai, Kuo, & Chung, 2017; Xu et al., 2018).

2.4.3 Fatigue

Fatigue, psychological stress and sleep problems are one of the most prevalent CRS among oncology patients during and after treatment (Ahlberg, Ekman, & Gaston-Johansson, 2005; Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003; Sonia Ancoli-Israel et al., 2014; Cleeland et al., 2013; Curt, 2000; Morrow, Andrews, Hickok, Roscoe, & Matteson, 2002; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003). Fatigue is the prevailing symptom experienced by cancer patients in treatment, affecting from 50% to 90% of patients (Campos et al., 2011; Miaskowski et al., 2010; Penttinen et al., 2014). Furthermore, a few studies provide evidence for the prevalence and persistence of this problem in cancer survivors. For instance, one third of BCS report significant levels of fatigue up to 10 years following treatment (Bower et al., 2000; Lindley et al., 1998), and approximately 30% of BCS report fatigue more than five years after completion of treatment (Bower et al., 2006, 2000; Ganz & Goodwin, 2015; Lindley et al., 1998; Servaes, Verhagen, & Bleijenberg, 2002).

The fatigue associated with cancer or its treatment is usually referred to as cancer-related fatigue (CRF) and has a broad designation (Piper & Cella, 2010). The most commonly used definition is the one suggested by the National Comprehensive Cancer Network (NCCN) Fatigue Guidelines Committee. According to the NCCN, CRF can be defined as an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning (Sonia Ancoli-Israel et al., 2014). This sense of tiredness is not relieved by rest or sleep, and is considered a distinct phenomenon of the fatigue experienced after muscle exertion (Morrow, 2007).

This symptom is widely recognized as the most distressing adverse effect experienced by breast cancer patients regardless of the therapy they underwent (Ahlberg et al., 2005, 2003; Sonia Ancoli-Israel et al., 2014; Bower et al., 2006; Cleeland et al., 2013; Curt, 2000; R. Morrow et al., 2002; Otte, Carpenter, Russell, Bigatti, & Champion, 2010; Stasi et al., 2003), with a higher

severity reported by chemotherapy than radiation patients (Cleeland et al., 2013; G. R. Morrow, Shelke, Roscoe, Hickok, & Mustian, 2005; Yeh, Wang, Chiang, Lin, & Chien, 2009)

In a population-based study with of 314 women with breast cancer 1 year after diagnosis, fatigue was identified as the strongest predictor of QoL. This data confirms the large impact of fatigue on limiting function and on overall QoL in breast cancer patients after treatment (Arndt, Stegmaier, Ziegler, & Brenner, 2006).

The impact of fatigue on breast cancer survivorship is not yet fully understood. However, it is believed that somatic and psychosocial factors are related to fatigue persistence in BCS (Dupont et al., 2014; Reinertsen et al., 2017; Saligan & Kim, 2012; Servaes et al., 2002). Some of the psychosocial factors include stress (Reinertsen et al., 2010), discomfort around breast area (Reinertsen et al., 2010) and neuroticism, which is a personality trait associated with feelings of anxiety, worry, fear, anger and others (Orre et al., 2008).

2.4.4 Stress

Stress is considered a QoL domain and is defined as a state of physiological or psychological response to internal or external stressors (Radhakrishnan et al., 2019). There is a growing interest in the occurrence of psychological stress among cancer survivors (Armaiz-Pena, Cole, Lutgendorf, & Sood, 2013; Elenkov & Chrousos, 2002; Henselmans et al., 2010; Low, Stanton, Thompson, Kwan, & Ganz, 2006; McCorry et al., 2013; Miller et al., 2002). It is already known that episodes of stress, anxiety, and depression experienced by BCS can negatively affect patient's QoL (Armaiz-Pena et al., 2013; Costanzo et al., 2007; Elenkov & Chrousos, 2002; Henselmans et al., 2010; Low et al., 2006; McCorry et al., 2013; Xiao et al., 2017), and that stressful life experiences are related to poorer quality of survivorship and to higher and premature mortality (Brem & Kumar, 2011; Chida, Hamer, Wardle, & Steptoe, 2008).

It is well documented that a cancer diagnosis can elicit a range of psychological symptoms and emotions, and that the stress associated with cancer can persist for a long time even after the treatment (Couzi et al., 1995; Hewitt et al., 2005). Fear of recurrence has been associated to both stress and anxiety post-treatment (Ziner et al., 2012). Other symptoms highly associated with this stress have been also reported by cancer survivors. For instance, around 25% of cancer survivors report depression or anxiety five years or more after treatment (Maass,

Roorda, Berendsen, Verhaak, & De Bock, 2015; Saboonchi et al., 2014). In a sample of 90 BCS within 6 months post diagnosis, 34.7% reported anxiety and 15.3% reported depression (McCorry et al., 2013).

Previous research suggests that besides the biological effects of stress, this symptom maintains a strong relationship with illness cognitions, which is defined as a range of cognitive process underlying psychological adjustment in response to an illness-related issue. i.e. attitudes and perceptions of illness and the ways to cope with it (Boltz et al., 2013). Two studies with BC patients demonstrated that even after controlling for disease-related variables, illness cognitions were correlated with a significant proportion of the variance in stress (Henselmans et al., 2010; Millar, Purushotham, McLatchie, George, & Murray, 2005).

In newly diagnosed BC patients, psychological stress along with fatigue have also been shown as predictors of the "length of time without recurrence". Fatigue was identified as a significant predictor of recurrence-free survival, and emotional function was identified as a significant predictor of overall survival. It means that lower is psychological distress and fatigue levels, lower are the chances of cancer recurrence (Groenvold et al., 2007).

A study with 558 BCS evaluated whether intrusive thoughts could predict lingering symptoms in the year following treatment. Intrusive thoughts are an unwelcome and distressing involuntary thought that is difficult to manage or eliminate and according to the authors, they are a potentially important risk factor for persistent symptoms in survivorship. Women who participated in this study completed psychosocial questionnaires within 4 weeks of post-treatment and again 2, 6, and 12 months later. Authors found that women with higher levels of intrusive thoughts had higher levels of fatigue at baseline and stayed worse over the following year compared with women with low levels of intrusive thoughts at baseline (Dupont et al., 2014). This same study also found that during the first year of survivorship, all symptoms analyzed improved moderately except for sleep quality and pain, which remained constant (Dupont et al., 2014).

Another study with 171 BC subjects reported that throughout 12 months postdiagnosis, 36.3% of women experienced no stress, 33.3% reported stress only in the active treatment phase, 15.2% experienced stress in the survivorship phase, and 15.2% reported stress throughout all phases (Henselmans et al., 2010). A research examined psychological adjustment during 3

months following treatment among 89 women with BC stages 0-III and found that in general, BCS were at risk for sustained distress (Henselmans et al., 2010).

2.4.5 Sleep problems

Sleep disorders can be defined as changes in sleeping patterns or habits. Signs and symptoms of sleep disorders include difficulty falling asleep, excessive daytime sleepiness, difficulty staying asleep, and/or nonrestorative sleep, and irregular breathing or increased movement during sleep (Dement, Kryger, & Roth, 2017).

The influence of sleep on BC development has been vastly investigated (Marinac et al., 2017; Schernhammer, Kroenke, Laden, & Hankinson, 2006; Vgontzas et al., 2001). There is considerable evidence indicating that sleep deprivation is intimately linked to BC predisposition due to metabolic changes such as endocrine function and glucoregulation (K. Spiegel, Leproult, & Van Cauter, 1999), and increased inflammation (Vgontzas et al., 2004). Nonetheless, only a few studies have explored the role of sleep on BC survivorship and prognosis (Marinac et al., 2017).

Poor sleep quality is commonly reported by BCS and can persist for many years after the diagnosis and completion of treatment (Cleeland et al., 2013; Couzi et al., 1995; Lindley et al., 1998). Up to 65% BCS report sleep problems immediately after cancer treatment and up to 42% experience persistent insomnia (Bower et al., 2011). Sleep problems reported by BCS include delayed sleep onset, difficulty in maintaining sleep, and early morning waking (Alfano et al., 2011; Bower, 2008). In cancer patients, sleep problems also have a high prevalence rate, which ranges from 24 to 95% (Graci, 2005). Similarly, sleep complaints among metastatic BC patients in treatment is up to 63% (Koopman et al., 2002).

One of the most comprehensive insomnia prevalence studies in cancer population included 1904 cancer survivors with approximately 52% of the subjects with at least six years past their initial diagnosis. They found that nearly 30% reported insomnia symptoms, compared to 17% of healthy controls (Mao et al., 2007).

Additionally, abnormal sleep behaviors might result in daytime dysfunction and poor QoL (Dreidi & Hamdan-Mansour, 2016; N. Li et al., 2017). A survey with 300 BCS (median time since diagnosis of 49 months) found that 51% of the subjects reported insomnia symptoms, 19%

met diagnostic criteria for insomnia disorder, 33% reported that insomnia occurred after they were diagnosed with cancer (Savard, Ivers, Villa, Caplette-Gingras, & Morin, 2011). In this same study, although two thirds were already having insomnia before the cancer diagnosis, 58% reported that having cancer aggravated their sleep problem (Savard et al., 2011).

Interestingly, studies have also shown an intrinsic relationship between sleep disorders and fatigue in cancer population. It has been hypothesised that fatigue may affect sleep and wake cycles, which in turn interferes in the intensity of the fatigue itself (Gedaly-Duff et al., 2006; Nishiura, Tamura, Nagai, & Matsushima, 2013). Nevertheless, although the relationship between fatigue and sleep in health and other illnesses has been widely studied, there is not a definite answer on how fatigue influences the quality or quantity of sleep or the biological circadian rhythmicity (Ancoli-Israel, Moore, & Jones, 2001).

2.5 Biological and Genetic Mechanisms of Cancer-Related Symptoms

The biological underpinning of CRS are yet to be fully understood. Although, several studies have explored the hypothesis of the immune system involvement in the genesis and etiology of CRS (Saligan & Kim, 2012; Saligan et al., 2015), more attention must be given to the contributions that basic science can make to CRS management and integrative oncology research.

Some mechanisms have been investigated in adults with cancer to explain the relationship of the immune system and CRS. These mechanisms include cytokine level dysregulation, hypothalamic-pituitary-adrenal axis (HPA) activity, serotonin (5-HT) neurotransmitter action, circadian rhythm dysregulation, changes in adenosine triphosphate (ATP) levels, genetic polymorphisms, and muscle metabolism (Dantzer et al., 2012; Morrow et al., 2002)

It is well known that the stress associated with cancer leads to disturbances in the HPA axis and defeats important aspects of the immune response. Particularly regarding fatigue, the following factors have been linked to the development of this symptom in cancer patients: the hypermetabolic state associated with tumor growth; the competition between the organism and the tumor for nutrients; the deleterious effects of chemotherapy and radiotherapy; inadequate nutritional intake associated with nausea and vomiting resulting from antineoplastic therapy; anemia; sleep disorders; uncertainty about the future; the fear of death and mutilation; and the

loss of family maintenance roles (Abrahão, Bomfim, Lopes-Júnior, & Pereira-da-Silva, 2019; De Jong, Candel, Schouten, Abu-Saad, & Courtens, 2006; Jean-Pierre et al., 2007).

An increase in the concentrations of proinflammatory cytokines, such as IL-1, IL-6 and TNF-α has been found in several chronic degenerative and autoimmune diseases including cancer (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010; Malekzadeh et al., 2015; Paulsen et al., 2017; Seruga, Zhang, Bernstein, & Tannock, 2008). Stress and fatigue have shown important correlations with inflammatory markers such as cytokines, telomerase length, cortisol and CRP in cancer patients (Law et al., 2016; Matousek, Pruessner, & Dobkin, 2011; Reyes-Gibby et al., 2013; Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007; Xiao et al., 2017). The action of pro- and anti-inflammatory cytokines has been recognized as an important element in the pathophysiology and the genesis of CRS during and after the treatment (Condon, 2018; Dupont et al., 2014; Laine, Iyengar, & Pandita, 2013).

Studies have shown a relationship between the levels of IL-6, TNF-α and fatigue severity in cancer patients (Condon, 2018; Saligan et al., 2015). Increased CRP levels were also found in association with fatigue in BC patients (Alexander, Minton, Andrews, & Stone, 2009; Alfano et al., 2012; Orre et al., 2011; Pertl et al., 2013; Wratten et al., 2004).

The stress experienced as the disease evolves decreases immune response, such as the Natural Killer (NK) cells activity and T cells proliferation, (Abrahão et al., 2019; Antoni et al., 2006; McDonald et al., 2005). These two cells play a vital role in the immune response against cancer, by fighting against tumor cells and monitoring their disordered growth (Abrahão et al., 2019; Armaiz-Pena et al., 2013; Elenkov & Chrousos, 2002). A study with 111 stage 0-III BCS at 1 year post-radiotherapy, found that depressive symptoms, CRP, IL-1β (antagonist receptor) and TNF- α (receptor 2) were risk factors of fatigue (Xiao et al., 2017).

Similarly, sleep problems seem to share a common underlying biological mechanism with fatigue and stress. Studies with cancer patients and other non-cancer populations have found correlations between several biomarkers and sleep quality, such as TNF-α (Clinton, Davis, Zielinski, Jewett, & Krueger, 2011; Wright et al., 2015), IL-10 (Wright et al., 2015), IL-6 (L. Liu et al., 2012a), CPR (L. Liu et al., 2012a; Wright et al., 2015), cortisol (Chang & Lin, 2017; Hoyt, Bower, Irwin, Weierich, & Stanton, 2016), oxalic acid (Weljie et al., 2015), diacylglycerol 36:3 (Seugnet, Boero, Gottschalk, Duntley, & Shaw, 2006), alpha-amylase (Sigurdardottir et al., 2015), melatonin (Innominato et al., 2016), urinary 6-sulfatoxymelatonin (A. H. Wu et al., 2012)

and serotonin (Payne, Held, Thorpe, & Shaw, 2008). Genetic variation in the IL-6 gene, as well as high serum concentrations of this cytokine, may contribute to differences in the severity of sleep disorders and fatigue experienced by cancer patients (Miaskowski et al., 2010).

Advances in molecular genetics have allow scientists to identify the genes encoding the biomarkers related to CRS (A. Barsevick et al., 2010). Genetic variations of these biomarkers have been also investigated in different cancer populations in the development of CRS (Illi et al., 2012; Lyon et al., 2011; Miaskowski et al., 2010; Reyes-Gibby et al., 2008).

For instance, research has shown that several CRS are susceptible to the influence of the effects of several genetic single nucleotide polymorphisms (SNP) (Reyes-Gibby et al., 2008). SNPs are the most common type of genetic variation. They are variants of only one nucleotide representing a difference in a single DNA building block (Schaefer, 2014)(Schaefer, 2014). Therefore, SNP's determine phenotypes that express in different amounts of the encoded proteins and are considered "functional polymorphisms", alongside variants that lead to modifications of the protein itself (Schaefer, 2014).

Fatigued BCS have shown SNPs in cytokines IL-1β and IL-6 (Reinertsen et al., 2011). Additionally, SNPs in the promoter region of IL-1β (--511) and IL-6 (--174) have been shown to control gene expression of cytokines associated with BC susceptibility and prognosis (Aouizerat et al., 2009; Illi et al., 2012). A study on functional SNP in the promoter region of TNF-α gene reported that individuals with common homozygous alleles reported higher levels of sleep disturbance when compared to those with heterozygous alleles. In a population of lung cancer survivors, a study found relationships between cytokines SNPs and the symptom of burden along with poor QoL (Rausch et al., 2010).

2.6 Factors Influencing the Persistence and Severity of Cancer-Related Symptoms

Although the exact physiopathology of CRS is unknown, the etiology and biological mechanisms that lead to some of these symptoms can be considered as part of a complex systemic and cellular feedback system. This system is characterized by pathophysiological, psychological, situational/environmental and genetic regulatory factors (Erickson, 2008; Saligan & Kim, 2012).

As for the pathophysiological factors, they include cytokine balance disturbance, cancer stage, hormone therapy, hemoglobin and hematocrit levels, chronic pain, albumin levels, C-reactive protein levels, prostaglandin levels, leukocyte count, monocyte count, the hydro-electrolytic imbalance, acid-base imbalance, dehydration, hypoxia, presence of cardiac abnormalities and thyroid disorders. Other factors related to the pathophysiology of cancer may also be associated with the severity and persistence of CRS, such as the hypermetabolic state associated with tumor growth, the deleterious effects of chemotherapy and radiotherapy and the competition between the body and the tumor for nutrients, which can be aggravated by inadequate nutrition (Erickson, 2008; Jean-Pierre et al., 2007; Kim et al., 2012; Orre et al., 2011; Paddison, Temel, Fricchione, & Pirl, 2009; Wang et al., 2002).

Psychological factors impacting CRS include chronic depression, chronic stress, fear of recurrence and social isolation. Situational factors include the type of treatment and protocol used, phase of treatment, patient's sleep and wakefulness pattern, infections, activity and rest pattern, among other environmental factors (Erickson, 2008). Genetic factors include cytokines genetic variations (i.e. SNPs) and epigenetic alterations (i.e. telomere length) (Kim et al., 2012; Okamoto & Seimiya, 2019; Reyes-Gibby et al., 2013; Saligan & Kim, 2012).

The co-occurrence of some of these factors generates a cumulative load that creates burden to an already overloaded biological system (Erickson, 2008). Consistently exploring all the possible interferences between these factors means capturing the dynamic and continuous response of the immune system to cancer, which may be associated with the persistency and severity of CRS.

The side effects of chemotherapy are one of the major factors associated with the persistence of CRS, with some authors referring to these symptoms as chemotherapy-induced symptoms. Side effects are intrinsically related to the individual's response to treatment, which seems to be related to the balance between pro and anti-inflammatory cytokines levels. For instance, in a study comparing cytokine levels with individuals' response to the first three cycle of chemotherapy, serum IL10 levels were found to be elevated in patients with poor treatment response and were found to be in lower levels in patients with good or consistent treatment response (Bien et al., 2013b).

Similarly, CRS also change in response to treatment. In general, CRS are more severe among those who underwent chemotherapy when compared to those who underwent radiotherapy

(Donovan et al., 2004). Fatigue in patients receiving chemotherapy usually follows a cyclic pattern, reflecting scheduled chemotherapy cycles; whereas fatigue in patients undergoing radiotherapy is cumulative and worsens after the end of treatment. For those patients under a multimodal therapy schedule the pattern of onset and severity of fatigue may overlap (Erickson, 2008).

Evidence has also shown that in animal models (murine), the use of chemotherapy drugs such as cyclophosphamide and etoposide alter the levels of IL-1β, IL-6 and TNF-α, and are linked to the development of fatigue in these animals (Smith et al., 2014; Wood et al., 2006).

The type and stage of cancer can also influence the severity and persistence of CRS. Severe fatigue was reported more frequently among patients with hematologic cancers when compared to those diagnosed with solid tumors (Wang et al., 2002). Likewise, in hematological malignancies, the prevalence of anemia, which is associated with fatigue and sleep problems, is approximately twice the frequency found in patients with solid tumors (Birgegård, Gascón, & Ludwig, 2006).

Persistent CRS are related to survivors' cancer stage. Often times, higher cancer stages experience more severe and frequent CRS. These changes are also seen in biological markers. For instance, in children with soft tissue sarcomas, stage I and II patients showed lower levels of IL-10 in comparison to stage III and IV patients (Bien et al., 2013a).

Different levels of CRS and cytokines have been identified at different time-points during treatment and after treatment. This shows that disease progression may have a relationship with the development of CRS (Bien et al., 2009, 2013a, 2013b). For instance, survivors of testicular cancer who are 1 year beyond diagnosis reported different severity and types of CRS in comparison to the same patient 20 years later (Miller, Pandey, Jain, & Mehta, 2015)

It is important to make progress in understanding the trajectory of each CRS and the mechanism that triggers changes in the severity of these symptoms at all levels (biological, social, psychological, physical, situational/environmental). Further steps need to be taken to identify the complex network of factors orchestrating the genesis and persistence of CRS. However, in oncology, defining a biological cause or mechanism is a complex task (A. Barsevick, Whitmer, Nail, Beck, & Dudley, 2006). A comprehensive and constant screening approach of CRS during and after treatment might help us in understanding the factors associated with its severity and persistence.

2.7 Cancer-Related Symptoms Management

2.7.2 Allopathic Approach

The allopathic approach to treat many CRS include a range of pharmacological interventions. For instance, some sleep problems can be treated with zolpidem, eszopiclone, ramelteon, trazodone among others (Dement et al., 2017; Pagel & Pandi-Perumal, 2007). Similarly, CRF can be treated with psychostimulants such as Ritalin and Modafinil have been also prescribed (Lyon et al., 2011). Clinical trials have also been testing new drug treatments for CRF such as hematopoietic growth factors, progestational steroids, methylphenidate, and paroxetine (Ollie Minton, Richardson, Sharpe, Hotopf, & Stone, 2008).

Moreover, the prescription of anti-depressants, muscle relaxants and antiemetics have been also documented to treat other CRS. In addition to the variety of side effects that these medications can cause, several patients refrain in using a pharmacological approach due to the risk of dependence and/or interactions with other medications (Couzi et al., 1995; Dement et al., 2017; Pagel & Pandi-Perumal, 2007).

2.7.3 Integrative Medicine Approach

According to the Academic Consortium Integrative Medicine and Health, integrative medicine (IM) can be defined as:

> The practice that affirms the importance of the relationship between the practitioner and the patient, focuses on the whole person, is informed by evidence and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals and disciplines to achieve optimal health and well-being (Tick & Nielsen, 2019).

Aiming to alleviate some of these symptoms, BC patients and survivors take advantage of several non-pharmacological treatments, including several modalities of integrative therapies (Antoni et al., 2006; Chandwani et al., 2012; Yates et al., 2005). There are four categories of integrative therapies according to the National Center for Complementary and Integrative Health (National Center for Complementary and Integrative Health, 2019). These categories are mind-body, energy-based, biologically based and whole medical system. Mind-body therapies include yoga, massage, art therapy, dance therapy, biofeedback, meditation. They focus on behavioral,

psychosocial and spiritual approaches. Energy-based therapies refer to diathermy, Reiki, healing touch, electroacupuncture etc. They involve the use of electromagnetic, ultrasonic, thermal or subtle energy. Biologically based practices include probiotics, orthomolecular medicine, botanical and herbal supplements, and diet. They refer to the use of natural or biologically sourced products that are internally or topically taken. The whole medical system therapies include chiropractic, osteopathy, homeopathy, Ayurvedic medicine, naturopathy, among others. They have an unifying theory of health-disease, healing, diagnosis and treatment options (National Center for Complementary and Integrative Health, 2019).

IM emphasizes a more inclusive collaborative way of viewing healthcare and wellness. It takes into account a holistic, patient-focused understanding, often including mental, emotional, functional, spiritual, social, and community aspects. Therefore, the underlying premise of IM is that optimal human health and wellbeing require merging and balancing the body, mind, and spirit.

The term IM is an emerging nomenclature that has been replacing the term complementary and alternative medicine (CAM), as more and more of these non-mainstream therapies are being used in an integrated approach to conventional medicine. According to the NCCIH, the terms "complementary," "alternative," and "integrative" are continually evolving (National Center for Complementary and Integrative Health, 2019). This shift to the term "integrative" communicates the importance of understanding the actual purpose of these therapies and how it should be used together with all appropriate therapeutic and lifestyle approaches in a coordinated way (National Center for Complementary and Integrative Health, 2019).

Another term used to define IM practices in the context of cancer care is integrative oncology, and it refers to the use of integrative therapies in association with conventional oncology care (Greenlee et al., 2017). A more comprehensive definition is that:

> Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment (Witt et al., 2017).

The slow recovery of CRS in the initial year after treatment may indicate persistent

difficulties in the years to come (Billhult, Stener-Victorin, et al., 2007). Overall, the literature highlights the promising effects of several integrative therapies in treating CRS in BC patients and BCS (Bernstein & Grasso, 2001; Greenlee et al., 2017; Kang et al., 2014; Patterson et al., 2013). A systematic review of the literature showed that, based on the quality and quantity of available evidence, the net benefit of the following integrative therapies is reliable and substantial in treating CRS in BCS: music therapy, meditation, stress management and yoga can be recommended for anxiety/stress reduction; meditation, relaxation, yoga, massage and music therapy can be used to manage depression/mood disorders; meditation and yoga to improve quality of life; acupressure and acupuncture can be used for reducing chemotherapy-induced nausea and vomiting (Greenlee et al., 2017).

The management of CRS during and after treatment is one of the top-ranked research priorities identified by the National Cancer Institute through a Clinical Trials Planning Meeting in 2010 (A. Barsevick et al., 2013). It is important for each cancer patient completing treatment to receive a comprehensive care plan particularly focused on the physical and psychological CRS being experienced following treatment. A few IM modalities have the potential of being safely incorporated into survivorship care, most of them, however, still need more scientific evidence to be generated (Brem & Kumar, 2011; Penttinen et al., 2014; Stanton et al., 2005).

2.8 An Introduction to Massage Therapy

MT is defined by the Academic Consortium Integrative Medicine and Health as:

> A practice that involves manipulation of soft tissue structures of the body to prevent or alleviate pain, spasm, tension, or stress and to promote health and well-being (Tick & Nielsen, 2019).

The definition of MT by the College of Massage Therapists of Ontario is also referred to as the "Scope of Practice" stated under the Massage Therapy Act, 1991 – a provincial legislation for MT in Ontario. According to this document, MT is:

> The assessment of the soft tissue and joints of the body and the treatment and prevention of physical dysfunction and pain of the soft tissue and joints by manipulation to develop, maintain, rehabilitate or augment physical function, or relieve pain (College of Massage Therapist of Ontatio, 2019).

In general, MT consists of manual manipulation of body's soft tissue — skin, muscles, tendons, ligaments, and fascia for the purpose of establishing and maintaining good health and promoting wellness (Braun & Simonson, 2008; Salvo, 2015).

MT is one type of integrative therapy that has been evolving for thousands of years in different cultures and regions around the world. Archeologist have found European cave paintings depicting what appears to be the use of MT in 15000s BC after battles. Later, around the sixth century AD, Chinese and Japanese people had well established MT practices. After that, massage gradually became popular as part of Hindu tradition (Braun & Simonson, 2008; Salvo, 2015).

Nowadays, there are more than 80 types of documented massage methods, a few examples are heated stone massage, lymphatic massage, reflexology, aromatherapy massage, scalp massage, light pressure effleurage massage, myofascial release, deep tissue and trigger point therapy and Swedish massage (Billhult et al., 2009; Braun & Simonson, 2008; Green et al., 2010; Imanishi et al., 2009; Salvo, 2015). Understanding the differences between each of these types is essential in choosing the most effective technique to obtain the maximum results. Based on the differences and similarities among all types of MT, a massage therapist who was cross-trained in several techniques may easily incorporate different massage techniques (Billhult et al., 2009; Braun & Simonson, 2008; Green et al., 2010; Imanishi et al., 2009; Salvo, 2015). Among the many specialized massage techniques being used today, the most commonly practiced and adopted by cancer patients is Swedish massage therapy (Braun & Simonson, 2008; Mustafa, Furmanek, Knapik, Bacik, & Juras, 2015; Salvo, 2015).

2.8.1 Swedish Massage

Swedish massage is a relaxation technique that focuses on improving blood flow to the skin and muscle and removing muscle tension (Cowen et al., 2006; Mustafa et al., 2015). The term Swedish massage is more recognized in English and Dutch speaking countries, and in Hungary. Elsewhere in Europe the style is referred to as classic massage (Calvert, 2002). Swedish massage was the first systematic method of therapeutic massage based on a physiological perspective (College of Massage Therapist of Ontatio, 2019).

Although Swedish massage techniques may vary from light to vigorous, it is considered a superficial massage technique, which is, for example, different from the Thai massage, which is classified as deep tissue massage (Cowen et al., 2006). This massage type is built around five basic strokes – effleurage (sliding or (gliding), petrissage (kneading), tapotement (rhythmic tapping), friction (steady pressure) and vibration or jostling (Mustafa et al., 2015; Salvo, 2015).

2.8.2 Biological Underpinnings and Effects of Massage Therapy

In general, MT has therapeutic effects on the body and improves health and well-being by acting on the muscular, nervous and circulatory system (College of Massage Therapist of Ontatio, 2019). Studies have shown that MT has a positive effect on stress, low back pain, muscle pain, sleep, physiological markers (i.e. blood pressure and heart rate), inflammatory biomarkers and mood in several cancer and non-cancer populations (Buttagat, Techakhot, Wiriya, Mueller, & Areeudomwong, 2019; Hodgson & Lafferty, 2012; Krohn et al., 2011; Liptan, Mist, Wright, Arzt, & Jones, 2013; Listing et al., 2010, 2009; Sritoomma, Moyle, Cooke, & O'Dwyer, 2014; Sturgeon et al., 2009; Supa'At, Zakaria, Maskon, Aminuddin, & Nordin, 2013). Particularly in BCS it has been used to promote relaxation, address muscle stiffness and pain, and resolve musculoskeletal complaints (Greenlee et al., 2017). Patient-oriented-report (PRO) research reported that MT was effective in reducing fatigue, pain, anxiety, tension, and creating a general feeling of wellness in different groups of cancer patients, including BC (Barnes et al., 2008; Billhult et al., 2009; Cassileth & Vickers, 2004; Drackley et al., 2012; Kashani et al., 2012; Krohn et al., 2011; Pruthi et al., 2009).

The growing body of molecular-based research on IM helped to increase the understanding biological underpinnings of MT and other integrative therapies. Many studies have showed positive biological effects of MT on IgA levels (Cantarero-Villanueva et al., 2011; Fernández-Lao et al., 2012), α-amylase (Cantarero-Villanueva et al., 2011; Fernández-Lao et al., 2012; Tiffany Field et al., 2005), salivary cortisol (Cantarero-Villanueva et al., 2011; Fernández-Lao et al., 2012; Tiffany Field et al., 2005), salivary flow rate (Hernandez-Reif et al., 2005), serum cortisol (Listing et al., 2010), serotonin (Field et al., 2005; Listing et al., 2010), NK cells (Billhult et al., 2009; Hernandez-Reif et al., 2005), lymphocytes (Green et al., 2010; Hernandez-Reif et al., 2005, 2004), catecholamines (Field et al., 2005; Hernandez-Reif et al., 2004), some

Th1 (Type 1 T helper) and Th2 (Type 2 T helper) molecules (Green et al., 2010), peripheral blood mononuclear cell (Billhult et al., 2009) and hemodynamic effects (Billhult et al., 2009).

However, many studies conducted so far did not show that there is high certainty of the net benefit of MT in addressing many of the CRS analyzed. Some studies demonstrate inconclusive benefits, creating equivocal evidence and indicating that there is moderate certainty of the net benefits of MT in managing CRS in BCS (Greenlee et al., 2017).

In May of 2017, the Society for Integrative Oncology through a systematic review of the literature released a clinical guideline making recommendations on the use of integrative therapies by BC patient and BCS (Greenlee et al., 2017). Conclusions were made based on the quality of studies, magnitude of effect, statistical significance, sample size, consistency of findings across trials, and if the outcomes were primary or secondary. Based on the analysis of the MT trials, there is high certainty of a net benefit of MT in depression/mood disorders only. They also concluded that there is no evidence up to date to assure that the net benefit of MT is substantial to treat other CRS, which is due to the fact that only a few rigorous trials have been conducted and the risk of bias in such trials is high (Greenlee et al., 2017).

Although MT has been less tested in BCS (Hodgson & Lafferty, 2012; Krohn et al., 2011; Listing et al., 2010, 2009; Rubin 1927- editor et al., 2013; Sturgeon et al., 2009), the following modalities of MT has been tested in BC patients in treatment: aromatherapy massage (Imanishi et al., 2009), light pressure effleurage massage (Billhult et al., 2009; Kashani et al., 2012), scalp massage and reflexology (Green et al., 2010), and lymphatic drainage therapy (Martín, Hernández, Avendaño, Rodríguez, & Martínez, 2011). Other studies have also examined multimodal methods by combining Swedish massage and acupressure (Boguszewski, Krupiński, & Białoszewski, 2017) meditation and massage (Dion et al., 2016) and massage and exercise (Cantarero-Villanueva et al., 2011), aromatherapy and acupressure massage (Kao et al., 2017) in different population types. Noteworthy that some studies, although performed with cancer population, did not specify the type of massage applied (Billhult, Bergbom, et al., 2007; Billhult, Stener-Victorin, et al., 2007; Drackley et al., 2012; Hernandez-Reif et al., 2005).

2.9 Bio-Behavioral Research in Integrative Oncology

Although some studies have investigated the biological effects of IT including MT in BCS, this still remains a largely unanswered question (Barnes et al., 2008; Bernstein & Grasso, 2001; Billhult et al., 2009; Cassileth & Vickers, 2004; Listing et al., 2010). It is unclear to what extent the observed effects of IT interventions are based on physical and biological adaptations or rather on psychosocial factors. More attention must be given to the contributions that basic science and bio-behavioral research can make to advance evidence-based practice on integrative oncology.

The bio-behavioral theory is a highly interdisciplinary philosophy and an emerging approach to analyzing the effectiveness of all types of IT. Fairly often, IT interventions can elicit positive PRO, without concomitant biological effects and vice and verse (i.e., dance increased cortisol levels, whereas yoga decreased them) (Matousek, Dobkin, & Pruessner, 2010), hence an approach such as the bio-behavioral framework that brings together the biological and behavioral factors and integrates them into a cohesive, holistic view, may be utilized to tackle IT research questions from a multifaceted view. Although several bio-behavioral concepts are suitable and applicable to IT research, such as the interactions between biological and behavioral aspects, rigorous and expanded studies in a multidisciplinary collaboration setting have been limited (Driscoll, Lyon, & McCain, 2011).

One of the most overlooked and used bio-behavioral framework is the psychoneuroimmunology (PNI), which proposes the existence of multidimensional interactions among psychosocial factors and physiological mechanisms of the neuroendocrine and immune systems (Kang, 2003). The PNI theory suggests a physiological relationship between stress, psychosocial-behavioral factors, and neuroendocrine-immune effects (Kiecolt-Glaser et al., 2014).

2.10 Barriers in the Use and Implementation of Integrative Medicine

There is a critical need to address the *quality* of survival after cancer, and this cannot be done without an analysis of the factors influencing patients, institutions and professionals in putting IM into practice.

The field of integrative oncology emerged as a result of cancer patients' advocacy for holistic care, leading to the need of patient-centered research to assess the safety and

effectiveness of integrative therapies (Berretta et al., 2017; Evans et al., 2007; Yates et al., 2005). Although the science of IM has significantly progressed in the past years, there are several barriers in the use and implementations of these therapies in clinical practice. It is of paramount importance to discuss the key components of an effective policy on the use of integrative therapies by BCS.

Legal, ideological and social obstacles in the implementation of IM practice in clinical oncology settings persist. Obstacles are found at professional, institutional and patient levels.

Professional barriers often include lack of a shared knowledge base and awareness, personal ideological beliefs; fear of indirect or shared liability, lack of research-based evidence on the reliability, validity, cost-effectiveness and effects of integrative therapies; a scarce number of specialists in integrative oncology and a lack of competency-based training models in IM at undergrad level in all health professions (Cohen & Ruggie, 2004; Latte-Naor & Mao, 2019).

Institutional barriers include lack of institutional evidence-informed policies and regulation in integrative care, fear of indirect or shared liability and lack of a personalized care policies (Cohen & Ruggie, 2004; Latte-Naor & Mao, 2019).

Patient-level barriers include lack of awareness and knowledge, insurance coverage and/or financial issues, ideological barriers, demanding treatment schedules and symptom burden (Cohen & Ruggie, 2004; Latte-Naor & Mao, 2019; Yabroff, Lawrence, Clauser, Davis, & Brown, 2004).

Interestingly, studies have shown that certain groups of people are more likely to use integrative therapies than others. Integrative therapies users tend to be female, middle-aged, highly educated, with a higher income, an interest in health knowledge, and have a diagnosis of at least one chronic disease (Astin, 1998; Eisenberg et al., 1993; Furnham & Smith, 1988; Wister et al., 2002). A study with 6016 noninstitutionalized adults found that higher odds of CAM use were associated with being young, female, living in the west, highly educated, employed, and with functional limitations (Rhee, Evans, McAlpine, & Johnson, 2016).

The information brought by these studies lead to an important reflection on the utilization of IM therapies among racial and ethnic minority populations and on health disparities in IM. Awareness, self-management, availability of services, accessibility, and affordability seems to be important factors influencing the use of integrative therapies (Saper, 2016).

Greater awareness at patient, professional and institutional levels will lead to greater demand among all. Particularly in historically low-income and minority groups, affordability seems to be a bigger issue (Saper, 2016). It becomes clear that the delivery of IM services for cancer patients and survivors must address not only the clinical aspects of CRS, but also socio-economic obstacles. Developing personalized survivorship care planning based on a more collaborative and multidisciplinary approach might lead us to offer an affordable, accessible integrative health care for all (Kamsu-Foguem & Foguem, 2014). Personalized cancer survivorship care model has been shown to help meet several patients' specific needs (Alfaro et al., 2014; Haq et al., 2013; Kamsu-Foguem & Foguem, 2014; Loonen et al., 2018; Tevaarwerk et al., 2019). Additionally, mobile health, electronic health and innovative open-access digital tools for the management of CRS (i.e. stress-management apps), can help address the lack of accessibility issue (Saper, 2016).

In the near future, multifaceted, personalized and multimodal care plans will be needed. Further steps include refinement of the different personalized cancer survivorship care models and its components, along with feasibility testing in all cancer types, and planning for more systemic implementation.

2.11 Summary of Chapter Two

The booming population of cancer survivors is the result of early cancer detection and improved cancer therapy. As a consequence of this increased number of survivors, one of the greatest challenges in oncology today is how to provide best care for these individuals after treatment. Many survivors have persistent CRS that can last for up to 10 years after treatment. Persistent CRS have been well studied in survivors of childhood cancers, but less is known about the survivorship experience for adult cancer survivors. Fatigue, stress and sleep problems are major symptoms reported by BCS and can significantly affect their QoL.

Interestingly, the biological mechanisms involved in the development of CRS has become progressively evident. The role of inflammatory markers has been associated with many CRS, and the current evidence supporting the relationships among proinflammatory cytokines, CRP, cortisol and CRS in individuals with cancer is very promising. This potential relationship between immune system, inflammation and CRS calls for a new approach on cancer survivorship

care that integrates biological, psychosocial, and behavioral determinants of CRS. Additionally, a few factors influencing the development, severity and persistence of CRS can be found at different levels, such as biological, social, psychological, physical and situational/environmental. Some examples of factors within these levels are type of cancer, markers of inflammatory and immune response, stage of the disease, hormonal therapy, type of cancer treatment and so on. Changes at any of these levels interferes in the severity of the symptoms at different stages of treatment and after treatment.

In other to reduce the burden of these symptoms, many BCS use non-pharmacological interventions including MT. Many MT therapeutic effects have been reported by cancer patients such as reduced fatigue, pain, anxiety, tension, and creating a general feeling of wellness. However, based on the quality and quantity of available evidence, the net benefit of many integrative therapies including MT is not substantial to create definite clinical guidelines. Patients, caregivers, families and clinicians need clarification and guidance regarding dosage, frequency, and timing of several IT modalities.

Due to its impact on patient's life, persistent CRS must be properly understood, prevented, and mitigated. Hence, continued symptom monitoring and management in early and late posttreatment survivorship is needed for BCS. It is suggested that novel survivorship care models include systematic symptom screening tools and management interventions.

However, there are numerous barriers in implementing integrative medicine into practice. These barriers can be found at patient, professional and institutional levels and include legal, ideological and social obstacles. For instance, the lack of understanding of the biomechanism of integrative therapies, its efficacy, and cost-effectiveness in managing CRS are important barriers. Additionally, awareness, insurance coverage and health discrepancies related to the use and access of IM are also significative barriers in implementing IM into practice.

To make informed decisions on the use of integrative therapies, clinicians and patients should understand the level of evidence of associated benefits and harms for each therapy. Information on IM must be accessible, available and trusted in order to positively change patients' and physicians attitude. Future steps in this field include developing more rigorous trials to incorporate evidence-based non-pharmacological modalities into survivorship care models.

CHAPTER 3

METHODS

3.1 Overview

This chapter describes the design, general methodology, ethical aspects, procedures and data analysis for the study. Additionally, this section provides an overview of important models and frameworks that guided this research.

3.2 Study Design

This is an interventional study, designed as a one-group longitudinal quasi-experiment.

3.3 Justification of using pre/post-test quasi-experimental design

An interventional study design was chosen as a prospective type of study since we were interested in evaluating the direct impact of an intervention.

A pre/post-test design was chosen to estimate the impact of an intervention through direct comparison within-subjects. Pre/Post-test design provides the possibility of having a repeated-measure evaluation plan around a proposed intervention with little control over the delivery of the intervention.

A quasi-experimental design was chosen to test our hypothesis due to its logistically moderate level of difficulty. This was the appropriate choice of study design since there were practical (i.e. personnel, budgetary, duration) barriers to conduct a genuine randomised experiment. Quasi-experimental designs are useful where there are political, practical, or ethical barriers to conducting a randomized controlled trial (Eccles et al., 2003). Due to its complexity, genuine randomised trials should only be considered when there is genuine uncertainty about the effectiveness of an intervention.

3.4 Philosophical underpinnings

In IM research, a philosophical foundation that can accommodate the complexity of assessing integrative therapies must prompt the inquirer to examine phenomena more holistically, researching it from multiple perspectives. In 1997, a British sociologist and philosopher introduced the idea of critical realism as an ontological and epistemological position from which it is possible to research subjects in a social/health context. Critical realism is, therefore, particularly apposite for IM research and has been chosen as part of the philosophical underpinnings for this study (Bryman, 2001).

Sharpe and Bhaskar (1976) posited that there are three realms of ontology: the 'empirical', the 'actual' and the 'real'. The 'empirical' which is what can be observed or experienced. The 'actual' represents occurrences and what is known that may not be observed but which is regulating the empirical. The final realm is the 'real' which is hidden or unobservable causal mechanisms but a necessary precondition for the 'actual' and 'empirical' (Sharpe & Bhaskar, 1976).

The application of Bhaskar's ontological levels to this study would be thus: at the 'empirical level' integrative therapies have been used by BCS to manage CRS. At the 'actual level' integrative therapies can ease CRS and inflammation. At the 'real level', inflammatory markers are related to the development of CRS. Thus, there are a series of mechanisms operating at the 'real' level that eventually impact on the benefits of integrative therapies in managing CRS at the 'empirical' level.

By relying on the critical realism position described above, the methodology chosen for this research has been designed based on an objectivist ontology that enquires about reality. When deciding on how that reality should be studied, we adopted a positivist paradigm in order to uncover the effects of MT by carefully and objectively measuring mechanisms and responses. (Bonell, Moore, Warren, & Moore, 2018). Indeed, the characteristics of interventional clinical research (i.e. RCT and *quasi*-experiments) are said to firmly situate this type of research in a positivist epistemological paradigm (Bonell et al., 2018; Marchal et al., 2013; Pearce & Raman, 2014; Rowe & Oltmann, 2016).

By following a positivists paradigm that seeks predictions and generalizations and attempts to reduce the complex to the simple, data is reduced to numerical symbols or quantifiers;

thus, a quantitative approach was undertaken in designing this study's methodology (Creswell, 2009; Pring, 2000). In aiming to yield a basis for prediction and generalization, a deductive approach was undertaken in this study. Correlation and experimentation were used to reduce complex interactions between variable and measurable evidence sought via repeated assessments and observation.

3.5 Theoretical Framework

This study was designed considering two theoretical frameworks: (i) the Middle Range Theory of Unpleasant Symptoms and (ii) the Psychoneuroimmunology Framework. Both provide the lens through which our research problem is being examined. They helped us in establishing a sense of structure to guide this research and the rationale for conducting it.

The Theory of Unpleasant Symptoms was developed and introduced in 1995 (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). It provides a model for the experience of, and relationships between concurrent symptoms. The three major components of this theory are: the symptoms, the consequences of the symptom experience, and the influencing factors. These influencing factors give rise to or affect the nature of the symptom and are classified in three categories: physiological, psychological, and situational. They are responsible for the variability in the experience reported by different individuals with the same symptoms (Lenz & Pugh, 2018; Lenz et al., 1997; Nguyen et al., 2011). Each symptom is designed to be a multidimensional experience, which can be measured separately or in combination with others. Although symptoms differ from each other, there are common dimensions among them: intensity, time, degree of affliction and perceived quality.

The psychoneuroimmunology (PNI) framework, is a valuable framework to guide the investigation of possible associations between biobehavioural aspects and the development of immunologically mediated diseases (Green et al., 2013; Kang, 2003; McCain et al., 2005). According to PNI, inflammatory and other innate immune mediators can signal back into the central nervous system, stimulate the production of cytokines, change neuronal function, and cause sickness behaviors and unpleasant symptoms as an adaptive response (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Green, O'Connell, & Lutgendorf, 2013). In the context of our conceptual schema, the PNI supports the idea that immune-to-brain communication cascades

might be related to cancer development and treatment-related symptoms such as fatigue, depression, cognitive dysfunction, and sleep disturbances (Green et al., 2013).

Combined, the PNI framework and the Theory of Unpleasant Symptoms constitute an effective way to comprehensively investigate the management of CRS in cancer patients since it unifies the core elements that are potentially modeling the genesis of CRS. These theories allowed us to comprehend the experience of CRS as a matter of multi-directional communication among psychological aspects, situational factors and neuroendocrine and immune systems.

3.6 Research Location

The study was conducted at the University of Saskatchewan in the province of Saskatchewan, Canada. BCS were recruited from Saskatoon Cancer Center (SCC) in Saskatoon (approximately population size of 273,000). The MT sessions occurred at the Massage Therapy Association of Saskatchewan and the McKay Career Training School. The venues for the MT sessions were chosen based on their location (easily accessible and favourable) and the availability of massage rooms that met the study specificities. Laboratory analysis were performed at Cancer Cluster Laboratory at the University of Saskatchewan, Health Sciences Building (4D40) under supervision of Dr. Franco Vizeacoumar.

3.7 Research Ethics

3.7.1 Behavioural and Biomedical Research Ethics Board Approval

Ethical approval was obtained from the Biomedical Research Ethics Board (Bio# 16-112) at the University of Saskatchewan - See Appendix B. In addition to this approval, a data access agreement was signed with the Saskatchewan Cancer Agency.

Prior to taking part in the study, all participants were asked to sign an informed consent to declare their willingness to participate in the study (Appendix C). This form was drafted in clear and objective language, through which the subjects were informed about the objectives of the study, data collection procedures, possible constraints. It was ensured that participants were not

exposed to unnecessary or avoidable risks and that, overall, the potential benefits would outweigh the foreseeable risks.

3.8 Participants & Sample Size

3.8.1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Confirmed diagnosis of cancer of non-metastatic BC - stages I to III.	• Pregnant or breastfeeding.
• BCS who have completed treatment in the last 6 months.	• Patients who have been receiving regular (i.e. at least twice a month) bodywork or any kind of MT over the past 6 months.
• Females over 18 years.	• Participants with potential for blood leakage into saliva by assessing oral health (*i.e.* "Did you observe bleeding gums in the past three days?")
• One treatment-related risk factor: chemotherapy/chemoprevention, surgery and/or breast radiation.	• Patients in use of cytokine-based treatments (*i.e.* interferon)
• Able to read, write and speak English.	• Known salivary gland disease
• Women on hormonal therapy, such as tamoxifen (Novaldex), raloxifene (Evista), anastrozole (Arimidex), exemestane (Aromasin), or letrozole (Femara).	• Known systemic infection or consistent fever > 38.5 °C.
• Ability to understand study procedures and to comply with them for the entire length of the study.	• Known upper respiratory infection (*i.e.* nasal drainage)
	• Known inflammation (*i.e.* sore throat, periodontitis)

3.8.2 Power Analysis

Similar studies in cancer population showed positive and statistically significant effects of MT by working with different sample sizes, ranging from 24 subjects (Keir, 2011) to 286 participants (Wilkinson et al., 2007).

Several studies suggest different methods to calculate sample size for feasibility studies (Hertzog, 2008). A safe range would be a minimum of 10 patients and a maximum of 30, but the most used approach suggests that a pilot study sample should be 10% of the sample projected for the larger correspondent study (Connelly, 2008; Treece, 1982). Other authors suggested 10 to 30 participants. In randomized clinical trials, authors suggest that a group of 12 participants per group is satisfactory (Julious, 2005; Moore, Carter, Nietert, & Stewart, 2011).

Hence, an initial sample size was projected for a larger correspondent study based on a previous work developed with similar design, same population and a similar intervention (Sturgeon et al., 2009). This previous study demonstrated an effect of MT in QoL with a subset of 50 subjects (Sturgeon et al., 2009). Our initial calculation was based on detecting a ten-point pre and post difference in the QoL score and an improvement of 15% on QoL pre and post intervention with an α level of .05, a desired power of 80%, and assuming a standard deviation of 15 points. This generated a sample size of at least 100 participants, already considering a 30% dropout rate. Therefore, considering 20% of our initial calculation of 100 patients for the larger-scale study, we fixed our sample in 20 patients for this feasibility study.

3.8.3 Subjects

A total of 24 females over 18 years who were diagnosed with non-metastatic BC - stages I to III and have completed the treatment in the last six months participated in this study (Figure 3.1).

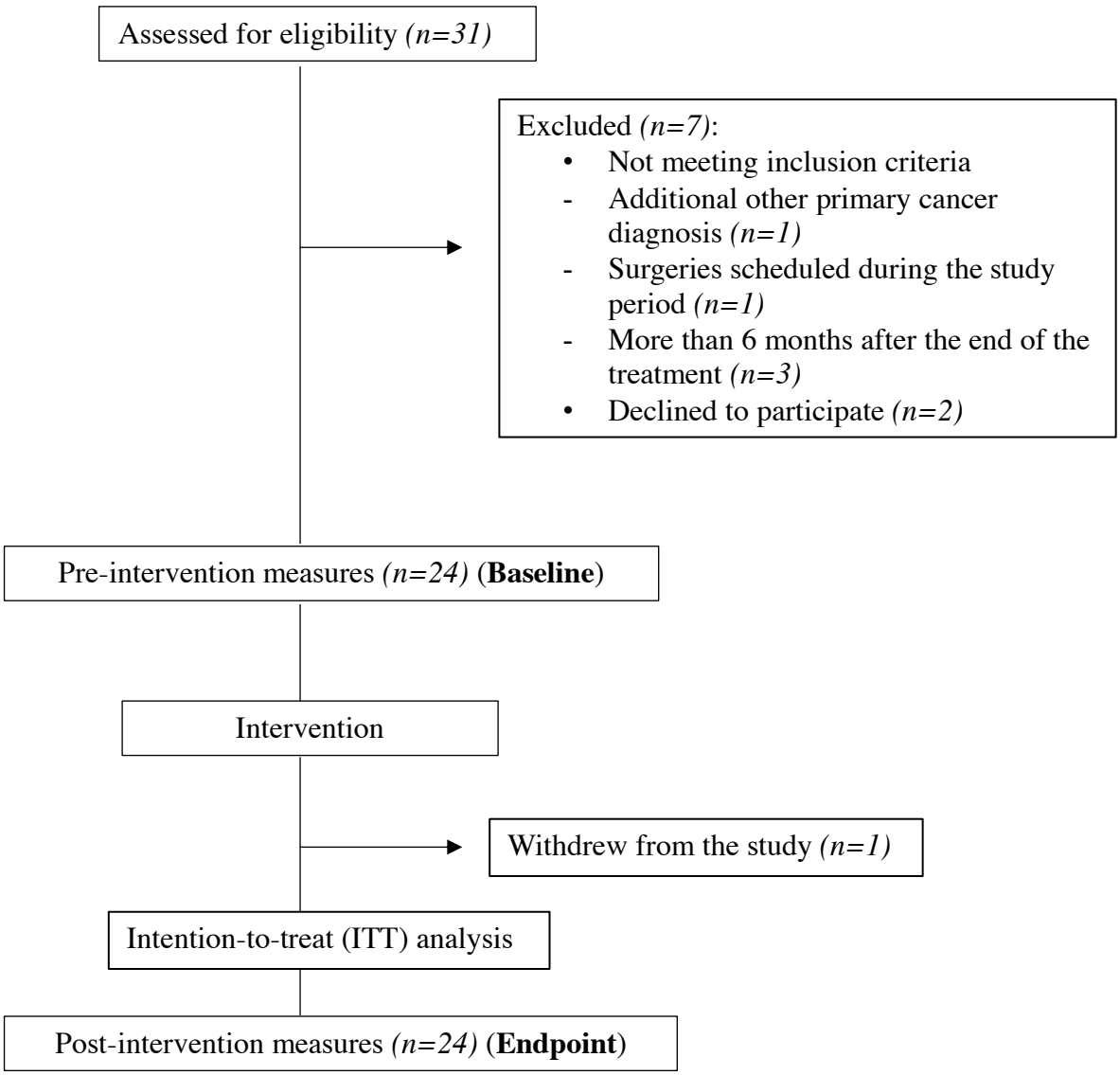
Convenience sampling – a non-probabilistic method was used to select participants; therefore, subjects were consecutively selected in order of appearance. Recruitment came to an end when sample saturation and time saturation was reached.

3.8.4 Dropouts

One participant withdrew from the study due to personal reasons (city relocation). An intention-to-treat (ITT) analysis was employed, which included data of all participants with at least one timepoint and one outcome measured. This patient withdrew from the study at week 3 (i.e. right before assessment 1), therefore, baseline data from this patient was included in the linear mixed methods analysis following the ITT approach (Figure 3.1).

Figure 3.1.

Flowchart of the study participants during data collection.



3.8.5 Recruitment

Participants were recruited from the SCC in Saskatoon. There were no study-specific costs to the patients if they decide to participate. As for recruitment strategies, brochures as flyers were used. Brochures were distributed: i) in the waiting rooms and elevator at the SCC; ii) during the sessions of the "Cancer Transitions Support Group" held at the SCC. This group is a six-week (once a week) program designed to help cancer survivors make the transition from active treatment to post-treatment life; and ii) at the cancer lodge center. (Appendix D)

Prospective participants were also identified with the help of medical oncologists from the SCC. Once the patients demonstrated interest in participating in the study, they were given a study folder and advised by their oncologist to contact the principal investigator or the primary researcher involved in this research. Those who responded directly to posters and/or flyers contacted the principal investigator or the primary researcher. After being accessed for eligibility and agreed on participating in this study, all participants signed the consent form (Appendix C). A Tim Horton's gift card of $10 was given to all participants at the end of the study in appreciation for their time.

3.9 Methods and Outcome Measures

QoL served as a primary outcome measure while stress, sleep and fatigue are considered secondary outcomes in this study. The biomarkers may not be considered as secondary outcomes as they are less critical than PRO in informing decisions, but they were taken into consideration in explaining the intervention effects at a biological level.

3.9.1 Quality of Life

QoL was assessed through the Functional Assessment of Cancer Therapy Version B (FACT-B). The FACT-B is an instrument that measures QoL among BC patients in five domains: Physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing and concerns specific to BC population. It has 38 items, 5-point Likert scale, self-administered (Brady et al., 1997; Webster, Cella, & Yost, 2003) (Appendix E).

3.9.2 Fatigue

Fatigue was assessed through the Functional Assessment of Cancer Therapy Fatigue (FACT-F) scale. The FACT-F is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities. The level of fatigue is measured on a 4-point Likert scale (4 = not at all fatigued to 0 = very much fatigued) (Minton & Stone, 2009; Wang et al., 2015; Webster et al., 2003). Both FACT-B and FACT-F were chosen due to its high reliability (α = .70-.80), feasibility and validity for the English language, and they also have been validated in several populations of cancer patients (Minton & Stone, 2009; Murray et al., 2013; Wang et al., 2015) (Appendix F).

3.9.3 Stress

Participants were asked to complete the Perceived Stress Scale (PSS-10), a 10-item questionnaire designed to assess individual's response to stress (Appendix G). Each question is rated on a 5-point scale from 0 (never) to 4 (very often). Higher scores indicate higher levels of stress. The scale scores range from 0-40. Scoring is completed by reverse scoring of four positively worded items and summing all item scores. To be identified as "stressed" by perceived stress scale, the score must be ≥ 12.1 for women (Cohen, Kamarck, & Mermelstein, 1983; Cohen & Williamson, 1988). The PSS was chosen because has demonstrated a good reliability of .87 of Cronbach's in previous studies with cancer population and also in the context of MT as a therapeutic intervention (Brennan & DeBate, 2006; Keir, 2011; Moraska & Chandler, 2009).

3.9.4 Sleep

Individual rest/activity cycle was measured noninvasively with a small-size wrist-worn accelerometer called Actigraph - Figure 3.2 (Basic Motionlogger®, Ambulatory Monitoring Inc.). Participants were asked to wear the device for 5 days at each assessment (baseline, assessment 1, assessment 2 and endpoint). The sleep devices and software for analysis were provided by the Sleep Lab and Sleep Disorders Center located at the Saskatoon City Hospital, Saskatoon.

Figure 3.2.

Actigraph Basic Motionlogger®, Ambulatory Monitoring Inc.

The Basic Motionlogger® (Ambulatory Monitoring, Inc, New York, USA), is similar to a watch and has an integrated piezoelectric accelerometer, which provides data related to daily activity and sleep pattern. This device infers sleep from the presence or absence of wrist movement. Based on previous literature, the sleep parameters assessed were sleep duration (SD), sleep efficiency (SE), sleep wake time after sleep onset (WASO) and sleep onset latency (SOL) (Sonia Ancoli-Israel et al., 2003; Landry, Falck, Beets, & Liu-Ambrose, 2015; Littner et al., 2003; Sadeh & Acebo, 2002). SD is a measure of quantity of sleep and represents the measure of time in minutes during down interval. SE is a measure of quality of sleep and represents the percentage of time asleep while in bed. WASO was measured in minutes and represents the minutes awake between sleep onset and wake time. SOL represents the length of time taken to fall asleep. Approximately 2,760 hours of sleep were recorded. In addition to the actigraphy data, patients were also asked to complete a 5-day sleep diary that was subsequently used to validate information from the actigraphy. By comparing two sources of data (subjectively and objectively assessed) concordance between measures was assessed (Appendix H).

The sleep scoring algorithm Cole-Kripke was used to score the sleep data, and the ActionW® and Action4® analysis software (Ambulatory Monitoring, Inc, New York, USA) were used to analyze data (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992). The Cole-Kripke algorithm is the most used algorithm to analyse actigraphy data in BC population (Berger, Farr, Kuhn, Fischer, & Agrawal, 2007; Berger, Wielgus, Hertzog, Fischer, & Farr, 2010; Madsen, Huang, & Gögenur, 2015; Moore, Schmiege, & Matthews, 2015).

3.9.5 Biomarkers

Saliva samples were collected using the passive drooling collection method. This method has been extensively used from previous studies and involves the collection of whole saliva by unstimulated passive drool (Ahlberg et al., 2005, 2003). The following biomarkers were analysed in this study: cortisol, CRP, IL-1β, IL-6, TNF-α, IFN-γ. The reasons why these analytes were chosen is supported by previous studies that showed a correlation between them and several aspects of inflammation, disease progression, recurrence and prognosis in breast cancer patients as well as survivors (Abdollahpour, Khosravi, Eskandari, & Haghighat, 2017; Derry et al., 2015; Fancourt et al., 2016; Jones et al., 2013; Kaur et al., 2018; Ma et al., 2017; Sephton, 2000; K. Spiegel et al., 1999; Wan, Couture-Lalande, Narain, Lebel, & Bielajew, 2016). Particularly, a few studies analysed these biomarkers in breast cancer subjects undergoing yoga and aerobic exercise programs (Abdollahpour et al., 2017; Derry et al., 2015; Jones et al., 2013).

- *Cortisol*: Salivary cortisol levels serve as a biomarker of chronic psychological stress (Debono et al., 2009; Stalder et al., 2016) and have been associated with sleep patterns and insomnia (Rodenbeck, Huether, Rüther, & Hajak, 2002; Vgontzas et al., 2001).
- *Cytokines and CRP*: Salivary levels of CRP, IL-1β, IL-6, TNF-α, IFN-γ were also measured in this study. Among other possibilities, cytokines and CRP can be sampled through human blood (serum, plasma) and saliva, which have been preferred by researchers for its non-invasive advantage (Corwin, 2000; Janssen, Caniato, Verster, & Baune, 2010). These molecules are a group of proteins released by a variety of cells. They have a major role in the inflammatory response and in the immune system (Corwin, 2000; Janssen et al., 2010).

Correlations between CRP, cytokines and the severity and development of CRS during treatment has been heavily investigated as detailed in the previous chapter. Most of these investigations report that high concentrations of IL-1β, IL-6, TNF-α, IL-13 and NF-kβ may contribute to the development of CRS and sleep problems in cancer patients in treatment and post-treatment (Alfaro et al., 2014; Bower, Ganz, Aziz, & Fahey, 2002; Illi et al., 2012; Miaskowski et al., 2010; Reyes-Gibby et al., 2008; Saligan & Kim, 2012).

3.9.6 Physiological Parameters

Oxygen saturation (SpO_2), heart rate (HR) and blood pressure (BP) were assessed by using an automated Vital Signs Monitor (Welch Allyn Vital Signs Monitor 6000 Series), as referred in previous studies (Muller et al. 2012; Wentworth et al. 2014).

Physiological parameters were assessed right before and after the intervention by the therapists or the primary researcher involved in the research. These measurements were not taken while the participant was resting on the massage table. Right after the massage session, patients were asked to dress up and walk to the next door where measurements were performed.

3.9.7 Clinical and Demographic Data

Clinical and demographic data were collected by using a questionnaire divided in four sections: i) Demographic data; ii) Disease characteristics; iii) Treatment details and iv) Other clinical information (Appendix I). Data was collected by reviewing participant's medical health record following authorization from SCA. The information from this questionnaire provided a clinical profile of each participant in the context of cancer disease, which has biological and statistical importance in the interpretation of the results.

3.10 Intervention Protocol

We aimed to create a reproducible, standardized and semi-structured Swedish MT protocol for BCS (Appendix J). Participants received the same one-hour, standardized MT upon each visit for 8 weeks (once a week). All the sessions were arranged in the afternoon from Mondays to Thursdays at the same time every week. Three participants missed a total of 5 sessions. These were contacted to reschedule the missed session to that same week. The same massage therapist was allocated for each participant during the entire duration of the study.

The MT protocol used in this study was designed by considering the advancements and limitations of previous studies with breast cancer patients (Billhult et al., 2009; Billhult, Stener-Victorin, et al., 2007; Hernandez-Reif et al., 2005, 2004; Kashani & Kashani, 2014; Krohn et al., 2011; Listing et al., 2010; Sturgeon et al., 2009). Limitations of previous studies included the massage being performed only in supine position (Kashani & Kashani, 2014) and by different therapists at each visit (Listing et al., 2009).

This protocol was developed in collaboration with Pam Fitchner, who is a registered massage therapist, and craniosacral and somatoemotional release therapist for over 12 years with a large experience MT for cancer patients. To assure consistency during protocol delivery, only standard Swedish strokes and massage techniques were used (i.e. effleurage, petrissage, little to no tapotement, vibration (gentling rocking), friction, and skin-rolling were used). The intervention protocol were as follows: a) prone position: the first phase encompassed a total of 32 minutes and involved foot massage (5 minutes), lower limb massage (10 minutes), back massage (10 minutes) and upper limbs (7 minutes); and b) supine position: a total of 28 minutes involving lower limbs (7 minutes), torso/breast area (5 minutes), upper limbs (6 minutes), neck, head and face (5 minutes) and neck (5 minutes).

The sessions took place in small, quiet and private rooms where lights were dimmed and soft. After checking for vital signs, participants were asked to undress (except for undergarments), and then make themselves comfortable on the MT table. Tables were properly sanitized before each session and draped with clean cotton sheets. Therapists were asked to refrain from talking during the sessions, except for asking about how the patient was feeling. All therapists used unscented fractioned coconut oil during the sessions. Therapists were also advised to do not treat muscles specifically or to do not deeper pressure as week progress. Some latitude was allowed if patient was unable to lie in prone or any area had lymphedema or swelling. Hence, if patient was unable to lie in prone, the sidelying position could be used; and if any area had lymphedema or swelling, the therapist was allowed to adapt by moving to another area. However, none of these adaptations were needed during the study. No music or aromatherapy was used in conjunction with the MT sessions.

A total of 5 registered massage therapists (RMT) and 10 senior massage therapy students participated in the study. All therapists were oriented and trained on how to perform the protocol by Pam Fitchner. Mock sessions were performed with each therapist and observed by the instructor in order to control for intra- and inter-therapist variability. Training included the theoretical aspects of the protocol (1hour) and hands-on practice (3 hours). Training sessions occurred at MTAS, for the RMT and at McKay school for the senior students. Each massage therapist received a certificate from the College of Medicine stating their participation in the study. The therapist remuneration rate per massage sessions was $35. In addition, MTAS offered 3 continuing education unit (CEU) credits for training participation.

3.11 Data Collection

Data was collected from September 2017 to May 2018. In this period, three rounds of data collection were performed. The first from September 2017 to November 2017 – total of 10 participants. The second round was carried out from February 2018 to early April 2018 – total of 8 participants. The third and final round was carried out from mid-March 2018 to May 2018 – total of 6 participants.

3.11.1. Piloting Saliva Collection Scheme

In order to predict potential issues and analyze the feasibility of the saliva collection scheme, we asked three graduate students to volunteer their time and kindly go over the saliva collection scheme. They received the exact same kit that were used by the study participants and were asked to go through this experience by following the same instructions, same timing and number of samplings that would be used in this study. This was an important step since it allowed us to get some critical feedback on the saliva collection scheme.

The participants judged their experience as very easy to perform, painless and handy. The drawbacks highlighted were the burden level due to the number of sampling and that it was easy to forget one or more collection samples.

3.11.2 Saliva Collection

All participants received a collection kit with all the material needed to collect and properly store the samples (Figure 3.3), along with instructions sheets (Appendix L and M). Approximately 1,152 saliva vials were collected to measure a total of six biomarkers, yielding a total of 6,912 readings using saliva specimens.

Participants were asked to follow the same instructions at every saliva collection. The instructions include asking the patients to tilt the head forward, allowing the saliva to pool on the floor of the mouth, passing the saliva into a polypropylene tube using a collection aid provided in the kit. Usually 1 min is enough to collect unstimulated passive drooled saliva using this method. To avoid contamination, participants were oriented to refrain from mouth cleaning, drinking

caffeinated beverages, smoking, having meals, snacks, or medications at least 1 hour before proceeding with the collection.

Figure 3.3.

Saliva Collection Kit.

Several molecules in the human body are secreted in a circadian rhythmicity, hence careful consideration of sampling times was employed in this study. The kinetics and time-release of several molecules in the saliva and blood specimens, as well as the reactivity (speed of change) of these molecules are still unclear (Bonz et al., 2003; Desborough, 2000; Pramanik et al., 2012; Smith, Kemp, Hemphill, & Vojir, 2002). For instance, cortisol, CRP, IL-1β, IL-6, TNF-α, IFN-γ have distinct peak release after an intervention and, therefore, studies with MT and other IM therapies have employed different data collection schemes when measuring biological markers. The study's research question (s) and the biomarkers of interest often determines the biological specimen (i.e. saliva, blood, urine) and the collection timepoints. Studies aiming to assess pre and post immediate changes tend to use blood specimens, while those aiming to assess late and/or long-term changes overtime employ saliva and urinary specimens. Likewise, studies have also employed a diverse scheme of collection timepoints. Previous studies have multiple collection points in the same day (Bernard, Hostinar, & Dozier, 2015; Bonz et al., 2003; Jäger, Schmidt, Conzelmann, & Roebers, 2014; Leardi et al., 2007;

Nilsson, 2009; Pędziwiatr et al., 2015; J. J. Wu et al., 2014), while others have characterized the whole diurnal profile by considering a multiple-time and multiple-day collection approach (Malarkey, Jarjoura, & Klatt, 2013; Matousek et al., 2011).

To reflect biomarkers' circadian pattern, collecting saliva samples at multiple times throughout the day for more than one day is the ideal approach. The following summarizes the most relevant studies' recommendations in regards to salivary sampling of biomarkers: (i) in order to reliably characterize within-person changes across interventions, at least 3 days of data collection are needed for the whole diurnal profile through Area Under the Curve (AUC) calculation (Jens Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003; Segerstrom, Boggero, Smith, & Sephton, 2014); (ii) collecting less than four samples per patient in 24 hours would not yield accurate results of the diurnal pattern (Stalder et al., 2016); (iii) instead of having many samples per day over the course of a few days, it is recommended collecting fewer samples, per day over more days (Segerstrom et al., 2014); (iv) sampling times throughout the day must be as evenly spread out as possible (Stalder et al., 2016) and (v) if multiple collections cannot be done, afternoon collection is preferable for adults to avoid the influence of the awakening response of some markers (Lovallo, Farag, & Vincent, 2010).

While it is desirable to acquire multiple measurements over time for finding individual variations with regard to response time and duration, the amount of data gathered is enormous and can represent a problem for the statistical analysis (Fekedulegn et al., 2007; Khoury et al., 2015; Jens Pruessner et al., 2003). When trying to identify possible relations between repeated measures and other outcomes, as well as to comprise biomarkers concentrations sampled in multiple measurements over time, the AUC has been routinely used to incorporate multiple time points (Fekedulegn et al., 2007; Khoury et al., 2015; Jens Pruessner et al., 2003). The exact number of measurements needed to create an accurate AUC depends on several factors such as the homogeneity of participants involved, the timing and interval of the measurements, and if clinically relevant cofounders are taken into account (Booij et al., 2015). For instance, in an attempt to estimate the exact number of measurements needed to create an accurate cortisol AUC, an author stipulated that 70 and 88 measurements would have been necessary to estimate between-individual differences with moderate reliability (Hruschka, Kohrt, & Worthman, 2005). However, up to date, only a few studies have sampled cortisol between 50 to 60 times (Peeters, Nicolson, & Berkhof, 2004; Van Eck, Berkhof, Nicolson, & Sulon, 1996).

For the purposes of this study, we were interested in the long-term effects of the intervention overtime (every two weeks). Immediate pre and post changes were not primarily intended to be captured in this study given that every biomarker of interest displays a different salivary reactivity and recovery pattern. Hence, based on these recommendations, three days of consecutive sampling were employed in this study, and the following time points were used for saliva collection: i) at day one: 5pm (roughly 1h after the MT session) and 8pm; ii) at day two: upon awake, 30 min. later, noon, 5pm and 8pm; and iii) at day three: upon awake, 30 min. later, noon, 5pm and 8pm (Appendix M). Awakening was either spontaneous or by alarm clock, since previous study has shown that the cortisol response is not affected by this factor (Pruessner et al., 1997).

3.11.3 Compliance

As for the compliance with saliva collection, the importance of collecting samples at designated times was emphasized, however we cannot confirm that participants strictly adhered to the collection scheme. Although it has been shown that the consistency of salivary measures is directly dependent on subject compliance, it has also been revealed that patient compliance rate is superior to that of healthy controls or volunteers (Broderick, Arnold, Kudielka, & Kirschbaum, 2004).

In order to help participants in remembering to collect the samples we used a bulk SMS system (RedOxygen™), which is able to send mass text messaging. The reasons for choosing this system were based on the fact that this tool allows to track message delivery, along with the cost-effectiveness and the capability to send SMS to several types of mobile devices. SMS were standardized and scheduled at specified times and dates. By using this tool, we were able to reach each participant by SMS according to the saliva collection scheme and remind them within approximately 10 minutes before each time point (Appendix N). A daily log was automatically generated by the system reporting the status of each SMS and allowing the researchers to confirm that the SMS was promptly delivered.

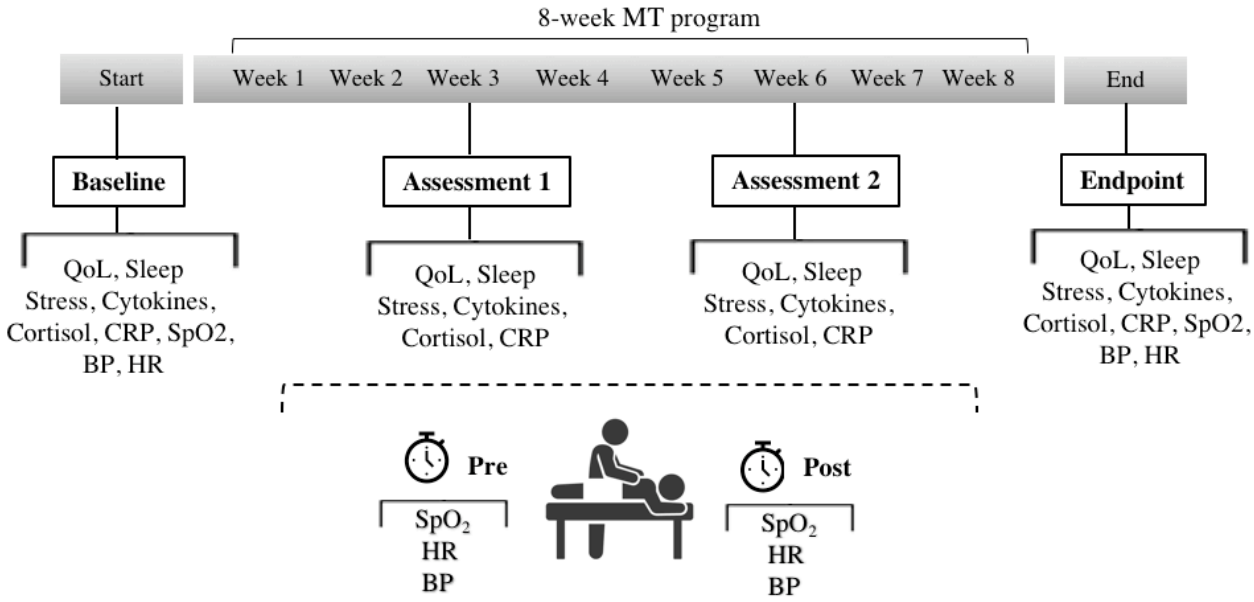
During the study, three participants opted out of receiving the SMS indicating that they had their own alerts/reminders set up in their personal mobile.

3.11.4. Study Assessments

As depicted in Figure 3.4, participants went through four assessments (i.e. baseline, assessment 1, assessment 2 and endpoint) over the course of 10 weeks. Participants received the intervention for 8 weeks, and the whole duration of the study was 10 weeks. The time points were selected based on results previously described in the literature and based on the most accurate methodologies to date applied (Bower et al., 2005; Carlson et al., 2013; Chan et al., 2006; Hsiao et al., 2012; Lipschitz, Kuhn, Kinney, Donaldson, & Nakamura, 2013; Nater, Rohleder, Schlotz, Ehlert, & Kirschbaum, 2007; Nunes et al., 2007; Stalder et al., 2016; Wan et al., 2016).

Figure 3.4.

Scheme summarizing the measurements according to the study phases.



Pre and post every MT session, the physiological parameters SpO_2, HR and BP were assessed, as well as at baseline and endpoint. QoL, fatigue, stress, fatigue and the biomarkers were assessed at all assessments. Hence, participants completed a battery of self-reported questionnaires (QoL, fatigue and stress), recorded sleep data for 5 days (actigraphy), and collected a 3-day cycle of saliva samples at:

- Baseline: the week prior to the first MT session.
- Assessment 1: upon week 3.
- Assessment 2: upon week 6.
- Endpoint: the week after the last MT session.

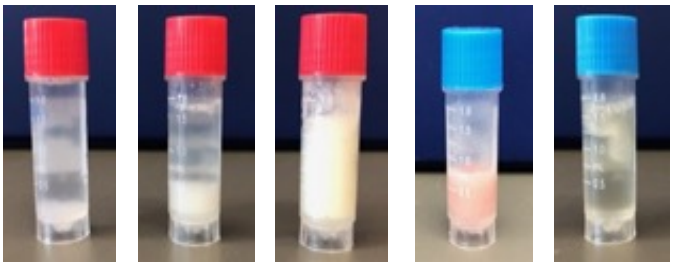
3.12 Laboratory Analysis

3.12.1 Saliva Sample Preparation

Saliva samples were labelled and stored at -80°C. Frozen samples were allowed to attain room temperature (RT) before analysis. Vortex followed by centrifugation at 10,000 × g for 5–10 minutes was performed. Even though saliva collection instructions were reinforced with all participants to prevent sample contamination with food debris, inevitably a few samples showed debris due to a possible food contamination (Figure 3.5).

Figure 3.5.

Saliva samples collected from study participants showing the differences in sample quality.



In order to achieve good and standard quality sample, any collection that presented contaminants were centrifuged a second time to remove cellular and food debris.

3.12.2 Saliva Sample Analysis

Saliva samples were analysed using Luminex technology® along with 6-plex Magnetic Bead ProcartaPlex® kits by ThermoFisher (Thermo Fisher Scientific, Waltham, MA). The Luminex technology enables multiple analytes to be measured at the same time. Previous studies

in cancer population have chosen this same technique to analyse saliva, serum, plasma and cell culture supernatant samples (Arellano-Garcia et al., 2008; Lee et al., 2018).

A MAGPIX®, Luminex® 100/200™ (serial number MAGPX13355701) was used to read the samples and the xPONENT® 4.2 software package was used to data acquisition. (Thermo Fisher Scientific, Waltham, MA).

Following the manufacture's recommendations, the reagents were allowed to attain RT before analysis. The analysis protocol constituted of six steps. The first step was the antigen standard preparation. Initially, each different antigen standard vial was centrifuged at 2,000 × g for 10 seconds. Standards were reconstituted by adding 50 µL of Universal Assay Buffer (1X) into each standard vial. Vials were then gently vortex for 10 seconds and centrifuged at 2,000 × g for 10 seconds. Vials were then incubated on ice for 10 minutes to ensure complete reconstitution. After complete reconstitution, the second step was pooling of standards. The entire content of standards vials was pooled into one single vial (total volume after this step will be 150uL). Vials were filled up with 100uL of Universal Assay Buffer (1X). (the final volume after reconstitution and pooling should be 250 µL). After gently vertexing the vial for 10 seconds, they were centrifuged at 2000 × g for 10 seconds to collect contents at the bottom of the vial.

The third step was the preparation of a 4-fold serial dilution. A provided PCR 8-tube strip was used to prepare the 4-fold serial dilution of the reconstituted standards. Tubes were labeled Std1, Std2, Std3, Std4, Std5, Std6, and Std7. A total of 200 µL of the reconstituted antigen standards were added into the Std1 tube of the strip. A total of 150 µL of Universal Assay Buffer were added into Std tubes 2 to 7. A volume of 50 µL of the reconstituted antigen standards was transferred from Tube 1 into Tube 2. The same amount (50 µL) of the mixed standards was transferred from Tube 2 into Tube 3 – and so on until Tube 7. A volume of 200 µL of Universal Assay Buffer was added into Tube 8 which served as a blank. These were kept on ice until ready to use (See Appendix O for 96-well plate template).

The fourth step was the preparation of the cortisol competitive conjugate solution (1X). A 25 µL of Competitive Conjugate Solution (50X) was mixed with 1,225 µL Universal Asssay Buffer (1X). Fifth step was the preparation of the cortisol beads. Cortisol beads were provided as concentrated 50x beads. Therefore, dilution of concentrated cortisol beads was required. Each cortisol bead vial (50X) was vortexed for 30 seconds and 50uL of the bead vial (50X) were added to a mixing bottle (Eppendorf tube). This bottle was filled up with 2,450uL of wash buffer (1X)

to a final volume of 5mL.

The sixth step of the protocol is the execution of the assay itself. The 6-plex Magnetic Bead vials was vortexed for 30 seconds. A volume of 50uL of the 6-plex Magnetic Bead solution was added into each well of the plate. In addition, 50uL of the diluted 1X cortisol beads were added into the same plate. Beads were washed from the plate (1x wash). After wash, a total of 25 µL of Universal Assay Buffer (1X) were added to each well, followed by 20 µL of the diluted Competitive Conjugate Solution (1X), and 25 µL of prepared standards and samples. After that, plate was sealed and covered with the black microplate lid and set to shake at 500 rpm for 60–120 minutes at RT. After incubation, plate was washed (2x wash) followed by the addition of the 25 µL of Detection Antibody Mixture (1X) to each well. A second incubation was performed with plate sealed and covered with the black microplate lid and set to shake for 30 minutes on a plate shaker at room temperature to 800 rpm for 1 min, back down to 600 rpm for remainder of time. After incubation, plate was washed (2x washes) followed by the addition of 50 µL of SAPE solution to each well. A third incubation was performed with plate sealed and covered with the black microplate lid and set to shake for 30 minutes on a plate shaker at room temperature to 800 rpm for 1 min, back down to 600 rpm for remainder of time. After incubation, plate was washed (2x washes) followed by the addition of 120 µL of reading buffer into each well. A third and final incubation was performed for 5 minutes on a plate shaker at 800 rpm for 1 minute, back down to 600 rpm for remainder of time.

Data analysis was performed using the Bio-Plex Manager™ 6.11 software®. The standard curves were fit with the designated model using those standards that encompassed the values for each marker obtained from the samples in each assay. A good percentage recovery was set from 80 to 120%. To reflect intra-assay precision, %C.V. were aimed to be less than 20-25%. The r^2 values for the linear fits were always between 0.80 and 0.95 and very often above 0.90. In each 96-well plate, the standards were run in duplicate, as well as the samples.

3.13 Statistical Analysis

3.13.1 Descriptive Statistics

Initial dataset was created in Microsoft Excel version 16.6 (Microsoft for MacBook Inc, Redmond, WA) and analyzed with Statistical Package for the Social Sciences (SPSS) version 19.0 (IMB Inc, Chicago, IL). Assumptions of independence, linearity and homoscedasticity were tested for all levels of independent variables. The Shapiro-Wilks test was used to assess the normality of the data. Measures of central tendency (e.g., mean and median) along with measures of dispersion (e.g., standard deviation and interquartile range) were calculated for continuous variables. Frequencies and percentages were used to present all categorical variables. Graphically displaying the data was considered as an additional aid in assessing patterns of dispersion in order to identify potential outlying values that may influence the results.

3.13.2 Inferential Statistics

Since this study proposed a quasi-experimental design, each participant was assessed by the same instruments at different points in time, and the results obtained for each individual during different measurements were compared; thus the statistical analyses was performed using paired methods such that each participant serves as her own comparison (i.e. two paired - dependent - samples).

For *research question one* (i.e. are there any changes in QoL, stress, fatigue and sleep in BCS submitted to an 8-week Swedish massage program?) a General Linear Model (GLM) and a Linear Mixed Model (LMM) were used.

General Linear Model:

Repeated-measures ANOVAs (RM-ANOVAs) were conducted to identify if there were significant changes in QoL, stress, fatigue and sleep data over the course of the program. For the RM-ANOVAs, measures at each of the four time points were entered as within-subject factors. Independent variables (i.e. age, cancer stage, sleep medications in use, months after treatment, type of treatment, presence of comorbidities, hormonal therapy) were entered as between-subject factors. If Mauchly's test was statistically significant, the Greenhouse-Geisser and Huynh-Feldt values were used as alternative corrections to the sphericity assumption. If both of these values are greater than 0.75, Huynh-Feldt was used, if lesser than 0.75, the Greenhouse-Geisser was chosen (Field, 2009). Absolute values of skewness and kurtosis were also checked. The variables that were not normally distributed but had good values for skewness and kurtosis were treated as

normally distributed after outliers removed. Skewness and kurtosis were expected to not exceed 0.8 and 2 respectively (George & Paul, 2010). The total sample size for the RM-ANOVAs was 23 subjects.

Linear Mixed Model:

Given the exploratory nature of the present study, only the variables that showed statistical significance in the RM-ANOVAs and significant interactions with the covariates were included in the LMM analysis. LMM allows modeling of subject-specific trajectories over time, as well as modeling the correlation between measurements within subject. In the case of the present study, the Satterthwaite approximations to degrees of freedom were used when testing fixed effects. Satterthwaite has shown to be more accurate especially when sample size is small or moderate (Luke, 2017). Second, in LMM, random effects and error terms express correlated and nonconstant variability in their results. It provides a fully specified model of the distribution of the outcome. Third, it allowed the analyses to be pragmatic and based on the intention-to-treat (ITT) principle, which included data on all participants with at least one timepoint and outcome measured. This procedure prevented listwise deletion due to missing data given that LMM use all data available at each time point; thus, missing data imputation was not undertaken. A total of twenty-three participants had data collected at all timepoints, and one participant had only baseline data collected. Because we applied ITT principle, LMM presented as a powerful alternative given its flexibility and robustness in dealing with missing data. Final sample used in the LMM analysis was 24 subjects.

For the LMM model, the response variables were the dependent variables (i.e. QoL, fatigue, sleep outcomes and the biomarkers) and the fixed effects were time and the predictor variables (i.e. age, type of treatment, cancer stage, hormone use, sleep aids in use, comorbidities, and months after treatment).

Careful application of model building strategies was employed to yield the best possible model within the constraints of the available data. Clinically biologically or scientifically meaningful independent variables (IVs) were chosen based on supporting literature, the biological theory related to the study, as well as on the RM-ANOVAs results. Following the forward/step-up selection strategy to fit multivariable models, the analysis of each variable to be included in the model was verified as follows: (i) starting with an intercept-only model (empty model), a model was initially generated with no predictors (fixed effects) in the model. This was

the base model for comparison; (ii) One at a time, IVs (potential predictors) were added to the model; (iii) an examination of AIC and BIC was performed; (iv) and a comparison of each estimated coefficient with the model containing only that variable; (v) variables that showed no significant main effect were removed from the final model, unless significant differences between categories and/or interactions were found (Harrison et al., 2018).

Additionally, variables with strong theoretical justification even if was statistically insignificant were retained, based on the assumption that explanatory power plays a major role in assessing predictive performance, whereas statistical significance does not. In fact, according to the literature, removing variables with small coefficients, even if they are statistically significant, results in improved prediction accuracy (Shmueli, 2010; Wu, Harris, & Mcauley, 2008).

Finally, we compared Akaike's Information Criterion (AIC) and Bayesian information Criterion (BIC) across each model. The difference in AIC and BIC values between models determines the strength of support for the model with the lowest AIC and BIC. AIC for model choice is commonplace in many scientific fields (Muth et al., 2016; Schober & Vetter, 2018; West, 2009). AIC measures predictive accuracy while BIC measures goodness of fit, and overall, lower values of these estimators mean that a model has a good fit (West, 2009). In addition to AIC and BIC values, the relationship between variables were also taken into account. Considering that the dependent variables (DVs) might be affected by the IVs, as well as by time, it is believed that the DVs will decrease or increase throughout the time. Any two distinct observations from the same patient have the same correlation coefficient ($0 < r \leq 1$). We assumed that factors and predictor variables have a linear relationship to the dependent variables, justifying the use of compound symmetry covariance structure, since its structure assumes constant variance and constant covariance (Muth et al., 2016; Schober & Vetter, 2018; West, 2009). Therefore, based on adherence values BIC and AIC, and on the assumption of relationship between variables, the compound symmetry covariance structure was used to adjust the LMM in this study.

Once we have identified a model that had the essential variables, the inclusion of interaction terms was undertaken. Significant interactions were retained and represented graphically. If not affecting the overall model goodness of fit, lower order effects were kept in the model when they were connected to higher order effects and vice versa.

For *research question two* (i.e. are there any changes in inflammatory markers in BCS submitted to an 8-week Swedish massage program?) the same procedure employed for *research question one*, were used to analyze the biomarkers data (GLM followed by LMM). Skewness and kurtosis were analyzed to detect whether biomarkers data was positively skewed (skewed to right, skew > 0) or negatively skewed (skewed to left, skew < 0). Because of a skewed non-normal distribution of the biomarkers data, data were logarithmically transformed. Since saliva samples were collected at multiple time points, indices representing total biomarkers' magnitude and production were calculated using AUC based on the log-trapezoidal method as described by previous studies (Fekedulegn et al., 2007; Khoury et al., 2015; Pruessner et al., 2003). Most of missing data was from the saliva collection (i.e. when a patient missed a collection, or the biological specimen did not meet the quality criteria). Missing values were handled by multiple imputation after missing patterns analysis. Littler's MCAR test ($p>0.05$) failed to reject the null hypothesis, determining randomness of missing data. Values were estimated based on data patterns. Linear regression is used to create values that are appropriate and realistic (Haukoos & Newgard, 2007; McKnight, 2007; Newgard & Haukoos, 2007; Sterne et al., 2009).

For *research question three* (i.e. what are the immediate changes in BP, HR and SpO_2 in BCS submitted to an 8-week Swedish massage program?) bivariate association analysis was performed to identify if there was any changes in BP, SpO_2 and HR using the nonparametric paired Wilcoxon for the variables not normally distributed and Paired T-test for the normally distributed. Mean Arterial Pressure (MAP) was calculated to analyse BP following previous studies methodology (Jane et al., 2009). MAP is defined as the average pressure in a patient's arteries during one cardiac cycle. MAP is considered a better indicator of perfusion to vital organs than systolic blood pressure (SBP) (Furlanis et al., 2018; Tee et al., 2017). To calculate a MAP, the diastolic blood pressure (DBP) was doubled, and the result added to the SBP, and then divided by 3.

For *research question four* (i.e. are there any correlations between the main variables in the study?) Spearman ϱ (rho) bivariate correlation tests were carried out to examine putative correlations between inflammatory markers with QoL, fatigue, stress and sleep measures. Following similar studies, we adopted Spearman's to examine correlation properties as a conservative measure, in order to avoid the effects of extreme values (Chowdhury, Chandra, Li, Ely, & Turner, 2019; Khosravi et al., 2018; Lopes-Junior et al., 2019; Nakamura et al., 2010)

All calculations were performed at a 95% confidence interval. Two-sided p values <0.05 were considered statistically significant. Effect sizes (Cohen's d) were also calculated as a measure of practical significance. For non-parametric data, log transformed data were used to calculate effect size based on previous studies recommendations (Rodríguez-Barranco, Tobías, Redondo, Molina-Portillo, & Sánchez, 2017).

3.14 Quality Assurance

A series of planned and systematic activities were conducted to ensure that this trial was performed in compliance with the study protocol. The following strategies were used to prevent, detect, and correct problems during the execution of the protocol, and to increase the quality of findings produced by this study:

- Participants that best represented the research topic were chosen;
- Student (primary researcher) received appropriate training to conduct the study (e.g. biosafety training, laboratory training, statistical training, ethics certification);
- A sustainable community-academic partnership was developed with the community partners to ensure long-term engagement throughout the study;
- The research processes were clearly generated, documented, and reported to the research supervisor and advisory committee;
- The decisions made throughout the study were summarized in an audit trial.

3.15 Knowledge Translation

The study results were presented to participants and key informants in a small gathering at MTAS on November 13th 2019. Medical oncologists, nurses, social workers and massage therapists who participated in the study were also invited, as well as the general public and anyone who were interested. Folders advertising the gathering were posted around the SCC and sent to our local partners which included: HOPE Cancer Help Centre (https://hopecancercare.com); McKay School Training (www.mckaysk.ca), SCC (www.saskcancer.ca), Breast Cancer Support Saskatoon

(http://breastcancersupportsaskatoon.com); Too Tired Fatigue Education Group, the Cancer Transition Group at SCC, Cancer Connection Network (https://survivornet.ca); Massage Therapists Association of Saskatchewan (MTAS) (https://www.saskmassagetherapy.com); Live Well program (www.saskatoonhealthregion.ca/locations_services/Services/cdm).

During this gathering session, Ms. Bomfim acknowledged the participation of all patients and recognized any supporter institutions, such as Saskatchewan Health Research Foundation (SHRF) and MTAS. Participants received a brochure with a summary of the principal results in layman's terms, although copies of the final research report were also available. They were encouraged to ask questions they may have. For those that were unable to attend, they were contacted individually by email or phone call to be informed of the results of this study. Our findings were also disseminated to the agencies and support groups that we partnered with through e-mail.

At an academic level, partial results have been presented at various international conferences (e.g. The Network: Towards Unit for Health in Darwin, Australia and CAPO/IPOS 21st World Congress of Psycho-Oncology in Banff, Canada, both in September 2019). Final results will be also disseminated in academic conferences. In addition, articles on the research findings will be submitted to indexed and peer-reviewed journals.

3.16 Summary of Chapter Three

This study is a one-group, longitudinal quasi-experiment without a control group. The study was carried out in Saskatoon at the University of Saskatchewan, Massage Therapy Association of Saskatchewan, the McKay Career Training School. The study is framed and guided by the Middle Range Theory of Unpleasant Symptoms and the Psychoneuroimmunology Framework.

Participants were females over 18 years who were diagnosed with breast cancer - stages I to III and have completed the treatment in the last month. The study involved the following methods and procedures: participants underwent 1 hour of Swedish relaxation massage over 8 weeks. Participants were assessed at: Baseline (T1); Assessment 1 (T2), Assessment 2 (T3) and Endpoint (T4). At all these assessments, all outcomes were assessed: QoL, stress, sleep, fatigue, physiological parameters, cortisol, CRP and cytokines. The FACT-F and FACT-B were chosen

to measure fatigue and QoL, and the Perceived Stress Scale was used to measure stress. Individual Rest/Activity Cycle was measured noninvasively with a small-size wrist-worn device (Basic Motionlogger®, Ambulatory Monitoring Inc.®). This tool is similar to a watch and the patients used it for at least 5 days. Saliva was collected to detect cortisol, CRP and cytokines levels. Also, physiological parameters (arterial oxygen saturation - SpO_2, heart rate and blood pressure) were measured pre and post every massage session.

The next chapter displays the results of this study. The results are presented in alignment with the study's research questions.

CHAPTER 4

RESULTS

4.1 Overview

In this chapter, the demographics of the participants and the results of the effects of the 8-week MT intervention on QoL, sleep, stress, fatigue and inflammatory markers in recently treated BCS are presented.

4.2 Characteristics of the Participants

A total of 23 participants completed the study, however, since ITT was employed, a total of 24 subjects were included in the final sample. Table 4.1 shows the main variables of the clinical-demographic profile. The average age of participants was 56.9 (±9.3). Most participants (n=11) went through all three types of treatment (chemotherapy, radiotherapy and surgery). All participants were diagnosed with a primary cancer. Most participants (n=13) enrolled in the study within the first three months after completion of treatment. The majority of BCS in our study were diagnosed with a stage I cancer (n=10), and the majority was in hormonal therapy (n=16). A total of 13 participants were taking sleep aids during the course of the study.

Table 4.1.

Descriptive statistics of the clinical-demographic variables of a sample of BCS, Saskatoon (n=24).

Variable	**M**	**SD**
Age (years)	56.9	9.3
Variable	**n**	**%**
Age Classification		
30-40	3	12.5
40-50	4	16.6
50-60	10	41.7
≥61	7	29.2

Table 4.1. (*continued*)

Education Level	**n**	**%**
Finished high school	7	29.1
College or Bachelor's degree	16	66.7
Post-degree education	1	4.2
Marital Status		
Married	19	79.1
Widowed	2	8.2
Not married	2	8.2
Divorced	1	4.5
Birth Country		
Canada	23	95.8
Out of canada	1	4.2
Work Status		
Not working	4	16.6
Part-time worker	4	16.6
Domestic worker	3	12.5
On medical leave	9	37.7
Pensioner	4	16.6
Disease Classification		
New primary	24	100
Months after treatment		
< 3 months	13	54.2
≥ 3 months	11	45.8
Cancer Stage		
I	10	41.6
II	7	29.2
III	7	29.2
Treatment Classification		
Unimodal therapy	3	12.5
Multimodal = 2 therapies	10	41.6
Multimodal > 2 therapies	11	45.9
Type of Treatment		
Chemo, Radiation and Surgery	11	45.9
Radiation and Surgery	5	20.8
Only Chemotherapy	2	8.2

Table 4.1. (*continued*)

Chemotherapy and Radiation	1	4.2
Surgery only	1	4.2
Chemotherapy and Surgery	4	16.6
Hormone Therapy		
Yes	16	66.7
No	8	33.3
Medications		
On sleep aids	13	54.2
Off sleep aids	11	45.9
Comorbidities		
Yes	14	58.3
No	10	41.7

4.3 Changes in QoL, Fatigue, Stress and Sleep

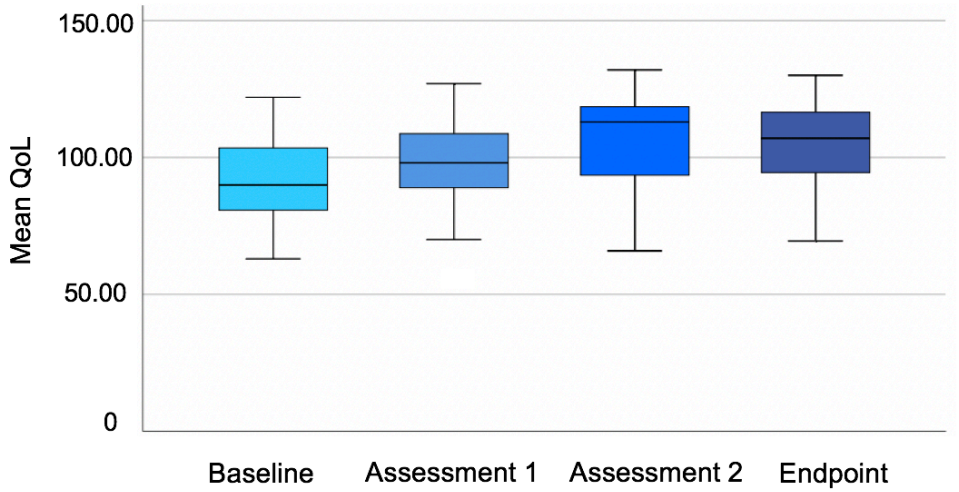
This subsection will address the findings of research question one: are there any changes in QoL, stress, fatigue and sleep parameters in BCS submitted to an 8-week Swedish massage program? Below, a detailed description of the results is presented for each outcome.

4.3.1 Quality of life

The trajectory of QoL throughout the 8-week MT program is depicted in Figure 4.1 (below). QoL scores measured with FACT-B questionnaire ranges from 0-144. Interpretation assumes that the higher the score, the better the QoL.

Figure 4.1.

Changes in QoL scores at each timepoint (n=24).



According to Figure 4.1, patients improved their QoL at the end of the 8-week MT program. Participants showed the lowest QoL at baseline (mean=92) and showed improvement of this construct at endpoint (mean=103.8). Among the study covariates tested in the LMM, only two (i.e. Months After Treatment and Cancer Stage) yielded statistically significant main effects and/or significant interaction terms in the QoL models, which are described below.

QoL and Months After Treatment

Table 4.2 (below) shows that Time had a significant effect on QoL [F=(3, 66.000)=12.328, p<0.0001], but Months After Treatment did not significantly affect QoL [F=(1, 22)=.682, p=0.418]. However, the interaction of Time and Months After Treatment had a significant effect on QoL [F=(3, 66.000)=3.053, p=0.034].

Table 4.2.

Type II tests of Fixed Effects Results for QoL Model 1 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	22	1037.07	.000
Time	3	66	12.32	.000
Months After Treatment	1	22	.682	.418
Interaction Time * Months After Treatment	3	66	3.05	.034

AIC: 708.57; BIC: 713.52

Table 4.3.

Estimates of Fixed Effects Results for QoL Model 1 (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	100.34	5.10	33.33	19.64	.000	89.95	110.72
Time							
Baseline	-9.66	3.68	66.00	-2.62	.011	-17.03	-2.30
Assessment 1	-8.69	3.68	66.00	-2.35	.021	-16.06	-1.33
Assessment 2	7.55	3.68	66.00	2.049	.044	.19	14.91
Endpoint[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
Months After Treatment							
< 3 months	7.06	6.93	33.33	1.01	.316	-7.04	21.17
≥ 3 months[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
Interactions[b]							
Assessment 2 *< 3 months	-9.77	5.01	66.00	-1.95	.055	-19.77	0.23
Endpoint * < 3 months[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

Estimates of fixed effects results displayed in Table 4.3, shows an interaction term between *Assessment 2 * < 3 months* with a *p* value marginally significant (β=-9.77, t=-1.95, *p*=0.055, CI 95%: -19.77, 0.23), indicating that those who finished treatment less than 3 months after study onset showed significantly lower QoL (9.77 points) when compared to those who finished treatment more or equal than 3 months after study onset at assessment 2 when compared to endpoint. This interaction is graphically displayed in Figure 4.2.

To describe how this interaction term indicates that there are differences in QoL scores for each group of Months After Treatment between Timepoints, and that, similarly, QoL scores

were different at each Timepoint for each level of the Months After Treatment variable, pairwise calculations were performed using the estimated means from the final LMM displayed in Table 4.3. For instance, to find the difference between QoL_1 [< than 3 months group at assessment 2] and QoL_2 [≥ 3 months group at endpoint], the following values were used for pairwise comparisons calculations:

- QoL_1 [≥ than 3 group * assessment 2] = $\beta_{intercept} + \beta_{Assessment2} + \beta_{\geq 3\ months} + \beta_{interaction}$
- QoL_1 [≥ than 3 group * assessment 2] = 100.34 + 7.55 + 0 + 0
- QoL_1 [≥ than 3 group * assessment 2] = 107.89

- QoL_2 [≥ than 3 group * endpoint] = $\beta_{intercept} + \beta_{Endpoint} + \beta_{\geq 3\ months} + \beta_{interaction}$
- QoL_2 [≥ than 3 group * endpoint] = 100.34 + 0 + 0 + 0
- QoL_2 [≥ than 3 group * endpoint] = 100.34

- $QoL_{1\text{-}2}$ = 107.89 – 100.34 = 7.55, meaning that QoL scores for those who finished treatment ≥ 3 months before study onset were 7.55 points higher at assessment 2 in comparison to endpoint.

Similarly, to find the difference between QoL_3 [< than 3 months group at assessment 1] and QoL_4 [≥ 3 months group at assessment 1], the following values were used for calculations:

- QoL_3 [< than 3 group * assessment 1] = $\beta_{intercept} + \beta_{Assessment1} + \beta_{<3\ months} + \beta_{interaction}$
- QoL_3 [< than 3 group * assessment 1] = 100.34 - 8.69 + 7.06 + 5.04
- QoL_3 [< than 3 group * assessment 1] = 103.75

- QoL_4 [≥ than 3 group * assessment 1] = $\beta_{intercept} + \beta_{Assessment1} + \beta_{\geq 3\ months} + \beta_{interaction}$
- QoL_4 [≥ than 3 group * assessment 1] = 100.34 - 8.69 + 0 + 0
- QoL_4 [≥ than 3 group * assessment 1] = 91.65

- $QoL_{4\text{-}3}$ = 103.75 – 91.65 = -12.1, meaning that QoL scores at assessment 1 were 12.1 points lower for those who finished treatment ≥ 3 months before study onset when compared to those who finished treatment < 3 months before study onset.

Results of all pairwise calculations are displayed in Tables 4.4 and 4.5. In addition to these calculations, a paired sample *t*-test was run to analyse if selected pairwise comparisons of interest were statistically significant.

Table 4.4.

Mean Difference of QoL scores for each group of Months after Treatment between Timepoints (n=24).

Moths After Treatment			**Mean Difference**
< 3 months	Baseline	Assessment 1	-9.00
		Assessment 2	-10.43*
		Endpoint	-12.65*
	Assessment 1	Baseline	9.00
		Assessment 2	-1.43
		Endpoint	-3.65
	Assessment 2	Baseline	10.43
		Assessment 1	1.43
		Endpoint	-2.21
	Endpoint	Baseline	12.65*
		Assessment 1	3.65
		Assessment 2	2.21
≥ 3 months	Baseline	Assessment 1	-0.97
		Assessment 2	-17.22*
		Endpoint	-9.67
	Assessment 1	Baseline	0.97
		Assessment 2	-16.25*
		Endpoint	-8.69
	Assessment 2	Baseline	17.22
		Assessment 1	16.25*
		Endpoint	7.55
	Endpoint	Baseline	9.67*
		Assessment 1	8.69
		Assessment 2	-7.55

*. The mean difference is significant at the .05 level (paired *t*-test).

Important differences in QoL scores for each group of Months after Treatment between Timepoints were found (Table 4.4 above). As shown in Table 4.4, for those who finished treatment < 3 months after study onset, QoL scores at baseline were significantly lower (12.65 points) in comparison to endpoint (p=0.003), showing improvement of this construct. Similarly, for those who finished treatment ≥ 3 months after study onset, QoL scores at endpoint were significantly higher (9.67 points) in comparison to baseline (p=0.011) (Table 4.4). For this same group, QoL scores at baseline and assessment 1 were significantly lower (17.22 points and 16.25 points, respectively) in comparison to assessment 2 (p<0.000) (Table 4.4).

Table 4.5.

Mean Difference of QoL scores at each Timepoint for each level of Months After Treatment (n=24).

Timepoints			Mean Difference
Baseline	< 3 months	≥ 3 months	4.07
	≥ 3 months	< 3 months	-4.07
Assessment 1	< 3 months	≥ 3 months	12.11
	≥ 3 months	< 3 months	-12.11
Assessment 2	< 3 months	≥ 3 months	-2.70
	≥ 3 months	< 3 months	2.70
Endpoint	< 3 months	≥ 3 months	7.06
	≥ 3 months	< 3 months	-7.06

Table 4.5 shows that, overall, those who finished treatment ≥ 3 months after study onset showed lower QoL (except at assessment 2), with no significant differences at timepoints. For instance, at assessment 1, a mean difference of 12.11 was found between groups, but this difference was not statistically significant (p=0.090) (Table 4.5).

QoL and Cancer Stage

Table 4.6 shows that Time had a significant effect on QoL [F=(3, 63.000)=11.337, p<0.0001], but main effect of Cancer Stage did not significantly affect QoL [F=(1, 21)=.242, p=0.787]. Main effect of the interaction *Time * Cancer Stage* was found to be not significant (Table 4.6), but the Estimates of Fixed Effects yielded significant interaction terms between these variables' categories (Table 4.7).

Table 4.6.

Type II tests of Fixed Effects Results for QoL Model 2 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	21	958.87	.000
Time	3	63	11.33	.000
Cancer Stage	2	21	.242	.787
Interaction Time * Cancer Stage	6	63	1.53	.180

AIC:686.01; BIC: 690.87

Table 4.7.

Estimates of Fixed Effects Results for QoL Model 2 (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	104.85	6.56	91.66	15.96	.000	9147	118.24
Time							
Baseline	-15.37	4.71	63.00	-3.26	.002	-24.79	-5.95
Assessment 1	-2.91	4.71	63.00	-.618	.539	-12.33	6.50
Assessment 2	-3.8	4.71	63.00	-.813	.419	-13.25	5.59
Endpoint[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Cancer Stage							
Stage I	2.73	8.56	31.66	.677	.751	-14.71	20.18
Stage II	-6.26	9.28	31.66	1.209	.505	-25.19	12.66
Stage III[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Interactions [b]							
Assessment 2 * Stage II	14.35	6.66	63.00	2.15	.035	1.03	27.68
Endpoint * Stage III	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

Estimates of fixed effects displayed in Table 4.7, shows a significant interaction term between *Assessment 2 * Stage II* (β=14.35, t=2.15, *p*=0.035, CI 95%: 1.03, 27.68) indicating that stage II patients showed significantly higher QoL (14.35 points) than stage III patients at assessment 2 in comparison to endpoint. This interaction term is graphically shown in Figure 4.9. To further assess this interaction, mean difference calculations (i.e. pairwise) were performed (Tables 4.8 and 4.9). Calculations were performed following the same procedures described on page 86. Table 4.8 presents the differences in QoL scores for each group of Cancer Stage between Timepoints. Similarly, Table 4.9 shows that QoL scores were different at each Timepoint for each level of the Cancer Stage variable. In addition to these calculations, a paired sample *t*-test was run to analyze if selected pairwise comparisons of interest were statistically significant.

Table 4.8.

Mean Difference of QoL scores for each group of Cancer Stage between Timepoints (n=24).

Cancer Stage			Mean Difference
Stage I	Baseline	Assessment 1	-3.17
		Assessment 2	-11.95*
		Endpoint	-11.21*
	Assessment 1	Baseline	3.17
		Assessment 2	-8.78
		Endpoint	-8.04
	Assessment 2	Baseline	11.95*
		Assessment 1	8.78
		Endpoint	0.74
	Endpoint	Baseline	11.21
		Assessment 1	8.04
		Assessment 2	-0.74
Stage II	Baseline	Assessment 1	-1.26
		Assessment 2	-17.83*
		Endpoint	-7.31
	Assessment 1	Baseline	1.26
		Assessment 2	-16.57*
		Endpoint	-6.05
	Assessment 2	Baseline	17.83*
		Assessment 1	16.57*
		Endpoint	10.52
	Endpoint	Baseline	7.31
		Assessment 1	6.05
		Assessment 2	-10.52
Stage III	Baseline	Assessment 1	-12.46
		Assessment 2	-11.54*
		Endpoint	-15.37*
	Assessment 1	Baseline	12.46
		Assessment 2	0.92
		Endpoint	-2.91
	Assessment 2	Baseline	11.54*
		Assessment 1	-0.92
		Endpoint	-3.83
	Endpoint	Baseline	15.37*
		Assessment 1	2.91
		Assessment 2	3.83

*. The mean difference is significant at the .05 level (paired *t*-test).

Important differences in QoL scores for each group of Cancer Stage between Timepoints were found (Table 4.8 above). As shown in Table 4.8, for Stage I and II patients, QoL scores at

baseline were significantly lower (11.95 and 17.83 points, respectively) in comparison to assessment 2 (p<0.000, for both). Also, for Stage III patients, QoL scores at baseline were significantly lower (15.37 points) in comparison to endpoint (p=0.006).

Table 4.9.

Mean Difference of QoL at each Timepoint for each level of Cancer Stage (n=24).

Timepoints			Mean Difference
Baseline	Stage I	Stage II	5.10
		Stage III	6.90
	Stage II	Stage I	-5.10
		Stage III	1.80
	Stage III	Stage I	-6.90
		Stage II	-1.80
Assessment 1	Stage I	Stage II	7.00
		Stage III	-2.39
	Stage II	Stage I	-7.00
		Stage III	-9.40
	Stage III	Stage I	2.39
		Stage II	9.40
Assessment 2	Stage I	Stage II	-0.78
		Stage III	7.31
	Stage II	Stage I	0.78
		Stage III	8.10
	Stage III	Stage I	-7.31
		Stage II	-8.10
Endpoint	Stage I	Stage II	9.00
		Stage III	2.74
	Stage II	Stage I	-9.00
		Stage III	-6.26
	Stage III	Stage I	-2.74
		Stage II	6.26

As shown in Table 4.9, overall, Stage III patients showed the lowest levels of QoL throughout the study (except at assessment 1), with no significant differences between stage groups at timepoints.

QoL and other covariates

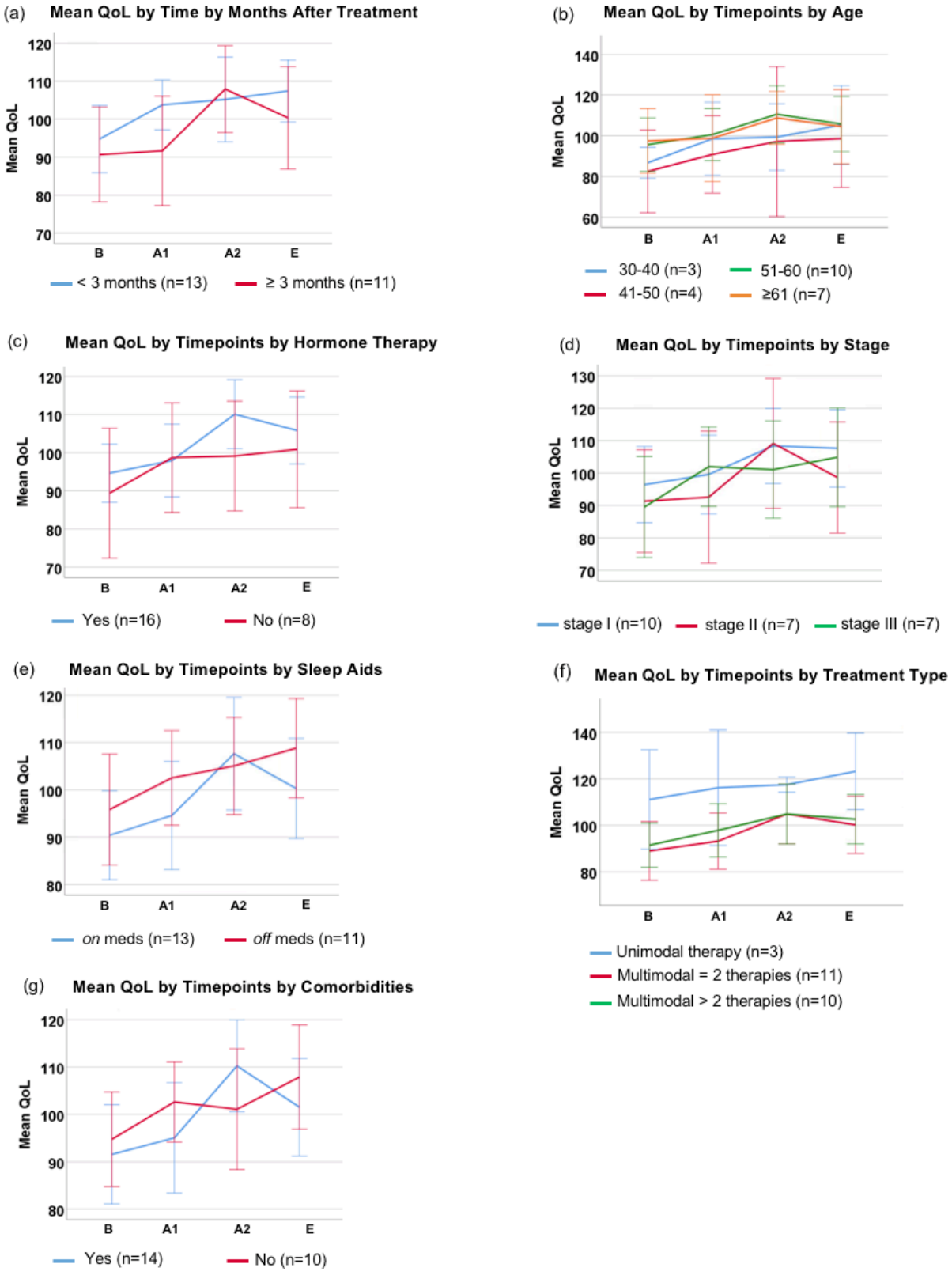
The inclusion of the other covariates (i.e. age of the participants, hormone use, presence of comorbidity, sleep aids use and treatment type) did not yield any statistically significant results in any of linear models tested. The trajectory of the QoL scores according to each independent variable throughout the 8-week MT program can be found in Figure 4.2 and in Appendix P, Table A.1 with descriptive statistics of QoL mean scores by each covariate at all timepoints.

Summary of QoL results

In summary, QoL increased after the 8-week MT program, with Time showing a significant effect on QoL. From all the covariates tested, only Cancer Stage and Months After Treatment showed significant interactions with Time. These interactions were broken down by conducting separate pairwise calculations for each level of Cancer Stage and Months After Treatment categories. Pairwise comparisons of interest were followed up with a paired-sample *t*-test. Results showed that QoL scores changed significantly between study timepoints for each category of Cancer Stage independently. In addition, Stage III patients showed the lowest levels of QoL throughout the study (except at assessment 1), with no significant differences at timepoints. Similarly, QoL scores changed significantly between study timepoints for each category of Months After Treatment independently. In addition, those who finished treatment ≥ 3 months before study onset showed lower QoL (except at assessment 2), with no significant differences at timepoints. In conclusion, QoL significantly improved after the 8-week MT program, regardless of the age of the participants, hormone use, presence of comorbidity, sleep aids use and treatment type.

Figure 4.2.

Changes in QoL scores by each independent variable (n=24).

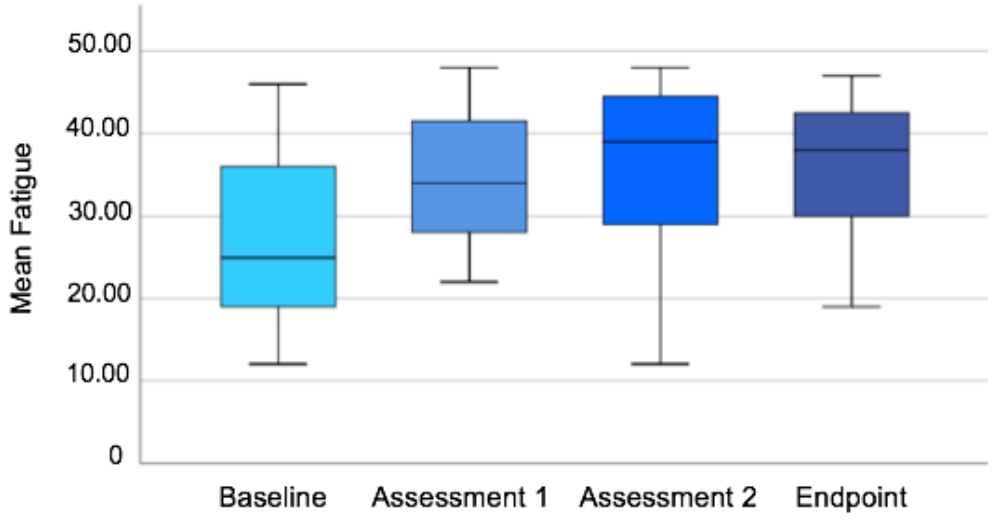


4.3.2 Fatigue

The trajectory of fatigue scores throughout the 8-week MT program is depicted in Figure 4.3. Fatigue scores measured with FACT-F questionnaire ranges from 0-52. Interpretation assumes that higher score indicates less fatigue.

Figure 4.3.

Changes in fatigue scores at each timepoint (n=24).



According to Figure 4.3, patients improved their fatigue at the end of the 8-week MT program. Participants were more fatigued at baseline (mean=28) and progressively showed improvement of this construct over time, reaching the lowest levels of fatigue assessment 2 (mean=35.8) and endpoint (mean=35.7). Among the study covariates tested in the LMM, only two covariates (i.e. Sleep Aids and Comorbidities) yielded statistically significant (or marginal significant) main effects and/or interaction terms in the fatigue models, which are described below.

Fatigue and Sleep Aids

Table 4.10.

Type II tests of Fixed Effects Results for fatigue Model 1 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	22	361.41	.000
Time	3	66.00	15.65	.000
Sleep Aids	1	22	.249	.623
Interaction Time * Sleep Aids	3	66.00	2.96	.038

AIC:591.69; BIC: 596.56

Table 4.10 shows that Time had a significant effect on fatigue levels [F=(3, 66.000)=15.605, p<0.0001], but main effect of Sleep Aids did not significantly affect fatigue [F=(1, 22)=0.246, p=0.623]. However, an interaction was found between Time and Sleep Aids in use [F=(3, 66.000)=2.961, p=0.038].

Table 4.11.

Estimates of Fixed Effects Results for fatigue Model 1 (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	29.44	2.85	30.36	10.29	.000	23.61	35.28
Time							
Baseline	5.40	1.82	66.00	2.95	.004	1.74	9.05
Assessment 1	3.54	1.82	66.00	1.93	.057	-.10	7.19
Assessment 2	5.59	1.82	66.00	3.06	.003	1.94	9.25
Endpoint[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
Sleep Aids							
on meds	-1.29	3.88	30.36	-.33	.742	-9.22	6.63
off meds [a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
Interactions[b]							
Assessment 2 * *on* sleep aids	7.14	2.48	66.00	.767	.005	2.18	12.10
Endpoint * *on* sleep aids [a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

Estimates of fixed effects results displayed in Table 4.11, shows a significant interaction term between *Assessment 2 * Sleep Aids/On* (β=7.14, t=2.87, p=0.005, CI 95%: 2.18, 12.10),

indicating that those *on* meds showed significantly higher fatigue scores (less fatigue) (7.14 points) when compared to those who were *off* meds at assessment 2 when compared to endpoint. This interaction is graphically displayed in Figure 4.4. To further assess the interaction term, pairwise calculations based on estimated means were performed following the same procedures described on page 86.

Tables 4.12 and 4.13 show all pairwise calculations based on estimated means. Table 4.12 presents the differences in fatigue scores for each group of Sleep Aids between Timepoints. Similarly, Table 4.13 shows that fatigue scores were different at each Timepoint for each level of the Sleep Aids variable. In addition to these calculations, a paired sample *t*-test was run to analyse if selected pairwise comparisons of interest were statistically significant.

Table 4.12.

Mean Difference of fatigue scores for each group of Sleep Aids between Timepoints (n=24).

Sleep Aids			**Mean Difference**
On Sleep Aids	Baseline	Assessment 1	-7.30
		Assessment 2	-10.69*
		Endpoint	-8.84*
	Assessment 1	Baseline	7.30
		Assessment 2	-3.38
		Endpoint	-1.54
	Assessment 2	Baseline	10.69*
		Assessment 1	3.38
		Endpoint	1.85
	Endpoint	Baseline	8.84*
		Assessment 1	1.54
		Assessment 2	-1.85
Off Sleep Aids	Baseline	Assessment 1	-5.40
		Assessment 2	-3.55
		Endpoint	-5.59*
	Assessment 1	Baseline	5.40
		Assessment 2	1.86
		Endpoint	-0.20
	Assessment 2	Baseline	3.55
		Assessment 1	-1.86
		Endpoint	-2.05
	Endpoint	Baseline	5.59*
		Assessment 1	0.20
		Assessment 2	2.05

*. The mean difference is significant at the .05 level (paired *t*-test).

As shown in Table 4.12, fatigue scores for those *on* sleep aids were higher at assessment 2 and endpoint (10.69 and 8.84 points, respectively) in comparison to baseline ($p<0.0001$, for both). Additionally, fatigue scores for those *off* sleep aids, were significantly higher at endpoint (less fatigue) in comparison to baseline (5.59 points) ($p=0.003$).

Table 4.13.

Mean Difference of fatigue scores at each Timepoint for each level of Sleep Aids (n=24).

Timepoints			Mean Difference
Baseline	*On* Sleep Aids	*Off* Sleep Aids	-1.29
	Off Sleep Aids	*On* Sleep Aids	1.29
Assessment 1	*On* Sleep Aids	*Off* Sleep Aids	0.61
	Off Sleep Aids	*On* Sleep Aids	-0.61
Assessment 2	*On* Sleep Aids	*Off* Sleep Aids	5.85
	Off Sleep Aids	*On* Sleep Aids	-5.85
Endpoint	*On* Sleep Aids	*Off* Sleep Aids	1.95
	Off Sleep Aids	*On* Sleep Aids	-1.95

As shown in Table 4.13, overall, patients *on* sleep aids showed higher fatigue scores (less fatigue) in comparison to patients *off* sleep aids. For instance, at assessment 2, there was a non-significant difference of 5.85 points in fatigue scores between patients who were *on* and *off* sleep aids, with those *on* sleep aids showing higher fatigue scores (less fatigue).

Fatigue and Comorbidity

Table 4.14.

Type II tests of Fixed Effects Results for fatigue Model 2 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	22.00	350.90	.000
Time	3	66.00	16.59	.000
Comorbidities	1	22.00	.013	.911
Interaction Time * Comorbidities	3	66.00	2.39	.076

AIC:593.26; BIC: 598.22

Table 4.14 shows that Time had a significant effect on Fatigue levels [F=(3,

66.000)=16.697, p<0.0001], but main effect of Comorbidity did not significantly affect fatigue [F=(1, 22)=.013, p=0.911]. In addition, a marginal statistically significant main interaction was found between Time and Comorbidity [F=(3, 66.000)=2.397, p=0.076] (Table 4.14).

Table 4.15.

Estimates of Fixed Effects Results for fatigue Model 2 (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	36.43	3.01	30.47	12.07	.000	30.27	42.59
Time							
Baseline	-9.04	1.94	66.00	-4.66	.000	-12.91	-5.16
Assessment 1[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Assessment 2	-2.17	1.94	66.00	11.12	.266	-6.04	1.69
Endpoint	.71	1.94	66.00	.369	.713	-3.15	4.59
Comorbidity							
Yes	-2.14	3.95	30.47	1.76	.591	-10.21	5.91
No[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Interactions[b]							
Assessment 2 * Yes	5.41	2.54	66.00	2.13	.037	0.34	10.48
Assessment 1 * No	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

Estimates of fixed effects results displayed in Table 4.15, shows a significant interaction term between *Assessment 2 * Comorbidity/Yes* (β=5.41, t=2.13, p=0.037, CI 95%: 0.34, 10.48), indicating that those who had a comorbidity showed significantly higher fatigue scores (less fatigue) (5.41 points) when compared to those who did not have a comorbidity at assessment 2 when compared to assessment 1. This interaction is graphically displayed in Figure 4.4. To further assess the interaction term, pairwise calculations based on estimated means were performed following the same procedures described on page 86.

Tables 4.16 and 4.17 (next page) show all pairwise calculations based on estimated means. Hence, Table 4.16 presents the differences in fatigue scores for each group of Comorbidities between Timepoints. Similarly, Table 4.17 shows that fatigue scores were different at each Timepoint for each level of the Comorbidities variable. In addition to these calculations, a paired sample t-test was run to analyse if selected pairwise comparisons of interest were statistically significant.

Table 4.16.

Mean Difference of fatigue scores for each group of Comorbidities between Timepoints (n=24).

Comorbidities			**Mean Difference**
Yes	Baseline	Assessment 1	-4.57
		Assessment 2	-7.81*
		Endpoint	-5.64*
	Assessment 1	Baseline	4.57
		Assessment 2	-3.24
		Endpoint	-1.07
	Assessment 2	Baseline	7.81*
		Assessment 1	3.24
		Endpoint	2.17
	Endpoint	Baseline	5.64*
		Assessment 1	1.07
		Assessment 2	-2.17
No	Baseline	Assessment 1	-9.04*
		Assessment 2	-6.86*
		Endpoint	-9.75*
	Assessment 1	Baseline	9.04*
		Assessment 2	2.18
		Endpoint	-0.72
	Assessment 2	Baseline	6.86*
		Assessment 1	-2.18
		Endpoint	-2.89
	Endpoint	Baseline	9.75*
		Assessment 1	0.72
		Assessment 2	2.89

*. The mean difference is significant at the .05 level (paired *t*-test).

As shown in Table 4.16, for both comorbidity groups (Yes and No), a significant increase in fatigue score (less fatigue) was detected at endpoint in comparison to baseline (5.64 and 9.75, respectively). For instance, for both groups of commodities, a significant difference in fatigue was found between baseline and assessment 2, with both groups (Yes and No) reporting significant higher fatigue scores (better fatigue) at assessment 2 in comparison to baseline (7.81 and 6.86 points higher, respectively) ($p<0.0001$, for both). Similarly, at endpoint, both groups (Yes and No) reported significant higher fatigue scores (less fatigue) in comparison to baseline (5.63 and 9.75 points higher, respectively) ($p<0.0001$, for both).

Table 4.17.

Mean Difference of fatigue scores at each Timepoint for each level of Comorbidities (n=24).

Timepoints			Mean Difference
Baseline	yes	no	2.32
	no	yes	-2.32
Assessment 1	yes	no	-2.15
	no	yes	2.15
Assessment 2	yes	no	3.27
	no	yes	-3.27
Endpoint	yes	no	-1.79
	no	yes	1.79

As shown in Table 4.17, overall, those who presented comorbidities showed slightly higher fatigue scores (less fatigue) in comparison to those who did not present any comorbidities. However, no statistically significant differences were found.

Fatigue and other covariates

The inclusion of the other covariates (i.e. age of the participants, hormone use, months after treatment, cancer stage and treatment type) did not yield any statistically significant results in any of linear models tested. The trajectory of the fatigue scores according to each independent variable throughout the 8-week MT program can be found in Figure 4.4 and in Appendix P Table A.2 with descriptive statistics of fatigue mean scores by each covariate at all timepoints.

Summary of fatigue results

In summary, fatigue improved after the 8-week MT program, with Time showing a significant effect on fatigue. From all the covariates tested, only Comorbidity and Sleep Aids showed significant interactions with Time. These interactions were broken down by conducting separate pairwise calculations for each level of Comorbidity and Sleep Aids use categories. Pairwise comparisons of interest were followed up with a paired-sample *t*-test. Results showed that fatigue scores changed significantly between study timepoints for each category of Sleep Aids independently. In addition, patients *on* sleep aids showed higher scores (less fatigue) in comparison to patients *off* sleep aids. However, no statistically significant differences were found.

Similarly, fatigue scores changed significantly between study timepoints for each category of Comorbidity independently. In addition, those who presented comorbidities showed slightly higher fatigue scores (less fatigue) in comparison to those who did not present any comorbidities. However, no statistically significant differences were found. In conclusion, fatigue significantly improved after the 8-week MT program, regardless of the age of the participants, hormone use, cancer stage, months after treatment, and treatment type.

Figure 4.4.

Changes in fatigue scores by each independent variable (n=24).

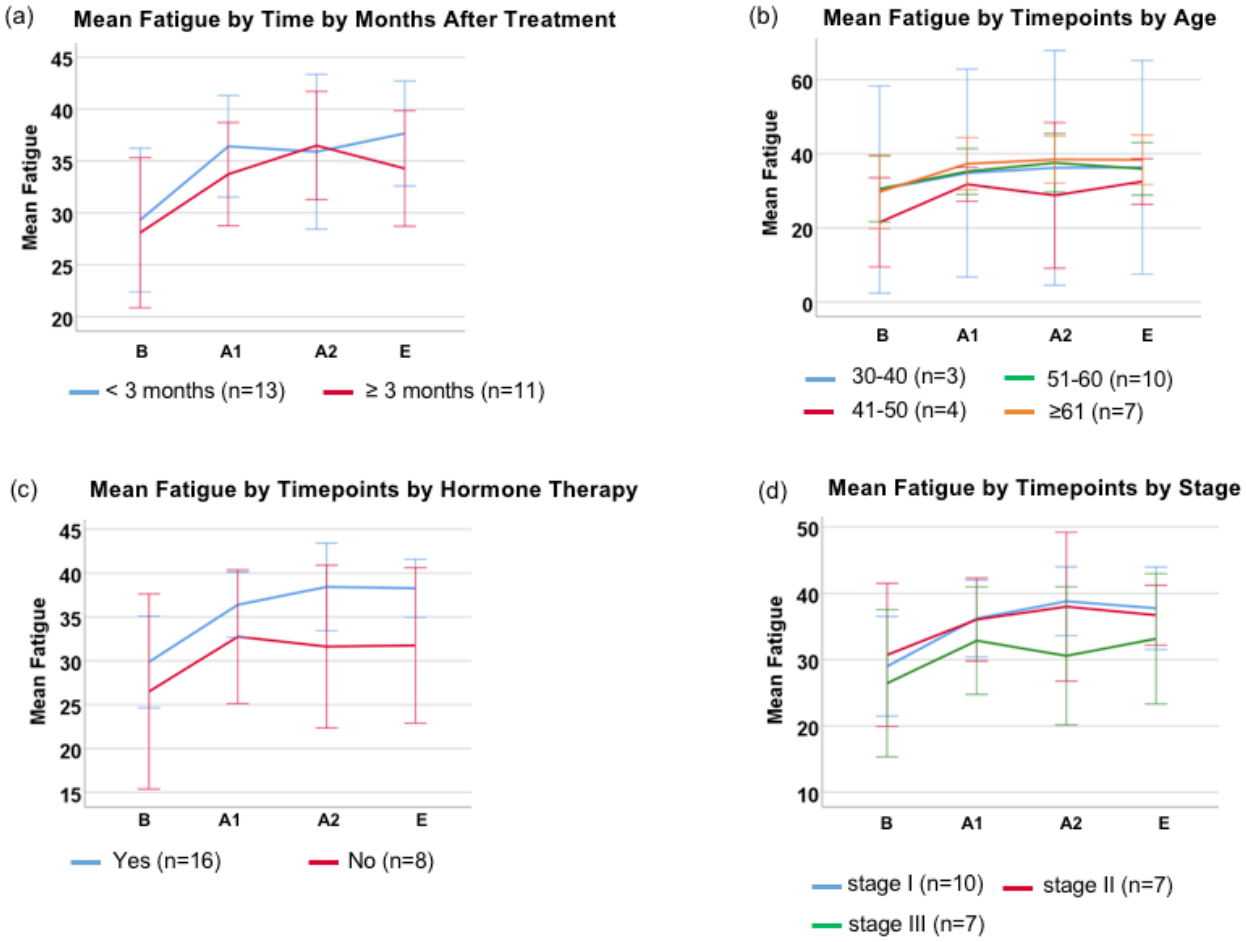
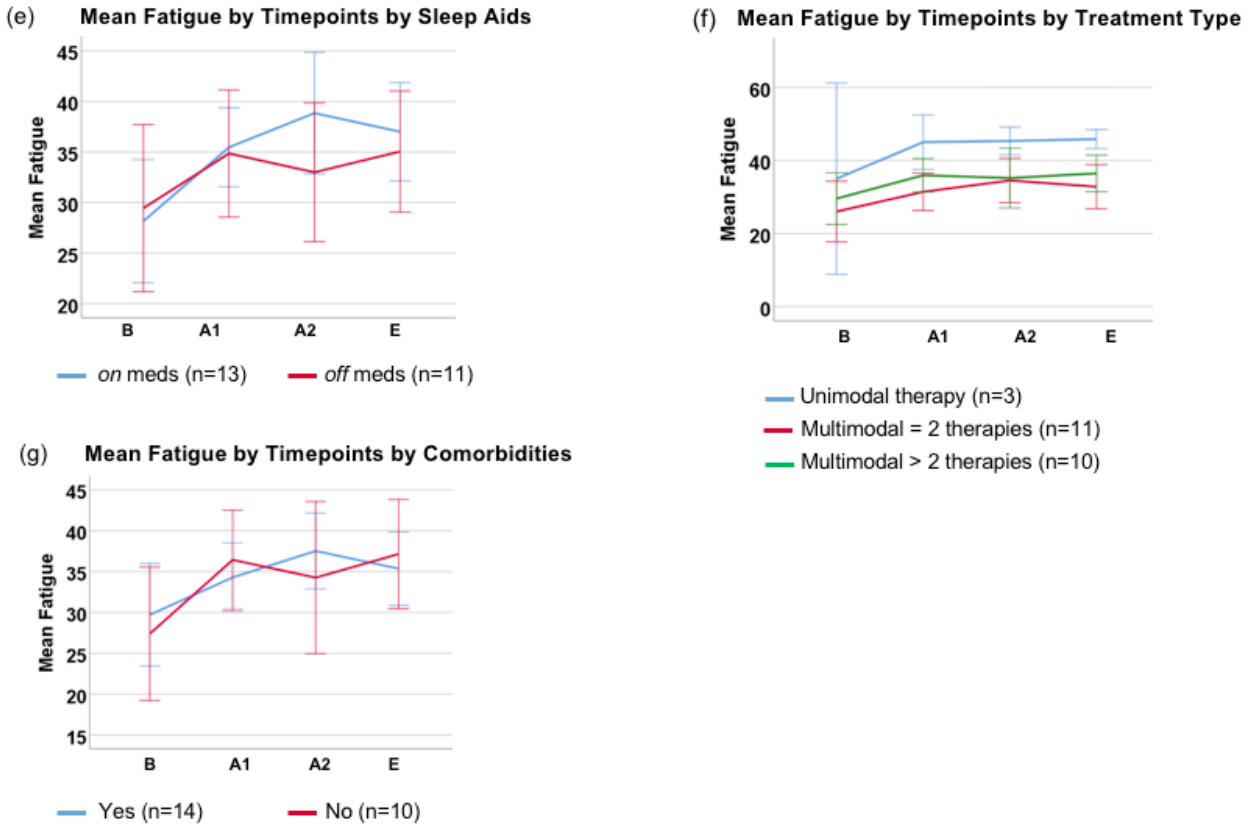


Figure 4.4. *(continued)*.

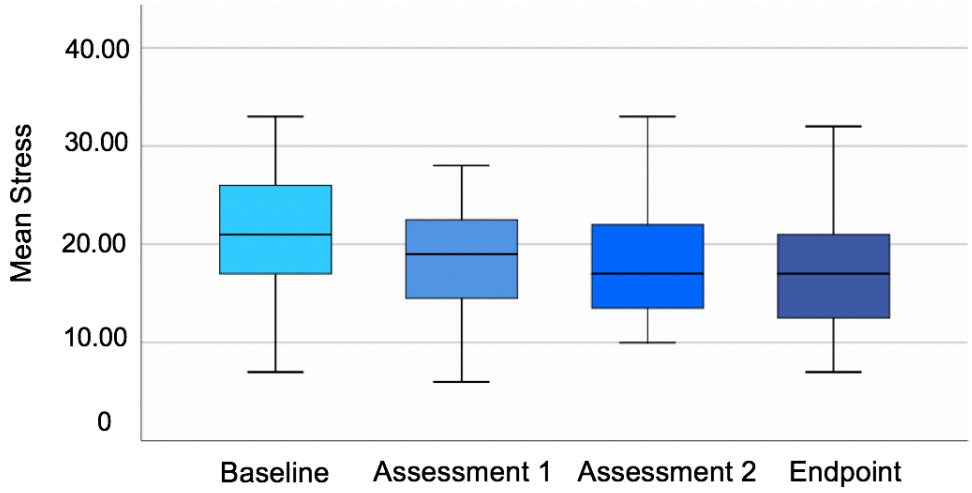


4.3.3 Stress

The trajectory of stress scores throughout the 8-week MT program is depicted in Figure 4.5 (next page). Stress scores measured with PSS questionnaire ranges from 0-40. Interpretation assumes that higher score indicates more stress.

Figure 4.5.

Changes in stress scores at each timepoint (n=24).



According to Figure 4.5, patients were more stressed at baseline (mean=20.9) and progressively showed improvement of this construct over time, reaching the lowest levels of stress at endpoint (mean=17.4). Among the study covariates tested in the LMM, only one (i.e. Cancer Treatment Type) yielded a statistically significant estimates of fixed effect in the stress models, with no significant interaction terms, as described below.

Stress and Treatment Type

Table 4.18.

Type II tests of Fixed Effects Results for stress (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	21.00	157.90	.000
Time	3	69.00	3.58	.018
Cancer Treatment Type	2	21.00	2.39	.116

AIC:569.98; BIC: 574.98

Based on Table 4.18, Time had a significant effect on stress levels [F=(3, 69.000)=3.584, p=0.018], but main effect of Cancer Treatment did not [F=(2, 21.000)=2.392, p=0.116]. However, the variable Cancer Treatment was kept in the model since it showed significant estimates of fixed effects (Table 4.19).

Table 4.19.

Estimates of Fixed Effects Results for stress (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	25.38	4.03	22.35	6.29	.000	17.02	33.74
Time							
Baseline	3.33	1.15	69.00	2.87	.005	1.02	5.64
Assessment 1	.33	1.15	69.00	.28	.775	-1.97	2.64
Assessment 2	.41	1.15	69.00	.35	.720	-1.89	2.72
Endpoint[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
Treatment Classification							
Unimodal therapy	-7.75	3.61	21.00	-2.14	.044	-15.25	-0.24
Multimodal = 2 therapies	-6.90	3.57	21.00	1.93	.067	-14.33	0.52
Multimodal > 2 therapies[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

According to Table 4.19, Stress improved by 3.33 points at endpoint, a significant difference (β=-3.33, t=2.87, *p*=0.005, CI 95%: 1.02, 5.64).

In addition, those who went through unimodal treatment reported less stress (7.75 points) than those who underwent multimodal treatment with only two therapies, a significant difference (β=-7.75, t=-2.14, *p*=0.044, CI 95%: -15.24, -0.24) (Table 4.19). Figure 4.6 (next page) depicts this difference in stress level reported by those who went through multimodal treatment and those who went through unimodal treatment. Similarly, those who went through unimodal treatment reported less stress (6.9 points) than those who went through multimodal treatment with more than two therapies, reaching only a marginal significant difference (β=-6.90, t=-1.93, *p*=0.067, CI 95%: -14.33, 0.52).

Stress and other covariates

The inclusion of the other covariates (i.e. age of the participants, hormone use, cancer stage, comorbidity, months after treatment, and sleep aids in use) did not yield any statistically significant results in any of linear models tested. The trajectory of the stress scores according to each independent variable throughout the 8-week MT program can be found in Figure 4.6 and in

Appendix P, Table A.3 with descriptive statistics of stress mean scores by each covariate at all timepoints.

Summary of stress results

In summary, stress significantly improved after the 8-week MT program, regardless of the age of the participants, hormone use, cancer stage, comorbidity, months after treatment, and sleep aids in use. Treatment type had an effect on stress, with those who went through unimodal treatment reporting significant less stress than those who underwent multimodal treatment with only two therapies, and those who went through multimodal treatment with more than two therapies.

Figure 4.6.

Changes in stress scores by each independent variable (n=24).

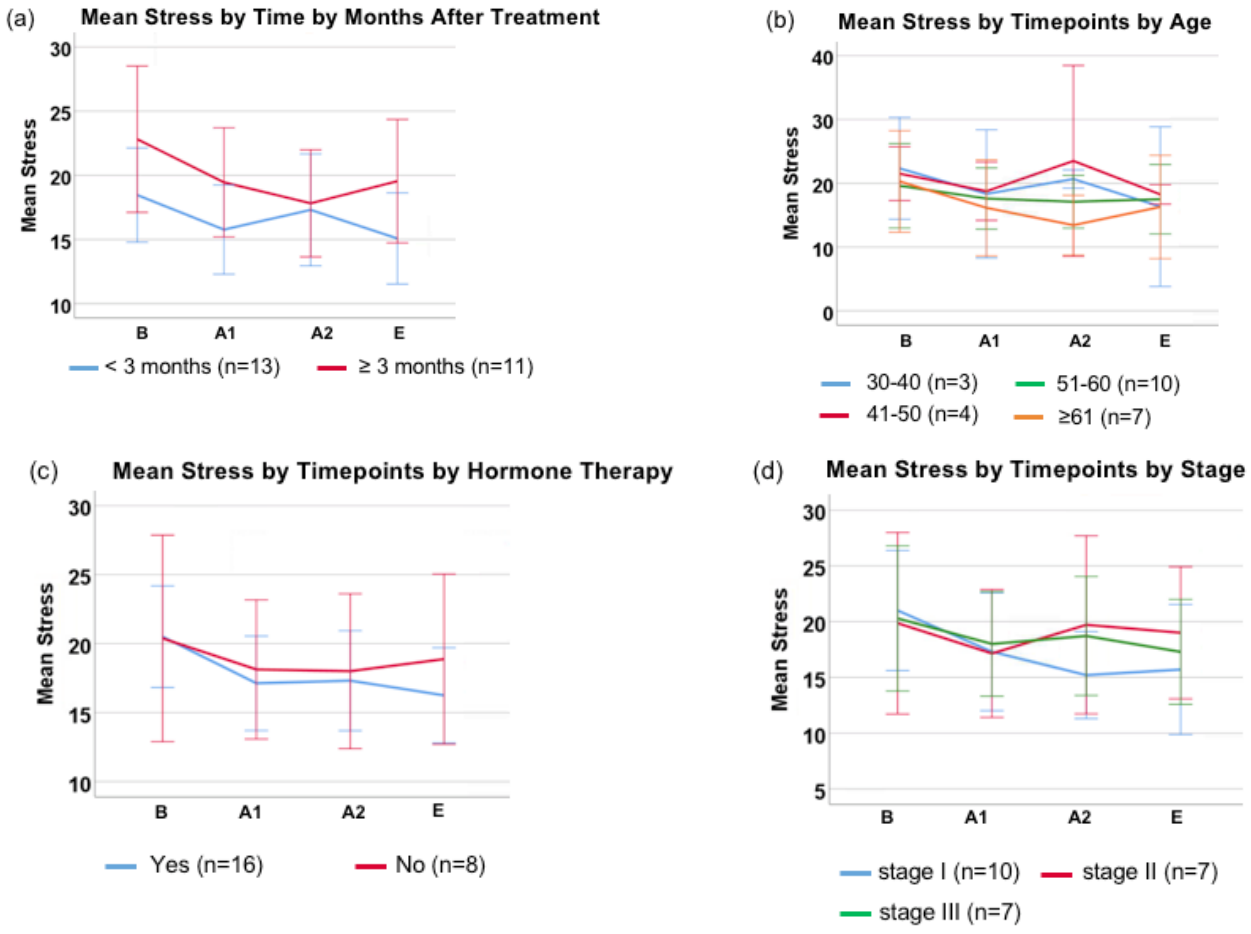
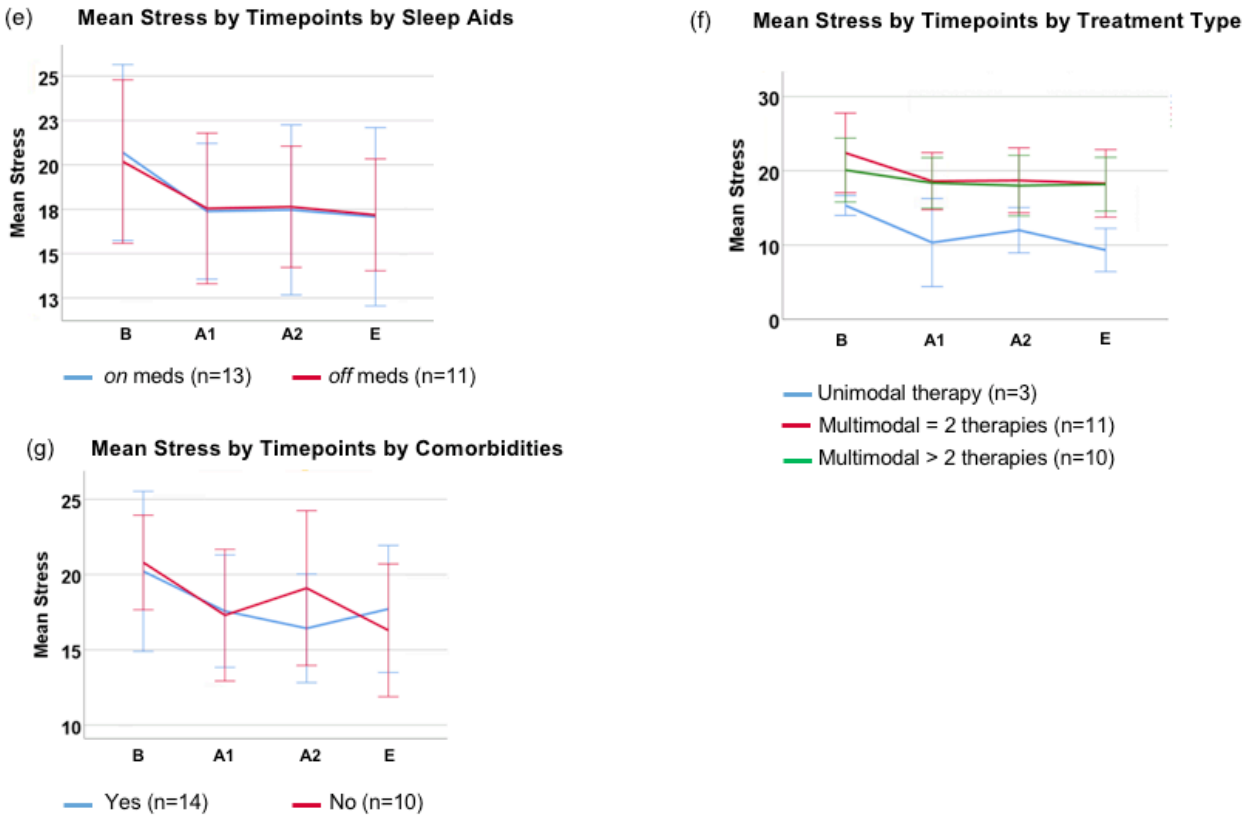


Figure 4.6. *(continued)*



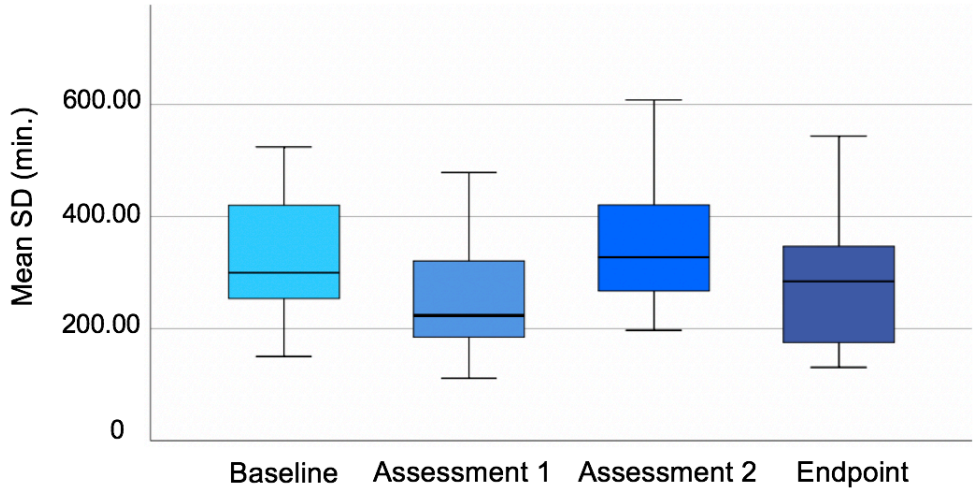
4.3.4 Sleep Duration

The trajectory of SD throughout the 8-week MT program is depicted in Figure 4.7. SD was measured with Actigraphy and are represented in minutes. Interpretation assumes that higher numbers indicate longer SD.

According to Figure 4.7, SD did not improve over time, with patients showing the shortest SD at assessment 1 (mean=255.5 min.) and reaching the longest SD at assessment 2 (mean=357.2 min.). Among the study covariates tested in the LMM, none yielded statistically significant main effects and/or interaction terms in the SD models. The final model for SD is presented next.

Figure 4.7.

Changes in SD (min.) at each timepoint (n=24).



Sleep Duration and Time

Table 4.20.

Type II tests of Fixed Effects Results for SD (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	22.77	327.01	.000
Time	3	66.59	7.75	.000

AIC: 1079.48; BIC: 1074.46

Table 4.20 shows that Time had a significant effect on SD [F=(3, 66.592)=7.753, p<0.0001].

Table 4.21.

Estimates of Fixed Effects Results for SD model (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	275.45	22.03	57.95	12.50	.000	231.35	319.56
Time							
Baseline	46.55	23.23	67.05	2.00	.049	.17	92.92
Assessment 1	-22.52	23.37	66.13	-.964	.339	-69.18	24.13
Assessment 2	79.74	23.37	66.13	3.41	.001	33.08	126.40
Endpoint[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

No significant improvement of sleep duration was detected after the 8-week MT program. Table 4.21 shows that, on average, patients at baseline showed higher sleep duration (46.5 minutes) in comparison to endpoint (β=46.55, t=2.00, p=0.0049, CI 95%: 0.17, 92.92). Additionally, patients at assessment 2 reported higher sleep duration (79.7 minutes) in comparison to endpoint, a statistically significant difference (β=79.74, t=3.41, p=0.0001, CI 95%: 33.08, 126.40) (Table 4.21). After changing reference category, it was also revealed that at assessment 1, patients reported significant lower sleep duration in comparison to baseline (β=-69.07, t=-2.97, p=0.004, CI 95%:-115.45, -22.70), and in comparison to assessment 2 (β=-102.28, t=-4.37, p<0.001, CI 95%: -148.92, 55.61) (Table 4.21, Figure 4.7).

SD and other covariates

The inclusion of the other covariates (i.e. age of the participants, hormone use, presence of comorbidities, sleep aids use, months after treatment, cancer stage and treatment type) did not yield any statistically significant results in any of linear models tested. The trajectory of the SD according to each independent variable throughout the 8-week MT program can be found in Figure 4.8 and in Appendix P, Table A.4 with descriptive statistics of mean SD by each covariate at all timepoints.

Summary of SD results

In summary, SD did not improve after the 8-week MT program. From all the covariates tested (i.e. age of the participants, hormone use, comorbidities, sleep aids use, months after treatment, cancer stage and treatment type), none showed any significant effects on SD or interactions.

Figure 4.8.

Changes in Sleep Duration (SD) by each independent variable (n=24).

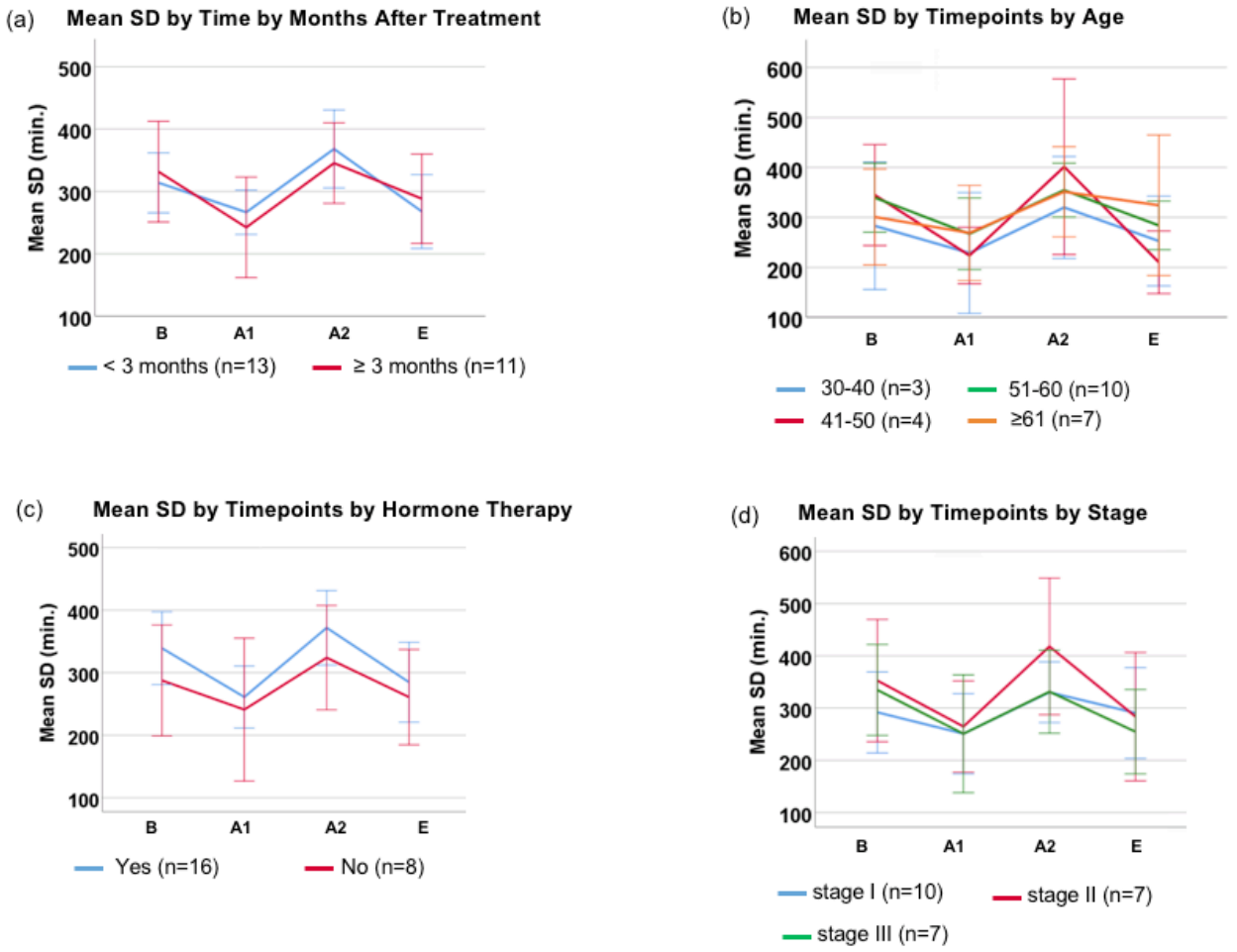
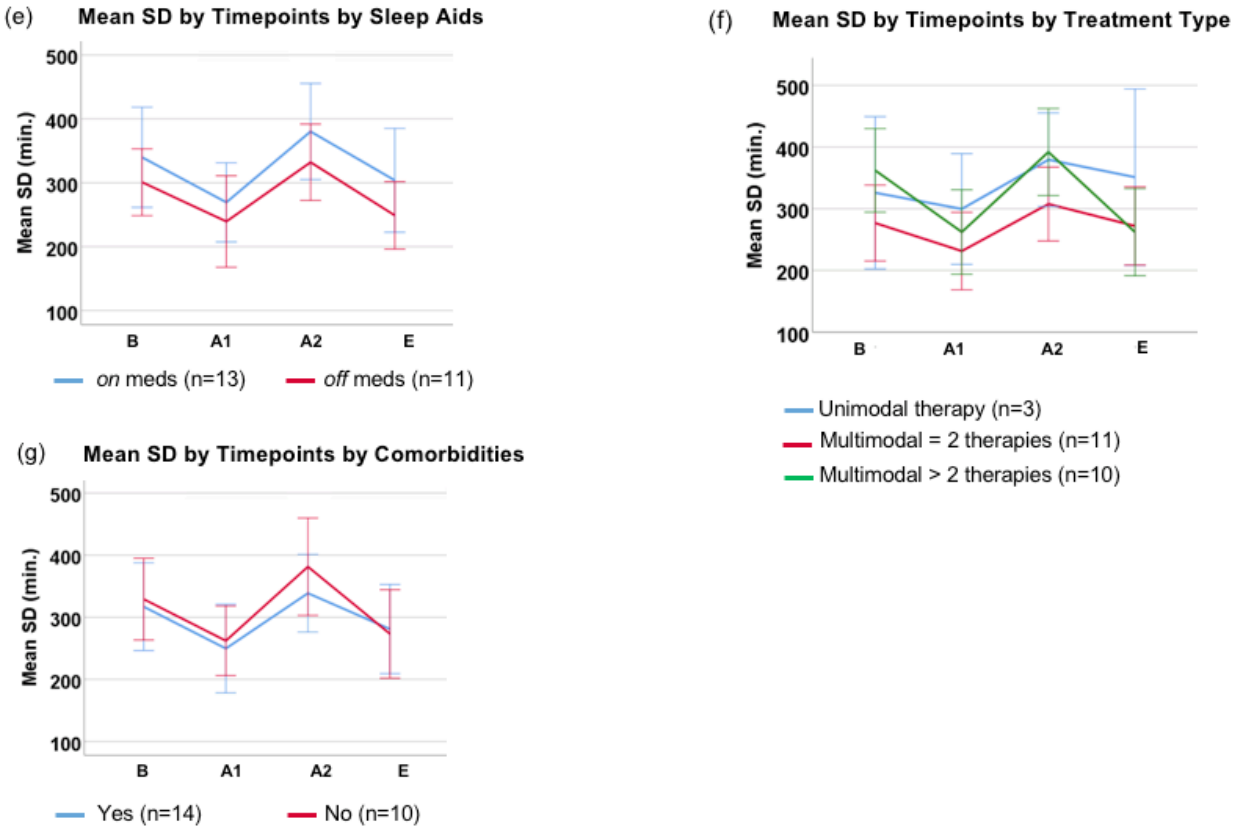


Figure 4.8. *(continued)*

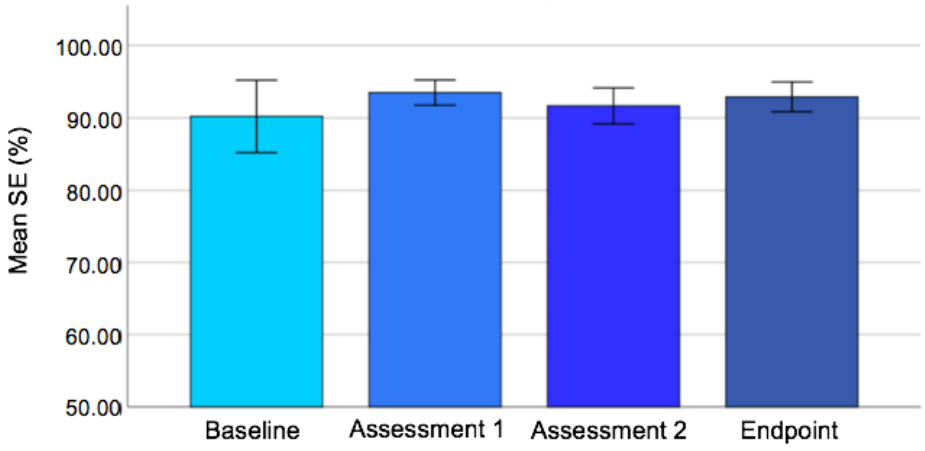


4.3.5 Sleep Efficiency

The trajectory of SE throughout the 8-week MT program is depicted in Figure 4.9. SE results measured with Actigraphy are represented in percentages and varies from 0-100%. Interpretation assumes that higher numbers indicate better SE.

Figure 4.9.

Changes in SE (%) at each timepoint (n=24).



As depicted in Figure 4.9, SE slightly improved after the 8-week MT program. A RM-ANOVA showed that changes in SE did not reach statistical significance [F (1.85, 57) = 2.832, p=0.076]), therefore, the main effect of Time did not show any significant difference in SE at the different timepoints. Patients showed the lowest SE at assessment 2 (mean=91.2), reaching the highest SE at assessment 1 (mean=93.9).

SE and other covariates

No statistically significant interactions were found between SE and the between-subject factors age, sleep aids use, stage, cancer treatment, presence of comorbidity, months after treatment and hormone therapy. The trajectory of the SE according to each independent variable throughout the 8-week MT program can be found in Figure 4.10 and in Appendix P, Table A.5 with descriptive statistics of mean SE by each covariate at all timepoints.

Summary of SE results

In conclusion, our findings suggest an improvement trend in SE during the MT program. SE improved regardless of the age of participant, cancer stage, treatment type, months after treatment, hormone use, sleep aids in use, and presence of comorbidities.

Figure 4.10.

Changes in Sleep Efficiency (SE) by each independent variable (n=24).

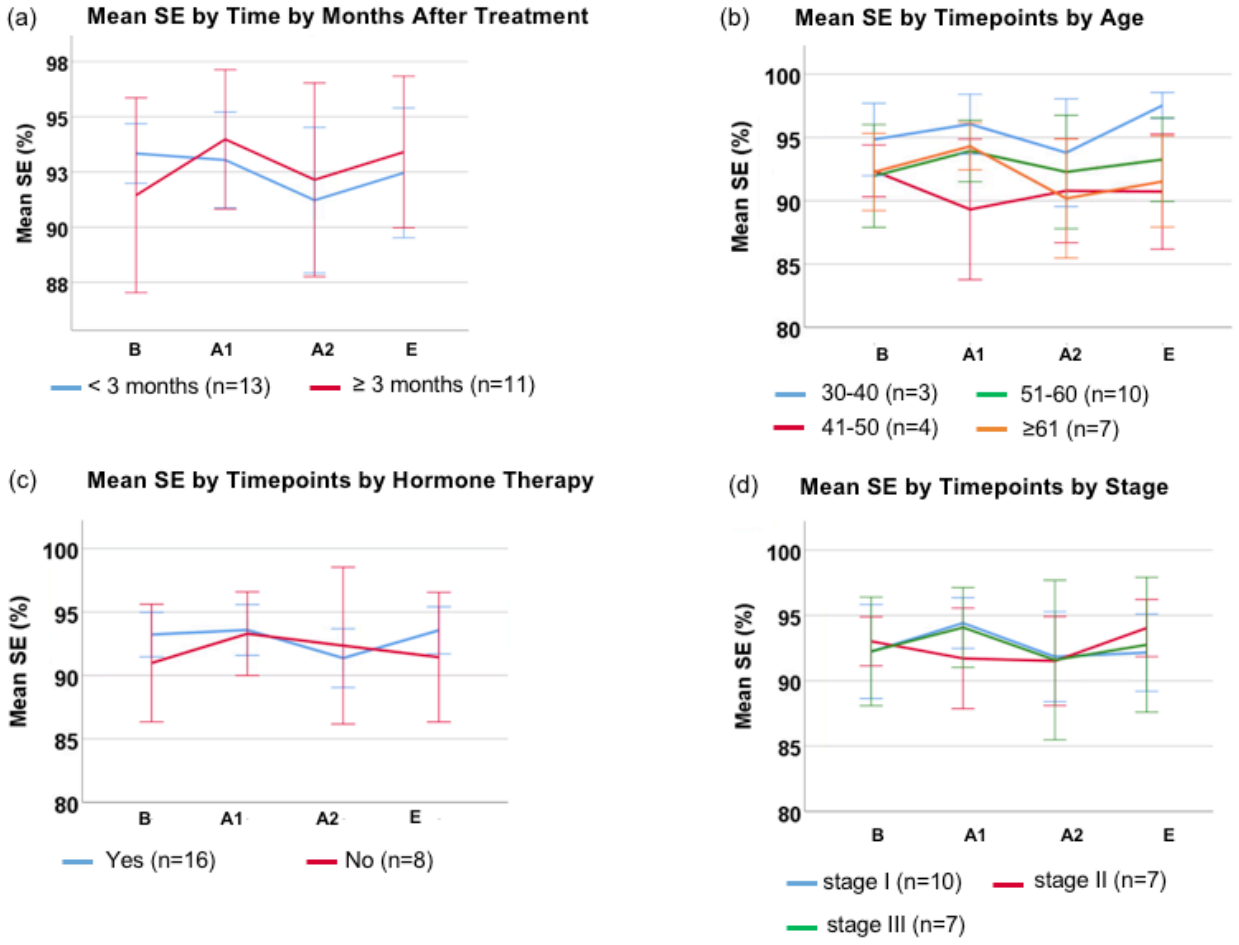
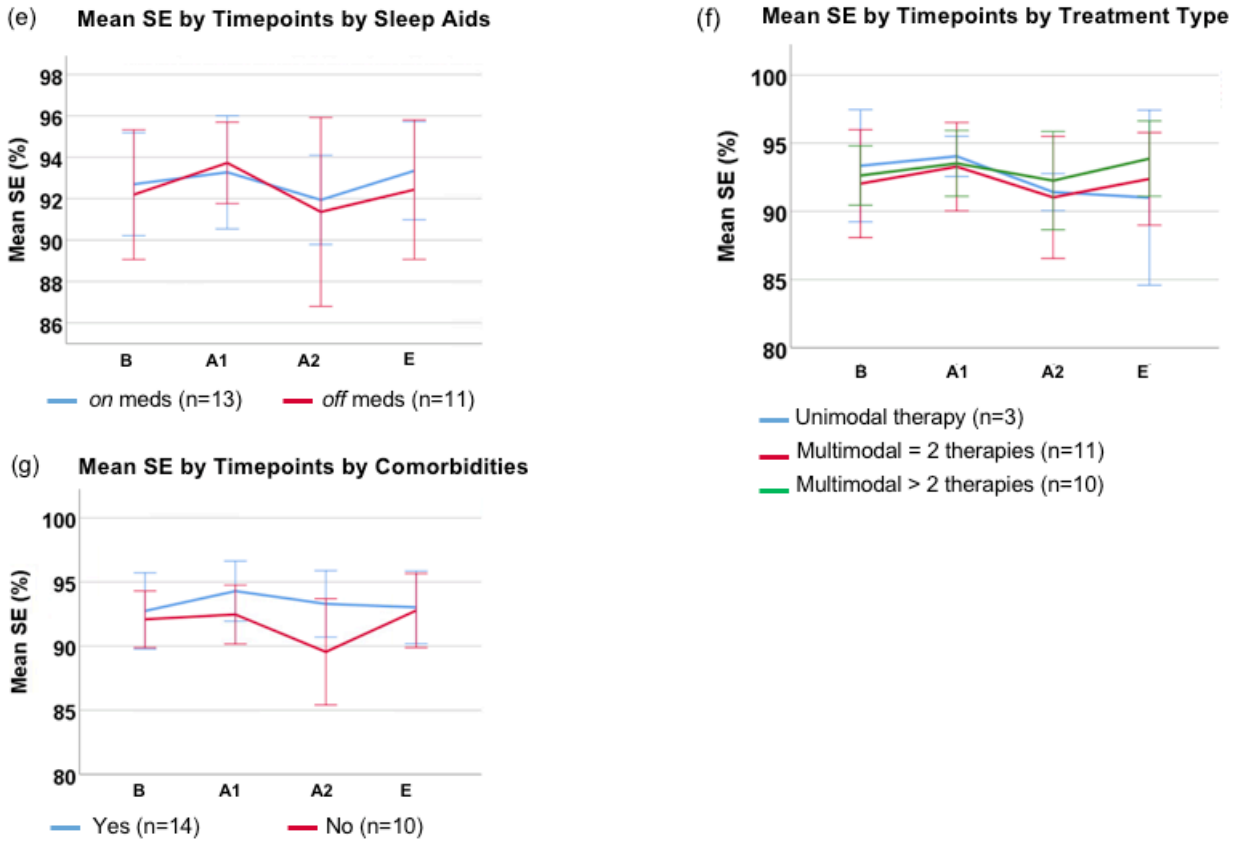


Figure 4.10. (*continued*)



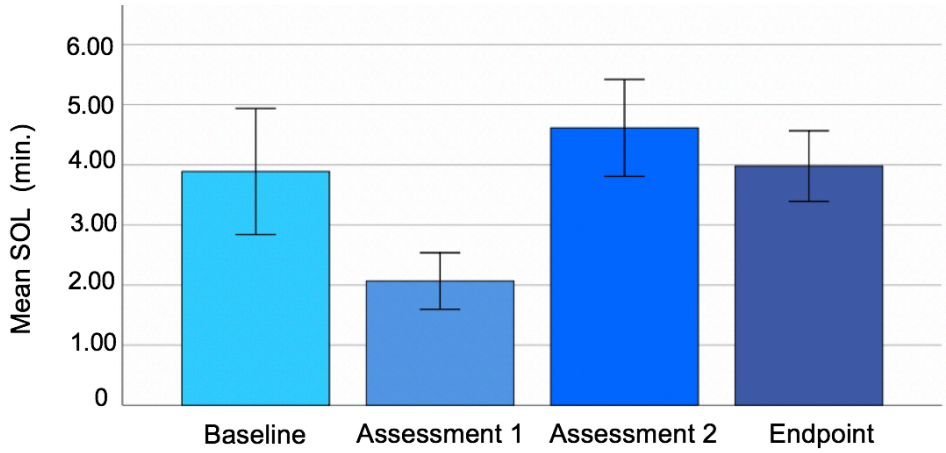
4.3.6 Sleep Onset Latency

The trajectory of the SOL throughout the 8-week MT program is depicted in Figure 4.11. SOL was measured with actigraphy and is denoted in minutes. SOL represents how long it takes to fall asleep. It is the length of time that it takes to accomplish the transition from full wakefulness to sleep. Along with WASO, SOL is the most used parameter in the assessment of insomnia, however, there is a lack of quantitative criteria and cut-off points for sleep quality assessment using actigraphy in several population types (Natale, Plazzi, & Martoni, 2009). Hence, the interpretation of SOL has to take into consideration a range of factors. For example, if it takes too fast for someone to fall asleep it can indicate a sleep debt, whereas, if it takes too long for someone to fall asleep it can indicate insomnia. Based on published literature (Blytt, Bjorvatn, Husebo, & Flo, 2017; Carskadon, 1986), the following SOL cut-off points were used in this study:

SOL (in min.)	INTERPRETATION
0 to 5 minutes	severe sleep deprivation
5 to 10 minutes	is troublesome
10 to 15 minutes	mild but manageable degree of sleep debt
15 to 30 minutes	little or no sleep debt
≥ 30	might indicate insomnia

Figure 4.11.

Changes in SOL (minutes) at each timepoint (n=24).



According to Figure 4.11 (previous page), patients showed the lowest SOL values at assessment 1 (mean=2.0), reaching the highest values at assessment 2 (mean=4.6 minutes). The trajectory of this measure shows that there was a slight trend towards SOL improvement over time, however, based on the overall mean (mean=3.6 minutes), patients in our study showed low SOL values, which is suggestive of sleep debt. Among the study covariates included in the LMM, only one (i.e. Cancer Stage) yielded statistically significant main effects and/or interaction terms in all the SOL models tested, as described below.

SOL and Cancer Stage

Table 4.22.

Type II tests of Fixed Effects Results for SOL (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	20.565	464.81	.000
Time	3	61.044	4.60	.006
Cancer Stage	2	20.583	.130	.879
Interaction Time * Cancer Stage	6	61.068	2.86	.016

AIC: 336.71; BIC: 341.50

Table 4.22 shows that Time had a significant effect on SOL [F=(3, 57.891)=5.398, p=0.002], but no significant effect of cancer stage on SOL was found. The interaction term *Time*Cancer Stage* was also found to be significant [F=(3, 61.068)=2.861, p=.0016] (Table 4.23), indicating that there are significant differences in SOL duration between stage groups at one or more levels of time point.

Table 4.23.

Estimates of Fixed Effects Results for SOL (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	4.76	61.32	80.95	7.7	.000	3.54	5.98
Time							
Baseline	-2.40	.86	60.82	-2.79	.007	-4.13	-.68
Assessment 1	-1.33	.86	60.82	-1.54	.128	-3.05	.39
Assessment 2	-.19	.86	60.82	-.22	.826	-1.91	1.53
Endpoint[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
Cancer Stage							
Stage I	-.73	.81	80.96	-.89	.372	-2.36	.89
Stage II	-.77	.81	80.95	.70	.373	-2.50	.94
Stage III[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
Interactions [b]							
Baseline x Stage I	3.15	1.13	61.51	2.77	.007	0.88	5.42
Endpoint x Stage III	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

Estimates of fixed effects results displayed in Table 4.23, shows a significant interaction term between *Baseline x Stage I* (β=3.15, t=2.77, *p*=0.007, CI 95%: 0.88, 5.42), meaning that, at baseline, stage I patients showed significantly higher SOL duration (3.15 minutes) when compared to stage III patients at endpoint. This interaction is graphically displayed in Figure 4.12.

To further assess the interaction term, mean difference calculations based on estimated means were performed (as shown on page 86). Hence, Table 4.24 (next page) presents the differences in SOL for each group of Cancer Stage between Timepoints. Similarly, Table 4.25 (page 118) differences in SOL at each Timepoint for each level of the Cancer Stage. In addition to these calculations, a paired sample *t*-test was run to analyse if selected pairwise comparisons of interest were significant.

Table 4.24 (next page) shows that for Stage I patients, SOL at assessment 1 was significantly higher (2.08 minutes) in comparison to baseline (*p*=0.007). For Stage III patients, SOL at endpoint was significantly higher (2.40 minutes) in comparison to baseline (*p*=0.007) (Table 4.24).

In addition, according to Table 4.25 (nex page), only at baseline significant differences between stages were found. At baseline, stage I patients showed significantly higher SOL in comparison to Stage II (2.34 minutes; *p*=0.004) and Stage III (2.42 minutes; *p*=0.003). All these changes are graphically depicted in Figure 4.12 (next pages).

Table 4.24.

Mean Difference of SOL for each group of Cancer Stage between Timepoints (n=24).

Cancer Stage			Mean Difference
Stage I	Baseline	Assessment 1	2.08*
		Assessment 2	1.07
		Endpoint	0.75
	Assessment 1	Baseline	-2.08*
		Assessment 2	-1.01
		Endpoint	-1.33
	Assessment 2	Baseline	-1.07
		Assessment 1	1.01
		Endpoint	-0.32
	Endpoint	Baseline	-0.75
		Assessment 1	1.33
		Assessment 2	0.32
Stage II	Baseline	Assessment 1	-0.52
		Assessment 2	-2.61
		Endpoint	-1.55
	Assessment 1	Baseline	0.52
		Assessment 2	-2.09
		Endpoint	-1.03
	Assessment 2	Baseline	2.61
		Assessment 1	2.09
		Endpoint	1.06
	Endpoint	Baseline	1.55
		Assessment 1	1.03
		Assessment 2	-1.06
Stage III	Baseline	Assessment 1	-1.08
		Assessment 2	-2.21
		Endpoint	-2.40*
	Assessment 1	Baseline	1.08
		Assessment 2	-1.14
		Endpoint	-1.33
	Assessment 2	Baseline	2.21
		Assessment 1	1.14
		Endpoint	-0.19
	Endpoint	Baseline	2.40*
		Assessment 1	1.33
		Assessment 2	0.19

*. The mean difference is significant at the .05 level (paired *t*-test).

Table 4.25.

Mean Difference of SOL at each Timepoint for each level of Cancer Stage (n=24).

Timepoints			Mean Difference
Baseline	Stage I	Stage II	2.34*
		Stage III	2.42*
	Stage II	Stage I	-2.34*
		Stage III	0.07
	Stage III	Stage I	-2.42*
		Stage II	-0.07
Assessment 1	Stage I	Stage II	-0.25
		Stage III	-0.73
	Stage II	Stage I	0.25
		Stage III	-0.48
	Stage III	Stage I	0.73
		Stage II	0.48
Assessment 2	Stage I	Stage II	-1.33
		Stage III	-0.86
	Stage II	Stage I	1.33
		Stage III	0.47
	Stage III	Stage I	0.86
		Stage II	-0.47
Endpoint	Stage I	Stage II	0.04
		Stage III	-0.73
	Stage II	Stage I	-0.04
		Stage III	-0.77
	Stage III	Stage I	0.73
		Stage II	0.77

*. The mean difference is significant at the .05 level (paired *t*-test).

SOL and other covariates

The inclusion of the other covariates (i.e. age of the participants, hormone use, comorbidities, sleep aids use, months after treatment and treatment type) did not yield any statistically significant results in any of linear models tested. The trajectory of the SOL according to each independent variable throughout the 8-week MT program can be found in Figure 4.12 and in Appendix P, Table A.6 with descriptive statistics of mean SOL by each covariate at all timepoints.

Summary of SOL results

In summary, SOL improved after the 8-week MT program, with Time showing a significant effect on SOL values. From all the covariates tested, only Cancer Stage showed significant interactions with Time. These interactions were broken down by conducting separate pairwise calculations for each level of Cancer Stage variable. Pairwise comparisons of interest were followed up with a paired-sample *t*-test. Results showed that SOL significantly changed between study timepoints for each category of Cancer Stage independently, with only Stage III patients showing significantly improved SOL at endpoint. In addition, only at baseline, Stage I patients showed significantly higher SOL in comparison to Stage II and Stage III. In conclusion, SOL statistically significantly improved after the 8-week MT program, regardless of the age of the participants, hormone use, sleep medications in use, months after treatment, comorbidities and treatment type.

Figure 4.12.

Changes in SOL by each independent variable (n=24).

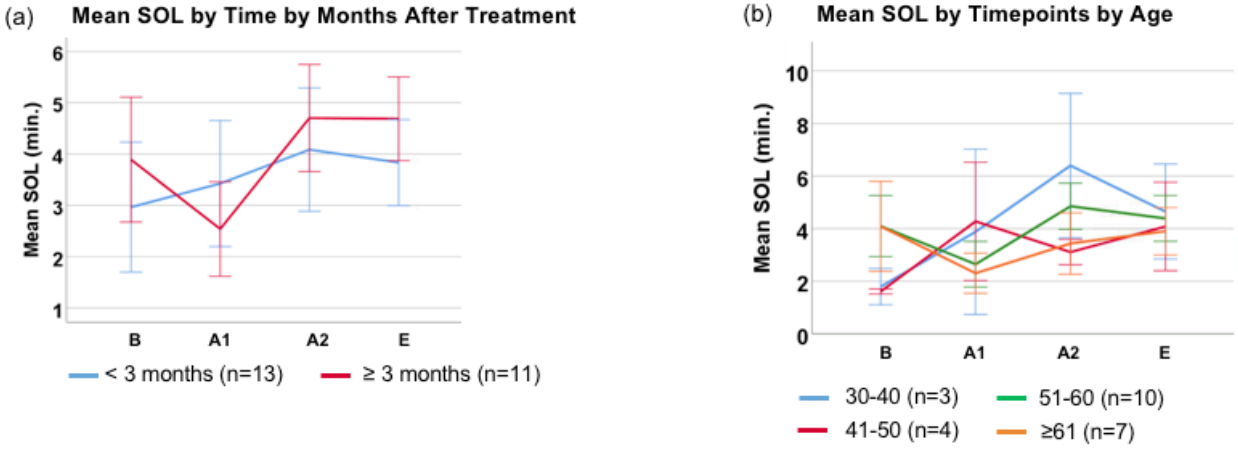
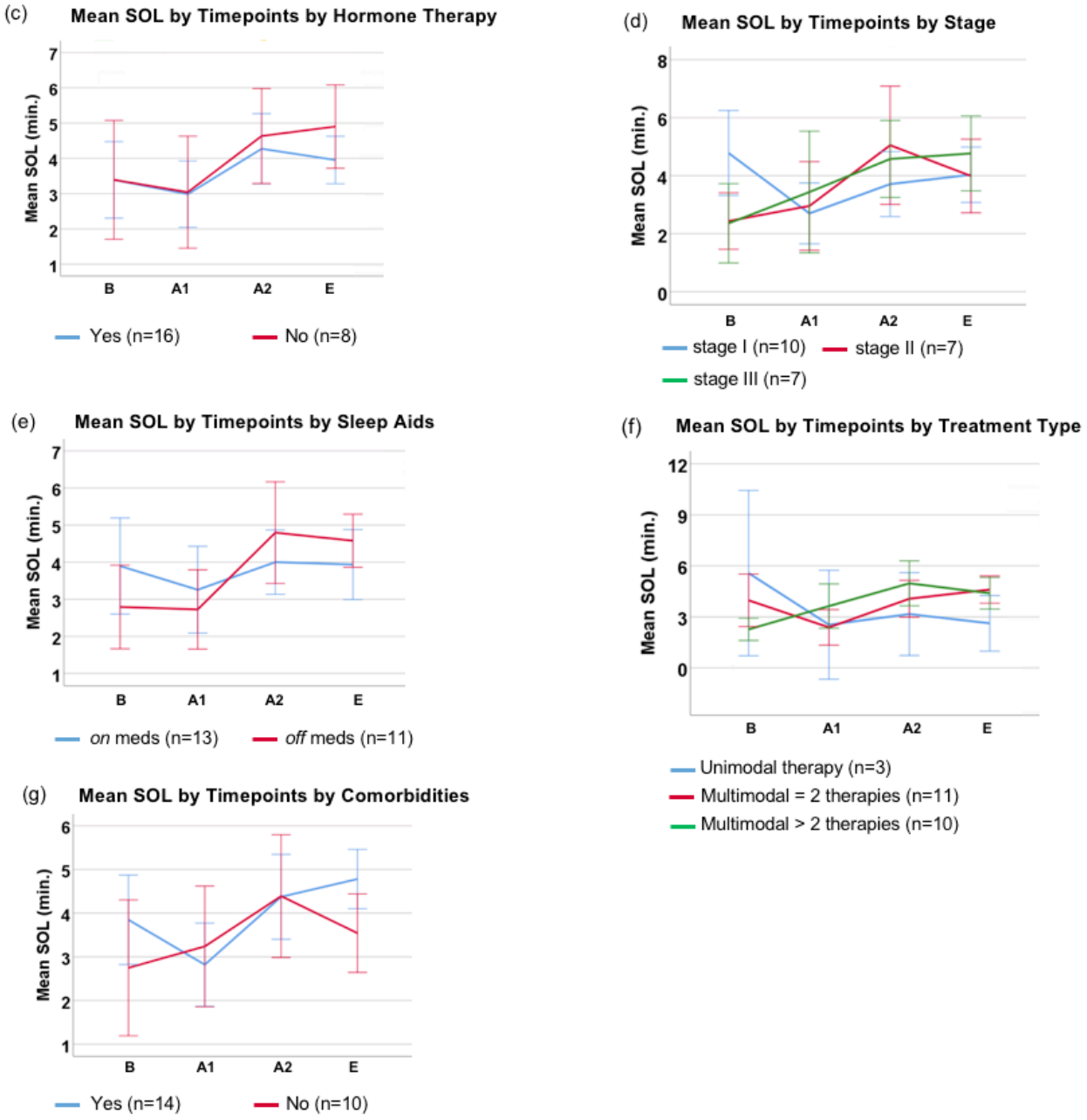


Figure 4.12. (*continued*)



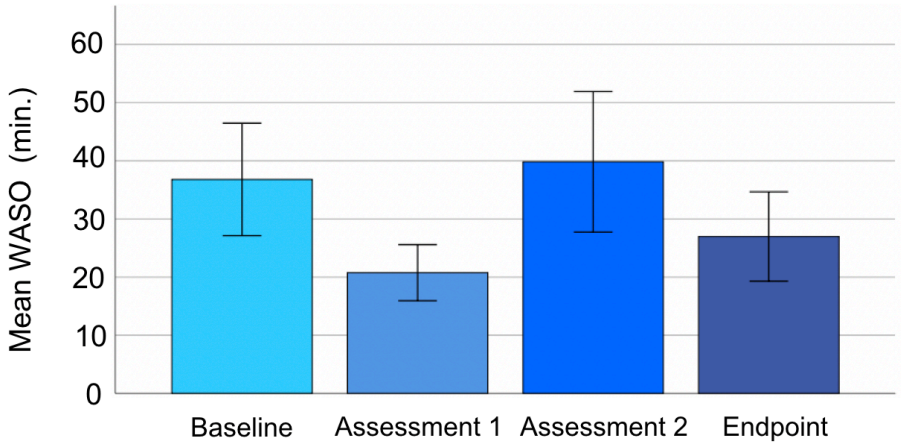
4.3.7 WASO

The trajectory of WASO readings throughout the 8-week MT program is depicted in Figure 4.13. WASO values measured with actigraphy are represented in minutes. WASO represents the minutes awake during the sleep period after sleep onset. Interpretation assumes

that higher numbers indicate worse sleep quality. Some authors state that a standard cut-off point for WASO measured with actigraphy is >30 minutes, which is suggestive of poor sleep quality (Blytt et al., 2017).

Figure 4.13.

Changes in WASO (minutes) at each timepoint (n=24).



According to Figure 4.13, patients showed the lowest WASO values at assessment 1 (mean=20.7 minutes), reaching the highest values at assessment 2 (mean=39.8 minutes). Among the study covariates tested in the LMM, none yielded statistically significant main effects and/or interaction terms in the WASO models. The final LMM for WASO is described below.

WASO and Time

Table 4.26.

Type II tests of Fixed Effects Results for QoL Model 2 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	22.40	99.26	.000
Time	3	66.29	7.06	.000

AIC: 793.87; BIC: 798.84

Table 4.26 shows that Time had a significant effect on sleep duration [F=(3, 66.298)=7.064, *p*=.000].

Table 4.27.

Estimates of Fixed Effects Results for WASO (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	27.42	4.33	61.79	6.32	.000	18.75	30.09
Time							
Baseline	10.53	4.74	66.77	2.21	.030	1.05	20.01
Assessment 1	-6.21	4.77	65.82	-1.30	.198	-15.75	3.32
Assessment 2	12.85	4.77	65.82	2.68	.000	3.31	22.39
Endpoint[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

A significant improvement of WASO was detected after the 8-week MT program. Table 4.27 shows that, on average, patients at baseline showed significantly higher WASO (10.53 minutes) in comparison to endpoint (β=10.53, t=2.21, p=0.030, CI 95%: 1.05, 20.01). Additionally, patients at assessment 2 reported higher WASO (12.8 minutes) in comparison to endpoint, a statistically significant difference (β=12.85, t=2.69, p<0.0001, CI 95%: 3.31, 22.39) (Table 4. 27). After changing reference category, it was also revealed that at assessment 1, patients reported significant lower WASO in comparison to baseline (β=-16.74, t=-3.52, p=0.001, CI 95%: 7.26, 26.22), and in comparison to assessment 2 (β=-19.06, t=-1.30, p<0.0001, CI 95%: -28.61, -9.52) (Figure 4.14).

WASO and other covariates

The inclusion of the other covariates (i.e. age of the participants, hormone use, comorbidities, sleep aids, months after treatment, cancer stage and treatment type) did not yield any statistically significant results in any of linear models tested. The trajectory of WASO readings according to each independent variable throughout the 8-week MT program can be found in Figure 4.14 (next page) and in Appendix P, Table A.7 with descriptive statistics of WASO by each covariate at all timepoints.

Summary of WASO results

In summary, WASO significantly improved after the 8-week MT program, with Time showing a significant effect on WASO values. Improvement was detected regardless of the age of the participants, hormone use, comorbidities, sleep aids use, months after treatment, cancer stage and treatment type.

Figure 4.14.

Changes in WASO by each independent variable (n=24).

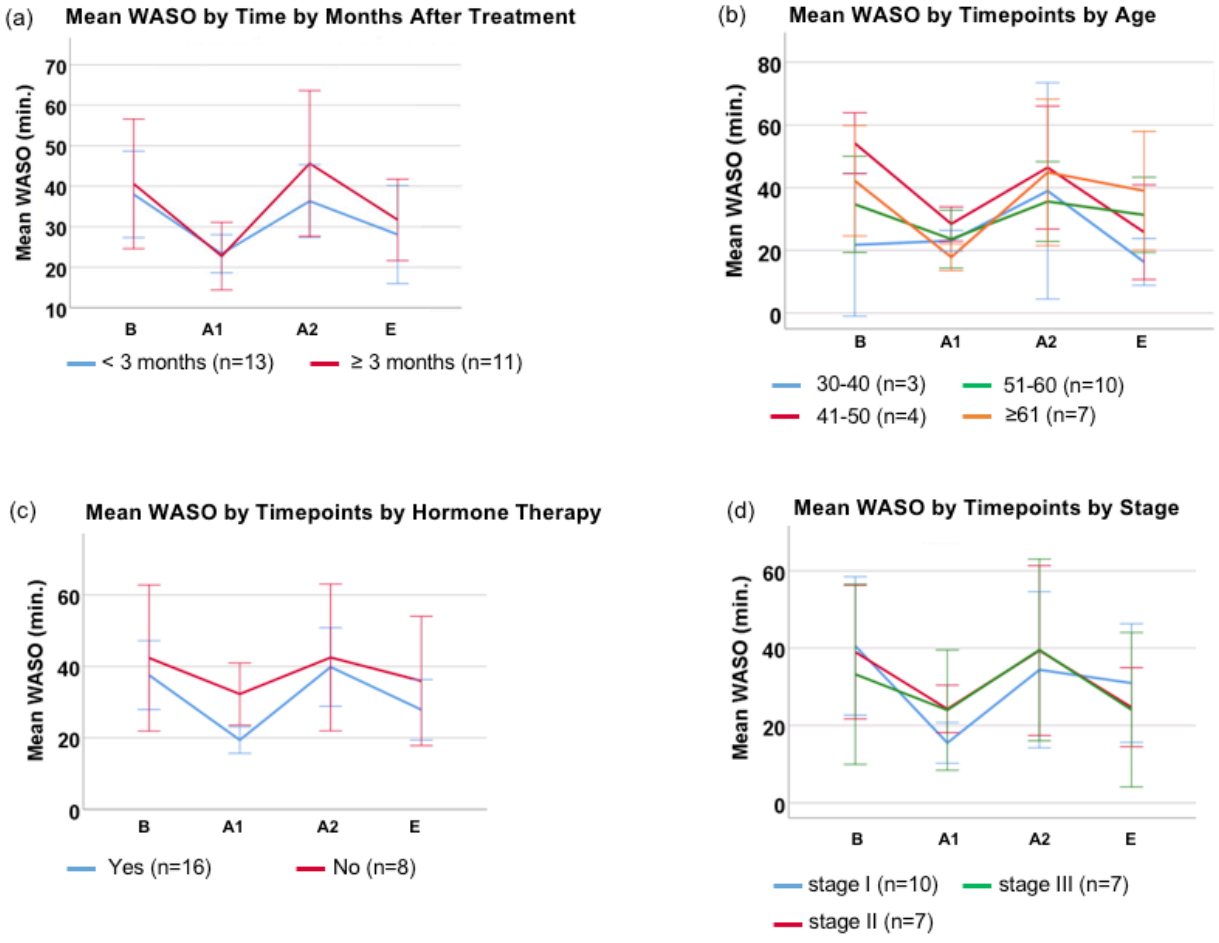
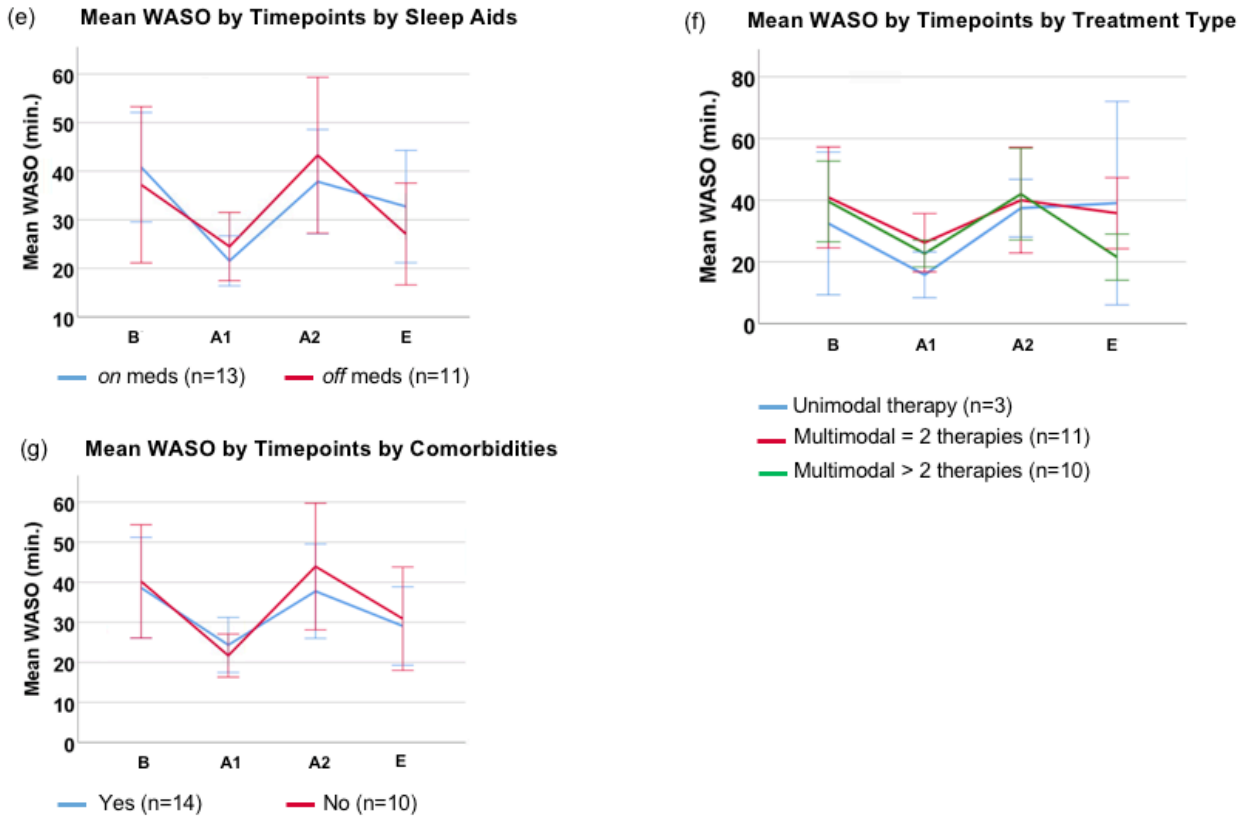


Figure 4.14. *(continued)*



4.3.8 Summary of Findings from Research Question One

- QoL, fatigue, stress, SOL and WASO showed improvements after the 8-week MT program.
- QoL improvements were significantly associated with time after cancer treatment completion and cancer stage.
- Changes in fatigue scores were significantly associated with sleep aids in use and comorbidities.
- Stress levels significantly improved at endpoint in comparison to baseline, regardless of any covariates tested.
- WASO significantly improved at endpoint in comparison to baseline, regardless of age, hormone use, comorbidities, sleep aids, months after treatment, cancer stage and treatment type.

- SOL changes were significantly associated with cancer stage.
- SD did not improve after the 8-week MT program.
- SE improved after the program, however, differences did not reach statistical significance.

4.4 Changes in Inflammatory Markers

This subsection will address the findings of research question two: are there any changes in inflammatory markers in BCS submitted to an 8-week Swedish massage program? Below, a detailed description of the results is presented for each outcome.

4.4.1 Cortisol

Figure 4.15 shows the trajectory of cortisol levels at each timepoint during the MT program.

Figure 4.15.

Changes in cortisol levels at each timepoint (n=24).

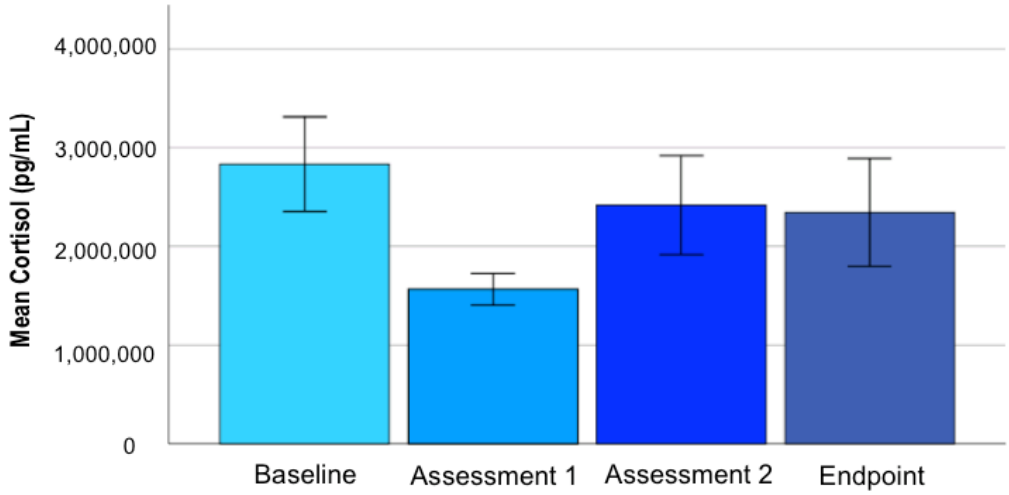


Figure 4.15 shows that there was a drop in cortisol levels from baseline to assessment 1, followed by an increase at assessment 2. Overall, cortisol levels decreased from baseline to

endpoint, showing an improvement. Among the study covariates tested in the LMM, none yielded significant main effects and/or significant interaction terms in the cortisol models. The final model for cortisol is presented next.

Cortisol and Time

Table 4.28.

Type II tests of Fixed Effects Results for cortisol (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	22.063	625.197	.000
Time	3	66.711	5.458	.002

AIC: 2734.55; BIC: 2739.53

Table 4.28 shows that Time had a significant effect on cortisol [F=(3, 66.711)=5.458, p=0.002].

Table 4.29.

Estimates of Fixed Effects Results for cortisol (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	2350956.98	217585.37	86.77	10.805	.000	1918466.71	2783447.24
Time							
Baseline	48359.49	318273.74	66.99	1.519	.133	-151818.89	1118737.89
Assessment 1	-780051.26	321965.23	66.42	-2.42	.018	-1422798.50	-137304.02
Assessment 2	72710.12	321965.23	66.42	.226	.822	-570037.11	715457.36
Endpoint[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

Cortisol levels decreased after the 8-week MT program. Table 4.29 shows that, on average, patients at assessment 1 showed significant lower cortisol in comparison to endpoint (β=-780051.26, t=-2.42, p=0.018, CI 95%: -1422798.50, -137304.02). Noteworthy that tables with a change in the reference category of Time are not shown, however all the significant results are described next. Patients at assessment 1 reported lower cortisol levels in comparison to baseline (β=-12635.76, t=-3.96, p<0.0001, CI 95%: -1232778.70, -123354.05) and in comparison

to assessment 2 (β=-852761.38, t=-2.64, *p*=0.010, CI 95%: -1782228.50, -130478.55).

Cortisol and other covariates

The inclusion of the other covariates (i.e. age of the participants, hormone use, comorbidities, sleep aids use, cancer stage, months after treatment and treatment type) did not yield any statistically significant results in any of linear models tested.

Summary of cortisol results

In summary, there was an overall improvement in cortisol levels after the 8-week MT program, however, cortisol changes from baseline to endpoint did not attain statistical significance. Significant improvements were seen in cortisol levels only in the middle of the MT program in comparison to endpoint. From all the covariates tested, none significantly affected cortisol levels or showed any interactions with Time.

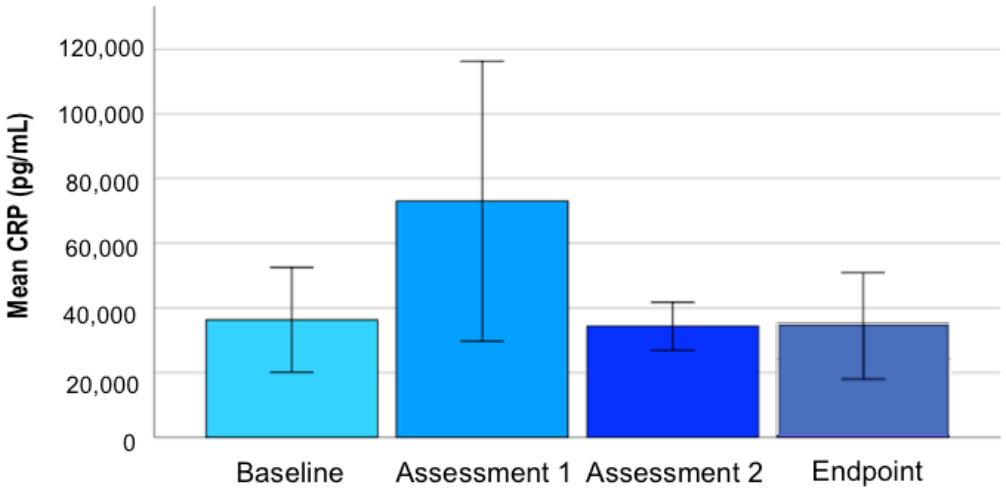
4.4.2 CRP

Figure 4.16 (next page) shows the trajectory of CRP levels at each timepoint during the MT program.

As depicted in Figure 4.16 (next page), CRP slightly improved after the 8-week MT program. A RM-ANOVA showed, however, that changes in CRP did not reach statistical significance [F (3, 66) = 1.268, *p*=0.293]. Overall, patients at assessment 2 (mean=34362.63 pg/mL) followed by patients at endpoint (mean=35027.47 pg/mL) showed the lowest CRP levels.

Figure 4.16.

Changes in CRP levels at each timepoint (n=24).



CRP and other covariates

No statistically significant interactions were found between timepoints and the following variables: sleep aids, months after treatment, cancer stages, hormone therapy, treatment type, and age, and presence of comorbidities.

Summary of CRP results

In summary, CRP levels decreased at endpoint, however, no statistically significant differences were found between timepoints. CRP levels varied regardless of the age of participant, cancer stage, treatment type, months after treatment, hormone use, sleep aids in use, and presence of comorbidities.

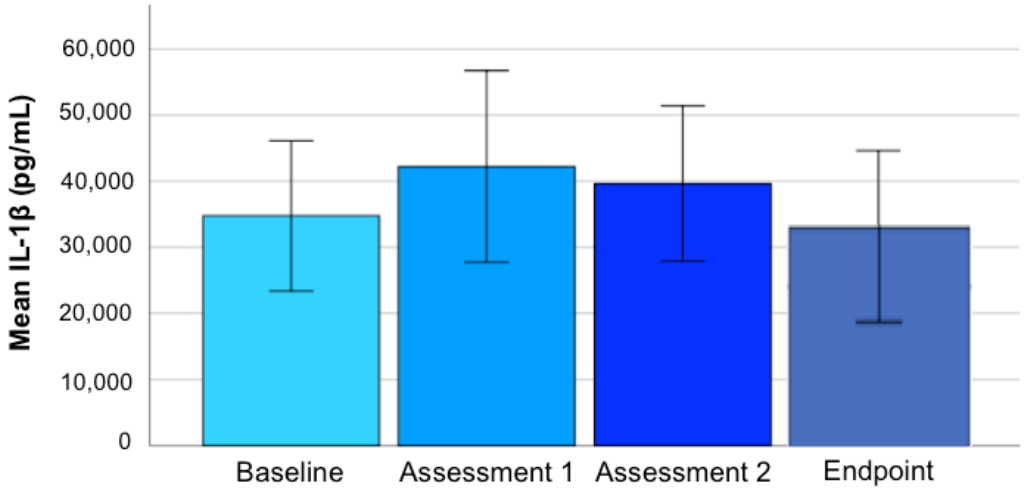
4.4.3 IL-1β

Figure 4.17 (next page) shows the trajectory of IL-1β levels at each timepoint during the MT program. According to Figure 4.24, IL-1β levels decreased at the end of the MT program in

comparison to baseline. Patients at endpoint (mean=32959.31 pg/mL) followed by patient at baseline (mean=35285.26 pg/mL) showed the lowest IL-1β levels.

Figure 4.17.

Changes in IL-1β levels at each timepoint (n=24).



Among the study covariates tested in the LMM, only two covariates (i.e. Cancer Stage and Hormone Therapy) yielded statistically significant main effects and/or significant interaction terms in the IL-1β models, which are described below.

IL1-β and Cancer Stage

Table 4.30.

Type II tests of Fixed Effects Results for IL1-β (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	21.02	46.49	.000
Time	3	60.41	2.16	.102
Cancer Stage	2	21.04	.064	.938
Interaction Time * Cancer Stage	6	60.42	2.35	.042

AIC: 1869.00; BIC: 1873.78

Table 4.30 shows that Time did not have a significant effect on IL1-β [F=(3, 60.412)=2.162, *p*=0.102], neither had Cancer Stage [F=(1, 21.045)=0.64, *p*=0.938]. However, the interaction of Time and Stage had a significant effect on IL1-β [F=(6, 60.429)=2.353, *p*=0.042].

Table 4.31.

Estimates of Fixed Effects Results for IL1-β Model 1 (n=24).

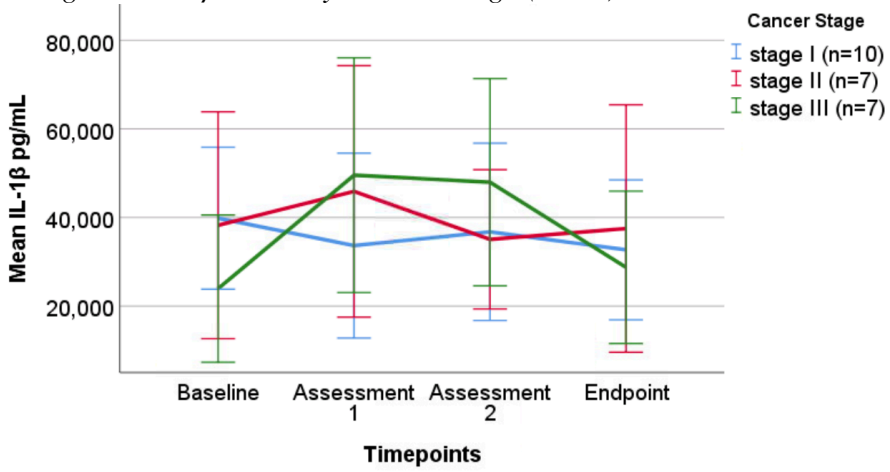
Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	23937.09	11089.75	31.91	2.15	.039	1345.72	4628.45
Time							
Baseline[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Assessment 1	25614.28	8118.13	60.23	3.15	.003	9376.89	4185.67
Assessment 2	24023.75	8118.13	60.23	2.95	.004	7786.36	40261.14
Endpoint	4813.21	8118.13	60.23	.593	.555	-11424.17	21050.61
Cancer Stage							
Stage I	15903.66	14459.27	31.91	1.10	.280	-13551.87	45359.20
Stage II	14312.29	15683.28	31.91	.913	.368	-17636.72	46261.31
Stage III	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Interactions [b]							
Assessment 1 x Stage I	-33239.86	10792.40	60.79	-3.08	.003	-54822.05	11657.66
Endpoint x Stage I	-28546.78	10792.40	60.79	-2.64	.010	-50128.98	6964.59
Endpoint x Stage II	-27214.47	11480.76	60.23	-2.37	.021	-50177.61	4251.33
Baseline x Stage III[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

Estimates of fixed effects results displayed in Table 4.31, show several significant interaction terms between Time and Cancer Stage (β=-33239.86, t=-3.08, *p*=0.003, CI 95%: -54822.05, 11657.66; β=-28546.78, t=-2.64, *p*=0.010, CI 95%: -50128.98, 6964.59, and β=-28546.78, t=-2.370, *p*=0.021, CI 95%: -50177.61, 4251.33), indicating that QoL varied differently at the different levels of Time and Cancer Stage. These interactions are graphically displayed in Figure 4.18 (next page).

Figure 4.18.

Changes in IL1-β levels by Cancer Stage (n=24).



To further assess these interaction terms, pairwise calculations based on estimated means were performed following the same procedures described on page 86. Hence, Table 4.32 (next page) presents the differences in IL1-β for each group of Cancer Stage between Timepoints. Similarly, Table 4.33 (page 132) shows that IL1-β levels were different at each Timepoint for each level of the Cancer Stage variable. In addition to these calculations, a paired sample *t*-test was run to analyze if selected pairwise comparisons of interest were statistically significant.

According to Table 4.32 (next page), only Stage III patients showed significant changes between timepoints. Hence, Stage III patients showed significantly lower IL1-β at endpoint in comparison to assessment 1 (mean=20801.06 pg/mL) and assessment 2 (mean=19210.53 pg/mL) (p=0.013). In comparison to baseline, this same stage group showed significantly higher levels of IL1-β at assessment 1 (25614.28 pg/dL higher), and assessment 2 (24023.75 pg/mL higher) (p=0.003 and p=0.004, respectively). No significant changes between baseline and endpoint were found for Stage III patients. In addition, no significant changes in Stage I and Stage II groups between timepoints were found.

Table 4.32.

Mean Difference of IL1-β levels for each group of Cancer Stage between Timepoints (n=24).

Cancer Stage			Mean Difference
Stage I	Baseline	Assessment 1	7625.58
		Assessment 2	4523.03
		Endpoint	8582.06
	Assessment 1	Baseline	-7625.58
		Assessment 2	-3102.54
		Endpoint	956.49
	Assessment 2	Baseline	-4523.03
		Assessment 1	3102.54
		Endpoint	4059.03
	Endpoint	Baseline	-8582.06
		Assessment 1	-956.49
		Assessment 2	-4059.03
Stage II	Baseline	Assessment 1	-7640.61
		Assessment 2	3190.72
		Endpoint	744.44
	Assessment 1	Baseline	7640.61
		Assessment 2	10831.32
		Endpoint	8385.04
	Assessment 2	Baseline	-3190.72
		Assessment 1	-10831.32
		Endpoint	-2446.28
	Endpoint	Baseline	-744.44
		Assessment 1	-8385.04
		Assessment 2	2446.28
Stage III	Baseline	Assessment 1	-25614.28*
		Assessment 2	-24023.76
		Endpoint	-4813.22
	Assessment 1	Baseline	25614.28*
		Assessment 2	1590.53
		Endpoint	20801.06*
	Assessment 2	Baseline	24023.76
		Assessment 1	-1590.53
		Endpoint	19210.53*
	Endpoint	Baseline	4813.22
		Assessment 1	-20801.06*
		Assessment 2	-19210.53*

*. The mean difference is significant at the .05 level (paired *t*-test).

Table 4.33.

Mean Difference of IL-β levels at each Timepoint for each level of Cancer Stage (n=24).

Timepoints			Mean Difference
Baseline	Stage I	Stage II	1591.36
		Stage III	15903.66
	Stage II	Stage I	-1591.36
		Stage III	14312.30
	Stage III	Stage I	-15903.66
		Stage II	-14312.30
Assessment 1	Stage I	Stage II	-13674.82
		Stage III	-17336.20
	Stage II	Stage I	13674.82
		Stage III	-3661.38
	Stage III	Stage I	17336.20
		Stage II	3661.38
Assessment 2	Stage I	Stage II	259.05
		Stage III	-12643.13
	Stage II	Stage I	-259.05
		Stage III	-12902.18
	Stage III	Stage I	12643.13
		Stage II	12902.18
Endpoint	Stage I	Stage II	-6246.26
		Stage III	2508.38
	Stage II	Stage I	6246.26
		Stage III	8754.64
	Stage III	Stage I	-2508.38
		Stage II	-8754.64

According to Table 4.33, no significant differences in IL1-β levels at each Timepoint for each level of Cancer Stage were found.

IL-β and Hormone Therapy

Table 4.34.

Type II tests of Fixed Effects Results for IL-β Model 2 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	22.66	42.99	.000
Time	3	64.01	2.34	.081
Hormone Therapy	1	22.66	.56	.459
Interaction Time * Hormone Therapy	3	64.01	2.83	.045

AIC: 1954.95; BIC: 1959.84

Table 4.34 (previous page) shows that Time did not have a significant effect on IL1-β [F=(3, 64.015)=2.347, *p*=0.081], neither had Hormone Therapy use [F=(1, 22.660)=0.568, *p*=0.459]. However, the interaction of Time and Hormone Therapy use had a significant effect on IL-β [F=(3, 60.015)=2.839, *p*=0.045].

Table 4.35.

Estimates of Fixed Effects Results for IL-β Model 2 (n=24).

Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	30979.98	10427.08	38.79	2.97	.005	9885.17	52074.78
Time							
Baseline	-13188.61	8197.68	65.22	-1.60	.112	-29559.46	3182.22
Assessment 1	7542.8	8274.40	63.38	.912	.365	-8990.33	24075.90
Assessment 2	9361.86	8274.40	63.38	1.13	.262	-7171.25	25894.99
Endpoint[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Hormone Therapy							
Yes	3037.35	12626.91	37.57	.24	.811	-22533.89	28608.59
No[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Interactions [b]							
Baseline x Yes	22382.66	9856.76	64.65	2.27	.026	-2695.36	42069.96
Endpoint x No	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.
b. Only statistically significant or marginally significant interactions are displayed.

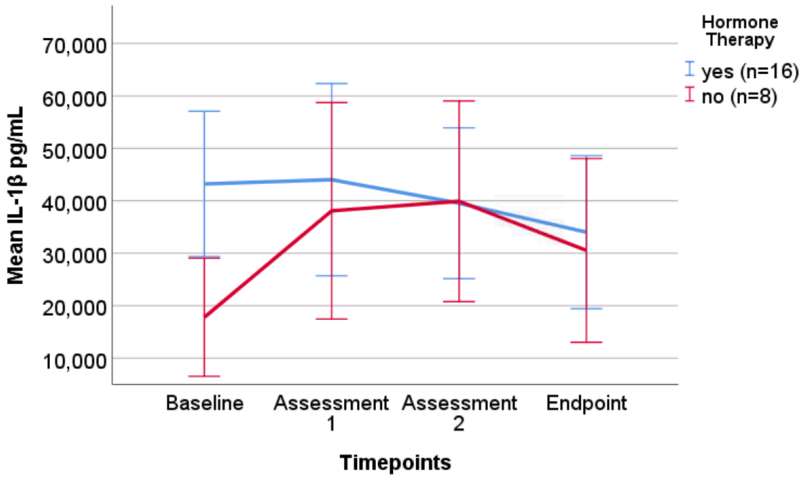
Estimates of fixed effects results displayed in Table 4.35, shows a significant interaction term between *Baseline x Hormone Therapy/Yes* (β=22382.66, t=2.271, *p*=0.026, CI 95%: -2695.36, 42069.96), indicating that those who were on hormone therapy showed significantly higher IL1-β (mean=22382.66 pf/mL) when compared to those who were not taking any hormones at baseline when compared to endpoint. This interaction is graphically displayed in Figure 4.19.

To further assess the interaction term, pairwise calculations based on estimated means were performed following the same procedures described on page 86. Hence, Table 4.36 (page 135) presents the differences in IL1-β for each group of Hormone Therapy between Timepoints. Similarly, Table 4.37 (page 135) shows that IL1-β levels were different at each Timepoint for

each level of the Hormone Therapy variable. In addition to these calculations, a paired sample *t*-test was run to analyse if selected pairwise comparisons of interest were statistically significant.

Figure 4.19.

Changes in IL1-β levels by Hormone Therapy (n=24).



In Table 4.36, noteworthy mentioning that, IL1-β levels for those *off* hormone therapy, were significantly higher at assessment 1 (20731.40 pg/mL) and assessment 2 (22550.48 pg/mL), respectively) in comparison to baseline (p=0.014, p=0.008, respectively). No significant changes between baseline and endpoint were found.

Table 4.36.

Mean Difference of IL1-β levels for each group of Hormone Therapy between Timepoints (n=24).

Comorbidities			Mean Difference
Yes	Baseline	Assessment 1	-812.93
		Assessment 2	3672.30
		Endpoint	9194.05
	Assessment 1	Baseline	812.93
		Assessment 2	4485.23
		Endpoint	10006.98
	Assessment 2	Baseline	-3672.30
		Assessment 1	-4485.23
		Endpoint	5521.75
	Endpoint	Baseline	-9194.05
		Assessment 1	-10006.98
		Assessment 2	-5521.75
No	Baseline	Assessment 1	-20731.40*
		Assessment 2	-22550.48*
		Endpoint	-13188.62
	Assessment 1	Baseline	20731.40*
		Assessment 2	-1819.08
		Endpoint	7542.78
	Assessment 2	Baseline	22550.48*
		Assessment 1	1819.08
		Endpoint	9361.87
	Endpoint	Baseline	13188.62
		Assessment 1	-7542.78
		Assessment 2	-9361.87

*. The mean difference is significant at the .05 level (paired *t*-test).

Table 4.37.

Mean Difference of IL1-β levels at each Timepoint for each level of Hormone Therapy (n=24).

Timepoints			Mean Difference
Baseline	yes	no	25420.01*
	no	yes	-25420.01*
Assessment 1	yes	no	5501.55
	no	yes	-5501.55
Assessment 2	yes	no	-802.77
	no	yes	802.77
Endpoint	yes	no	3037.35
	no	yes	-3037.35

*. The mean difference is significant at the .05 level (paired *t*-test).

As shown in Table 4.37, overall, throughout the MT program, patients *on* hormone therapy showed higher IL1-β levels in comparison to patients *off* hormone therapy. For instance, at baseline patients who were *on* hormone therapy, showed significantly higher IL1-β levels (25420.01 pg/mL) in comparison to those who were not (p=0.047).

IL1-β and other covariates

The inclusion of the other covariates (i.e. age of the participants, comorbidities, sleep aids use, months after treatment and treatment type) did not yield any statistically significant results in any of linear models tested.

Summary of IL1-β results

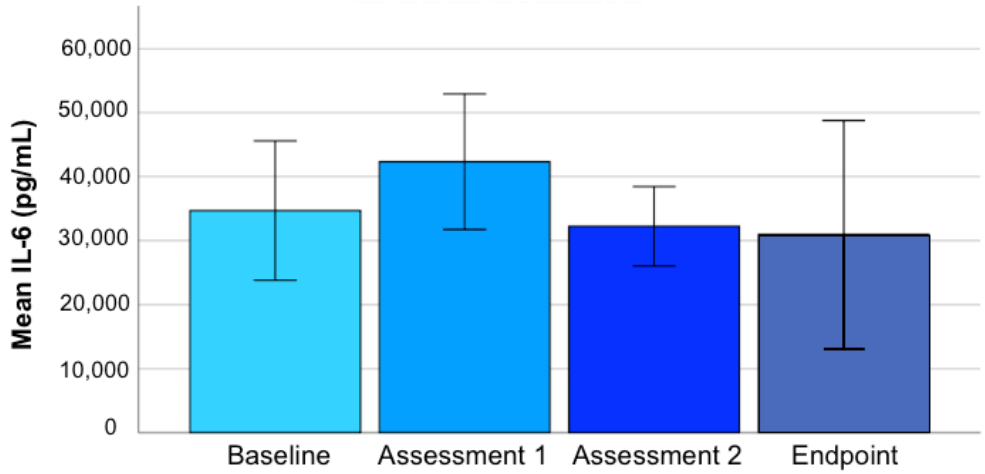
In summary, IL1-β improved after the 8-week MT program, with only Hormone Therapy and Cancer Stage showing significant interactions with Time. These interactions were broken down by conducting separate pairwise calculations for each level of Cancer Stage and Hormone Therapy categories. Pairwise comparisons of interest were followed up with a paired-sample *t*-test. Results showed that IL1-β levels changed significantly between study timepoints for stage III group only. In addition, IL1-β levels between Cancer Stage groups were not significantly different at each timepoint. Similarly, IL1-β levels changed significantly between study timepoints for those who were not in hormone therapy. In addition, patients *on* hormone therapy showed significantly higher IL1-β levels in comparison to patients *off* hormone therapy at baseline. In conclusion, a slight non-statistical improvement in IL1-β levels were detected after the 8-week MT program, regardless of the age of the participants, months after treatment, sleep aids use, comorbidities and treatment type.

4.4.4 IL-6

Figure 4.20 shows the trajectory of IL-6 levels at each timepoint during the MT program.

Figure 4.20.

Changes in IL-6 levels at each timepoint (n=24).



A RM-ANOVA revealed that there was not a statistically significant change in IL-6 during the MT program [F (3, 66)=0.785, *p*=.507]. According to Figure 4.20, IL-6 levels decreased over time reaching its lowest levels at endpoint. Patients at endpoint (mean=30,969.85 pg/mL) followed by patient at assessment 2 (mean=32,256.64 pg/mL) showed the lowest IL-6 concentrations.

IL-6 and other covariates

No statistically significant interactions were found between timepoints and the following variables: sleep aids, months after treatment, cancer stages, hormone therapy, treatment type, presence of comorbidity, and age.

Summary of IL-6 results

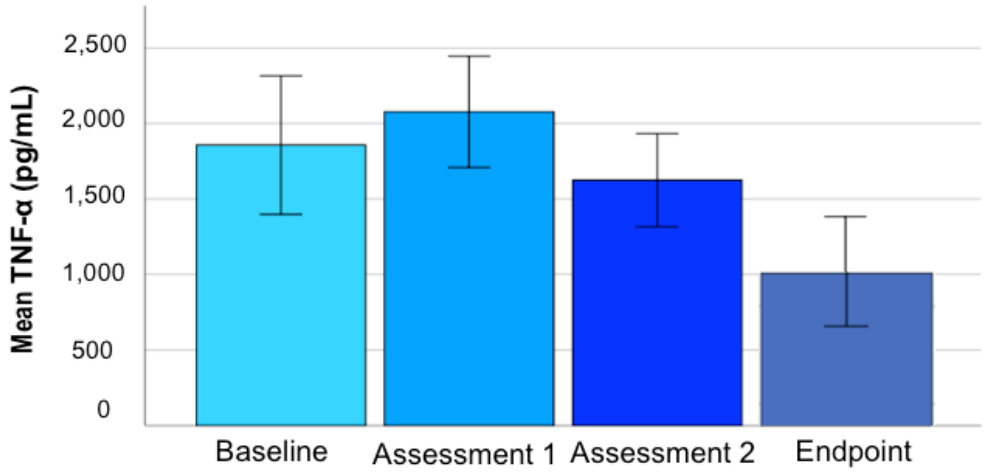
In conclusion, there were improvement trends in IL-6 levels during the MT program, however, these failed to reach statistical significance. IL-6 levels slightly improved regardless of the age of participant, cancer stage, treatment type, months after treatment, hormone use, sleep aids in use, and presence of comorbidities.

4.4.5 TNF-α

Figure 4.21 shows the trajectory of TNF-α levels at each timepoint during the MT program.

Figure 4.21.

Changes in TNF-α levels at each timepoint (n=24).



According to Figure 4.21, TNF-α levels decreased at the end of the MT program in comparison to baseline, and in comparison to all other time-points. Overall, patients at endpoint showed the lowest TNF-a levels (mean=1013.12 pg/mL). Among the study covariates tested in the LMM, only three (i.e. Age, Treatment Classification, and Cancer Stage) yielded statistically significant main effects in the TNF-α models, which are described below.

TNF-α and Age

Table 4.38 shows that Time had a significant effect on TNF-α levels [F=(3, 66.537)=6.835, p=0.000], when Age was in the model. The same table shows that Age also had a significant effect on TNF-α levels [F=(2, 18.980)=4.126, p=0.021].

Table 4.38.

Type II tests of Fixed Effects Results for TNF-α Model 1 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	18.92	06.60	.000
Time	3	66.53	6.83	.000
Age	3	18.98	4.12	.021

AIC: 1427.67; BIC: 1432.58

Table 4.39.

Estimates of Fixed Effects Results for TNF-α Model 1 (n=24).

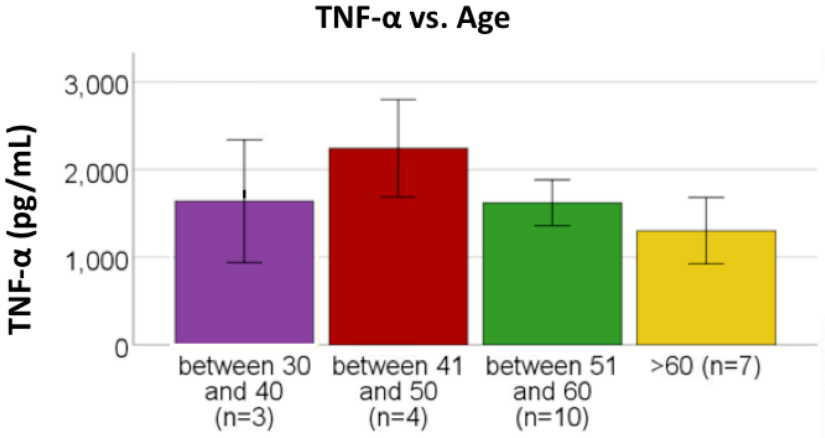
Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	660.54	229.15	54.15	2.88	.006	201.16	1119.93
Time							
Baseline	857.91	247.05	66.91	3.47	.001	364.77	1351.04
Assessment 1	1062.89	249.59	66.15	4.25	.000	564.58	1561.20
Assessment 2	610.94	249.59	66.15	2.44	.017	112.63	1109.25
Endpoint[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Age							
Between 30-40	346.39	296.95	19.07	1.17	.258	-274.97	967.74
Between 41-50	950.28	270.72	19.15	3.51	.002	383.96	1516.60
Between 51-60	326.99	215.61	19.41	1.52	.146	-123.66	777.63
> 60	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

According to Table 4.39, TNF-α levels improved by the end of the 8-week MT program. In comparison to endpoint, TNF-α levels were increased at baseline (β=857.91, t=3.47, p=0.001, CI 95%: 364,78, 1351.04), assessment 1 (β=1062.90, t=4.26, p<0.0001, CI 95%: 564.59, 1561.21), and assessment 2(β=610.95, t=2.45, p=0.017, CI 95%:112.64, 1109.25) (Figure 4.21).

In regard to age, in comparison to patients >60 years old, those between 41-50 years old showed significant higher levels of TNF-α (β=950.27, t=3.510, p=0.002, CI 95%: 383.96, 1516.60) (Table 4.39). Noteworthy that tables with a change in the reference category of Time and Age are not shown, however all the significant results are described next. Additionally, those between 30-40 years old showed marginally significant lower TNF-α levels in comparison to patients between 41-50 years old (β=-603.89, t=-1.871, p=0.077, CI 95%: -1280.29, 75.50). The trajectory of TNF-α by Age groups is showed in Figure 4.22 (below).

Figure 4.22.

Changes in TNF-α by Age groups (n=24).



TNF-α and Stage

Table 4.40.

Type II tests of Fixed Effects Results for TNF-α Model 2 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	19.93	337.69	.000
Time	3	66.53	6.83	.000
Cancer Stage	2	19.95	4.74	.021

AIC: 1443.39; BIC: 1448.32

Table 4.40 shows that Time [F=(3, 66.535)=6.836, *p*=0.000] had a significant effect on TNF-α levels when cancer stage was in the model. The same table shows that Cancer Stage also had a significant effect on TNF-α levels [F=(2, 19.957)=4.741, *p*=0.021].

Table 4.41.

Estimates of Fixed Effects Results for TNF-α Model 2 (n=24).

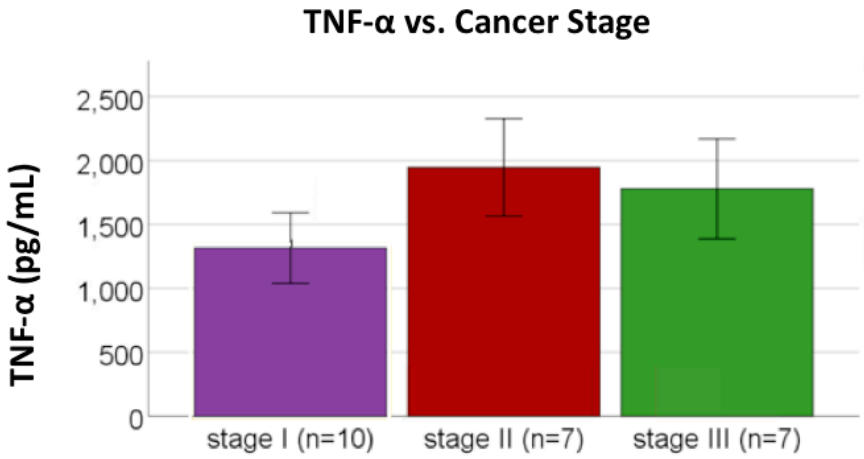
Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	1145.15	224.69	56.33	5.10	.000	695.10	1595.20
Time							
Baseline	858.06	247.05	66.91	3.47	.001	364.93	1351.19
Assessment 1	1062.89	249.58	66.15	4.25	.000	564.61	1561.18
Assessment 2	610.94	249.58	66.15	2.44	.017	112.65	1109.23
Endpoint[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Cancer Stage							
Stage I	-469.77	218.60	20.06	-2.15	.044	-925.66	-13.88
Stage II	167.66	233.26	19.71	0.72	.481	-319.37	654.69
Stage III[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.

According to Table 4.41, TNF-α levels decreased after the 8-week MT program. On average, in comparison to endpoint, patients showed significant higher TNF-α at baseline (β=858.06, t=3.47, *p*=0.001, CI 95%: 364.93, 1351.20), at assessment 1 (β=1032.89, t=4.259, *p*<0.0001, CI 95%: 112.66, 1109.23), and at assessment 2 (β=610.94, t=2.44, *p*=0.017, CI 95%: 695.10, 1595.20) (Table 4.41, Figure 4.21). Table 4.41 also shows that those diagnosed with stage I showed significant lower TNF-α levels in comparison to stage III patients (β=-469.77, t=-2.156, *p*=0.044, CI 95%: -925.66, -13.88). Noteworthy that tables with a change in the reference category of Time and Cancer Stage are not shown, however all the significant results are described next. Those diagnosed with stage I showed significant lower TNF-α levels in comparison to stage II patients (β=-637.43, t=-2.916, *p*=0.009, CI 95%: -1093.32, -181.53). The trajectory of TNF-α by Cancer Stage groups is showed in Figure 4.23 (next page).

Figure 4.23.

Changes in TNF-α by Cancer Stage (n=24).



TNF-α and Treatment Classification

Table 4.42.

Type II tests of Fixed Effects Results for TNF-α Model 3 (n=24).

Source	Num df	Den df	F	Sig.
Intercept	1	19.76	203.03	.000
Time	3	66.40	6.80	.000
Treatment Classification	2	19.85	3.54	.048

AIC: 1444.78; BIC: 1449.72

Table 4.42 shows that Time had a significant effect on TNF-α levels [F=(3, 66.400)=6.804, p<0.0001], when Treatment Classification was in the model. The same table also shows that Treatment Classification also had a significant effect on TNF-α levels [F=(2, 19.851)=3.54, p=0.048].

Table 4.43.

Estimates of Fixed Effects Results for TNF-α Model 3 (n=24).

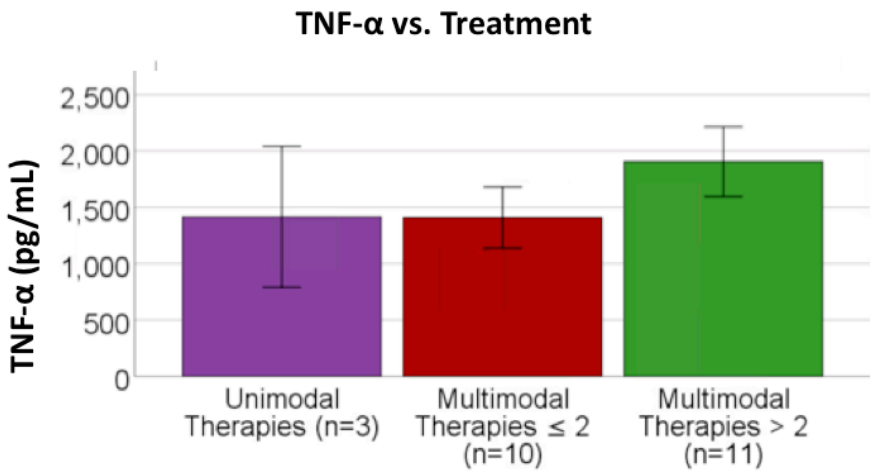
Parameter	Estimate	SE	df	t	Sig.	95% CI	
						Lower	Upper
Intercept	1273.13	205.16	68.79	6.21	.000	863.83	1682.44
Time							
Baseline	855.34	247.43	66.80	3.46	.001	361.44	1349.24
Assessment 1	1062.90	249.91	66.00	4.25	.000	563.94	1561.86
Assessment 2	610.95	249.91	66.00	2.44	.017	111.99	1109.90
Endpoint[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Treatment Classification							
Unimodal therapy	-490.05	295.79	19.60	-1.66	.131	-1107.87	127.75
Multimodal = 2 therapies	-506.00	202.48	20.06	-2.50	.021	-928.29	-83.72
Multimodal > 2 therapies[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

a. Reference category.

According to Table 4.43, TNF-α levels decreased after the 8-week MT program. On average, in comparison to endpoint, patients showed significant higher TNF-α at baseline (β=855.34, t=3.46, *p*=0.001, CI 95%: 361.44, 1349.24), at assessment 1 (β=1062.90, t=4.25, *p*<0.0001, CI 95%: 563.94, 1561.86), and at assessment 2 (β=610.95, t=2.44, *p*=0.017, CI 95%: 111.99, 1109.90) (Table 4.43, Figure 4.21). Table 4.43 also shows that those who went through multimodal therapies with only two therapies showed significant lower TNF-α levels in comparison to those who went through multimodal therapies with more than two therapies (β=-506.00, t=-2.50, *p*=0.021, CI 95%: -928.29, -83.72). The trajectory of TNF-α by Treatment Classification groups is showed in Figure 4.24 (next page).

Figure 4.24.

Changes in TNF-α by Treatment Classification (n=24).



Summary of TNF-α

Overall, TNF-α levels significantly decreased at the end of the MT program in comparison to baseline, and in comparison to all other time-points. Only Age, Treatment Classification, and Cancer Stage yielded statistically significant main effects in the TNF-α models. Therefore, during the MT program, TNF-α levels significantly varied between Age, Treatment Classification, and Cancer Stage groups.

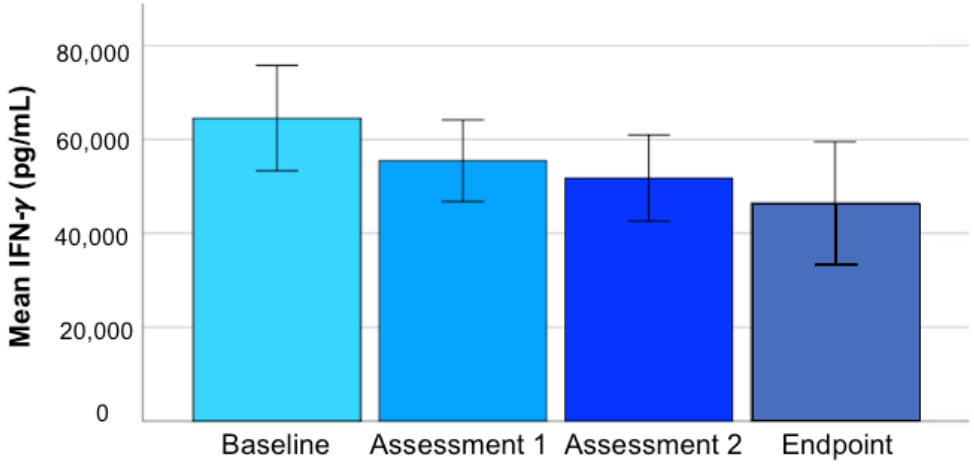
4.4.6 IFN-γ

Figure 4.25 (next page) shows the trajectory of IFN-γ levels at each timepoint during the MT program.

A RM-ANOVA revealed that there was not a statistically significant change in IFN-γ during the MT program [F (3, 66)= 2.518, p=0.066]. According to Figure 4.25, IFN-γ levels progressively decreased throughout the MT program reaching its lowest level at the end of the MT program. Overall, patients at endpoint (mean=46526.59 pg/mL) followed by patient at assessment 2 (mean=51781.18 pg/mL) showed the lowest IFN-γ levels.

Figure 4.25.

Changes in IFN-γ levels at each timepoint (n=24).



IFN-γ and other covariates

No statistically significant interactions were found between IFN-γ and the between-subject factors age, sleep aids use, stage, cancer treatment, presence of comorbidity, months after treatment and hormone therapy.

Summary of IFN-γ results

In conclusion, there were improvement trends in IFN-γ levels during the MT program, however, these failed to attain statistical significance. IFN-γ levels varied regardless of the age of participant, cancer stage, treatment type, months after treatment, hormone use, sleep aids in use, and presence of comorbidities.

4.4.7 Summary of Findings from Research Question Two

- Significant changes in inflammatory markers in BCS submitted to an 8-week MT program were found.
- Overall, all the biomarkers decreased at endpoint in comparison to baseline. Statistically significant results were found in the cortisol, IL1-β and TNF-α models.

- Although there was an overall improvement in cortisol levels after the 8-week MT program, significant improvements were seen in cortisol levels only in the middle of the MT program in comparison to endpoint.
- IL1-β levels improved after the 8-week MT program, with Hormone Therapy and Cancer Stage showing important interactions.
- Overall, TNF-α levels significantly decreased at the end of the MT program in comparison to baseline and in comparison to all other timepoints. In addition, TNF-α levels significantly varied between Age, Treatment Classification, and Cancer Stage groups.
- Improvement trends in the IFN-γ, IL-6 and CRP levels were found throughout the MT program, however, these failed to reach statistical significance.

4.5 Changes in Physiological Parameters

This subsection will address the findings form research question three: what are the immediate changes in BP, HR and SpO_2 in BCS submitted to an 8-week Swedish massage program? Below, a detailed description of the results is presented for each outcome.

4.5.1 Blood Pressure Changes Following MT Session

Tables 4.44 and 4.45 (next page) show the results of SBP and DBP at each week of the study. Contrary to our hypothesis, SBP and DBP increased right after the MT sessions at all weeks. Tables 4.44 and 4.45 also show that SBP increased right after the MT sessions at all weeks. The increase in SBP, however, was only statistically significant at week 1 (p=0.003), week 2 (p=0.003), week 4 (p=0.006) and week 7 (p=0.022). Similarly, DBP increased right after the MT sessions at most all weeks. Pre and post differences on DBP were statistically significant at week 3 (p=0.007). There was a decrease in the SBP from baseline to endpoint, whereas DBP increased from baseline to endpoint. However, these differences failed to reach significance for both variables SBP (p=0.112), and DBP (p=0.247).

Table 4.44.

Median SBP pre and post MT sessions (n=24).

Variable	Median (IQR)	Median (IQR)	Difference	*p* value
Systolic Blood Pressure (mmHg)	**Baseline (n=23)**	**Endpoint (n=23)**		
	133.5 (121.2-142.7)	129.0 (114.2-138.7)	4.5	.112
Systolic Blood Pressure (mmHg)	**Pre (n=23)**	**Post (n=23)**		
Week 1	130.0 (116.2-146.0)	143.5 (120.5-152.25)	-13.5	.003*
Week 2	132.5 (118.0-144.0)	138.0 (128.0-150.5)	-5.5	.003*
Week 3	128.5 (117.0-143.7)	134.0 (124.2-145.5)	-5.5	.063
Week 4	128.0 (116.0-125.2)	137.5 (125.2-147.0)	-9.5	.006*
Week 5	132.0 (118.5-141.1)	138.0 (127.0-148.5)	-6	.113
Week 6	134.5 (122.0-143.5)	135.5 (126.0-148.5)	-1	.249
Week 7	130.0 (124.2-136.5)	136.5 (122.0-145.2)	-6.5	.022*
Week 8	130.5 (114.2-139.0)	133.5 (133.0-140.5)	-3	.133

*p-values reflect Wilcoxon test <0.05.

Table 4.45.

Median DBP pre and post MT sessions (n=24).

Variable	Median (IQR)	Median (IQR)	Difference	*p* value
Diastolic Blood Pressure (mmHg)	**Baseline (n=23)**	**Endpoint (n=23)**		
	80.0 (73.5-86.5)	85.0 (75.0-89.0)	-5	.247
Diastolic Blood Pressure (mmHg)	**Pre (n=23)**	**Post (n=23)**		
Week 1	77.5 (72.0-90.75)	80.5 (74.2-91.5)	-3	.108
Week 2	83.0 (71.2-76.2)	83.5 (76.2-90.0)	-.5	.116
Week 3	79.0 (70.2-83.7)	83.5 (74.2-89.7)	-4.5	.007*
Week 4	77.0 (74.0-88.5)	83.5 (72.2-89.0)	-6.5	.209
Week 5	81.0 (70.2-91.7)	80.0 (72.2-86.0)	1	.951
Week 6	82.5 (74.5-87.5)	81.5 (75.2-91.2)	1	.831
Week 7	79.5 (70.2-92.7)	80.0 (75.2-90.0)	-.5	.474
Week 8	76.5 (67.7-89.0)	81.5 (78.2-89.5)	-5	.777

*p-values reflect Wilcoxon test <0.05

4.5.2 Oximetry Changes Following MT Session

Oximetry values increased right after MT sessions at each week of the program, validating our hypothesis. This increase was only statistically significant at week 2 (p=.008), week 4 (p=.040), week 7 (p=.014), and week 8 (p=.033).

4.5.3 Heart Rate Changes Following MT Session

HR values decreased right after MT sessions at each week of the program, validating our hypothesis. This decrease was statistically significant between baseline and endpoint (p=.001). Immediate pre and post changes were also statistically significant at week 2 (p=.000), week 3 (p=.000), week 5 (p=.000), week 6 (p=.000), week 7 (p=.001), and week 8 (p=.000). No statistical significance was found at week 1 and week 4.

4.5.4 Summary of Findings from Research Question Three

There were immediate changes in BP, HR and SpO_2 in BCS submitted to an 8-week Swedish massage program. Overall, HR and oximetry values improved right after MT sessions, validating our hypothesis. On the other hand, contrary to our hypothesis, SBP and DBP increased right after the MT sessions at all weeks.

4.6 Correlations Between Inflammatory Markers and PRO

This subsection will address the findings form research question four: are there any correlations between the levels of inflammatory markers and QoL, stress, fatigue and sleep efficiency? Below, a detailed description of the results is presented for each outcome.

4.6.1 Inflammatory Markers, Sleep and Patient-Reported Outcomes

Our results demonstrate associations between inflammatory markers, PROs and sleep parameters. These confirm our hypothesis that these outcomes are symbiotically correlated and can potentially influence one another.

There were statistically significant relationships between sleep parameters and inflammatory markers. Overall, the higher the levels of inflammatory markers, the poorer the sleep quality. Table 4.46 (next page) summarizes the statistically significant correlations between inflammatory markers and sleep parameters. On the other hand, QoL, stress and fatigue did not show any statistically significant association with inflammatory markers. However, there was a negative correlation between IL-6, TNF-α and IFN-γ and the QoL subscale "additional concerns" at different time-points (r=-.474, *p*=.022; r=-.463, *p*=.026; r=-.421, *p*=.046, respectively). The "QoL additional concerns" is a subscale of FACT-B provides a disease-specific QoL assessment for breast cancer (e.g., cancer-specific questions). It evaluates concerns such as shortness of breath, swollen arms, hair loss, weight change and so on. Higher scores mean less additional concerns. Hence, the negative correlations found between IL-6, TNF-α and IFN-γ and this construct mean that the higher the additional concerns score (denotating less concerns), the lower the levels of inflammatory markers.

Additionally, there was a statistically significant relationship between CRP and the QoL subscale emotional well-being at baseline (r=-.565, *p*=.005). The QoL emotional well-being is a subscale of FACT-B that covers aspects such as feeling of sadness, fear of death, hope and so on. Higher scores mean a better sense of wellbeing. Hence, the negative correlation found between CRP and this construct means that the higher the well-being score, the lower the levels of CRP.

No statistically significant correlations between inflammatory markers and patient-reported outcomes were found at endpoint. However, noteworthy that TNF-α and IFN-γ negatively correlated to sleep duration and almost attained statistical significance at endpoint (r=-0.393, *p*=.063; r=-.380, *p*=.073, respectively).

Table 4.46.

Statistically significant correlations between inflammatory markers and sleep parameters using Spearman's rho (n=24).

Variable		Time Point	Correlation coefficient (ϱ)	*p* value
Cortisol	Wake after sleep onset	A2	.427	.042
	Sleep onset latency	A2	-.428	.020
CRP	Sleep duration	B	-.499	.015
	Emotional wellbeing	B	-.565	.005
	Sleep onset latency	A1	.504	.014
IL-6	Additional concerns	A2	-.474	.022
IL-1β	Sleep duration	A1	-.544	.007
TNF-α	Additional concerns	A2	-.463	.026
IFN-γ	Additional concerns	A2	-.421	.046

4.6.2 Sleep and Patient-Reported Outcomes

Our results demonstrate associations between PROs and sleep parameters. These confirm our hypothesis that QoL, fatigue and stress are correlated and can potentially play a role in the development and severity of each other.

Hence, important statistically significant relationships between sleep parameters and PROs were found. Generally, the better the QoL, the better the fatigue and stress. Table 4.47 (below) summarizes the statistically significant correlations between these outcomes.

Table 4.47.

Statistically significant correlations between patient-reported outcomes using Spearman's rho (n=24).

Variable		Time Point	Correlation coefficient (ϱ)	*p* value
QoL	Fatigue	B	.765	.000
	Stress	B	-.735	.000
	Fatigue	A1	.770	.000
	Stress	A1	.-732	.000
	Fatigue	A2	.748	.000
	Stress	A2	-.813	.000
	Fatigue	E	.766	.000
	Stress	E	-.836	.000
Fatigue	Stress	B	-.676	.000
	Stress	A1	-.654	.001
	Stress	A2	-.603	.002
	Stress	E	-.716	.000
Sleep Efficiency	Wake after sleep onset	B	-.969	.000
	Wake after sleep onset	A1	-.807	.000
	Wake after sleep onset	A2	-.949	.000
	Wake after sleep onset	E	-.734	.000
Sleep Onset Latency	Wake after sleep onset	B	.452	.031

Table 4.47 shows that there was a strong statistically significant relationship between QoL and stress and fatigue at all time points. A negative correlation between QoL and stress means that the higher the levels of stress, the lower the QoL ($p<.000$). In addition, QoL showed positively strong correlations with fatigue at all time-points. That means that the higher the fatigue score (denotating less fatigue), the better the QoL ($p<.000$).

Of particular relevance are the significant associations between sleep parameters found at all time points. Strong statistically significant relationships between the WASO and SD show that the lower the WASO, the higher the sleep duration (r=-0.969, p=0.000 at baseline; r=-0.807, p=0.000 at assessment 1; r=-0.949, p=0.000 at assessment 2 and r=-0.734, p=0.000 at

endpoint). Similarly, WASO was associated to SOL meaning that the longer patients took to fall asleep, more awakening episodes they had after sleep onset (r=0.452, *p*=0.031 at baseline).

4.6.3 Inflammatory Markers

Our results demonstrate associations between several cytokines with each other. These confirm our hypothesis that cytokines follow an orchestrated mechanism of expression, suppression and production, and are correlated to each other, influencing one another.

There were important statistically significant relationships between all pro-inflammatory cytokines as well as between the cytokines and CRP levels. No correlations were found between cortisol and cytokines or CRP. Overall, the higher the cytokine levels, the higher the CRP levels. Table 4.48 summarizes the statistically significant correlations between these outcomes.

Table 4.48.

Statistically significant correlations between inflammatory markers using Spearman's rho (n=24).

Variable		Time Point	Correlation coefficient (ϱ)	*p* value
CRP	IL-6	B	.537	.008
	IL-6	A2	.765	.000
	IL-1β	A2	.854	.000
	TNF-α	A2	.728	.000
	IFN-γ	A2	.441	.035
	Il-6	E	.836	.000
	IL-1β	E	.674	.001
	TNF-α	E	.736	.000
	IFN-γ	E	.496	.016
IL-6	TNF-α	B	.620	.002
	TNF-α	A1	.555	.006
	IL-1β	A2	.588	.003
	TNF-α	A2	.802	.000
	IFN-γ	A2	.632	.001
	IL-1β	E	.603	.002
	TNF-α	E	.818	.002
	IFN-γ	E	.584	.003

Table 48. (*continued*)

IL-1β	TNF-α	A2	.59	.003
	TNF-α	E	.530	.009
	IFN-γ	E	.520	.011
TNF-α	IFN-γ	B	.665	.001
	IFN-γ	A1	.560	.005
	IFN-γ	A2	.632	.001
	IFN-γ	E	.671	.000

Of particular relevance are the strong significant associations between IL-6 and TNF-α (r=0.818, p=0.002), between CRP and IL-6 (r=0.836, p<0.0001) and between CRP and IL-1β (r=0.854, p=0.000).

4.6.4 Summary of Findings from Research Question Four

Our results demonstrate associations between several inflammatory markers, PROs and sleep parameters. Overall, the higher the levels of inflammatory markers, the poorer the sleep quality. Associations between QoL ("additional concerns" subscale) and cytokines were also found. Findings also showed associations between PROs and sleep parameters. In general, the better the QoL, the better fatigue and the stress. Our results also demonstrate associations between several cytokines with each other. For instance, there were important statistically significant relationships between all pro-inflammatory cytokines as well as between the cytokines and CRP levels. No correlations were found between cortisol and cytokines or CRP.

4.7 Effect Sizes

The effect sizes of the MT intervention were also calculated as a measure of practical significance. This measure can be understood as the difference that is clinically meaningful (Tran, 1997). It is determined by calculating the mean difference between two groups (i.e. baseline and endpoint), and then dividing the result by the pooled standard deviation (Hinton, 2014). Interpretation of Cohen's d suggests that a $d\approx0.2$ is considered a 'small' effect size, $d\approx0.5$

represents a 'moderate' effect size and $d \approx 0.8$ is considered a 'large' effect size (Cohen, 2013). Effect sizes results can be found in Table 4.49 (below).

Table 4.49.

Effect sizes from the 8-week MT intervention (n=24).

Outcome	Cohen's *d* Effect Size[a]	Magnitude of Effect Size
QoL	0.70	Moderate to large
Fatigue	0.80	Large
Stress	0.50	Moderate
SD	0.45	Small to moderate
SE	1.12	Very large
SOL	0.05	Very small
WASO	0.46	Small to moderate
Cortisol	0.59	Moderate
CRP	0.08	Very small
IL-6	0.28	Small
IL-1β	0.02	Very small
TNF-α	0.82	Large
IFN-γ	0.75	Moderate to large

[a] Effect size calculated using Cohen's *d* [d= mean1 – mean2 / $\sqrt{((SD_1^2 + SD_2^2)/2}$]

4.8 Summary of Results

Overall, QoL, fatigue and stress improved at the end of the MT program. QoL improvements were significantly associated with time after treatment completion and cancer stage. Changes in fatigue scores were significantly associated with sleep aids in use and comorbidities. Stress levels significantly improved at endpoint in comparison to baseline, regardless of any covariates tested. Wake after sleep onset was the only sleep variable that significantly improved at endpoint. Changes in sleep onset latency (SOL) were significantly associated with cancer stage. Sleep duration did not show any significant improvement. Sleep efficiency improved after the MT program, however, it did not reach statistical significance. Overall, all the biomarkers decreased at endpoint in comparison to baseline; however, only cortisol, IL-1β and TNF-α reached significant changes, with IL-1β showing important associations with cancer stage and hormone therapy. Only improvement trends were detected in CRP, IL-6 and IFN-γ levels. Heart rate and oxygen levels improved right after sessions, and blood pressure slightly increased.

CHAPTER 5

DISCUSSION AND CONLCUSION

5.1 Discussion of the results

In this final chapter, the study results are discussed in light of what is known from the literature and aligned with the study's philosophical underpinnings and theoretical framework. The results are discussed under the four major research questions. In addition, this chapter also presents the limitations and strengths of the research along with the clinical implications and recommendations for future research. A final section presents the study's conclusion.

The Middle Range Theory of Unpleasant Symptoms (Lenz & Pugh, 2018; Lenz et al., 1997) and the PNI (Green et al., 2013; Kang, 2003; McCain et al., 2005) frameworks provided the lens through which the results of this study were discussed. They Middle Range Theory of Unpleasant Symptoms framework assisted in establishing a sense of structure to guide the discussion around the changes in QoL, fatigue, stress and sleep. Similarly, the PNI framework provided the lens to comprehensively investigate the multi-directional synchronicity among patient-oriented reports, sleep measures and neuroendocrine and immune systems markers. Together, these frameworks allowed us to better comprehend how MT can assist in the management of CRS in BCS since it unifies the core elements that are potentially modeling the genesis of CRS.

5.1.1 Changes in QoL, Fatigue, Stress and Sleep

5.1.1.1 QoL

In the present study, QoL improved after the 8-week MT program. Participants experienced a statistically significant improvement in QoL after only 3 weeks in the MT program (i.e. assessment 1) and at the end of the program (i.e. endpoint). Our findings on QoL improvement are in accordance with other studies that found an increase in QoL after MT in

breast cancer patients in treatment (Listing et al., 2010; Ovayolu, Seviğ, Ovayolu, & Sevinç, 2014; Sturgeon et al., 2009), and other populations such as gynecologic cancer survivors (Donoyama, Satoh, Hamano, Ohkoshi, & Onuki, 2018), patients with brain tumor (Keir, 2011) and advanced cancer (Kutner et al., 2008).

Although only some of the independent variables explored in our study showed a statistically significant influence on QoL, it is well known that several aspects might affect QoL in breast cancer survivorship (e.g. demographic, medical and psychosocial variables). Interestingly, psychosocial aspects (i.e. family support, financial concerns) seems to play a greater influence on QoL in comparison to medical and demographic variables (Carver, Smith, Petronis, & Antoni, 2006).

QoL and cancer stage

As a result of a significant interaction between Cancer Stage and Timepoints found in this study, important differences in QoL scores for each group of cancer stage between timepoints were revealed. These differences can be explained by the fact that different cancer stages will have a different impact on BCS' QoL after treatment (Caan et al., 2005; Carver et al., 2006; Lidgren, Wilking, Jönsson, & Rehnberg, 2007).

In this study, we found that Stage III patients showed the lowest levels of QoL throughout the study (except at assessment 1), with no significant differences at timepoints. This is in accordance to previous findings that show that patients who were diagnosed with higher cancer stages showed poorer QoL right after treatment (Caan et al., 2005; Carver et al., 2006; Lidgren et al., 2007).

QoL and Months After Treatment

A significant interaction between the variables Months After Treatment and Timepoints was found in this study. This interaction revealed that those who finished treatment ≥ 3 months after treatment showed lower QoL (except at assessment 2), with no significant differences at timepoints. This is not in accordance with previous studies, as it is expected that BCS and other cancer patients will recover their QoL as more time elapses after the end of treatment (Gordon &

Siminoff, 2010b; Imran, Al-Wassia, Alkhayyat, Baig, & Al-Saati, 2019; van Leeuwen et al., 2018).

Important differences in QoL scores for each group of Months after Treatment between Timepoints were also found, which can be explained by the fact that patients at different survivorship stages, will report different QoL after treatment (Gordon & Siminoff, 2010b; Imran et al., 2019; van Leeuwen et al., 2018).

QoL and Hormonal Therapy

The use of hormonal therapy can also influence QoL as endocrine treatments can elicit varying side effects (e.g. increased tumor or bone pain, hot flashes, nausea) (Fallowfield, Leaity, Howell, Benson, & Cella, 1999). Interestingly, our study showed that women taking hormonal therapy reported better QoL. This result is in accordance with a previous study, which indicates that despite the side-effects associated with adjuvant treatments, women taking endocrine treatments reported significantly higher QoL after breast cancer treatment (Fallowfield et al., 1999). On the other side, a second study contradicts this finding by reporting an association between endocrine treatments and decreased overall QoL (Browall et al., 2008). Finally, some studies reported that side effects of tamoxifen and aromatase inhibitors did not lead to significant differences in perceived QoL in breast cancer patients (Buijs, de Vries, Mourits, & Willemse, 2008; Fan et al., 2005).

QoL and sleep aids

Another interesting finding in our study was that patients *on* sleep aids (17.4%) reported lower QoL. Sleep medications are expected to ultimately lead to a better QoL by improving sleep–wake disturbances, however, a previous study has shown that sleep aids are valuable to improve mental and cognitive QoL, but it might reduce the physical and functional QoL, due to adverse effects (Sasai et al., 2010). In addition, a study with 124 breast cancer patients found that those patients prescribed sleep medications during treatment were significantly more likely to be taking psychiatric medications (Costantini, Ale-Ali, & Helsten, 2011).

QoL and MT

Given the limited number of interventional studies testing MT in BCS, our findings provide new evidence on how MT can improve BCS' QoL in the transition period. It contributes to the understanding of how QoL can be managed after cancer treatment by the incorporation of a popular IM therapy. QoL is an indispensable outcome measure in clinical trials and patient-oriented research. The full therapeutic potential of MT and other IM therapies are in part dependent of its effects on self-reported QoL. Therefore, it is an essential part of MT research to assess QoL and additional outcomes encompassing the whole person health—physical, mental, social, and spiritual.

5.1.1.2 Fatigue

The current study revealed that fatigue improved after the 8-week MT program, with significant interactions between the variable sleep aids and timepoints, as well as the variable comorbidities and timepoints. Similar studies also found beneficial effects of full-body MT programs on fatigue in different types of cancer patients and survivors (Donoyama et al., 2018; Fernández-Lao et al., 2012; Kinkead et al., 2018; Listing et al., 2010, 2009). A study with 63 breast cancer patients reported that a one to two sessions of 20 minutes of neck and shoulder massage and relaxing background music decreased fatigue (Pruthi et al., 2009). Additionally, a significantly great reduction of fatigue has been reported in a systematic review on MT in cancer palliation (Ernst, 2009) and a lessening in fatigue according to a metanalysis on MT interventions and treatment-related side effects of breast cancer (Pan, Yang, Wang, Zhang, & Liang, 2014).

Fatigue and sleep aids

In our study, a statistically significant interaction between sleep aids and timepoints revealed significant differences in fatigue scores for each group of Sleep Aids between Timepoints. More interesting is that, overall, patients *on* sleep aids showed non-significantly higher fatigue scores (less fatigue) in comparison to patients *off* sleep aids. Similarly, other

studies have reported how sleep medications affect fatigue in cancer patients (Clanton et al., 2011; Liu et al., 2012b).

Another interesting finding of our study was that patients *on* medications for sleep started the study more fatigued, and throughout the program showed superior improvement of this symptom in comparison to patients *off* meds. Patients *on* meds also seemed to sustain the effects of massage, since this group did not show a worsening of fatigue at assessment 2, in comparison to the group of patients *off* meds. These results indicate that, in our sample, a combined approach (massage *plus* medication) showed greater impact on fatigue. However, our outcome validity is limited due to a small study population.

Fatigue and Comorbidities

In our study, a statistically significant interaction between sleep aids and timepoints revealed significant differences in fatigue scores for each group of Comorbidities between Timepoints. Overall, those who presented comorbidities showed slightly higher fatigue scores (less fatigue) in comparison to those who did not present any comorbidities. The relationship between fatigue and other diseases has been studied in previous studies, which have pointed out to the role of comorbidities as a predictor or an effect modifier of fatigue levels in several types of cancer (Hoffman, Given, Von Eye, Gift, & Given, 2007; Kozachik & Bandeen-Roche, 2008; Rao & Cohen, 2004).

Fatigue and hormonal therapy

There is little published work with respect to hormonal therapy and severity of fatigue in cancer patients. Our findings pointed that patients who were under hormonal therapy (i.e. Tamoxifen or Aromatase Inhibitors) showed less fatigue (non-significant difference). It is possible that adjuvant hormonal treatment for breast cancer, which lowers serum estradiol levels, may have a significant influence on fatigue levels (Fan et al., 2005). Contrary to our results, previous studies found that different types of cancer patients, including breast cancer, who were taking adjuvant hormonal therapy showed higher levels of fatigue and cognitive function

problems (Castellon et al., 2004; Fan et al., 2005; P. Stone, Hardy, Huddart, A'Hern, & Richards, 2000; Tannock, Mar Far, Houédé-Tchen, Qi-Long, & Vardy, 2005).

Fatigue and treatment type

Treatment type is a well-researched aspect and potential predictor of fatigue severity during and after treatment. Overall, the severity of the fatigue is worse in patients who underwent chemotherapy in comparison to radiotherapy (Donovan et al., 2004; Karthikeyan, Jumnani, Prabhu, Manoor, & Supe, 2012). Additionally, cancer patients who went through combined therapy (i.e. chemotherapy and radiotherapy) have reported higher levels of fatigue compared to those who went through single therapy (Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Mendoza et al., 1999; Woo, Dibble, Piper, Keating, & Weiss, 1998). In this study, we observed differences in fatigue severity in our subgroup analyses, however, our findings are not generalizable as the study sample is small.

Fatigue and MT

In summary, our study shed some light on how BCS can benefit from MT in the transition period after treatment. Fatigue is the most common symptom reported by cancer patients in treatment - of any kind, and can linger well past treatment's completion, however, as of yet, no single cause or the mechanisms behind fatigue persistence in BCS had been discovered. Similarly, how MT actually affects BCS is also not well described, but it is believed that MT increases blood circulation and oxygen flow throughout the body, decreasing muscle tension. The mechanical pressure employed during MT results in important biomechanical mechanisms that could explain fatigue improvement after MT in BCS, such as increased recovery of joint motion, joint fluid collection and diminished joint stiffness. Pressure might also change muscle tissue temperature from rubbing, and it might have a role in how MT helps with fatigue (Field, 1998; Waters-Banker, Dupont-Versteegden, Kitzman, & Butterfield, 2014).

We argue that the Swedish gliding strokes and broad muscle compression techniques in our study protocol led to an increase in blood flow, neurological excitability, thereby speeding the tissues' recovery and the overall physical performance, and therefore decreasing fatigue in

our participants. Although allopathic treatments are available to treat fatigue in BCS (i.e. psychostimulants), IM therapies have the potential to ease persistent fatigue in BCS, therefore, further studies are merited in this arena.

5.1.1.3 Stress

In the present study, stress improved after the 8-week MT program. Participants experienced a statistically significant improvement in stress after the MT program (i.e. assessment 1) and at the end of the program (i.e. endpoint). MT has been nominated as an established therapy in reducing perceived immediate stress in healthy individuals (Moyer, Dryden, & Shipwright, 2009). Although our study did not assess any immediate effect on perceived stress, we showed a sustained and significant reduction of stress over the course of our MT program. Our findings correspond to studies that also found a reduction in stress levels over time in cancer patients undergoing MT programs (Billhult, Bergbom, et al., 2007; Hernandez-Reif et al., 2004; Listing et al., 2010; Pan et al., 2014) and aromatherapy massage programs (Wilkinson et al., 2007). However, a few previous studies in patients with cancer found contradictory results concerning reduction of stress by showing that perceived stress did not show significant changes after four sessions of MT twice-week (Wilkie et al., 2000) and after an 8-week course of massage, with or without the addition of a blend of essential oils (Corner, Cawley, & Hildebrand, 1995). The inconsistency of existing results may be caused by variations on the measuring instrument applied to assess stress, as well as sample heterogeneity.

Moyer and colleagues (2009) argue that MT reduces stress by being able to reduce the perceived effect of negative stressors (Moyer et al., 2009). The stress buffering effect of MT is also explained by considering MT as a direct positive *stimuli* to recipient's affective state (Moyer, 2008) and as a form of emotion-focused coping practice (Folkman & et al, 1986).

Stress and MT

In light of the increased number of BCS using MT to decrease stress, our study brings important contributions to this arena by providing evidence of an improvement in stress levels after the MT program, which was sustained until the end of the program. Although there is no

evidence indicating a causal relationship between stress and cancer recurrence in BCS, there has been a link between fear of recurrence or progression as a mechanism underlying stress states in cancer survivors. Therefore, managing stress and other somatic symptoms can improve QoL and emotional well-being in BC survivorship ((Hall, Lennes, Pirl, Friedman, & Park, 2017; Todd, Moskowitz, Ottati, & Feuerstein, 2014). Gauging BCS's risk of severe levels of stress or cancer-related Post-Traumatic Stress (PTS) are crucial in clinical care. Recommendations are that cancer patients must be screened for stress early in the course of treatment and at critical points along the course of care and survivorship period.

It is possible to speculate that stress improvement could be related to a relaxation response following MT sessions. An overarching potential reason for this relaxation reaction after MT is related to decreased muscle tension, along with diminished activity of the sympathetic nervous system (SNS), increased parasympathetic activity and vagal outflow (Field, 1998; Waters-Banker et al., 2014). Noteworthy that some of these effects are dependent on the pressure massage (i.e. moderate pressure or a light pressure massage) (Diego & Field, 2009; Porges, 2001), as it will be discussed further in this chapter.

5.1.1.4 Sleep

Slight improvements in sleep quality were found in our study. All measures, except for SD, showed a trend to improvement at endpoint in comparison to baseline, however baseline-to-endpoint improvements failed to reach statistical significance. On the other hand, SD, WASO and SOL showed statistically significant improvements in the middle of the MT program. Previous studies indicated the effectiveness of MT in the management of sleep disorders in cancer patients. In this regard, the study by Kashani et al. (2004) showed an improvement in the mean scores of quality of sleep before and after a 4-week (20 min.) MT program (effleurage and petrissage) in breast cancer patients (Kashani & Kashani, 2014). Neck and shoulder massage on a chair for 20 minutes has been also reported to increase the sense of well-being, and improve sleep quality in breast cancer patients (Pruthi et al., 2009).

In non-breast cancer patients, a study that tested a Swedish massage protocol for 1 week (15-30 min.) also found it effective in reducing pain, stress, and sleep disorders in hospitalized cancer patients (Smith et al., 2002). In another investigation with patients with bone metastasis,

MT (45-minute full-body massage) was shown to have beneficial effects on sleep quality (Jane et al., 2011). In non-cancer population, 30 min. of superficial and deep MT showed decrease in pain and sleep disorder on 14 patients with back pain and sleep disorder (Field, Hernandez-Reif, Diego, & Fraser, 2007). Back massage once a week for 4 weeks (30 min.), significantly improved sleep in hospice patients (Soden, Vincent, Craske, Lucas, & Asley, 2004).

In all of the mentioned studies, to assess the patients' quality of sleep, no actigraphy was recorded, but the following scales were used instead: Pittsburgh Sleep Quality Index (Kashani et al., 2014), Verran and Snyder-Halpern (VSH) sleep scale (Solden et al., 2004; Smith et al. 2002; Field et al., 2007), Richards-Campbell Sleep Questionnaire (Jane et al. 2011) and Pruthi and colleagues (2009) did not mention if any instrument was used to assess sleep, indicating that sleep was assessed by just directly asking participants about their sleep quality.

Sleep Duration

In our study, the SD mean was 326.6 minutes at baseline, and 277.5 minutes at endpoint. Healthy adults usually sleep from 420–540 minutes per night (American Academy of Sleep Medicine, 2005). This suggests that sleep was already disturbed when participants started the study. Similar to our study, SD ranged from 386–480 minutes in BCS who went through chemotherapy and an average of 420 minutes in BCS who went through radiotherapy (Berger et al., 2003). Berger et al. measured actigraphy for only 48 hours. Another study that assessed sleep for 3 consecutive nights in a sample of metastatic breast cancer patients reported a SD of 478.5 minutes (Palesh et al., 2008). With actigraphy measured during seven nights, SD in BCS was less than 360 minutes (Otte, Payne, & Carpenter, 2011) and 314.21 minutes (Alexander et al., 2009). Similar results were found in breast cancer patients before starting chemotherapy (Sonia Ancoli-Israel et al., 2006; Berger et al., 2007), confirming the hypothesis of Ancoli-Israel et al. (2006) that breast cancer patients are already sleep deprived prior to chemotherapy (Sonia Ancoli-Israel et al., 2006).

Sleep Efficiency

Our findings also showed that the SE mean was 92% at baseline, and 92.8% at endpoint. SE is calculated by dividing the number of minutes of sleep by the number of minutes in bed, multiplied by 100. A cut-off of 85% for SE is suggestive of a good night's sleep, therefore, a SE lower than 85% is an indicator of poor sleep (American Academy of Sleep Medicine, 2005). According to the available literature, we found that our patients presented comparable SE to other groups of cancer survivors as other studies showed that SE was not drastically affected (Berger et al., 2007; Dean et al., 2013; Dhruva et al., 2012; Enderlin et al., 2011; Palesh et al., 2014; Reinsel, Starr, O'Sullivan, Passik, & Kavey, 2015). In BCS who went through chemotherapy, SE was about 82%–92% (Berger et al., 2003), and greater than 85% in those who went through radiotherapy (Dhruva et al., 2012). Interestingly, two studies that measured actigraphy during seven nights found a low SE of 78% (Otte et al., 2011) and 92.92% (Alexander et al., 2009) in BCS.

Sleep Onset Latency

In regard to SOL, the trajectory of this measure shows minor improvement at assessment 2 (= 4.6 minutes) and endpoint (=3.9 minutes) in comparison to baseline (=3.8). A desirable SOL is usually less than 20 minutes (American Academy of Sleep Medicine, 2005).

As a result of a significant interaction between Cancer Stage and Time found in this study, important differences in SOL for each group of Cancer Stage between Timepoints were revealed. These differences can be explained by the fact that factors like cancer stage, cancer type and treatment side-effects are likely to precipitate sleep problems (Berger et al., 2007; Miaskowski et al., 2004).

When comparing results from our patients to available polysomnography (PSG) and actigraphy values in the literature, we found that our patients reported quite lower SOL compared to other groups of cancer patients (Berger et al., 2007; Dean et al., 2013; Enderlin et al., 2011; Palesh et al., 2014; Reinsel et al., 2015) and to samples of healthy women in a similar age range (Mitterling et al., 2015; Ram, Seirawan, Kumar, & Clark, 2010; Vitiello et al., 1996; Webb, 1982). For instance, according to the literature, cancer patients reported a SOL of 11 to 72 minutes, on average (Berger et al., 2007; Dean et al., 2013; Enderlin et al., 2011; Palesh et al., 2008). In healthy adults SOL ranges from 19 to 24 minutes (Enderlin et al., 2011; Mitterling et

al., 2015; Ram et al., 2010; Vitiello et al., 1996; Webb, 1982). In BCS, previous studies reported a SOL mean of 13.1 minutes (Reinsel et al., 2015), 17.4 minutes (Epstein & Dirksen, 2007), average 15 minutes after radiotherapy completion (Dhruva et al., 2012), and 34.8 minutes in patients who went through chemotherapy (Enderlin et al., 2011). Additionally, studies reported mean SOL of 67 minutes (Otte et al., 2011) and 26.66 minutes (Alexander et al., 2009) based on seven nights of actigraphy. Our patients showed a significant low SOL at baseline and during the course of the study, possibly meaning severe sleep deprivation (Blytt et al., 2017; Carskadon, 1986). It must be emphasized that, SOL can be influenced by other aspects such as mood, depression and BMI, which were not evaluated in this study, making it difficult to establish any definite conclusion on why our patients showed lower SOL (Berger, Hertzog, Geary, Fischer, & Farr, 2012; Dhruva et al., 2012; Palesh et al., 2008; Talbot, Hairston, Eidelman, Gruber, & Harvey, 2009).

Wake After Sleep Onset

According to the results of the present study, WASO significantly decreased from baseline (=36.7) to assessment 1 (=20.7) and from assessment 2 (=39.8) to endpoint (=26.9). According to the American Academy of Sleep Medicine, in adults sleeping an average of 420 minutes per night, WASO is usually less than 42 minutes (American Academy of Sleep Medicine, 2005). In BCS submitted to chemotherapy WASO was 50 minutes (Berger et al., 2003), and 71.44 minutes as demonstrated by another study (Palesh et al., 2008).

It should be noted, however, that studies in BCS have found that WASO is either influenced or predicted by other aspects such as depression, fatigue, BMI (Berger et al., 2012; Dhruva et al., 2012; Palesh et al., 2008). For instance, a study found that BMI predicted variability in WASO in a sample of 73 BCS (Dhruva et al., 2012). At one-year follow-up for chemotherapy, a BMI of 30 significant correlated with circadian parameters, anxiety, fatigue, and physical functioning in BCS (Berger et al., 2012). In addition, depression and fatigue have been also found as predictors of longer WASO in BCS (Palesh et al., 2008). Therefore, even though our patients presented lower WASO in comparison to other BCS populations, which is reflected in the SE values found in our sample, other aspects must have been taken in consideration when analysing these results.

Sleep and MT

Sleep problems are among the most commonly reported problems by BCS (Campos et al., 2011; Couzi et al., 1995; Davidson et al., 2002; Lindley et al., 1998; Miaskowski et al., 2010). Our study provided preliminary evidence that MT has the potential ability to produce beneficial effects in sleep in BCS.

MT is commonly regarded as a therapeutic tool to manage stress, but far less studied as a plausible sleep improving modality. Its capacity in managing sleep problems has been previously showed by improving insomnia in postmenopausal women (Hachul, Oliveira, Bittencourt, Andersen, & Tufik, 2014), improving sleep quality in cancer patients (Kashani & Kashani, 2014; Pruthi et al., 2009), with less focus on BCS population. However, how MT actually works in improving sleep is not well understood. As previously mentioned in this chapter, MT is known to stimulates the venous, arterial and lymphatic vessels' flow, the connective tissue and muscle physiology. It is speculated that the muscle-cutaneous *stimuli* act on receptors for touch, pressure, heat, vibration, and pain, which can trigger neurochemical reactions capable of improving sleep, inducing relaxation, tranquility along with physiological changes (i.e. HR, BP, oxygen levels, peristalsis) (Field et al., 2005).

These dermal and pressure *stimuli* are transduced via the peripheral and autonomic nervous systems (ANS) to the central nervous system and are hypothesized as inducers of serotonin production - a chemical precursor to melatonin. Therefore, as a positive sleep-inducing hormone, melatonin production following MT can influence the sleep quality and other aspects of an BCS's circadian rhythm. Noteworthy that this possible link calls for further research exploring the direct effects that MT has on serotonin and melatonin (Agarwal et al., 2000; Field et al., 2005; Jane et al., 2011).

5.1.2 Changes in Inflammatory Markers

Table 5.1 shows the principal actions of the selected biomarkers, although each marker contains multiple other functions (Andoniou, Andrews, & Degli-Esposti, 2006; Corwin, 2000; Dunlop & Campbell, 2000; Kang et al., 2011).

Table 5.1.

Principal action of selected biomarkers.

Biomarker	**Principal Actions**
Cortisol	Steroid-based hormone, in the glucocorticoid class of hormones. It is known as a stress hormone involved in the response to physical and/or emotional stress, but it also controls blood sugar levels, regulates metabolism, manufacturing glucose from fatty acids, helps reduce inflammation, and assists with memory.
CRP	Clinically established marker for inflammation. It is an acute-phase protein that increases following IL-6 secretion by macrophages and T cells. IL-6 is reported to be the main inducer of CRP gene expression, with IL-1 enhancing the effect.
IL-6	Secreted by a wide range of cells. Has roles in B-cell differentiation and in promoting inflammation. Inducer of acute phase proteins and "sickness behaviour". Its biological activities partly overlap those of IL-1 and TNF.
IL-1β	Synthesized as a larger precursor, which is then converted to the active forms IL-1α or IL-1β. Modulates hematopoietic cell growth, regulates acute phase reaction, and induces tissue repair. Activates lymphocytes, induces hematopoietic cell growth, and infiltration of leukocytes at sites of infection. Related to fever and anorexia.
TNF-α	Produced by macrophages. It is an endogenous pyrogen; also induces tumor cell apoptosis, cachexia and inflammation. Causes widespread tissue damage to the gastrointestinal tract, kidneys, and lungs during septicaemia.
IFN-γ	Wide range of effects. Inhibits viral and bacterial replication and enhances natural killer cell activity. It is an important activator of macrophages and orchestrates activation of the innate immune system.

5.1.2.1 Cortisol

In our study, MT contributed to cortisol responses in a positive direction. Levels of this biomarkers decreased at the end of the intervention and showed statistically significant improvements from baseline to assessment 1, and from assessment 1 to assessment 2.

The positive MT effect in cortisol levels has been shown by previous studies with breast cancer patients (Listing et al., 2010; Stringer, Swindell, & Dennis, 2008) and in different populations such as children with cancer (Post-White et al., 2008), pregnant woman (Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2004), adolescents (Field et al., 1998) victims of sexual abuse (Field 1997), HIV patients (Ironson et al., 1996), family caregivers of cancer patients (Pinar & Afsar, 2016), among other populations (Hart et al., 2001; Ouchi et al., 2006) – in saliva, urine and blood specimens. Different from the reduction in cortisol levels in our study, other studies did not find any decrease in salivary and blood cortisol levels in BCS (Fernández-Lao et al., 2012) and breast cancer patients (Billhult et al., 2009; Green et al., 2010; Hernandez-Reif et al., 2004). Nevertheless, a recent metanalysis did not find any significant effect of different forms of MT in cortisol levels in patients who suffered from different diseases (Moyer, Seefeldt, Mann, & Jackley, 2011). Contradictory findings were also found by two studies on MT effects in urinary cortisol levels in breast cancer patients (Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2004; Field et al., 2005), and other studies on MT and urinary cortisol levels in different population types (Bost & Wallis, 2006; Field et al., 2004; Ironson et al., 1996; Taylor et al., 2003).

To compare our raw cortisol values with other studies is particularly challenging due to important differences between studies' methodologies. The main drawback is that our study was not designed to assess immediate effects of MT, therefore, no pre and post measurements were taken, whereas the majority of the studies performed single measurements (immediate pre and post intervention), cortisol awakening response (CAR) or cortisol diurnal slope, which are different from the reactivity indicator used in our study (i.e. AUC). Moreover, AUC values tend to be much higher than the other indices (i.e. single measurements, CAR and diurnal slope), as it represents total daily cortisol production and requires a higher number of saliva samples across days.

Additional factors also create great heterogeneity among published studies regarding cortisol results. First, the method of saliva collection shows great variability across studies (i.e., passive drool or salivary swab), along with the specimen of choice (salivary, urinary, serum), and characteristics of the collection tubes. Steroid hormones such as cortisol can lead to different results when collected in different plastic tubes or containers. Low affinity plastic containers are considered the most appropriate ones (Mert et al., 2013). Secondly, different detection methods,

such as commercial luminescence immunoassay, radioimmunoassay (RIA), multi-analyte profiling bead-based assay and enzyme-linked immunosorbent assay (ELISA). Different detection techniques have great implications in the interpretation of the studies since different methods detect cortisol in different measuring units (ng/mg, ng/ml, μg × min^{-1}, nmol/l), as well as based on different detection limits. For instance, the study by Fernandez-Lao et al. (2012) in BCS and MT assessed salivary cortisol (using ELISA detection method) in μg × min^{-1} (Fernández-Lao et al., 2012). Two other studies in breast cancer patients reported serum cortisol mean in ng/mg (Hernandez-Reif et al., 2004) and in ng/ml (Green et al., 2010) – both using ELISA method. Other studies with BCS and patients presented means of log-transformed salivary cortisol values making it difficult to proceed with any comparison (Bower, Ganz, Dickerson, et al., 2005; Campo et al., 2015; Listing et al., 2010).

Diurnal cortisol concentrations found in this study were within the range of the laboratory assay and in accordance to the manufacture's standards. Our mean cortisol values were lower than the normal range in healthy subjects, which is not in line with previous studies that showed no difference in diurnal cortisol profiles between BCS and healthy controls (Couture-Lalande, Lebel, & Bielajew, 2014; Hsiao et al., 2012; Wan et al., 2019). Our values were also a bit lower than those found in long-term BCS (Couture-Lalande et al., 2014; Wan et al., 2019), and lower than in breast cancer patients in treatment (Webster, Chandrasekaran, Vijayaragavan, & Sethu, 2016). One factor that must be taken into consideration is how shortly after the completion the treatment the patient is being assessed for cortisol. Noteworthy that a major difference between these studies is that our participants were short-term BCS, while Wan at al. (2019) recruited BCS who completed treatment at least 6 months prior to the study start date (hormonal treatment excepted) and Couture-Lalande et al. (2014) recruited long-term BCS (more than 4 years since diagnosis).

In different types of population, salivary cortisol have yielded inconsistent results, however, it is well known that cortisol has a relatively stable circadian pattern secretion in healthy individuals (Foley & Kirschbaum, 2010; Stone et al., 2001). In addition, the pattern of cortisol production in BCS and patients is not fully understood (Sephton, 2000; Spiegel, Giese-Davis, Taylor, & Kraemer, 2006; Wan et al., 2016). The hormonal system HPA axis is thought to be involved in this scenario since it triggers the production of the stress hormone cortisol (Stephens & Wand, 2012). One possible explanation to the lower cortisol levels in our sample is

the hyporeactivity of HPA axis, which has been reported in BCS populations (Bower, Ganz, & Aziz, 2005; Couture-Lalande et al., 2014; Spiegel et al., 2006). One possible explanation is that, during cancer trajectory, a prolonged accumulation of stressors activates the stress system leading to a HPA axis dysregulation. This dysregulation and chronic stress are carried forward to the survivorship period, which has been suggested as one of the causes leading to HPA axis hyporeactivity in cancer survivors (Bower, Ganz, Dickerson, et al., 2005; Van Der Pompe, Antoni, & Heijnen, 1996). Thus, a sustained accumulation of stressors, and therefore, a chronic activation of the HPA axis may lead to its 'wear and tear' and may be potentially associated with a diminished physiological cortisol reactivity (Couture-Lalande et al., 2014).

Cortisol levels are strongly correlated with stress in healthy population and in a range of diseases (e.g. depression, pain, eating disorders, asthma, chronic fatigue, HIV and breast cancer) (Field et al., 2005). Salivary cortisol relation to serum cortisol have been determined by radioimmunoassay showing a strong non-linear correlations between the cortisol concentrations in serum and saliva, which is suggestive that salivary cortisol may be used in situations where blood sampling is difficult to perform (Aardal & Holm, 1995; Teruhisa et al., 1981).

Overall, lower levels of cortisol would provide a psychological index of less stress (Billhult et al., 2009). Benefits of MT on stress levels had been shown to be mediated by the activation of brain's areas involved in the relaxation process. A study by Ouchi (2006) showed a reduction of cortisol levels and increase in blood flow in the parietal and occipital regions of the brain after MT (Ouchi et al., 2006). Other studies have shown in different types of population, including paediatric population, a variety of possible mechanisms of stress reduction after MT, such as, increased incidence of delta waves in the brain (Field et al., 2004), stimulation of *nervus vagus* (Diego, Field, & Hernandez-Reif, 2005), increased levels of oxytocin, which is a modulator of stress in several areas of the limbic system (Uvnäs-Moberg & Petersson, 2005), and parasympathetic response mediated by the stimulation of type 3 and 4 mechanoreceptors (Purves et al., 2012).

5.1.2.2 CRP

There was not a statistically significant change in CRP during the study. Therefore, our findings do not suggest any improvement trends in CRP levels after the MT program. No studies in BCS and MT were found in the literature. The only similar study found on cancer population

was on the effects of prostatic massage on CRP levels in prostate cancer patients. This study showed that four and six weeks of MT showed a significant reduction in CRP and PSA levels (Fathollahi, Dabidiroshan, Sheikh, & Nuri, 2016).

In non-cancer population, MT has been found to reduce CRP levels in coronary artery bypass graft patients (Sheikhsaraf et al., 2016). On the other hand, in healthy individuals, muscle massage before strength training exercise showed no significant differences on CRP levels between control (n=12) and treatment (n=12) groups (Garrido, Oliveira, Mendes, Sousa, & Sousa, 2013).

Plasma and serum CRP are general and reliable indicators of systemic inflammation and are easily measured in daily clinical practice. Salivary CRP relation to serum and/or plasma CRP have been determined by radioimmunoassay showing a strong correlation under specific conditions (Ouellet-Morin, Danese, Williams, & Arseneault, 2011). For instance, salivary CRP may reflect low-grade inflammation and have the potential to serve as a screening marker for cardiovascular risk status (Out, Hall, Granger, Page, & Woods, 2012), as biomarker for metabolic syndrome (Dezayee & Al-Nimer, 2016) and rheumatic disease (Sikorska et al., 2018). Nevertheless, in healthy adults, concentrations of CRP in saliva did not correlate significantly with those in serum (Kopanczyk et al., 2010).

In young healthy adults, salivary CRP concentration ranged from 0.05 to 64.3 ng/mL (median=1.2 ng/mL) when measured through ELISA (Kopanczyk et al., 2010) and around 950 pg/mL according to another study in healthy young adults (22–26 years) also through ELISA (La Fratta et al., 2018). CRP concentrations found in this study were within the range of the laboratory assay and in accordance to the manufacture's standards. Our mean CRP concentrations (all three days) were 677.18 pg/mL (67.7 ng/mL) at baseline and 672.06 pg/mL (67.2 ng/mL) at endpoint. In comparison to BCS, our CRP findings were lower than salivary CRP concentrations found in a previous study with BCS at least six months from the completion of the adjuvant therapy (4899.04 pg/ml; SD 1085.25) (Lozano-Lozano et al., 2019), as well as in serum and plasma CRP in BCS diagnosed on average 3.6 years previously to the study start date (Bower et al., 2014), in overweight postmenopausal BCS (Thomson et al., 2009), in BCS 12 months after diagnosis (Villaseñor et al., 2011), and postmenopausal BCS at any time after treatment (Fairey et al., 2005).

One possible explanation to why our CRP levels were lower in comparison to other BCS populations is that it is associated with several additional factors, such as waist circumference, smoking status, tamoxifen use and treatment underwent. Tamoxifen, for instance, have been shown to decrease serum CRP (Bonanni et al., 2003; Cushman et al., 2001). In addition, the studies found in the literature worked with heterogeneous samples of BCS (i.e. short and long-term survivors, postmenopausal, overweight).

5.1.2.3 Cytokines

Our results showed that TNF-α levels significantly decreased at endpoint. No statistically significant differences were found in IL-6, IL-1β and IFN-γ over time, however, all biomarkers decreased in concentration at endpoint in comparison to baseline, therefore, responding in a positive direction at the end of the MT program.

Our study is the first to show significant improvements in salivary TNF-α concentration after an 8-week MT intervention. Previous studies with BCS did not find any changes in TNF-α concentration after a 6-week MT intervention (Krohn et al., 2011). However, a study on exercise-induced muscle damage found that MT attenuated the production of the TNF-α and IL-6 in young male (Crane et al., 2012). Interestingly, TNF-α is a cell signaling protein involved in systemic inflammation and tumor progression in cancer. The fact that, in our study, this cytokine showed significant decrease after the MT program, along with important associations with Cancer Stage, among other covariates, reveals a promising finding with important implications in the c-Jun N-terminal kinase (JNK) signaling pathway. The JNK pathway is one of the major signaling cassettes of the mitogen-activated protein kinase (MAPK) pathway that regulates TNF-α, having a crucial role in the TNF paradox in cancer progression and immunotherapy (Montfort et al., 2019).

As a result of two significant interactions found in this study, the first one between Cancer Stage and Timepoints, and the second one between Hormone and Timepoints, important differences in IL-1β concentrations for each group of Hormone Therapy and Cancer Stage were revealed. Although not all these differences were statistically significant, it is worth mentioning that, both hormone therapy and cancer stages, are important factors that are likely to alter IL-1β concentrations in cancer patients even after treatment (Mantovani et al., 2000; Tas et al., 2005; V

et al., 2014). In fact, IL-1 is a major pleiotropic cytokine in tumor–host interactions, and therefore, might play an important role in how patients navigate through cancer survivorship (Apte & Voronov, 2002). Interestingly, a previous study has also reported how in non-cancer perimenopausal women, hormone replacement therapy increases serum soluble IL1ra (Abrahamsen, Bonnevie-Nielsen, Ebbesen, Gram, & Beck-Nielsen, 2000).

Taken together, the overall improvements in cytokine levels seemed to show favorable immune changes in this study. This overall decrease on cytokine levels found in our study is, to some extent, comparable with other studies that have found an increase of cellular immunity after MT. Similar to our findings, several studies found a trend towards improvement of immunological markers, but could demonstrate significant changes concerning immune cell counts, cytokine concentration and immune system activations after MT in breast cancer patients (Billhult et al., 2009; Hernandez-Reif et al., 2005, 2004; Krohn et al., 2011), HIV-1 positive patients (Shor-Posner et al., 2006) and healthy individuals (Rapaport, Schettler, & Bresee, 2012). The results of the present study are consistent with findings of most of the previous studies which revealed no significant changes in IFN-γ concentration after 6-week MT intervention in BCS (Krohn et al., 2011), and IL-6 and IFN-γ (Kang et al., 2011).

One speculation for the non-statistical significance of some cytokines in our study is insufficient power. It must be also taken into consideration that BCS are recovering from therapy and their immune responsivity to a relaxation activity (i.e. MT practice) might have been diminished by slow recovery of immune system and chronic stress (Kang et al., 2011). Furthermore, even though we designed a comprehensive 3-day scheme for saliva sampling to account for diurnal variations, other host and environmental factors also play an important role in the expression of cytokines, cortisol, CRP, and therefore, variability of immune response. Many of these factors were not explored in this study, such as the genetic make-up of the host (i.e. genetic polymorphisms), the intestinal microbiome, diet, physical activity levels, hormone levels, BMI (Ice, 2005; Stachowicz & Lebiedzińska, 2016; ter Horst et al., 2016).

Cytokine concentrations found in this study were within the range of the laboratory assay and in accordance to the manufacture's standards. Noteworthy that there are still not definite reference values or normative data concerning salivary cytokines and their changes under each medical condition and therapeutic interventions (Pollmächer, Haack, Schuld, Reichenberg, & Yirmiya, 2002). Relating to the reliability of the blood and saliva to measure cytokines, previous

studies have showed a significant plasma-saliva correlation in several populations (La Fratta et al., 2018; Riis et al., 2014).

Noteworthy that our study showed higher concentrations of some cytokines in comparison to baseline results from studies with BCS. For instance, our IFN-γ were higher in comparison to plasma IFN-γ levels in breast cancer patients (Krohn et al., 2011) and our IL-6 levels were higher than salivary IL-6 in BCS (Lozano-Lozano et al., 2019) - both at baseline. On the other hand, our study showed lower IL-6 and IFN-γ in comparison to IL-6 and IFN-γ salivary concentrations in a study with BCS and MT at baseline (Kang et al., 2014). The lack of consensus on cytokine levels between studies can be explained by the fact that it has been not well explored in cancer patients, and precisely in BCS. However, it should be noted that inflammation has emerged as one important aspect in cancer survivorship. In addition to an increased persistence of CRS, prominent increases in proinflammatory cytokine activity occur in cancer survivors (Irwin, Olmstead, Ganz, & Haque, 2013).

The higher concentrations found in our study in comparison to blood samples can be explained by the fact that, although there is a correlation between salivary and plasma cytokine concentration, salivary concentration tend to be higher than the plasmatic level (La Fratta et al., 2018). This difference in concentration could be associated with the salivary glands' faster reactivity in comparison to circulating cellular production of cytokines (La Fratta et al., 2018).

Inflammatory Markers and MT

Our study provided important preliminary evidence of immunomodulatory effects of MT in BCS by assessing cortisol, CRP, IL-1β, IL-6, TNF-α and IFN-γ. All biomarkers showed a decrease after the MT program, suggesting that salivary immunological measures are potentially sensitive to immunomodulatory effects of MT in BCS.

In MT research, it is critical to continue exploring the effects of mechanical manipulation of body tissues and immunomodulation. Besides the changes in the inflammatory markers presented by our study, previous works have shown positive biological effects of MT on IgA levels (Cantarero-Villanueva et al., 2011; Fernández-Lao et al., 2012), α-amylase (Cantarero-Villanueva et al., 2011; Fernández-Lao et al., 2012; Tiffany Field et al., 2005), serotonin (Field et al., 2005; Listing et al., 2010), NK cells (Billhult et al., 2009; Hernandez-Reif et al., 2005),

lymphocytes (Green et al., 2010; Hernandez-Reif et al., 2005, 2004), catecholamines (Field et al., 2005; Hernandez-Reif et al., 2004), some Th1 and Th2 molecules (Green et al., 2010) and peripheral blood mononuclear cell (Billhult et al., 2009).

Other studies on sport-related muscle injuries in animal models, have also brought remarkable insights on immunomodulatory effects of MT. For instance, a study in rats found that the immunomodulatory response exerted by MT is dependent upon the applied load. Utilizing a custom-fabricated massage mimetic device, this study assessed the effects of various loading magnitudes on healthy skeletal muscle in rats. Animals received massage for 30 min, once a day, for 4 consecutive days using four loading conditions: control, low, moderate, and high. Different cyclic compressive loads provoked different profile expression in 534 genes between the three groups and modulation of key immune cells involved in the inflammatory response in rats (Waters-Banker, Butterfield, & Dupont-Versteegden, 2014). Additionally, another study in rats found that MT promotes enhanced skeletal muscle regrowth and remodelling even on contralateral non-massaged hindlimb, indicating that there is a systemic response to MT (Miller et al., 2018).

Therefore, MT seems to have a potential in manipulating the host inflammatory response and attenuating the potentially negative consequences of CRS in BCS. To explain our results on how inflammatory markers are capable of responding to MT and changes in mechanical activity exerted on muscles, we conjectured that: (1) cell signaling is activated by mechanotransduction provoked by MT, which transfers mechanical energy into a chemical response in the cells; (2) As suggested in previous studies, MT might alter the behavior of NFkB, causing less of this key inflammatory mediator to be released. Consequently, the NFkB-regulated cytokines (i.e. IL-6, TNF) become less active, a sign of less cellular stress and inflammation; (3) due to muscle manipulation, MT can cause the release of cytokines and myokines (cytokines synthesized by myocytes in the muscle tissue and released in response to contractions, which are intricately involved in the inflammatory response of skeletal muscle); (4) MT activates the SNS to cause muscle relaxation through direct neural mechanisms as well as endocrine-like mechanisms (Crane et al., 2012; Miller et al., 2018).

Although it is becoming clear that the perceived positive effects of MT are a result of an attenuated production of inflammatory markers, it remains to be determined whether all cancer types respond in similar fashion and if these results can reach statistical significance in a larger

clinical trial. Therefore, biological mechanism(s) behind the beneficial effect of MT still require further investigation.

5.1.3 Physiological Parameters

5.1.3.1 Blood Pressure Changes Following MT Session

Contrary to our hypothesis, SBP and DBP increased right after the MT sessions at all weeks. There was a decrease in the SBP from baseline to endpoint, whereas DBP increased from baseline to endpoint. However, these differences failed to reach significance for both diastolic and systolic blood pressure. Worth pointing out the changes were small and likely not relevant clinically.

MT has been widely studied in healthy patients, however, additional scientific research with BCS is warranted. Our results are not in accordance with previous studies that support the ability of MT to improve BP in breast cancer patients (Billhult et al., 2009; Ferrell-Torry & Glick, 1993; Post-White et al., 2003) and other population types such as family caregivers of patients with cancer (Pinar & Afsar, 2016), middle-aged women (Lee & Yeun, 2017), hypertensive women (Hernandez-Reif et al., 2000; Supa'At et al., 2013), patients undergoing autologous bone marrow transplantation (Ahles et al., 1999), and in women with pre-hypertension (Moeini, Givi, Ghasempour, & Sadeghi, 2011). It should be noted that, the above mentioned study with breast cancer patients found that MT lowered SPB, but not DBP (Billhult et al., 2009).

Conflicting results have been also found in the literature regarding BP and MT. In a sample of patients with metastatic bone cancer, no significant changes on BP were found after MT (Jane et al., 2011). Hand massage in cancer patients receiving radiotherapy, elicited a non-statistically significant decrease of SBP, and a statistically significant decrease in DBP in the experimental group (Park & Suh, 1995).

Although we did not find a statistically significant reduction in BP we view the reductions in SBP at endpoint as noteworthy, and we speculate that due to sample size we were not able to attain statistical significance. In regard to the immediate increase of BP right after the MT sessions, one possible reason for that is that physiological measurements were not taken while the participant

was still in supine position on the massage table. Instead, right after the massage session, patients were asked to get up from the massage table, get dressed and walk to the next room - approximately 7 meters distance to perform the measurements. Most importantly, our patients did not raise any concerns with their BP being slightly elevated after MT, by already knowing that their blood pressure at home is under consistent control, which is clinically more relevant than getting isolated readings at a clinic or ambulatory setting (Pierdomenico, Bucci, Lapenna, Cuccurullo, & Mezzetti, 2001).

Different pressure massage (i.e. moderate pressure or a light pressure massage) has been also speculated as a possible effect moderator in MT studies. Moderate pressure massage has been shown to increase vagal activity, which in turn, is associated with lower HR and BP and decreased cortisol levels (Diego & Field, 2009; Porges, 2001). Inversely, light pressure has been shown to decrease vagal activity, and has been associated with increased cortisol levels (Diego & Field, 2009; Spangler, 1997).

5.1.3.2 Heart Rate Changes Following MT session

In our study, HR values decreased right after MT sessions at each week of the program, validating our hypothesis. In addition to the immediate pre and post significant changes throughout the MT program, this decrease was also statistically significant between baseline and endpoint.

MT has been widely studied in healthy patients, but scarcely in BCS. It is already known that MT elicits a slight change HR due to a vagal activity, possibly through the activation of vagal afferent fibers. Therefore, the stimulation of dermal pressure receptors leads to an increase in vagal activity, and therefore, exhibits a parasympathetic nervous system response characterized by a decreased HR (Field, Diego, & Hernandez-Reif, 2010).

In healthy subjects, previous studies suggest that there is a relationship between maximum HR slowing and the degree of vasodepression during massage (range 2-80 msec/mmHg) in several populations (Kaye et al., 2008; Mcintosh, Lawson, & Kenny, 1994). The stimulation of pressure receptors by MT is associated with decreased heart rate. The MT effects on HR might be mediated by increased vagal activity (Field, 2014).

In conformity with our results, several studies have found that MT elicited a decrease in HR in breast cancer patients (Billhult et al., 2009; Post-White et al., 2003). Billhult et al. (2009), for instance, found that a single full-body light pressure effleurage massage in women with breast cancer who were undergoing radiation therapy lowered the HR. HR also decreased in a sample of HIV adolescents submitted to moderate massage (Diego et al., 2001), in healthy elderly subjects (Mcintosh et al., 1994), and family caregivers of patients with cancer after back massage (Pinar & Afsar, 2016).

Conflicting results were also found by previous studies. For instance, in a sample of patients with metastatic bone cancer, no significant changes on HR were found after MT (Jane et al., 2011).In a sample of healthy individuals who received a moderate pressure massage an increase in HR was detected. However, the same study also detected that those who received a light pressure massage showed a decreased heart rate (Diego & Field, 2009). A third study aimed to assess the effects of three different types of massage (1) moderate pressure massage, (2) light pressure massage, or (3) vibratory stimulation group. The moderate pressure massage group exhibited a decrease in HR. In contrast, the light pressure massage and vibratory stimulation groups showed an increase in HR after massage (Diego, Field, Sanders, & Hernandez-Reif, 2004). Additionally, one study did not detect any statistically significant changes on heart rate variability in BCS (Fernández-Lao et al., 2012). Opposing results were also found by a study assessing short-term effects of manual therapy in patients with chronic tension-type headache. They found that the a single session of manual therapy elicited an immediate increase of heart rate variability, although it also prompted a decrease in tension, anger status, and perceived pain (Toro-Velasco, Arroyo-Morales, Fernández-de-las-Peñas, Cleland, & Barrero-Hernández, 2009).

5.1.3.3 Oximetry Changes Following MT session

Our findings show that oximetry values increased right after MT sessions at all weeks of the program, validating our hypothesis. This increase was only statistically significant at weeks 2, 4, 7 and 9, but not between baseline and endpoint. Our findings are in line with previous studies that reported an increase in oxygen saturation after several modalities of MT in patients with metastatic bone cancer (Jane et al., 2011), middle-aged women (Lee & Yeun, 2017), congestive heart failure (Chen et al., 2013), in neonates (Elsagh, Lotfi, Amiri, & Gooya, 2019) and in liver

transplant patients (Demir & Saritas, 2019). Two other studies, however, found that MT decreased oxygen saturation (Rudnicki et al., 2012; Valizadeh, Hosseini, Asghari Jafarabadi, & Ajoodanian, 2012).

One of the most reported effect of MT is an increase in tissue blood flow (Fritz, 1995; Moyer, Rounds, & Hannum, 2004; Munk, Symons, Shang, Cheng, & Yu, 2012; Weerapong, Hume, & Kolt, 2005). Changes in parasympathetic activity following MT result in a relaxation response. Therefore, as found in our study, an increase in oximetry is expected after massage. The conjectured mechanisms behind it, is that MT increases blood supply and oxygen by improving circulation throughout the body. MT incites an increase in circulation due to the pressure created by massage strokes and techniques (i.e. effleurage and petrissage) that actually moves blood through the vessels promoting an increase in oxygenation (Li, Li, Lin, & Li, 2017). However, MT effects on tissue blood flow are conflicting and inconclusive mainly due to design and measurement limitations of previous studies (Munk et al., 2012; Weerapong et al., 2005).

5.1.4 Correlations Between Outcomes

QoL and Cytokines Correlations

In our study, correlations were also demonstrated between IL-6, TNF-α and IFN-γ and the QoL subscale "additional concerns". Additionally, there was a statistically significant relationship between CRP and the QoL subscale "emotional well-being". These correlations mean that less concerns and better emotional well-being (higher QoL) were associated with lower levels of inflammatory markers.

Associations between inflammatory markers and both total QoL score and its subscales have been reported before. In patients with advanced cancer, the EORTC-QoL subscale "appetite loss" was independently associated with high serum IL-6 and CRP; and the subscale "role function", was independently associated with serum IL-6 and CRP concentrations (Paulsen et al., 2017). Moreover, in a second study with patients with advanced cancer, "appetite", "fatigue", and "role function" were the only EORTC-QoL subscales independently associated with systemic inflammation (Laird et al., 2016).

Similar to our findings, correlation between QoL and both IL-6 and IL-1β in cancer patients were found (Meyers, Albitar, & Estey, 2005), as well as QoL and TNF-α (Fung et al., 2013; Panju, Danesh, Minden, Kelvin, & Alibhai, 2009) and QoL and IFN-α (Panju et al., 2009). In addition, Panju et al., (2009) reported significant correlations between QoL and IL-2, IL-5 and IL-8 (Panju et al., 2009). More recently, one study showed that among men with early-stage lung cancer, a marginal significance was observed for IL-1A C-889T. Man with C/T or T/T genotype had a lower risk of severe fatigue compared with those with genotype C/C (Reyes-Gibby et al., 2013).

On the other hand, in a sample of patients with acute myeloid leukemia no correlation between QoL and IL-1β were found (Fung et al., 2013; Panju et al., 2009). Also, in accordance to our findings, no significant relationships between perceived stress the cytokines IL-1β, IL-6, TNF-α, and CRP were reported in a sample of breast cancer patients (Xiao et al., 2017). Relationships between stress and CRP and IL-6 were only found in a sample of women receiving radiation for breast cancer, but only among those patients with a history of childhood trauma (Han et al., 2016).

Part of these symptoms occurring in cancer patients were observed for the first time in laboratory animals submitted to the induction of infectious conditions and the injection of pro-inflammatory cytokines. The result of this induction was a phenomenon called *sickness behavior*. This term was coined in 1992 by Stephen Kent and collaborators and is characterized, in animals, by a set of physiological responses (fever, pain, increased activity of the HPA axis and ANS) and behavioral responses (fatigue, dysphagia, changes in sleep patterns, apparent loss of interest in daily activities, depressive behavior, decreased social interaction and sexual interest) (Kent, Bluthé, Kelley, & Dantzer, 1992). Interestingly, in humans, fatigue, pain, insomnia, depression and cognitive disorders were observed in cancer patients who presented high levels of pro-inflammatory cytokines (Barsevick, 2007). Therefore, to consistently explore all these possible correlations, it is crucial to capture the dynamic and continuous response of the immune system to cancer, considering the involvement of cells, organs and pro and anti-inflammatory biological markers.

QoL, Fatigue and Stress Correlations

Our results demonstrated several correlations between PROs (i.e. QoL, Fatigue and Stress). Generally, the higher the levels of stress, the lower the QoL; as well as the higher the fatigue score (denotating less fatigue), the better the QoL. These confirm our hypothesis that QoL, fatigue and stress are correlated and can potentially play a role in the genesis and severity of each other. Fatigue and its correlation with QoL - both following and during breast cancer treatment, have been reported by previous studies (Canário et al., 2016; Charalambous & Kouta, 2016; Gupta, Lis, & Grutsch, 2007; Kluthcovsky & Urbanetz, 2015; Paraskevi, 2012; Tabrizi & Alizadeh, 2017). In accordance to our findings, a study with 202 BCS, found that total and subscale fatigue scores were correlated to lower QoL (Kluthcovsky & Urbanetz, 2015). Similarly, in a sample of 215 breast cancer patients, mean scores for QoL were significantly lower among fatigued women (Canário et al., 2016). Another study in patients with lung cancer found similar results reporting that the higher the levels of pain, fatigue, sleep disorders and stress, the lower the QoL (Lin, Chen, Yang, & Zhou, 2013).

QoL is considered an important endpoint in cancer care and in clinical trials, while fatigue is one of the most troublesome and frequent symptoms described by cancer patients and survivors. QoL is often associated with symptoms such as fatigue, insomnia, and psychological stress (Ahlberg, Ekman, Wallgren, & Gaston-Johansson, 2004; Portenoy, 2000; Stone, Richardson, et al., 2000; Vogelzang et al., 1997; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). Our findings corroborate the argument that QoL and CRS are intrinsically correlated in the cancer trajectory, influencing one another as a cluster of symptoms, in both patients and BCS (Cleeland, 2007; Cleeland et al., 2013; Dantzer et al., 2012; Dodd, Miaskowski, & Paul, 2001; Dodd, Miaskowski, & Lee, 2004).

Sleep Parameters Correlations

Significant associations between sleep parameters were found at all time points. Strong statistically significant relationships between the WASO and SD were found. Similarly, WASO was associated with SOL meaning that the longer patients took to fall asleep, more awakening episodes they had after sleep onset.

The significant correlations between sleep parameters in our sample represent to some extent the microstructure of sleep architecture. To further explore these relationships, we tested

for other correlations between sleep and PROs (i.e. QoL, fatigue and stress). However, no correlations were found between QoL, fatigue and/or stress and the actigraphy sleep measurements in our study. These observations correspond to findings from other trial that failed to find relationships between actigraphy sleep measurements and subjective health-related measures (i.e. PROs and health-related symptoms) (Aili, Åström-Paulsson, Stoetzer, Svartengren, & Hillert, 2017). In patients with atopic dermatitis, among the 9 actigraphy sleep measures, only 5 approached significant correlations with QoL (Bender, Leung, & Leung, 2003). In addition, other study where sleep was assessed subjectively also failed to find relationships between sleep and QoL (Sonia Ancoli-Israel et al., 2003). Similarly, in the same study mentioned above with atopic dermatitis patients, of the 8 subjective sleep measures, none correlated with the QoL score (Bender et al., 2003).

The low overall correlation between actigraphy sleep measurements and PROs in our study creates a number of discussion points. First, as proposed by Ancoli-Israel et al. (2003), is it that the actigraphy measurements are not reliable enough to capture the relationship between sleep changes and PRO's measures, or, is it that, in fact, there is no relationship between sleep and PRO's measures? (Sonia Ancoli-Israel et al., 2003). These findings might suggest that actigraphy measurements and subjective health-related measures do not correlate, but rather complement each other. Albeit a definite explanation for these results are not clear-cut, one speculation is that the participant responses to the FACT (i.e. QoL and fatigue) and PSS (ie.e stress) scales have a 1-week recall period, whereas the actigraphy recorded sleep during another timeframe.

Different from our results, a previous study have shown an inversely proportional relationship between fatigue in cancer patients and actigraphy sleep measurements (Berger, 1998). Also, in adolescents with cancer, a correlation between QoL and sleep was also observed (n=20) (Erickson et al., 2011). Indeed, the relationship between fatigue and sleep in health and other illnesses has been widely studied. It is unknown, however, how fatigue influences the quality or quantity of sleep or its actual relationship with the biological circadian rhythmicity (Ancoli-Israel, Moore, & Jones, 2001). Sleep/wake circadian rhythm cycle, independent of its relationship to fatigue, may play an important role in CRS. There is robust evidence to suggest, however, that disruptions in sleep/wake circadian rhythm cycle are relevant to cancer and other

chronic diseases (Mormont & Lévi, 1997; Wang et al., 2017; Zhang, Xie, Yu, Zhang, & Qian, 2019).

A lack of correlation has been also identified between actigraphy measures and subjective measures of sleep. As demonstrated by previous studies, a discrepancy between objective sleep/wake measures (i.e., actigraphy) and self-reported sleep (i.e., the PSQI and CSD) has been found (Aili et al., 2017; Ancoli-Israel et al., 2003; Berger et al., 2007; Girschik, Fritschi, Heyworth, & Waters, 2012). By no means it is suggested that any of these measures are unimportant. Actigraphy reflects an important aspect of sleep quality, as is true for subjective measures. Clearly, subjective and objective measures of sleep quality target very different aspects of sleep quality—each providing valuable insights (Sonia Ancoli-Israel et al., 2003; Landry, Best, & Liu-Ambrose, 2015), therefore, the best practice would be including both subjective and objective measures when examining sleep quality in BCS (Landry, Best, et al., 2015).

Relationship between Sleep Onset Latency and Sleep Duration

Although we did not find any significant correlations between Sleep Onset Latency (SOL) and Sleep Duration (SD), the relationship between these two variables is worth discussion given their important role in the microstructure of sleep architecture. On average, our patients showed an ultra-short (≤5 min.) SOL, along with a short SD. Therefore, on the assumption that there is a strong synchronicity between these two variables, we hypothesize that SOL and SD are positively correlated. However, there is insufficient knowledge regarding SOL and SD in BCS population to compare our data. In other population types, strong correlations have been found between SD and SOL (Ishihara, 2002), as well as associations of increased SOL with insufficient total sleep duration (Gau & Soong, 1995; Liu & Zhou, 2002). Contrary to that, a previous study found that an increase in SD was associated with an enhanced risk of prolonged SOL (Alexandru et al., 2006). Interestingly, in mice, prolonged or delayed SOL was associated with chronic sleep restriction, in other words, SOL increased as a function of sleep restriction or lower SD. (Kim, Hwang, Kim, & Choi, 2013).

Sleep and Cortisol Correlations

Overall, the higher the levels of inflammatory markers, the poorer the sleep quality. For instance, our study showed that high cortisol levels correlated with worse WASO. The association between cortisol and sleep have been previously studied in several types of populations. In old adults, it has been demonstrated that impaired nighttime sleep is associated with elevated plasma cortisol (Vgontzas et al., 2003). Alterations in cortisol concentrations can interfere with sleep (Vgontzas et al., 2001), which may trigger elevations in proinflammatory cytokines and fatigue, creating a positive feedback loop (Vgontzas, Mastorakos, et al., 1999; Vgontzas, Papanicolaou, et al., 1999). The current findings indicate that sleep deprivation modulate cortisol levels and increases plasma concentrations of pro- and anti-inflammatory proteins – such as cytokines (Wright et al., 2015).

Sleep and Cytokines Correlations

Short SD was also correlated with higher IL-1β levels in our study. Elevated plasmatic pro-inflammatory cytokines have been associated with sleep disturbances in BCS and breast cancer patients (Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006; L. Liu et al., 2012a). Inflammation has been associated to disrupted sleep in cancer survivors, with a few key endogenous factors leading to inflammatory activity, such as nuclear factor-ϰB (NF-ϰB), and major inflammatory cytokines, such as IL-1β, IL-6, and TNF-α (Karin, 2006). Decreased SD and disrupted sleep have deleterious effects that shift the metabolism and produce a chronic elevation of plasmatic CRP, IL-6 and TNF-α (Rico-Rosillo & Vega-Robledo, 2018; Rockstrom et al., 2018; Vgontzas et al., 2001). It's been also demonstrated that inflammatory cytokines IL-1β, IL-6, and TNF-α increase non-rapid eye movement sleep, whereas anti-inflammatory cytokines such as IL-4 and IL-10 decrease it (Rico-Rosillo & Vega-Robledo, 2018). In contrast, other investigators have noted that IL-6, but not IL-1β or TNF-α, was related to a symptom cluster composite of sleep quality, pain, fatigue, depression, weight loss, and cognitive disturbance in patients with advanced pancreatic cancer (Tobias, Rosenfeld, Pessin, & Breitbart, 2015).

Sleep and CRP Correlations

We also identified that, high CRP levels correlated with worse SOL. The relationship between salivary CRP and sleep is not fully understood in BCS and have been scarcely researched to date. Elevated CRP in plasma have been associated with sleep disturbances in BCS (Collado-Hidalgo et al., 2006) and breast cancer patients (L. Liu et al., 2012a). The importance of this molecule as a predictive element in cancer survivorship has been supported by previous studies suggesting an increased mortality rate associated with higher CRP levels (Pierce et al., 2009). Furthermore, previous studies reported a relationship between elevated levels of CRP and circadian misalignment in night-shift workers (Kim et al., 2016; Morris, Purvis, Mistretta, Hu, & Scheer, 2017). By contrast, other investigators have reported inconsistent correlations between CRP and sleep disturbance over 2 years in women with early-stage breast cancer (Starkweather et al., 2017).

The interplay between cytokines, CRP and cortisol in modulating sleep and CRS have been investigated before. Accumulating data suggest an interaction among sleep, circadian rhythms, and circulating concentrations of IL-6 in relation to the secretory profiles of cortisol, and melatonin (AlDabal, 2011; Bauer et al., 1994; Redwine, Hauger, Gillin, & Irwin, 2000). Sleep deprivation may decrease IL-6 levels, with effects on the integrity of immune system functioning (AlDabal, 2011; Bauer et al., 1994; Redwine et al., 2000). Interestingly, CRP is synthesized in response to IL-1 and IL6 stimulation, and it has been found in association with fatigue in breast cancer patients (Alexander et al., 2009; Alfano et al., 2012; Orre et al., 2011; Pertl et al., 2013; Wratten et al., 2004). Fatigued BCS showed elevations in serum markers associated with pro-inflammatory cytokines activity an average of 5 years after diagnosis (Bower et al., 2002). Furthermore, elevations in IL-6 and alterations in cortisol have been reported in a variety of cancers, and both have been associated with fatigue (Murali, Hanson, & Chen, 2007; Schrepf et al., 2013).

The pursuit of timely, cost-effective, accurate, and non-invasive methodologies to measure sleep quality and sleepiness have led scientists to explore saliva (Seugnet et al., 2006), exhaled breath and exhaled breath condensate (Carpagnano, 2011) as promising mediums of diagnostic and prognostic value (Michael, Valle, Cox, Kalns, & Fogt, 2013; Yoshizawa et al., 2013). In sleep medicine, inflammatory markers such as IL-6, TNF-α, von Willebrand factor, α-amylase and CRP have drawn considerable attention (Clinton et al., 2011; Miller, 2011).

However, most of the previous studies are in fruit flies (*Drosophila melanogaster*) and humans (Seugnet et al., 2006), but not BCS.

Inflammatory Markers Correlations

Several correlations between inflammatory markers were found in our study. There were important statistically significant relationships between all pro-inflammatory cytokines as well as between the cytokines and CRP levels. These confirm our hypothesis that inflammatory markers are influencing one another as a result of an orchestrated symbiosis in the human body.

Overall, the higher the cytokine levels, the higher the CRP levels. The relationship between CRP and the cytokines measured in our study is not well understood in BCS. The relationship between CRP and IL-6 has been well studied in other populations, such as patients with systemic sclerosis, acute coronary syndrome, schizophrenia and bipolar disorder (Daniels, 2017; Misiak et al., 2018; Muangchan & Pope, 2013). CRP is synthesized in response to IL-1 and IL-6 stimulation, therefore, a relationship between these two cytokines were expected. Interleukin-6 works upstream of CRP and downstream of IL-1β and activates its proinflammatory response via stimulation of membrane-bound IL-6 receptors on the cell surface (Daniels, 2017). Interestingly, CRP and IL-1β have been linked to the development of fatigue. A study with 111 stage 0-III BCS at 1 year post-radiotherapy, found that depressive symptoms, CRP, IL-1β (antagonist receptor) and TNF- α (receptor 2) were risk factors of fatigue (Xiao et al., 2017).

As of particular importance, our study showed that all cytokines positively correlated to each other. Cytokines are small signaling proteins released by a variety of cells acting in cell development and growth. These proteins play a central role in the immune system, in which they influence the host's responses to infections, inflammations, chronic and acute diseases (Corwin, 2000; Roshene & Ramesh, 2017). Initially they were categorized as mediators of interactions between immune system cells, recently however, they have been also considered essential factors for the interaction between the immune system and the central nervous system (Haack et al., 1999). Members of this large and diverse family of signaling polypeptides, produced by cells of different embryonic origins, are traditionally classified as lymphokines (cytokines produced by activated lymphocytes), interleukins (cytokines that act as mediators between leukocytes), or

chemokines (cytokines) (Hiscott & Ware, 2011; Janssen et al., 2010; Ransohoff & Benveniste, 2006).

Although their specific biological activities vary, two general categories of cytokines can be distinguished, pro-inflammatory and anti-inflammatory. The first group consists of cytokines that are directly or indirectly involved in inflammatory processes, such as IL-1, IL-6 and TNF-α. The other group consists of cytokines that are known to regulate the immune response by decrease cell activation and the production of pro-inflammatory mediators. This group includes IL-4, IL-10 and IL-13, among others (Hiscott & Ware, 2011; Meager, 1991; Schiepers, Wichers, & Maes, 2005).

Cytokines are pleiotropic (i.e. one cytokine can have different effects on different cells), they can be redundant (i.e. different cytokines can have the same effects), they are able to synergize and antagonize with each other and they can induce a cascade effect (i.e. some cytokines enhance or inhibit the action of other cytokines in complex ways).

The results of our study support the idea that cytokines follow an orchestrated mechanism of expression, suppression and production. Their expression and their receptors are highly regulated and correlated to each other, influencing one another. TNF- α, IL-1β and IL-6 have been most extensively studied given its roles in the inflammatory process (Hazelzet, van der Voort, Lindemans, ter Heerdt, & Neijens, 1994; Kowsar, Keshtegar, & Miyamoto, 2019; Schindler et al., 1990). In general, inflammation involves signalling through IL-1β, TNFα and IL-6 cytokines as the biological activities of IL-6 partly overlap those of IL-1 and TNF. In addition, IL-6 is probably also involved in the regulation of TNF and IL-1 production (Hazelzet et al., 1994; Schindler et al., 1990).

Correlations Between Outcomes and MT

Several correlations between inflammatory markers, sleep and PRO were found in our study. We provide preliminary evidence of a sustained pattern of correlation between the symptoms itself and between these with inflammatory markers throughout a MT program in BCS across different timepoints. These confirm our hypothesis that these outcomes are synergistically correlated and can potentially influence one another.

In the context of a MT trial, these correlations are particularly meaningful given its consistency throughout the program. For instance, stress and fatigue correlated to each other at all timepoints. It means that improvement in these symptoms at each timepoint were accompanied by a repetitive pattern of correlations between them. This consistent correlation pattern endorses the necessity of screening and managing CRS simultaneously, and not as isolated symptoms. Although the actual hierarchy between these symptoms' occurrence is not well understood, our results corroborate the hypothesis that these symptoms occur together as a cluster due to a possible common underlying inflammatory, neuroendocrine and immunologic etiology. Additionally, because most of these correlations were statistically significant, we can also assume that these associations were not attributed to chance.

There has been a paucity of studies identifying the occurrence of symptom clusters in BCS across different points in the post-treatment trajectory. Currently, it is not known if these symptoms coexist after treatment or whether the clustering became weaker or stronger post treatment. Therefore, besides the persistence of CRS even after treatment detected in our study, the strong correlations between these symptoms might be an indicative of persistent symptom clustering. Evaluating and treating persistent CRS is an important part of survivorship care and MT seems to be a promising approach in this regard, since according to our results, it improved both CRS and inflammatory markers.

5.2 Strengths and Limitations of the study

5.2.1 Strengths

Assessing the biological effects of MT by taking into account the circadian reactivity of inflammatory markers has been one of the major difficulties of earlier studies. A unique feature of this study was the repeated assessment of inflammatory markers for 3 consecutive days and at four timepoints throughout the study. The findings may prove useful for determining optimum sampling times for future studies, as well as it provides pioneering data of some salivary inflammatory markers in short-term BCS.

While few studies have been done in assessing the effects of MT, it has been mainly done in cancer patients in treatment. This study amplifies the understanding of the benefits of MT to short-term BCS for the first time using salivary inflammatory markers. Our findings help to

reinforce and amplify the relationships between the sleep architecture's variables in BCS, as well as the relationship between salivary markers and sleep in BCS.

Another strength of this study is the fact that only one patient withdrew from the study (representing a drop-out rate of 4.1% of the original sample). A low drop-out rate is a good indicator of study adherence and feasibility of the MT protocol.

This study also expands on previous work by designing a fairly long intervention period (8 weeks) and by assessing the long-term and cumulative MT effects rather than immediate effects. Hence, our findings provide rich insights in establishing an accurate dose-response for MT and to guide treatment protocols, as an important aspect for patient care. The theoretical basis of the research and the MT protocol development were also a strength of this study, since careful analysis of previously published MT protocols and input from experienced RMT were appraised before putting together an intervention protocol for this study.

Despite the limitations, the study's findings would serve as a basis for many forthcoming investigations in BCS on sleep, stress, fatigue, QoL, immune response, and MT practice, dose effects, adherence, and more.

5.2.3 Limitations

There are numerous challenges in integrative oncology research, particularly in therapeutic massage research. These challenges create methodological restrictions to interventional studies, and a number of these merit discussion. Due to budgetary limitations, a within-subjects, single group design was used for testing our hypotheses. Additionally, due to a small sample size, the study was underpowered, being more representative of a pilot or a feasibility study. Hence, findings should be replicated with a larger sample, as less study participants may not be accurately representative of patient homogeneity observed in larger studies. The consistency of this study's results over a number of variables, suggests that the differences found in our study are likely to be real and replicable in a larger sample. In addition, it may be possible that an 8-week MT can induce longer-lasting effects, however, due to the lack of a follow-up assessment, we could not elucidate this assumption.

Among the many inherent challenges associated with MT research, there is the consistency in the delivery of massage, or in other words, the limitations around inter and intra-

therapist variability at each MT session. Due to feasibility reasons, it was not possible to have less therapists involved in the study. To overcome this problem in our study, each patient had the same therapist during the entire study. On the other hand, having the same therapist or a reduced number of therapists performing all sessions in all patients may limit the generalizability of the results; since it is expected that any trained therapist must be able to deliver the same MT protocol with similar results.

Given that the current literature does not provide a reasonable estimate of expected differences in the inflammatory markers investigated, our power analysis had to be done based only on our primary outcome's expected change (i.e. QoL). Another important limitation of our study is that past medical history of sleep disorders was not collected from participants. Patients were only asked if they were currently on any medication for sleep problems or any sleep aids. The analysis of personality traits on the adherence to MT program, was not included in our study either. The inclusion of other psychological covariates in this study (i.e. personality traits) could have better explained the trajectories of this study's outcomes.

In home-based clinical trials, in which the majority of the patient's data and/or samples are obtained from their own home, ensuring protocol compliance is a challenge. Even though we asked for participants to record the date and time for each saliva collection, some of them forgot to do so, and some participants reported difficulties in complying with the collections. An event monitoring system is a gold standard in home-based clinical trials, and it could have been used in this study to increase compliance. It is a simple, yet expensive small-box size device, that records and stores up to 4,000 events corresponding to the date and time when a patient opens it to get the sample collection aids and collectors. In our study, in order to mitigate the effects of noncompliance, the use of scheduled text messages (RedOxygen™) was employed to remind participants of sample collection times.

The variability across findings and some methodological drawbacks in published studies limited the extent to which our data could be compared to the literature. A significant heterogeneity among the studies were found in regard to comparison groups, varying lengths of intervention, varying assessment instruments, different compliance criteria, or included subjects with various types of cancer.

5.3 Implications on Clinical Practice

The study's findings suggest that an 8-week MT program has positive effects on multiple immune responses and in QoL, fatigue, stress and sleep in short-term BCS. Results of this research represent a significant contribution to integrative oncology by bringing scientific evidence to support mainstream clinical guidelines and the decision-making process in BC survivorship care. Providing scientific evidence on MT benefits gives BCS a choice for symptom management and supports acceptance of the use of MT by institutions, patients and clinicians. However, further studies with rigorous design and larger sample sizes are demanded to validate our findings. Once our findings are validated, the outcomes measured in this study should be routinely assessed in clinical practice to provide healing-oriented medicine encompassing the whole person.

Results of our study also adds to the discussion of multimodality treatment regimen, reinforcing that integrative medicine therapies must be provided to patients and their families using a patient-centered approach and in concert with mainstream care to manage symptoms, improve QoL, and psychological and physical health.

Symptom control in short-term BCS is an under researched area of study. Our study provided evidence that can enable researchers, health care practitioners, and policy makers to foster the development and implementation of health promotion initiatives. The high adherence rate of this study demonstrates a current demand of BCS in Saskatchewan willing to receive massage treatment to manage their symptoms during the transition period after BC treatment. The study's logistics was also set with local partners to deliver MT in a manner that can be incorporated into survivorship cancer care services provided in Saskatchewan. As such, partnerships could be potentially arranged between SCC and our partners in order to provide MT services for BCS without requiring any physical space or new infra-structure to be implemented at SCC.

Many cancer patients use integrative medicine therapies or are interested in these therapies. Yet, the majority of patients frequently neglect to disclose its use to their oncologists. Reasons for non-disclosure include lack of inquiry from medical providers, fear of physician disapproval, physician's disinterest, belief providers lacked integrative therapies knowledge, lacking time, and belief integrative therapies are safe (Cramer, Cohen, Dobos, & Witt, 2013;

Foley, Steel, Cramer, Wardle, & Adams, 2019). Therefore, by providing evidence that MT can help BCS with CRS management, our study helps to close this gap between professionals' and patients' practices and believes. As a patient-oriented research, our study endorses that research needs to be done in partnership with patients, their families and communities to substantially answer questions that matter to them and aims to improve health care. Given the frequent number of IM users it is important that more studies are done, and that health care professionals, educators, and patients engage in a dialog about useful integrative therapies during and after cancer treatment.

5.4 Research Contributions Summary

There are limited interventional studies exploring how IM therapies can help BCS in the transition period. Our findings provide new evidence on how MT can improve BCS' QoL, fatigue, stress and sleep during the transition period. It contributes to the understanding of how CRS can be managed after cancer treatment by the utilization of IM therapies.

Given the link between inflammation and breast cancer, our study provides new evidence to understand the potential salutary associations between inflammatory markers, sleep problems and persistent CRS in BCS. Hence, it contributes to the understanding of how cortisol, CRP, IL-1β, IL-6, TNF-α and IFN-γ can be potentially involved in the development and persistence of CRS and sleep problems.

In addition, our study also provides preliminary evidence of saliva as a promising body fluid to detect and measure biomarkers related to sleep problems and CRS in BCS. This is an important contribution to the emerging field of interdisciplinary salivary bioscience. In the oncology context, it serves as a foundational reference guide to the collection, analysis, and interpretation of inflammatory salivary data in BCS, as well as its myriad applications in health care (e.g. surveillance, public health etc.).

To the best of our knowledge, this is the first trial to report correlations between salivary cytokines and CRP, as well as correlations between cytokines in BCS. These findings add to the literature by suggesting that salivary inflammatory markers might also act within an extensive tightly orchestrated biochemical network. Understanding inflammatory markers' interactions under different biological, clinical or experimental conditions is of great importance and should

be considered, especially in case of therapeutic treatment. Comprehend the hidden relations between pro- and anti-inflammatory cytokines can lead to new important understanding in cell signalling and inflammation. Clearly, the study of the correlations among inflammatory markers in cancer survivorship is particularly warranted given the well-established connection between cancer and inflammation (Coussens & Werb, 2002; Murata, 2018; Singh, Mishra, & Aggarwal, 2017).

Correlations between PROs also adds to the literature by suggesting that several symptoms might niche-adapt in clusters during breast cancer survivorship, even under the benefits of BCS. That means that even though there were improvement of all CRS, they were still highly correlated with each other throughout the program. The understanding of symptoms clustering can help in the management of CRS and in the design of new interventions.

This study provides a better understanding of the mechanisms underlying the psychological, physiological and immunomodulatory effects of MT in BCS and serve as an aid for patients' informed decision, as well as to sensitize the general public and clinical practitioners by raising awareness of the potential benefits of MT.

5.5 Recommendations

There is an eminent need for more scholarly inquiry in IM field, along with more standardized education, training, and regulation of integrative therapies in clinical and academic settings. World Health Organization (WHO) has repeatedly reinforced its support of integrative therapies. In 2008, the WHO Congress of Traditional Medicine promulgated the Beijing Declaration, which has as one of its major policy directions, to strengthen the communication between allopathic health professionals and integrative therapists, along with the need to develop appropriate IM training programs for health professionals and health-related fields students (World Health Organization, 2013). Reverberating WHO's endorsements, and to close the gap between perceptions and reality around IM, it is recommended to incorporate evidence-based IM education for health professionals, especially for those who work in primary health care. The relevance of training health professionals who are not specialists in integrative medicine, is endorsed, particularly in the recognition of patients, families and communities who would benefit from integrative therapies. Therefore, it is reinforced the creation of a minimum competency

profile in integrative medicine to be adopted in all universities at both undergraduate and postgraduate levels.

Strengthening IM research in clinical settings to help establish IM services into standard cancer care is one of the major recommendations of this study. Clinical audits are crucial to evaluate the cost-benefit and relevance of MT integration into standard cancer care in hospital settings. In North America, a number of hospitals offer a range of IM services among the spectrum of integrative oncology services offered as standard of care (Cramer et al., 2013). In Saskatchewan, the SCC has not yet implemented integrative services for either cancer survivors or patients in treatment. This represents a disparity in cancer care as several other provinces in Canada have already established IM services (e.g. Cancer Care Manitoba, Integrative Health Institute in Edmonton, and Tom Baker Cancer Centre in Calgary).

Prevention of new and recurrent cancers are important aspects of cancer survivorship, but surveillance must also rigorously incorporate behavioral, psychosocial and sleep screenings. Therefore, future practical recommendations include establishing screening and evaluation of CRS and sleep problems throughout cancer trajectory and survivorship. By monitoring the onset and progression of symptoms, whether they started before treatment, after treatment or during one of the treatment phases, a relationship to the phase of treatment (or not) can be suspected.

5.6 Future Research Directions

Although this study used a one-group pre/post-test design with adequate, but relatively small sample size, it opens new research avenues on integrative oncology, salivary bioscience, symptomatology and management in BC survivorship. Future steps in this field include creating more evidence to support informed decisions on the use of integrative therapies by cancer patients and survivors. A larger replication of this study must consider a follow-up assessment, stricter control of saliva specimens' collection, and a control group. It is also strongly suggested that future studies should test different dosages and durations of MT interventions. In addition, giving detailed information of both research methods and interventions protocols is another important aspect to be acknowledged by further studies.

Not many studies have been interested in understanding the biopsychosocial aspects in cancer survivorship. Future investigations should focus on the study of early predictors of

prolonged recovery in BC survivorship, as well as the evaluation of underlying biopsychosocial changes during cancer survivorship. In addition, subsequent studies in BCS should attempt to evaluate the possible clinical long-term outcomes of the use of MT and other non-pharmacological interventions.

Incorporation of qualitative data collection in another recommendation for future research, as this type of data is able to capture experiences, perceptions, and factors that can help researches in evaluating the impact of an intervention. Rigorous qualitative research can provide meaningful conclusions that can inform policy and practice in clinical settings.

Areas for further research include understanding and identifying the pitfalls of implementing a comprehensive practical screening for sleep-wake disturbances, fatigue and psychological stress throughout cancer trajectory, along with identifying ways of overcoming the barriers in offering integrative oncology services as part of standard cancer treatment. Additionally, more scholarly research is warranted on patient safety, dosage, potential harms, discomforts, side effects and contraindications on integrative therapies.

Future steps in salivary biomarkers field include defining what target sensitivity and specificity values might confer clinical utility. Therefore, to identify whether salivary cytokines, cortisol and CRP are possible markers and/or predictors of persistent CRS and sleep quality in BCS, further early phase biomarker studies must determine target performance values for sensitivity and specificity of these molecules. In addition, further studies must also determine the effectiveness of MT on other sleep-reactive physiological measures such as serotonin and melatonin.

One important aspect to consider when investigating the immunomodulatory effects of MT is the pressure-dependent response. As described before, different pressure massages (i.e. moderate pressure or a light pressure massage) has been shown to yield different physiological outcomes (Diego & Field, 2009; Porges, 2001). Therefore, further studies should investigate to what extent the immunomodulatory response exerted by MT is dependent upon the applied pressure.

Our findings show that oximetry values increased right after MT sessions at each week of the program, validating our hypothesis. However, this increase was only statistically significant at week 2, 4m 7 and 8. Future studies should consider the use of near-infrared spectroscopy (NIRS), which provides a non-invasive technology to assess the concentration change in oxy-

hemoglobin (HbO_2), deoxy-hemoglobin (Hb), and blood volume. It is possible that because we used pulse oximetry in the present study, we were not able to identify more significant changes. Pulse oximeter assesses only the arterial compartment, while NIRS assesses all of the vascular compartments (arterial, venous and capillary). It also measures hemodynamics and gives the exact oxygen level in the blood (microcirculation).

There are a number of psychological factors which were not explored in this research that are warranted to be assessed in future studies. One of these factors is the influence of personality traits and personal beliefs on adherence to MT programs and other IM practices. It is known that personality types and other psychosocial aspects have an influence on reported adherence to pharmacological therapies, non-pharmacological interventions and e-therapies (Axelsson, Brink, Lundgren, & Lötvall, 2011; Donkin et al., 2011; Emilsson et al., 2011; Hilliard, Brewer, Cornelius, & Raalte, 2014; Jerant, Chapman, Duberstein, Robbins, & Franks, 2011; Sirois & Purc-Stephenson, 2008). However, more methodological work is needed on how to robustly determine the influence of personality traits on adherence to IM practices, including MT.

5.7 Conclusion

This study sought to examine the effects of an 8-week Swedish MT program on quality of life, fatigue, stress, sleep, cortisol, CRP and pro-inflammatory cytokines in BCS. It revealed evidence of a positive effect of MT in QoL, fatigue, stress and sleep quality in BCS. Oxygen levels and heart rate also demonstrated improvements. Our findings also indicated significant improvement in cortisol, IL-1β and TNF-α levels in BCS and showed improvement trends in most of the other inflammatory markers analyzed. Besides that, this study provides pioneering data of salivary inflammatory markers in BCS.

MT has been associated with alleviating CRS in cancer patients, nevertheless, given the number of restrictions of previous studies, inconsistencies and methodological drawbacks, long-term and biological effects of MT interventions in BCS are still inconclusive. Overall, it highlights the importance of testing non-pharmacological interventions for the management of CRS and sleep problems in BCS, as well as understanding its burden in this population.

With regards to CRS clustering, this study further supports the concept of the development of symptoms clustering during cancer survivorship. For instance, important relationships within PROs, and between PROs with sleep and cytokines were found in this study,

indicating that these symptoms might have the same biological underpinnings, leading to a possible interconnection between its development, severity and persistence. To our knowledge, our study provides new data on associations between salivary inflammatory biomarkers, sleep and PROs in the setting of an intervention trial with BCS. Therefore, findings from this dissertation employed the use of objective and biological measures in combinations with subjective symptom assessment.

The results concerning inflammatory markers indicate that there is a potential in MT's effects in reducing inflammation, however, larger studies are needed to determine immunomodulatory changes under MT in BCS.

Results of our study must be interpreted with caution given its limitations. However, based on our findings, MT for BCS has potential clinical value for relieving CRS and improving sleep, QoL, stress and decreasing fatigue. Our results on the biological effects of MT also provide promising evidence that manipulative therapies may be justifiable in clinical practice. Therefore, integration of MT during treatment phase and/or survivorship care, particularly in the breast cancer context, seems to be recommendable according to the present study.

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APPENDICES

Appendix A – Permission to Reproduce

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Appendix B - Certificate of Approval Behavioral Research Ethics Board

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Kalyani Premkumar	Community Health and Epidemiology	16-112

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Saskatoon Cancer Centre
20 Campus Drive
Saskatoon SK S7N 4H4

STUDENT RESEARCHER(S)
Emiliana Bomfim

FUNDER(S)
UNIVERSITY OF SASKATCHEWAN

TITLE
Protocol : Effects of Swedish Massage on Quality of Life, Sleep, Stress, Fatigue and on Biological Markers Levels in Recently Treated Patients with Breast Cancer

ORIGINAL REVIEW DATE	APPROVED ON	APPROVAL OF	EXPIRY DATE
22-Apr-2016	19-Jul-2016	revised Application for Biomedical Research Ethics Review (May 6, 2016) revised Research Protocol (July 14, 2016) revised Participant Information and Consent Form (July 19, 2016) Letter of Initial Contact (May 6, 2016) Recruitment Flyer (May 6, 2016) Recruitment Brochure (May 6, 2016) revised Clinical Questionnaire (July 14, 2016) Functional Assessment of Cancer Therapy version B (FACT-B) Functional Assessment of Cancer Therapy Fatigue (FACT-F) NCCN Distress Thermometer for Patients PRO-Diary Motion tool to measure sleep (May 6, 2016) Massage Therapy Protocol Patient General Questionnaire Data Collection Tool (July 14, 2016) Acknowledgement of: McMaster Certificate of Completion for Emiliana Bomfim (434999) 2016-05-04	18-Jul-2017

Delegated Review ☒ Full Board Meeting ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. If a protocol has been reviewed at a full board meeting, a subsequent study of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://research.usask.ca/for-researchers/ethics/index.php.

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Kalyani Premkumar	Community Health and Epidemiology	16-112

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research studies involving human participants under section 29 of The Health Information Protection Act (HIPA).

Gordon McKay, PhD., Chair
University of Saskatchewan
Biomedical Research Ethics Board

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Re-Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Kalyani Premkumar	Community Health and Epidemiology	16-112

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Saskatoon Cancer Centre
20 Campus Drive
Saskatoon SK S7N 4H4

STUDENT RESEARCHER(S)

Emiliana Bomfim

FUNDER(S)

UNIVERSITY OF SASKATCHEWAN

TITLE

Effects of Swedish Massage on Quality of Life, Sleep, Stress, Fatigue and on Biological Markers Levels in Recently Treated Patients with Breast Cancer

RE-APPROVED ON	EXPIRY DATE
19-Jun-2017	18-Jun-2018

Delegated Review ☒ Full Board Meeting ☐

IRB 1 Registration #00001471 ☐ IRB 2 Registration #00008358 ☐ Not Applicable ☒

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named research study. The study was found to be acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2-2014).

Gordon McKay, PhD., Chair
University of Saskatchewan
Biomedical Research Ethics Board

Please send all correspondence to:

Research Services and Ethics Office
University of Saskatchewan
Room 223 – Thorvaldson Building
110 Science Place
Saskatoon, SK Canada S7N 5C9

Appendix C - Consent Form

UNIVERSITY OF SASKATCHEWAN | www.usask.ca

Participant Consent Form

HEALTH SCIENCES DEPARTMENT

You are invited to participate in a research project entitled:

Effects of Swedish massage on quality of life, sleep, stress, fatigue and on biological markers levels in recently treated patients with breast cancer

You are invited to take part in this research because you may potentially qualify for the study since you have been diagnosed with breast cancer and have finished the treatment in the last month.

Your participation is voluntary. It is up to you to decide whether or not you wish to take part. If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision. If you do not wish to participate, you will not lose the benefit of any medical care to which you are entitled or are presently receiving. It will not affect your relationship with the Saskatoon Cancer Centre.

Please take time to read the following information carefully, and feel free to ask questions you might have.

You can ask the researcher to explain any words or information that you do not clearly understand. Please feel free to discuss this with your family, friends or family physician before you decide.

Supervisor:
Kalyani Premkumar MBBS MD MSc(Med Ed) PhD MBA (c)
Director (Acting), Division of Faculty Development,
Associate Professor,
Room 3226, E Wing,
Department of Community Health & Epidemiology,
College of Medicine, University of Saskatchewan,
Saskatoon, SK Canada S7K 5E5
Phone: (306) 966 1409 Fax: (306) 966 7920
email: kalyani.premkumar@usask.ca

Student researcher:
Emiliana Bomfim, RN, MSc, PhD Student
University of Saskatchewan, College of Medicine
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Saskatoon (SK), Canada, S7N 5E5
E-mail: e.bomfim@usask.ca
Phone: (613) 406-1977

Co-investigator: one
Franco Vizeacoumar, MSc ,PhD
Saskatchewan Cancer Agency
4D01.5 Health Sciences Bldg.
107, Wiggins Road
Saskatoon (SK), Canada, S7N 4E5
Phone: (306) 966 7010

Purpose(s) and Objective(s) of the Research:

- This study is being done to uncover and support the use of massage therapy - its efficacy and efficiency that help to define standards and trustworthy clinical practice guidelines. In other words, this study aims to explore the effects of Swedish massage on quality of life, sleep patterns, stress and fatigue in a population of patients with a recent history of breast cancer and also investigate the effects of Swedish massage on some substances, called biomarkers, that our body produces and that might be related to sleep, fatigue and stress in patients with cancer or who was recently treated for cancer.
- The main research question of this study is: in recently treated breast cancer patients, could a 1-hour session of Swedish massage improve self-reported quality of life, sleep quality and, decrease stress, fatigue and biomarkers levels?

Procedures:

- Women over 18 years with a diagnosis of breast cancer who have completed therapy in the last 1 month will be invited to participate in this research. The weekly massage sessions be held at the Massage Therapist Association of Saskatchewan Inc. located at 1724 Quebec Ave, Saskatoon, SK S7K 1V9. As a participant, you will undergo 1 hour of massage therapy (MT) sessions, given by professional therapists using standardized protocol, over 8 weeks.

Measurements:

1. ***Quality of Life, stress and fatigue***: will be measured four times during the study: (i) In the beginning of the study; (ii) upon week 4 and week 7 (iii) In the end of the study. They will be assessed by using appropriate scales (questionnaires). (see Figure 1 for an overview of data collection phases).

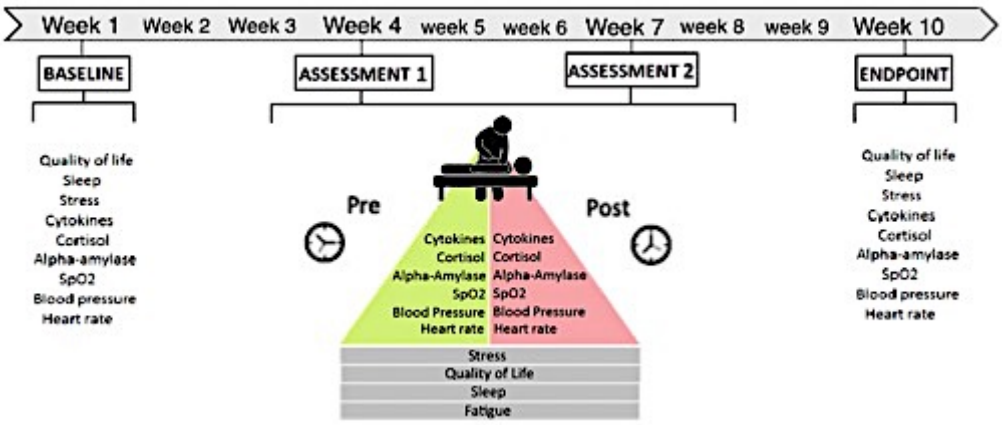


Figure 1. Description of when each assessment will be done.

2. ***Sleep Quality***: will be measured four times: (i) In the beginning of the study; (ii) upon week 4 and week 7 (iii) In the end of the study. Sleep will be assessed by a wrist actigraph, which is a tool similar to a watch and the participants will use it for at least 5 days (see Figure 2)

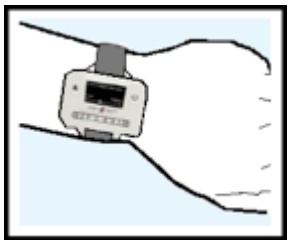


Figure 2. Sleep watch.

3. ***Biomarkers***: are those substances that our body produces and that might be related to sleep, fatigue and stress in patients with cancer or in those who were recently treated for cancer. They will be measured four times: (i) In the beginning of the study; (ii) upon week 4 and week 7, right after and before the massage therapy sessions; (iii) In the end of the study. The levels biomarkers will be assessed through saliva collection (see Figure 3). These saliva kits are intended for use in the non-invasive collection of saliva samples. They are suitable to easily measure molecules that are present in the human saliva and have medical relevance. The saliva samples to assess these biomarkers will be collected using the passive drooling collection method (Figure 3). This method involves the collection of whole saliva by unstimulated passive drool. You will be asked to tilt your head forward, allowing the saliva to pool on the floor of the mouth, then pass the saliva into a polypropylene tube. Usually 1 min is enough to collect passive drooled

saliva using this method. Two saliva collections will be performed per day of massage session (pre and post intervention). One additional collection will be performed in the beginning of the study and another one in the end of the study. In total, each participant will deliver 48 tubes of saliva.

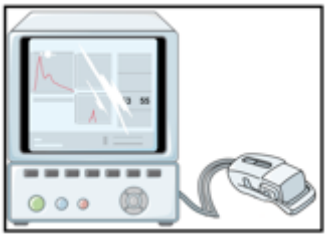


Figure 3. Saliva tube.

4. ***Physiological parameters****:* these are biological characteristic that help us to understand the physiological function of human body. The oxygen saturation, blood pressure and heart rate are the physiological parameters that this study will measure in four times: (i) In the beginning of the study; (ii) upon week 4 and week 7, right after and before the massage therapy sessions; (iii) In the end of the study. Physiological parameters will be assessed by using an automated vital signs monitor, which is a non-invasive method, versatile, very simple and widely used in medical services to provide physiological parameters reading without needing someone to operate the cuff or listen to the blood flow sounds (please see Figure 4).

Figure 4. Vital Signs Monitor.

5. ***Clinical Information****:* will be collected (type and stage of breast cancer, details about the treatment performed and some latest lab results), by the researchers reviewing your medical health records with your permission. See the end of the consent form for checkbox.

Please feel free to ask any questions regarding the procedures and goals of the study or your role.

Funded by:

- This study is being supported by internal funds from the Vice-Dean's office.

Potential Risks:

- Transient physical discomfort due to massage therapy sessions.
- Activation of any embarrassment from answering questions that trigger memories of an unpleasant event.
- Since personal medical information will be collected, the breach of confidentiality is a potential risk, however, many procedures will be followed to minimize this risk (please see the topic: "*Confidentiality*" below).

***Potential Benefits*:**

- This study may directly benefit you at the time of your involvement by providing the MT sessions and a potential relief sensation, plus periodic symptoms evaluations.
- It is hoped the information gained from this study can be used in the future to benefit other people with a similar condition.
- Advice, care, and support by trained clinical staff who understand about the occurrence of late cancer-related symptoms.
- Closer monitoring of your late symptoms, care and treatment
- The opportunity to access a promising new treatment being the first to benefit from a new approach under study

Safeguards to alleviate these risks:

- There is no information on rates of harm related to massage therapy sessions in patients with cancer according to previous publications, however, you will be asked to report as soon as possible any side effects to the investigator. In general population, some rare side effects may occur in approximately 1.1% of clients receiving massage, such as: (i) physical discomfort; (ii) bruising; (iii) headache and (iv) tiredness. This study will receive the collaboration and supervision of Pam Fitchner, a registered massage therapist, and cranio-sacral and somato-emotional release therapist for over 12 years. If any participant experiences any worries or discomfort, she will be referred to Ms. Fitcher who will be able to manage any side effects. Also, if you experience any worries or discomfort you will be informed about the possibility of withdrawing from the study. You may withdraw from the study at any time without any penalty or loss of benefits to which you are otherwise entitled (please see the topic "*Right to Withdraw*" below)

Compensation:

- There are no study-specific costs to the participants. Participants will be given a gift card of $10 in appreciation for their time in the study.
-

Confidentiality:

- As a procedure to safeguard confidentiality of responses, handwritten notes taken during the data collection will be assigned an alpha-numeric code (each participant will receive a study code, which means that your name will be de-identified) and no identifying information will be associated with any name. In reporting findings, only summaries of the results will be disseminated, and your identity will not be revealed.
- In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected. The study data will be stored securely (in a locked cabinet contained within a

locked office under the supervision of the principal investigator Dr. Premkumar) by the study team for a minimum of 5 years after the final results are published.

- Research records and medical records identifying you may be inspected by the University of Saskatchewan Biomedical Research.
- Ethics Board, or regulatory authorizes for quality assurance and monitoring purposes.
- It is the intention of the research team to publish results of this research in scientific journals and to present the findings at related conferences and workshops, but your identity will not be disclosed.

Storage of Data:

- To protect the confidentiality of the participant data collection instruments will not contain information that could readily identify participants. Instead will be used study codes. Each sample will receive a unique study ID, comprising of an alphanumeric code (e.g.: mts01, mts02, mts03), which will be inserted onto their data document (questionnaires, medical chart, saliva tubes etc.). To link each participant with their responses/ data the study ID will be assigned to each participant prior to collecting data. On a separate file participants' name will be typed along with their unique study ID - master list. Digitalized data will be coded and stored on researcher's personal computer as encrypted data and with a secured password. Paper data will be scanned and stored electronically and paper data will be destroyed after five (5) years. After the 5-year storage period the paper and electronic data will be destroyed by confidential shredding and permanent deletion, respectively. All saliva samples remaining will be unlabeled and then discarded in the lab facility according to the applicable institutional policies, and local and national regulations to handle discarding specimens process. No biobank or biorepository is intended to be created.
- Ms. Bomfim will transport any data collected in a locked backpack from collection site to Health Sciences Building Hsc E wing room# 3226 at the University of Saskatchewan - 107, Wiggins Road. The saliva samples will be transferred into a small container using a sponge. Saliva samples collected using the method proposed by this study are stabilized and can be transported and/or stored long-term at ambient/room conditions. During the duration of the study, the saliva tubes will be also coded accordingly and stored at the Cancer Cluster Laboratory 4D01 Health Sciences Bldg. 107, Wiggins Road Saskatoon, SK at the University of Saskatchewan.

Dissemination of Results:

- The research data may be used to create poster presentations and/or conference abstracts, as well as for writing a journal article for submission to an academic journal.

Right to Withdraw:

- Your participation is voluntary, and you can answer only those questions that you are comfortable with. You may withdraw from the research project for any reason, at any time without explanation or penalty of any sort.
- If you do not wish to participate, you will not lose the benefit of any medical care to which you are entitled or are presently receiving. It will not affect your relationship with the Saskatoon Cancer Centre.

- Should you wish to withdraw by any reason, for example: if you experience any worries or discomfort or even if you are not able to cope with the duration of the study. Regardless the reason, if you withdraw from the study your data and samples collected so far will be also discarded unless the data have been already de-identified.
- Your right to withdraw statement to explain the point at which data withdraw may no longer be required. Your right to withdraw data from the study will apply until results have been disseminated. After this date, it is possible that some form of research dissemination will have already occurred and it may not be possible to withdraw your data.

What happens if something goes wrong?

- It is important to mention that by signing this consent form it is ensured that you do not waive any of your legal rights.

Follow up:

- The study results will be presented to all participants and key informants in a small gathering in a location that will be favourable for all by the end of September 2018. During this gathering session, I will acknowledge the participation of all participants and thank any supporter institution, such as Saskatchewan Cancer Agency. You will receive a brochure with a summary of the principal results in layman's terms, although copies of the final research report will be available and send to you via mail or e-mail (please see below). You will be encouraged to ask any questions you may have or express their concerns about the research. For those that will be unable to attend, you will be contacted individually by call to be informed about the results of this study.

Would you like to be informed about the final results of this study ?

☐ NO

☐ YES If yes:
by email: _____
by mail: _____

Questions or Concerns:

- Contact the researcher(s) using the information at the top of page 1;
- This research project has been approved on ethical grounds by the University of Saskatchewan Research Ethics Board. Any questions regarding your rights as a participant may be addressed to that committee through the Research Ethics Office ethics.office@usask.ca (306) 966-2975. Out of town participants may call toll free (866) 966-2975.

If you have any questions concerning the research project, please feel free to ask at any point; you are also free to contact the researcher at the number provided if you have other questions. Your signature below indicates that you have read and understand the description provided; I have had an opportunity to ask questions and my/our questions have been answered. I consent to participate in the research project. A copy of this Consent Form has been given to me for my records.

Effects of Swedish massage on quality of life, sleep, stress, fatigue and on biological markers levels in recently treated patients with breast cancer
CONSENT TO PARTICIPATE

By signing this document, I am confirming that:

- **I have read the information in this consent form.**
- **I understand the purpose and procedures and the possible risks and benefits of the study.**
- **I was given sufficient time to think about it.**
- **I had the opportunity to ask questions and have received satisfactory answers.**
- **I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future medical care.**
- **I agree to tell the study doctor at once if I feel I have had any unexpected or unusual symptoms.**
- **I understand that this study may not provide any benefits to me.**
- **I give permission for the use and disclosure of my de-identified personal health information collected for the research purposes described in this form.**
- **I give permission for the access of my identifiable personal health information for the research purposes described in this form.**
- **I understand that by signing this document I do not waive any of my legal rights.**
- **I understand I will be given a signed and dated copy of this consent form.**

Would you permit that the researchers of this study have access to your medical chart to collect additional clinical data regarding your previous condition and health history?

☐ NO

☐ YES

_____	_____	_____
Name of Participant	*Signature*	*Date*
_____	_____	_____
Name of Researcher	*Signature*	*Date*

A copy of this consent will be left with you, and a copy will be taken by the researcher

Appendix D - Material for Recruitment

Photo credit: http://flickr/p/v8stAn

IF I AM INTERESTED, WHAT SHOULD I DO NEXT?

Contact your doctor to let him or her know that you would like to learn more about the study and he will put you in contact with the researchers. Make time to talk to the researchers in detail about what is involved in the study and to find out whether you qualify to participate.

WHAT IF I AGREE TO TAKE PART, BUT THEN CHANGE MY MIND? CAN I WITHDRAW MY CONSENT?

Yes. You may withdraw from the study at any time without any penalty or loss of benefits to which you are otherwise entitled. If you choose to withdraw after having agreed to participate, you just have to contact any of the researchers involved in the study.

Saskatchewan Cancer Agency

University of Saskatchewan
College of Medicine

McKAY CAREER TRAINING

MTAS
Massage Therapist Association of Saskatchewan

LiveWell

Saskatoon Health Region

Sleep Lab & Sleep Disorders Center
Saskatoon Health Region's LiveWell Chronic Disease Management (CDM)

RESEARCHERS CONTACT:

Emiliana Bomfim
Ph.D. Student
College of Medicine, University of Saskatchewan
E-mail: e.bomfim@usask.ca
Phone: (306) 250-0148

Dr. Kalyani Premkumar
Professor
College of Medicine, University of Saskatchewan
Email: kalyani.premkumar@usask.ca
Phone: (306) 966-1409

SWEDISH MASSAGE THERAPY AND CANCER

RESEARCH STUDY

PARTICIPANT RECRUITMENT INFORMATION

TITLE OF THE STUDY: Effects of Swedish massage on quality of life, sleep, stress, fatigue and biological markers levels in recently treated patients with breast cancer

Your doctor has given you this brochure to provide you with a general idea of what would be involved in participating in this study.

WHY HAS MY DOCTOR GIVEN ME THIS BROCHURE?

Your doctor feels that you may be an appropriate candidate for this new medical study.

WHAT IS THE PURPOSE OF THIS STUDY?

This study intends to understand the effects of Swedish massage therapy on sleep patterns, stress, quality of life, fatigue and some biological markers in patients with history of breast cancer.

Photo credit: https://flickr/p85tpWs

WHAT WILL I HAVE TO DO IF I PARTICIPATE IN THE STUDY?

If you meet the criteria necessary to take part in the study and choose to participate, you will receive one-hour weekly massage session for 8 weeks from a trained massage therapist.

WHAT HAPPENS ONCE THE STUDY STARTS?

If you choose to participate in this study you will be requested to:

- Commit approximately one hour per week of your time for 8 weeks.

- You will participate on the data collection process, which involves:

a. Wearing a wrist monitor* (similar to a watch) to record your sleep patterns for 5 days at the beginning, middle and end of the study.

b. Having your physiological parameters (blood pressure, heart rate, and oxygen saturation) assessed before and after the massage therapy.

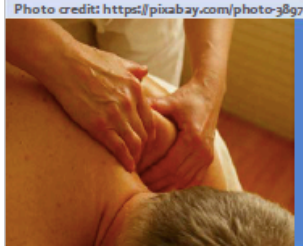
c. Having your saliva sample collected on a few occasions (the saliva will be used to measure some biomarkers that might be related to stress, fatigue and sleep).

d. Answering 3 questionnaires about quality of life, fatigue and sleep at the beginning, middle and end of the study.

WILL TAKING PART IN THE STUDY HELP ME FEEL BETTER?

There is no guarantee that you will benefit from taking part in this study. You may benefit from having access to massage therapy sessions and periodic symptoms evaluation. The purpose of the study is to investigate the effects of massage therapy, so we cannot yet say whether or not it will be beneficial. However, you will be given "gold standard" medical attention and your participation will help us to learn things about complementary treatment options that could benefit others in the future facing the same situation.

Photo credit: https://pixabay.com/photo-3897161/



WHAT IF I'M NOT INTERESTED IN TAKING PART IN THE STUDY? WILL THAT AFFECT MY RELATIONSHIP WITH MY DOCTOR?

Taking part in this - or any clinical trial - is entirely voluntary. You should not feel any pressure to enroll. If you are not certain that you wish to participate or if you decide not to take part, you will not suffer any penalty or lose any benefits to which you are otherwise entitled.

*WHAT IS A WRIST MONITOR?

Wrist monitor is a tool similar to a watch used to assess sleep. Participants will use it for at least 5 days.

This tool has an integrated accelerometer, which provides data related to daily activity and sleep pattern (such as sleep efficiency, frequency and duration).

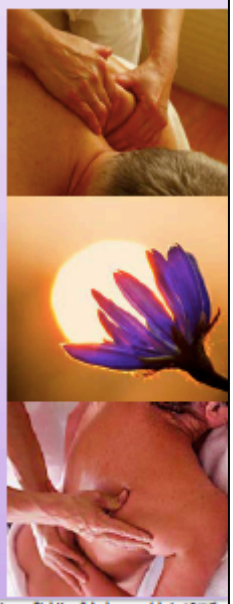
We are looking for volunteers to participate in an upcoming clinical research study about massage therapy & breast cancer survivors

RESEARCH STUDY

BREAST CANCER SURVIVORS NEEDED

YOU MAY QUALIFY IF YOU ARE:

- Female over 18 years
- A breast cancer survivor - stages I to III
- Have completed the treatment in the last month



QUALIFIED PARTIPANTS WILL:

- Receive one-hour weekly massage session for 8 weeks from a trained massage therapist.

- Be asked to answer questionnaires about quality of life, stress, fatigue and have their sleep quality assessed.

- Have your saliva sample collected during set intervals to measure substances related to stress, fatigue and sleep.

Everything will be provided free of any cost.

Photo credit: https://pixabay.com/photo-3839/
Photo credit: https://pixabay.com/photo-3879/
Photo credit: https://flic.kr/p/6dsAn

TO PARTICIPATE, PLEASE CONTACT US:

Emiliana Bomfim
Ph.D. Student
Health Sciences Graduate Program
College of Medicine
University of Saskatchewan
E-mail: e.bomfim@usask.ca
Phone: (306) 250-0148

Dr. Kalyani Premkumar
Professor
Department of Community Health and Epidemiology
College of Medicine
University of Saskatchewan
Email: kalyani.premkumar@usask.ca
Phone: (306) 966-1409

MTAS Massage Therapist Association of Saskatchewan

Saskatchewan Cancer Agency

University of Saskatchewan College of Medicine

LiveWell Saskatoon Health Region
Sleep Lab & Sleep Disorders Center

McKAY CAREER TRAINING

Appendix E - Functional Assessment of Cancer Therapy Version B (Fact-B)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble eating the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

.....

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4

B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix F - Functional Assessment of Cancer Therapy Fatigue (Fact-F)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix G - Perceived Stress Scale (PSS)

Perceived Stress Scale

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.

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

	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

Please feel free to use the *Perceived Stress Scale* for your research.

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www.mindgarden.com

References

The PSS Scale is reprinted with permission of the American Sociological Association, from Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*, 386-396.

Cohen, S. and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) *The Social Psychology of Health*. Newbury Park, CA: Sage, 1988.

Appendix H - Sleep Diary

SLEEP DIARY

PARTICIPANT ID: _____

Complete the diary each morning (answer in the morning after waking for the day). Do not worry too much about giving exact answers. An estimate will do it.

Start date: ____/____/___ **Day of week:**	**DAY 1** _____	**DAY 2** _____	**DAY 3** _____	**DAY 4** _____	**DAY 5** _____
Time you went to bed last night					
Time you got out of bed this morning					
Number of times you woke up during the night					
Took off the sleep watch? ***(e.g. to take a shower)***	Yes N	Yes No	Yes No	Yes No	Yes No
	If yes, for how long? _____	If yes, for how long? _____	If yes, for how long? _____	If yes, for how long? _____	If yes, for how long? _____
Took a nap?	Yes No	Yes No	Yes No	Yes No	Yes No
	If yes, for how long? _____	If yes, for how long? _____	If yes, for how long? _____	If yes, for how long? _____	If yes, for how long? _____
Medications you took today (if any)					
Have you consumed caffeinated drinks?	**If yes, how many cups?**	**If yes, how many cups?**	**If yes, how many cups?**	**If yes, how many cups?**	**If yes, how many cups?**
How did you feel when you woke up?	☐Refreshed ☐Somehow refreshed ☐Fatigued	☐Refreshed ☐Somehow refreshed ☐Fatigued	☐Refreshed ☐Somehow refreshed ☐Fatigued	☐Refreshed ☐Somehow refreshed ☐Fatigued	☐Refreshed ☐Somehow refreshed ☐Fatigued

This Sleep Diary was developed based on the National Sleep Foundation Sleep Diary from U.S. Access: https://sleepfoundation.org/sleep-diary/SleepDiaryv6.pdf

Appendix I - Clinical and Demographic Questionnaire

i. DEMOGRAPHIC DATA	
Participant ID#:	
File Number:	
Age:	
Level of education:	☐ No formal education ☐ Less than high school ☐ High School ☐ College or Bachelor's degree ☐ Less than high school
Marital status:	☐ Married ☐ Not married ☐ Stable Union ☐ Divorced ☐ Widowed ☐ Other:_____
Birth country:	
Work:	☐ Not working ☐Full time worker ☐Part-time worker ☐Domestic worker ☐Pensioner
Religion:	1. ☐ Christian 2. ☐Other:_____
Ethnicity:	1. ☐ Black 2. ☐White 3. ☐Native American
ii. DISEASE CHARACTERISTICS	
Diagnosis:	
Date of diagnosis:	
Stage:	☐ Stage I ☐ Stage II ☐ Stage III
Disease Classification:	1.☐ Primary neoplasm 2. ☐ Recurrent neoplasm
If recurrent:	1. Date of recurrence:
Week after the treatment:	1. Number of week (s) after the completion of treatment:
Other characteristics:	1. Type of tumor: 2. Size: 3. Location: 4. T (size):_____ N(node):_____ M(metastasis):_____
Medications in use: _____	

iii. TREATMENT CARACTHERISTICS	
Treatment:	**1. Chemotherapy:** ☐ No ☐ Yes: **1.1** First day of treatment: _____ **1.2** Last day of treatment: _____ **1.3** Type of treatment: _____ **2. Radiotherapy:** ☐ No ☐ If yes: **2.1** First day of treatment: _____ **2.2** Last day of treatment: _____ **2.3** Type of treatment: _____ **3. Surgery:** ☐ No ☐ If yes: **3.1** Date of procedure: **3.2** Type of surgery: ☐ lumpectomy ☐ quadrantectomy ☐ partial mastectomy ☐ radical mastectomy **3.3** Reconstructive or breast implant surgery: ☐ No ☐ If yes, which:_____ When: _____ **3.4** Lymph node surgery: ☐ No ☐ If yes: ☐ Sentinel node ☐ Axillary node dissection ☐ Other **4. Hormone Therapy:** ☐ No

	☐ If yes, which:_____ When: _____ **5. Other:** ☐ No ☐ If yes, which:_____ When: _____
iv. OTHER CLINICAL INFORMATION	
Comorbidities:	☐ None ☐ If yes, which: _____
Latest lab results:	Hemoglobin: Hematocrit: Date:
In use of any medication:	☐ No ☐ If yes, which one (s): 1._____ How long: _____ 2. _____ How long: _____ 3. _____ How long: _____

Appendix J - Swedish Massage Therapy Protocol

This protocol was developed based on previous studies with breast cancer population [27,28,35,36,37,39,40,41,260,135]. Women will receive 1-hour massage sessions (1 massage per week for 8 weeks).

Observations before starting the protocol:

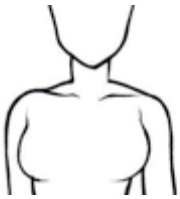
1. No talking during massage except for asking for pressure and how they are feeling
2. Same oil usage for all participants- fractioned coconut oil
3. Relaxation massage – not treating muscles specifically or doing deeper pressure as week progress. Do light to moderate pressure. Little to no tapotement.
4. If patient is unable to lie prone, then she can use the sidelying position
5. If any area has lymphedema or swelling, the therapist can adapt by moving to another area.

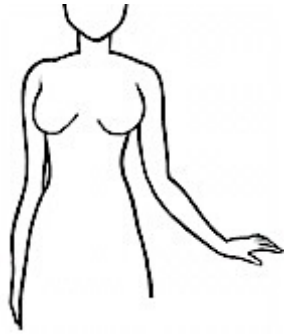
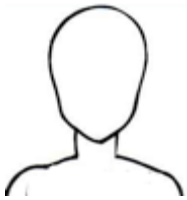
PRONE (OR SIDELYING)

BODY PART	TIMING	TECHNIQUE
	5 min. [1 foot at a time for 2.5 minutes each]	**FOOT MASSAGE:** Along with diaphragm breathing. Begin with 3 diaphragm breaths with your hand on the back of the participant's diaphragm. Bring the kneed into 90 degrees' flexion if possible. Flex/extend the foot – Get the patient to breathe in, do plantar flexion (foot down towards the table) and then breathe out, dorsiflexion (foot upwards towards the ceiling). Massage the bottom and top of the feet squeezing the heel. Could do some frictions, along with compressions.
	10 min. [1 leg at a time for 5 minutes each]	**LOWER LIMBS:** Stroke and knead the calf muscles. Shake (gently rocking) the leg with the knee flexed onto therapist's shoulder (if able to). Effluarge and Petrissage Strokes from the heel up to and over the buttock, circular stroking to the buttock area and stroking from the buttock and back down to the feet.

	10 min.	**BACK**: Effleurage 2 x on either side of the spine. Stroke from the base of the shoulders. Do deeper palmar or fingertip/thumb kneading. Squeeze neck and shoulder areas with compressions. Can use the edge of hand to rub alongside the spine from the top to the bottom of the back. Squeeze and stretch the neck muscles
	7 min. [1 arm at a time for 3.5 minutes each]	**UPPER LIMBS:** Effleurage, Petrissage. Light stroke and gentle palmar or fingertip kneading; stroke from the base of shoulders to out over the arms to the elbow and effleurage back up to the neck

SUPINE

	7 min. [1 leg at a time for 3.5 minutes each]	**LOWER LIMBS:** Ending together. Effleurage and Petrissage. Stroke and knead the anterior thigh region. Stroke from the hip to the calf and foot, holding both legs together at the heels and then pulling them with traction. Also, do a gentle pulling of the legs together to the right and to the left.
	5 min. [1 side of the chest at a time for 2.5 min.]	**TORSO/ BREAST AREA:** Effleurage, Petrissage. Start with one hand on top of the other at the sternum and do a gentle compression with 3 deep breaths. Stroke and knead into the shoulder; do range of motion with the shoulder on the same side, then treat opposite side of chest. Do rib raking and stroking along rib cage- 3 spots 3x each from below to axilla, depending on scar tissue and sensitivity. do slow progressive compressions from the armpit to the chest- alternate stroking from sternum along pectoralis minor to shoulder and fingertip kneading and stroking. Do compressions along the arm starting at the shoulder.

	6 min. [1 arm at a time for 3 minutes each]	**UPPER LIMBS:** Effleurage and Petrissage. Stand at head facing towards chest. Press down on the shoulders with the palms of the hands and into any mid-shoulder trigger points. Stroke from the sternum to the armpit. Then, move to the wrist and stand facing towards the chest. Stroke from the wrist to the shoulder and do range of motion with each arm.
	5 min.	**NECK, HEAD AND FACE:** Effleurage and Petrissage. Stroke and fingertip knead and strip along neck. Circular knead, gentle stroke on face and scalp.
	5 min.	**NECK:** Lengthening of the neck by doing cervical traction with one hand on each side of the head and gently pulling. Stroke forehead, circular stroke and stretch jaw area.

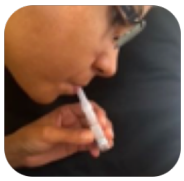
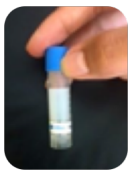
Appendix L - Instructions on Collecting Saliva Samples

Before Saliva Collection:

Avoid foods with high sugar (e.g. pop), acidity (e.g. alcoholic beverages), or high caffeine content (e.g. coffee), 60 min. before sample collection.

Do not eat, brush your teeth or smoke within 60 minutes of sample collection.

During Saliva Collection:

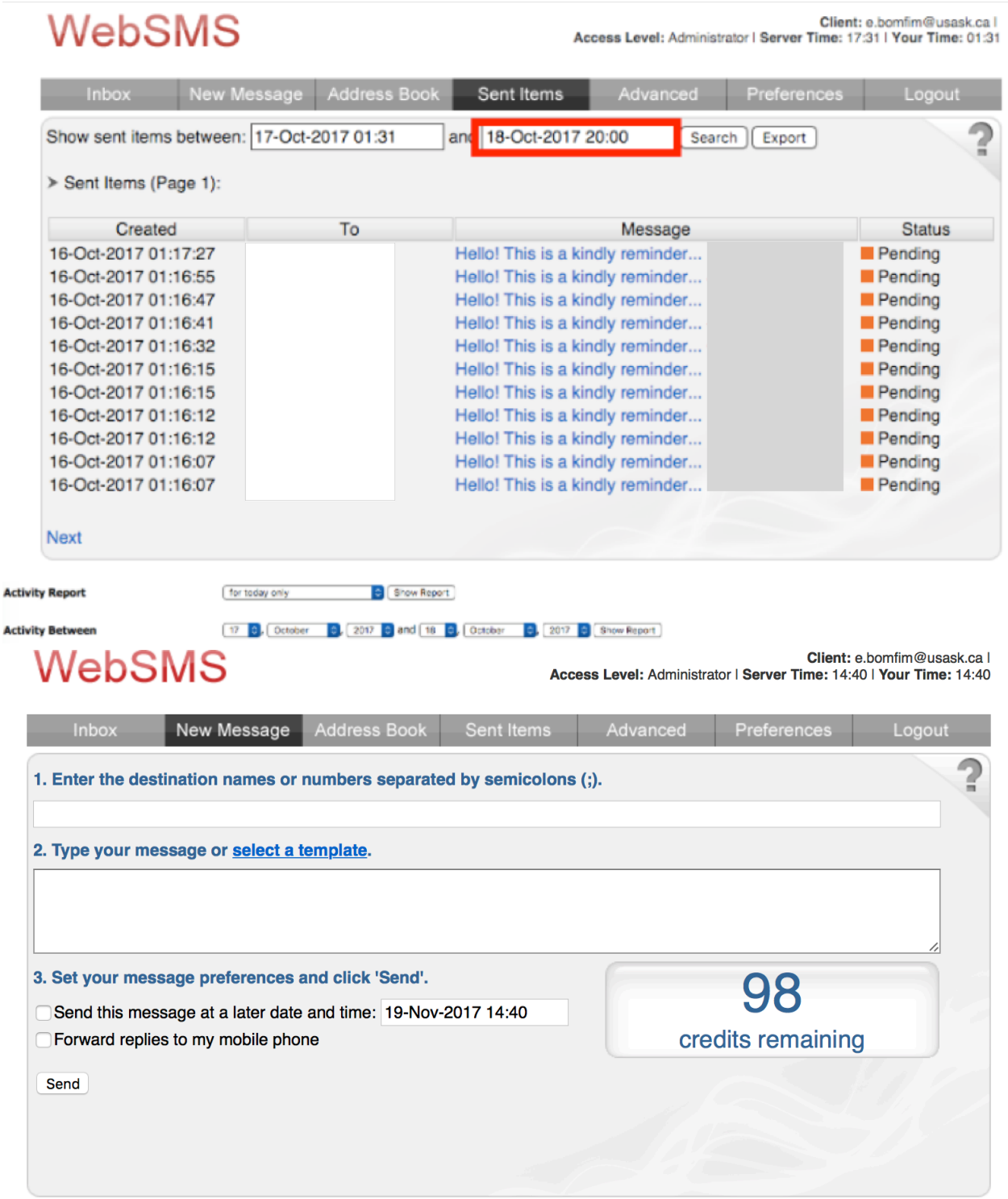
	STEP 1: Rinse mouth with water to remove food residue**.**
Wait at least 10 minutes after rinsing to collect the saliva	
	STEP 2: Open foil pouch and remove the Saliva Collection Aid.
	STEP 3: Place the ribbed-end of the Saliva Collection Aid securely into the correct collection tube.
	**STEP 4**: Allow saliva to pool in mouth. Then, with head tilted forward, gently force saliva through the Saliva Collection Aid into the tube. Fill to 2mL. Reserve a small amount of air space in the tube to accommodate liquid expansion during freezing.
	**STEP 5**: Remove and discard Saliva Collection Aid. Attach cap to collection vial and tighten.

After Saliva Collection: Immediately after collection, freeze samples at or below -20°C (regular household freezer). If freezing is not possible

Appendix M - Saliva Collection Sheet

DAY	CAP COLOR	WHEN TO COLLECT SAMPLE	COLLECTION START/ STOP TIME		COMMENTS
_____	Orange	5pm	_____:_____ ☐ p.m.	_____:_____ ☐ p.m.	
	Orange	8pm	_____:_____ ☐ p.m.	_____:_____ ☐ p.m.	
_____	Blue	Upon awake	_____:_____ ☐ a.m.	_____:_____ ☐ a.m.	
	Blue	30 min after awake	_____:_____ ☐ a.m.	_____:_____ ☐ a.m.	
	Blue	Noon	_____:_____ ☐ p.m.	_____:_____ ☐ p.m.	
	Blue	5pm	_____:_____ ☐ p.m.	_____:_____ ☐ p.m.	
	Blue	8pm	_____:_____ ☐ p.m.	_____:_____ ☐ p.m.	
_____	Green	Upon awake	_____:_____ ☐ a.m.	_____:_____ ☐ a.m.	
	Green	30 min after awake	_____:_____ ☐ a.m.	_____:_____ ☐ a.m.	
	Green	Noon	_____:_____ ☐ p.m.	_____:_____ ☐ p.m.	
	Green	5pm	_____:_____ ☐ p.m.	_____:_____ ☐ p.m.	
	Green	8pm	_____:_____ ☐ p.m.	_____:_____ ☐ p.m.	

Appendix N - Bulk Messaging Communication Platform



Appendix O - Template of the 96-well plate Used for Saliva Analysis

	1	2	3	4	5	6	7	8	9	10	11	12
A	**Std1**	**Std1**										
B	**Std2**	**Std2**										
C	**Std3**	**Std3**										
D	**Std4**	**Std4**										
E	**Std5**	**Std5**										
F	**Std6**	**Std6**										
G	**Std7**	**Std7**										
H	**Blank**	**Blank**										

Appendix P - Tables of Descriptive Statistics at All Timepoints

Table A.1. Descriptive statistics of the total fatigue (FACT-B) scores at respective time-points and independent variables' categories in a sample of BCS, Saskatoon.

Outcome	Baseline	Assessment 1	Assessment 2	Endpoint
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Total QoL	92.0 ± 16.14	97.6 ± 17.4	106.1 ± 17.8	103.8 ± 17.14
QoL by Age				
30-40	86.7 ± 3.0	98.5 ± 7.2	99.3 ± 6.5	105.3 ± 7.7
41-50	82.5 ± 12.7	90.8 ± 11.9	97.2 ± 23.1	98.6 ± 15.1
51-60	95.6 ± 18.44	100.6 ± 17.8	110.5 ± 19.6	105.7 ± 18.9
≥61	95.0 ± 17.48	96.6 ± 24.42	108.2 ± 15.2	103.2 ± 21.3
QoL by Stage				
I	94.6 ± 16.4	98.1 ± 17.3	107.9 ± 17.1	107.1 ± 17.6
II	91.2 ± 17.1	92.5 ± 21.9	109.1 ± 21.6	98.5 ± 18.5
III	89.4 ± 16.8	101.9 ± 13.2	101.0 ± 16.1	104.8 ± 16.4
QoL by Months After Treatment				
< 3 months	93.3 ± 14.2	103.0 ± 11.0	104.6 ± 19.1	107.0 ± 14.0
≥ 3 months	90.6 ± 18.5	91.6 ± 21.4	107.8 ± 17.0	100.3 ± 20.0
QoL by Sleep Aids in Use				
On	88.5 ± 14.7	93.1 ± 18.9	107.2 ± 20.5	99.2 ± 17.8
Off	95.8 ± 17.4	102.5 ± 14.8	105.0 ± 15.2	108.7 ± 15.6
QoL by Treatment Type				
Chemo only	113.8 ± 10.0	117.1 ± 13.9	117.8 ± 1.6	122.5 ± 9.1
Chemo and radiation	122 ± 0.0	126 ± 0.0	126 ± 0.0	130 ± 0.0
Radiation and surgery	79.5 ± 11.8	83.9 ± 13.0	100.9 ± 19.0	93.5 ± 18.1
Surgery and chemo	86.0 ± 8.3	91.5 ± 1.5	102 ± 21	97.3 ± 5.5
Surgery only	105.5 ± 0.0	114.1 ± 0.0	116.8 ± 0.0	124.6 ± 0.0
All three	91.4 ± 14.1	97.8 ± 17.0	104.8 ± 19.1	102.6 ± 15.8
QoL by Hormone Therapy				
Tamoxifen	100.0 ± 13.7	103.5 ± 14.4	109.7 ± 24.2	107.6 ± 12.7
Aromatase Inhibitors	91.3 ± 14.2	94.6 ± 19.6	110.2 ± 12.3	104.7 ± 18.8
None	86.1 ± 19.6	96.8 ± 17.6	97.2 ±17.1	99.2 ± 19.2

Table A.2. Descriptive statistics of the total fatigue (FACT-F) scores at respective time-points and independent variables' categories in a sample of BCS, Saskatoon.

Outcome	Baseline	Assessment 1	Assessment 2	Endpoint
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Total Fatigue	28.0 ± 10.6	34.8 ± 7.6	35.8 ± 10.3	35.7 ± 8.3
Fatigue by Age				
30-40	30.3 ± 11.2	34.7 ± 11.2	36.1 ± 12.7	36.3 ± 11.5
41-50	21.5 ± 7.5	31.7 ± 2.8	28.7 ± 12.3	32.5 ± 3.8
51-60	30.5 ± 12.3	35.2 ± 8.6	37.5 ± 11.0	35.9 ± 9.9
≥61	27.3 ± 9.4	36.1 ± 7.7	37.5 ± 7.0	37.4 ± 7.3
Fatigue by Stage				
I	27.3 ± 9.6	35.3 ± 8.0	38.2 ± 7.4	37.0 ± 8.9
II	30.7 ± 11.6	36.0 ± 6.7	37.9 ± 12.1	36.7 ± 4.8
III	26.4 ± 12.0	32.8 ± 8.7	30.5 ± 11.2	33.1 ± 10.6
Fatigue by Months After Treatment				
< 3 months	28.0 ± 11.0	35.7 ± 8.1	35.2 ± 12.6	37.1 ± 8.5
≥ 3 months	28.0 ± 10.7	33.7 ± 7.4	36.4 ± 7.7	34.2 ± 8.2
Fatigue by Sleep Aids in Use				
On	26.8 ± 9.2	34.7 ± 6.1	38.4 ± 10.2	36.4 ± 8.1
Off	29.4 ± 12.3	34.8 ± 9.3	32.9 ± 10.2	35.0 ± 8.9
Fatigue by Treatment Type				
Chemo only	34.5 ± 14.8	45 ± 4.2	44.5 ± 0.7	45.2 ± 0.3
Chemo and radiation	46 ± 0.0	43 ± 0.0	41 ± 0.0	42 ± 0.0
Radiation and surgery	20 ± 3.5	28.8 ± 2.1	33.8 ± 4.8	31.4 ± 8.5
Surgery and chemo	23.3 ± 11.0	27.6 ± 6.0	30.3 ± 13.5	28.3 ± 6.1
Surgery only	36 ± 0.0	45 ± 0.0	47 ± 0.0	47 ± 0.0
All three	29.5 ± 10.5	35.9 ± 6.8	35.1 ± 12.2	36.4 ± 7.4
Fatigue by Hormone Therapy				
Tamoxifen	32.8 ± 12.4	39.0 ± 7.1	40.2 ± 13.9	39.4 ± 5.7
Aromatase Inhibitors	28.0 ± 8.0	34.8 ± 6.7	37.3 ± 5.9	37.6 ± 6.6
None	24 ± 12.17	31.1 ± 8.5	29.8 ± 10.7	30 ± 10.0

Table A.3. Descriptive statistics of stress (PSS) total score at respective time-points and independent variables' categories in a sample of BCS, Saskatoon.

Outcome	Baseline	Assessment 1	Assessment 2	Endpoint
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Total Stress	20.9 ± 7.2	17.8 ± 6.0	17.9 ± 6.5	17.4 ± 6.6
Stress by Age				
30-40	22.3 ± 3.2	18.3 ± 4.0	20.6 ± 0.57	16.3 ± 5.0
41-50	21.5 ± 2.6	18.7 ± 2.8	23.5 ± 9.39	18.2 ± 0.9
51-60	19.6 ± 9.2	17.6 ± 6.7	17.1 ± 5.7	17.5 ± 7.6
≥61	22.1 ± 7.6	17.3 ± 8.2	14.1 ± 5.1	17.5 ± 8.9
Stress by Stage				
I	22.3 ± 6.6	18.2 ± 7.2	15.8 ± 5.3	16.4 ± 8.2
II	19.8 ± 8.8	17.1 ± 6.2	19.7 ± 8.6	19.0 ± 6.4
III	20.2 ± 7.0	18.0 ± 5.0	18.7 ± 5.7	17.2 ± 5.0
Stress by Months After Treatment				
< 3 months	19.2 ± 5.6	16.3 ± 5.6	18 ± 7.0	15.5 ± 5.8
≥ 3 months	22.8 ± 8.4	19.4 ± 6.3	17.8 ± 6.2	19.5 ± 7.1
Stress by Sleep Aids in Use				
On	21.6 ± 7.7	18.0 ± 6.0	18.1 ± 7.8	17.7 ± 8.2
Off	20.1 ± 6.8	17.5 ± 6.1	17.6 ± 5.0	17.1 ± 4.6
Stress by Treatment Type				
Chemo only	15 ± 1.4	7.5 ± 2.1	10.5 ± 0.7	10.5 ± 2.1
Chemo and radiation	7 ± 0.0	10 ± 0.0	13 ± 0.0	13 ± 0.0
Radiation and surgery	25.8 ± 5.6	19.4 ± 3.9	21.2 ± 7.3	20 ± 8.7
Surgery and chemo	26.3 ± 0.5	23.3 ± 4.1	19.6 ± 5.1	20.3 ± 3.0
Surgery only	16 ± 0.0	16 ± 0.0	15 ± 0.0	7 ± 0.0
All three	20.0 ± 7.1	18.3 ± 5.6	18 ± 6.7	18.1 ± 5.9
Stress by Hormone Therapy				
Tamoxifen	18 ± 7.0	15.1 ± 8.2	17.3 ± 8.5	16 ± 4.8
Aromatase Inhibitors	22 ± 6.7	18.3 ± 5.1	17.3 ± 6.0	16.4 ± 7.5
None	22 ± 8.3	19.4 ± 5.1	19.2 ± 6.1	20.2 ± 6.7

Table A.4. Descriptive statistics of SD readings (in minutes) at respective time-points and independent variables' categories in a sample of BCS, Saskatoon.

Outcome	Baseline	Assessment 1	Assessment 2	Endpoint
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Total Sleep Duration (SD) (in minutes)	326.6 ± 108.6	255.0 ± 100.7	357.2 ± 105.9	277.5 ± 108.5
SD by Age				
30-40	283.0 ± 110.2	228.7 ± 104.6	319.9 ± 88.1	252.7 ± 77.7
41-50	344.7 ± 101.0	223.7 ± 56.4	401.3 ± 175.7	210.1 ± 62.6
51-60	339.4 ± 109.2	266.9 ± 113.2	354.5 ± 85.4	283.8 ± 76.9
≥61	315.1 ± 132.6	268.9 ± 116.5	351.2 ± 110.3	324.2 ± 172.2
SD by Stage				
I	300.3 ± 111.3	250.8 ± 99.9	330.2 ± 75.5	290.5 ± 112.95
II	352.5 ± 126.5	264.5 ± 94.2	417.9 ± 141.2	283.6 ± 132.8
III	334.6 ± 94.1	250.7 ± 122.0	331.3 ± 86.0	254.7 ± 87.2
SD by Months After Treatment				
< 3 months	322.1 ± 85.1	266.6 ± 61.3	368.1 ± 108.4	267.6 ± 102.4
≥ 3 months	331.6 ± 134.0	242.3 ± 133.7	345.3 ± 107.08	288.2 ± 118.8
SD by Sleep Aids in Use				
On	350.3 ± 129.7	269.3 ± 97.4	380.3 ± 118.5	303.8 ± 128.0
Off	300.8 ± 77.7	239.3 ± 106.7	332.1 ± 88.9	248.8 ± 78.4
SD by Treatment Type				
Chemo only	320.5 ± 150.5	343.8 ± 17.9	364.7 ± 85.4	354.4 ± 174.9
Chemo and radiation	279.8 ± 0.0	175.2 ± 0.0	197 ± 0.0	148.0 ± 0.0
Radiation and surgery	242.2 ± 88.4	248.4 ± 102.7	261.0 ± 19.3	264.2 ± 107.5
Surgery and chemo	354.2 ± 113.7	221.5 ± 109.4	422.1 ± 17.2	326.1 ± 27.9
Surgery only	336.3 ± 0.0	211.1 ± 0.0	408.6 ± 0.0	344.2 ± 0.0
All three	362.0 ± 112.2	262.2 ± 113.4	391.8 ± 117.1	261.9 ± 117.0
SD by Hormone Therapy				
Tamoxifen	332.8 ± 125.1	282.2 ± 65.7	402.1 ± 127.7	293.2 ± 11.0
Aromatase Inhibitors	342.9 ± 105.5	248.4 ± 107.5	353.6 ± 103.6	279.6 ± 130.4
None	298.0 ± 110.1	241.0 ± 123.5	324.0 ± 90.1	260.9 ± 82.4

Table A.5. Descriptive statistics of SE at respective time-points and independent variables' categories in a sample of BCS, Saskatoon.

Outcome	Baseline	Assessment 1	Assessment 2	Endpoint
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Total Sleep Efficiency (SE)	92.0 ± 5.0	93.9 ± 3.0	91.3 ± 5.9	92.8 ± 4.6
SE by Age				
30-40	94.8 ± 2.4	96.0 ± 2.0	89.3 ± 5.5	97.5 ± 0.8
41-50	89.2 ± 3.2	92.3 ± 2.0	92.1 ± 6.9	90.7 ± 4.1
51-60	92.2 ± 6.4	93.6 ± 3.9	90.1 ± 5.7	93.0 ± 5.1
≥61	92.1 ± 4.3	94.2 ± 2.2	97.5 ± 0.8	91.5 ± 4.4
SE by Stage				
I	91.8 ± 5.8	94.4 ± 2.9	92.1 ± 5.4	91.9 ± 4.2
II	91.8 ± 3.8	93.5 ± 2.3	90.6 ± 5.3	92.7 ± 4.3
III	92.4 ± 5.8	93.6 ± 4.1	91.0 ± 7.7	94.0 ±5.8
SE by Months After Treatment				
< 3 months	92.9 ± 3.5	93.3 ± 1.9	90.4 ± 5.2	93.0 ± 4.0
≥ 3 months	91.0 ± 6.4	94.5 ± 3.9	92.3 ± 6.9	92.6 ± 5.4
SE by Sleep Aids in Use				
On	91.8 ± 5.0	94.3 ± 2.9	91.7 ± 4.6	92.0 ± 4.5
Off	92.1 ± 5.3	93.4 ± 3.2	90.9 ± 7.2	93.6 ± 4.8
SE by Treatment Type				
Chemo only	92.5 ± 3.2	93.3 ± 0.1	92.0 ± 0.3	89.3 ± 6.6
Chemo and radiation	80.9 ± 0.0	87.1 ± 0.0	84.5 ± 0.0	83.3 ± 0.0
Radiation and surgery	91.3 ± 2.9	94.4 ± 3.3	92.9 ± 3.9	91.5 ± 4.7
Surgery and chemo	94.9 ± 1.1	95.6 ± 4.0	90.7 ± 11.4	94.0 ± 4.8
Surgery only	95.0 ± 0.0	95.5 ± 0.0	90.0 ± 0.0	94.3 ± 0.0
All three	92.1 ± 1.3	93.8 ± 2.6	91.3 ± 6.1	94.4 ± 3.6
SE by Hormone Therapy				
Tamoxifen	92.6 ± 4.5	92.8 v 4.3	91.1 ± 4.8	91.5 ± 4.5
Aromatase Inhibitors	92.5 ± 3.7	91.1 ± 4.8	91.1 ± 5.6	93.6 ± 3.8
None	90.8 ± 7.3	91.1 ± 5.6	91.8 ± 7.8	92.7 ± 6.1

Table A.6. Descriptive statistics of SOL at respective time-points and independent variables' categories in a sample of BCS, Saskatoon.

Outcome	Baseline	Assessment 1	Assessment 2	Endpoint
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Total SOL	3.8 ± 2.4	2.0 ± 1.0	4.6 ± 1.8	3.9 ± 1.3
SOL by Age				
30-40	1.4 ± 0.79	1.7 ± 0.9	6.4 ± 2.3	4.6 ± 1.5
41-50	3.7 ± 2.3	1.3 ± 0.4	4.2 ± 2.2	3.1 ± 0.47
51-60	4.0 ± 2.2	2.2 ± 1.3	4.9 ± 1.5	4.0 ± 1.6
≥61	4.9 ± 2.7	2.3 ± 0.9	3.4 ± 1.4	4.1 ± 1.0
SOL by Stage				
I	5.2 ± 2.6	2.3 ± 1.2	3.9 ± 1.4	4.0 ± 1.4
II	2.9 ± 1.6	1.9 ± 0.8	5.2 ± 2.4	3.7 ± 0.8
III	3.0 ± 2.0	1.7 ± 1.1	4.9 ± 1.5	4.1 ± 1.7
SOL by Months After Treatment				
< 3 months	3.7 ± 2.5	1.8 ± 0.9	4.5 ± 1.9	3.4 ± 1.1
≥ 3 months	4.0 ± 2.3	2.2 ± 1.2	4.6 ± 1.8	4.5 ± 1.3
SOL by Sleep Aids in Use				
On	3.9 ± 2.7	2.3 ± 1.2	4.0 ± 1.6	3.8 ± 1.5
Off	3.7 ± 2.0	1.8 ± 0.8	5.1 ± 2.0	4.0 ± 1.1
SOL by Treatment Type				
Chemo only	6.0 ± 3.7	3.0 ± 1.3	3.16 ± 1.3	3.7 ± 1.0
Chemo and radiation	5.2 ± 0.0	1.6 ± 0.0	4.7 ± 0.0	4 ± 0.0
Radiation and surgery	4.3 ± 3.0	1.9 ± 1.5	3.2 ± 2.0	4.6 ± 1.0
Surgery and chemo	1.0 ± 1.1	1.9 ± 1.2	5.1 ± 0.1	4.2 ± 1.8
Surgery only	7.0 ± 0.0	1.5 ± 0.0	3.1 ± 0.0	1.8 ± 0.8
All three	3.6 ± 1.7	2.0 ± 0.9	5.4 ± 1.8	3.9 ± 1.2
SOL by Hormone Therapy				
Tamoxifen	3.7 ± 2.9	2.5 ± 0.9	5.0 ± 2.2	3.9 ± 0.9
Aromatase Inhibitors	4.0 ± 2.5	1.6 ± 0.9	4.1 ± 1.8	3.7 ± 1.4
None	3.7 ± 2.1	2.3 ± 1.3	4.9 ± 1.5	4.2 ± 1.6

Table A.7. Descriptive statistics of WASO at respective time-points and independent variables' categories in a sample of BCS, Saskatoon.

Outcome	Baseline	Assessment 1	Assessment 2	Endpoint
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Total WASO	36.7 ± 22.3	20.7 ± 11.1	39.8 ± 27.9	26.9 ± 17.7
WASO by Age				
30-40	54.1 ± 13.6	15.3 ± 11.2	38.9 ± 29.8	16.3 ± 6.4
41-50	34.6 ± 9.7	28.4 ± 5.4	59.9 ± 35.9	25.8 ± 15.0
51-60	38.4 ± 24.2	21.9 ± 14.0	28.9 ± 22.3	26.6 ± 17.9
≥61	15.3 ± 23.0	16.3 ± 5.6	44.8 ± 28.6	33.5 ± 23.1
WASO by Stage				
I	37.8 ± 24.9	15.5 ± 6.8	34.3 ± 26.2	30.9 ± 19.9
II	38.9 ± 18.7	24.2 ± 6.6	47.0 ± 34.5	24.7 ± 11.0
III	33.2 ± 25.1	23.9 ± 16.8	39.5 ± 25.3	24.0 ± 21.5
WASO by Months After Treatment				
< 3 months	33.3 ± 18.1	23.3 ± 8.1	40.8 ± 25.1	24.5 ± 19.1
≥ 3 months	40.5 ± 26.5	17.9 ± 13.5	38.7 ± 31.9	29.5 ± 16.6
WASO by Sleep Aids in Use				
On	38.8 ± 19.8	19.2 ± 9.0	39.5 ± 28.0	28.4 ± 19.2
Off	34.5 ± 25.6	22.3 ± 13.3	40.1 ± 29.1	25.3 ± 16.7
WASO by Treatment Type				
Chemo only	34.9 ± 27.6	17.8 ± 7.6	33.3 ± 5.7	46.9 ± 35.4
Chemo and radiation	77.8 ± 0.0	49.9 ± 0.0	45.9 ± 0.0	63.5 ± 0.0
Radiation and surgery	39.4 ± 26.6	18.6 ± 9.6	30.7 ± 23.5	30.4 ± 15.2
Surgery and chemo	23.0 ± 11.5	17.4 ± 18.1	53.4 ± 32.0	25.6 ± 16.7
Surgery only	27.5 ± 0.0	11.8 ± 0.0	45.5 ± 0.0	23.2 ± 0.0
All three	36.7 ± 21.7	21.2 ± 8.0	40.3 ± 34.2	19.1 ± 11.4
WASO by Hormone Therapy				
Tamoxifen	33.9 ± 22.5	22.2 ± 8.6	41.3 ± 33.6	31.1 ± 22.6
Aromatase Inhibitors	36.8 ± 18.5	16.5 ± 6.0	40.8 ± 27.8	23.7 ± 12.5
None	39.1 ± 29.6	25.3 ± 16.8	36.9 ± 27.22	27.9 ± 21.4