THE PSYCHONEUROIMMUNOLOGY OF WOMEN EXPERIENCING STRESSFUL LIFE EVENTS:

TESTING THE OXIDATIVE MODEL

A thesis submitted for the Degree of

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by

Jodie Merle Oliver-Baxter

B. A. (Hons)

School of Psychology

The University of Adelaide

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ABSTRACT

It has been acknowledged that psychological stress can impact on one's health. A definitive link between psychological state, immune suppression, and disease has yet to be established. A possible mechanism has been termed The Oxidative Model. This refers to the oxidative imbalance of cells associated with antioxidant status and psychological distress. The aim of this dissertation was to use this theoretical model to establish an evidence basis for future interventions in vulnerable populations. For cancer patients the post-treatment period has been identified as psychologically challenging. In addition bio-psycho-immunological models remain underexplored in post-treatment breast cancer samples to date.

Two longitudinal studies were employed. The first, an observational study of a sample of women (N=17) concluding treatment (chemotherapy and/or radiotherapy) for early stage (I-III) breast cancer at the Royal Adelaide Hospital, South Australia. The second study tested the benefits of antioxidants during prolonged stress using an 8-week RCT. A sample of general population women (N=60) reporting mild to severe psychological distress was recruited. Psychological parameters measured included Psychological Distress, Defense Styles, Loneliness, Anger Expression, Psychological Adjustment, the Impact of Events Scale (IES-R), and State-Trait Depression, Curiosity, Anxiety, and Anger. Biochemical parameters included 5'-ectonucleotidase (NT), homocysteine (HCY), tissue ascorbate (VIT C), c-reactive protein (CRP), cholesterol (CHOL), folate (FOLATE), Vitamin B12 (VIT B12), and inflammatory cytokines (IL-1 β, IL-5, IL-6, IFN-γ, TNF-α, TNF-β, and IL-10).

Findings from study 1 indicated severe psychological distress was experienced for a subset of breast cancer patients post-treatment. Fluctuating levels of psychological distress, anger, anxiety, and curiosity were observed across the 20-weeks. A pro-oxidant state was evident during this period. Pro-inflammatory measures were low and relatively stable. Associations between psychological measures and biomarkers supported Oxidative Model relationships. The second study revealed improved pro-oxidant and pro-inflammatory biomarkers favoured the multivitamin supplemented group. Collectively both studies reveal the influence of demographic and health behaviours on bio-psycho-social measures central to the Oxidative Model propositions. This thesis brings out the case for exploring complementary interventions, like multivitamin use, in the post-treatment period for those patients experiencing distress.

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To my family and friends- especially Ben and Fletcher, and our baby in waiting I appreciate your patience and understanding-

'Life is what happens when you are doing a PhD'!

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Structure of the Dissertation

This dissertation is dedicated to the Psychoneuroimmunology of women. It comprises one longitudinal observational investigation, followed by a randomised controlled trial of women experiencing stressful life events. Due to the multidisciplinary nature of the topics studied, a thorough introduction to each study will be provided in the respective chapters. A brief overview of the chapters follows:

Chapter 1 focuses on briefly describing the paradigm of Psychoneuroimmunology. This chapter provides a review of the immune system prior to the presentation of a theoretical model- The Oxidative Model- in Chapter 2. Chapter 1 is not intended as a comprehensive description of the field of immunology but rather a review of the literature important to the Psychoneuroimmunology framework as it exists currently. It involves a brief introduction to Psychoneuroimmunology, identifying general trends, the conceptual, methodological, and design challenges for research in this area. It also discusses proposed Models of immune change during stress.

Chapter 2 introduces one specific PNI model - The Oxidative Model. This chapter provides a detailed review and critique of the literature applying to this Model to date. This chapter encompasses a detail of the pro-oxidant and pro-inflammatory biomarkers employed, followed by a thorough critique of the previous research which has employed this theoretical Model. This chapter sets the background for designing studies for this dissertation based on previous research findings and limitations.

Chapter 3 introduces a population for which The Oxidative Model has yet to be applied: women treated for early stage breast cancer. This section focuses on the first

6-months following the conclusion of active treatment. The focus of this review is specific to literature on psychosocial implications during this period. It attempts to highlight both the disparities and similarities of this period with psychological constructs utilized in The Oxidative Model. These constructs include both positive and negative, and include a spectrum of constructs which incorporate distress, anxiety, depression, anger, curiosity, post traumatic stress disorder (PTSD), coping styles, and social needs. The aim is to clarify this period as one which has chronic stress characteristics like previous Oxidative Model research.

This chapter also presents a review of psychoneuroimmunological studies undertaken on breast cancer patients' once active treatment has ceased. It aims to provide the framework for the proposed research questions. This section comprises both psychosocial and psychoneuroimmunological research in order to align this research with The Oxidative Model literature to date.

Chapter 4 outlines the thesis rationale in the context of the literature reviews provided in the previous chapters. Principal research questions are proposed.

Chapter 5 describes Study 1, an observational study of breast cancer patients. It involves the measurement, longitudinally, of psychological and biochemical markers that have been associated with chronic stress. The associations between psychological and biochemical variables are explored and discussed in view of psychoneuroimmunological findings from previous Oxidative Model research. In addition trends, in psychological constructs like distress, anxiety, depression, anger, curiosity, PTSD and coping are investigated. Pro-oxidant and pro-inflammatory biomarkers are assessed, based on propositions of a bio-psycho-immunological model

relating chronic stress to a pro-oxidant and pro-inflammatory internal state; The Oxidative Model (Blake-Mortimer, Winefield, & Chalmers, 1996).This chapter provides a generic methodology section which describes data collection and laboratory assay techniques used across both studies in this dissertation.

Results from Study 1, explore both cross-sectional and longitudinal data. Limitations of this study are discussed, including sample size, inter-individual variability, and heterogeneity. The heterogeneous nature of the sample was highlighted by several areas of disparity. This included how stressful individuals found the post-treatment period, demographic differences, varied treatment regimes prior to the study and diversity in individuals' health behaviours.

This level of diversity was a major challenge for drawing conclusions for this study. Several health behaviours and demographic variables were identified as confounders. The Oxidative Model proposes vitamins, specifically those with antioxidant properties, to alleviate the negative impact of chronic stress on pro-oxidant and pro-inflammatory biomarkers. This was partially supported by findings from study 1; regular vitamin-taking by patients was identified as a confounder for only one Oxidative Model biomarker, HCY. In light of this relationship and based on gaps in past Oxidative Model literature, a randomised controlled trial (RCT) to further assess the influence of vitamin-taking during chronic stress was proposed in a larger and more homogeneous sample.

Chapter 6 is based on previous Oxidative Model research and the findings and limitations from Study 1 of this dissertation. A new direction away from the oncology population was taken with regard to the sample utilized. In order to attain a more

homogenous sample with less 'nuisance' variables (i.e. treatment confounders), a sample of healthy women screened to be experiencing chronic stress were recruited from the general population. Eligible participants were randomised to either an Active or Placebo Group. The Active Group was the intervention group and consisted of an 8-week course of multivitamins targeted to be beneficial during periods of stress. Conversely, those allocated to the Placebo Group received a placebo; an identical capsule with non-active ingredients. The data collection methodology outlined in Chapter 3 was adhered to. Pre- to post-intervention changes, plus group comparisons are discussed. Correlational analyses were also employed to clarify psychoneuroimmune associations. Partial support was observed for Oxidative Model mechanisms.

In Chapter 7, major conclusions from Study 1 and Study 2 are reviewed. Strengths and Limitations of the dissertation are presented. Future directions for The Oxidative Model are discussed.