



**Persistent fatigue and endocrine function in women after  
radiotherapy for breast cancer**

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## **Declaration**

I hereby declare that this thesis is my original work. To the best of my knowledge it contains no previously published material unless otherwise acknowledged or has been accepted for an award or diploma by any other institution of higher learning.

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## Abstract

The experience of persistent fatigue after breast cancer treatment is estimated to affect approximately one in four women, but fatigue development and factors associated with cancer-related fatigue are poorly understood. Gaining a better understanding of these issues is important because persistent fatigue after radiation therapy can be a debilitating experience for cancer survivors. The objectives of this study were: (1) to determine fatigue prevalence in women with breast cancer at standardised timepoints after radiation therapy; (2) to investigate the relationships between fatigue, salivary cortisol rhythm and thyroid function; (3) to investigate the amount of radiation dose received by the thyroid gland in different radiation therapy treatment techniques; and (4) to investigate the relationship between irradiation of the thyroid, thyroid function and fatigue.

Participants in this research were women diagnosed with non-metastatic breast cancer and all were referred for adjuvant radiation therapy treatment. One cohort of participants ( $n = 48$ ) was assessed prior to the start of radiation therapy and then six months after treatment, and a second cohort ( $n = 15$ ) was assessed at six months and then at 12 months after treatment. Behavioural assessments included questionnaires that measured the level of multidimensional fatigue (MFSI-SF), the degree of fatigue and depression symptoms (SPHERE-12), impact that fatigue had on participants' functioning (FIS) and aspects of quality of life (EORTC QLQ-C30). Biological assessments included a three day measurement of salivary cortisol rhythm and an assessment of thyroid function (TSH, free T4 and free T3). Radiation doses to the thyroid gland were determined from participants' treatment plans.

Six months after completing adjuvant radiation therapy, women receiving treatment for breast cancer experienced significant improvements in emotional fatigue, role functioning and social functioning. High fatigue levels were prevalent in 29% of women at six months and 33% of women at 12 months after treatment, but newly developed fatigue that was not present before treatment was only found in 5% of participants. There were no significant changes in cortisol rhythm over time or between fatigued and non-fatigued participants; however, significant positive correlations were found between fatigue and morning cortisol. Regarding thyroid function, significant decreases in free T4 hormone levels were seen from six months to 12 months after radiation therapy with larger decreases in free T4 levels being related to higher fatigue. Radiation doses to the thyroid gland were significantly higher in participants who received treatment to the regional lymphatics with a supraclavicular fossa radiation field compared to participants who received localised treatment to the breast or chest wall only. In the former, changes in thyroid function were observed, as were relationships between mean radiation dose to the thyroid and thyroid function.

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# Table of Contents

<b>List of Figures.....</b>	<b>x</b>
<b>List of Tables .....</b>	<b>xii</b>
<b>Abbreviations .....</b>	<b>xiv</b>
<b>1 Introduction.....</b>	<b>1</b>
<b>2 Literature Review .....</b>	<b>3</b>
2.1 <i>Breast cancer survivorship and health-related quality of life</i> .....	4
2.1.1 Breast cancer epidemiology, aetiology and treatment .....	4
2.1.2 Quality of life.....	5
2.2 <i>Cancer-related fatigue</i> .....	13
2.2.1 Fatigue - theoretical frameworks and definition.....	13
2.2.2 The experience of cancer-related fatigue.....	15
2.2.3 Prevalence of cancer-related fatigue.....	16
2.2.4 Factors related to cancer-related fatigue.....	24
2.2.5 Limitations of previous research.....	29
2.3 <i>Endocrine functioning and fatigue</i> .....	30
2.3.1 Hypothalamic-Pituitary-Adrenal axis .....	30
2.3.2 Hypothalamic-Pituitary-Thyroidal axis .....	37
2.3.3 Hormone inter-relationships .....	44
2.4 <i>Summary</i> .....	46
<b>3 Methodology.....</b>	<b>47</b>
3.1 <i>Study design, aims and hypotheses</i> .....	47
3.2 <i>Setting</i> .....	50
3.3 <i>Participants</i> .....	51
3.3.1 Study population .....	51
3.3.2 Eligibility .....	51
3.3.3 Sample size estimates .....	52
3.3.4 Radiation therapy treatment protocol .....	52
3.4 <i>Ethics approval and funding</i> .....	54
3.5 <i>Data acquisition</i> .....	55
3.5.1 Recruitment.....	55
3.5.2 Fatigue assessment session .....	55
3.5.3 Saliva collection protocol and cortisol analysis.....	63
3.5.4 Blood tests.....	67
3.5.5 Radiation dose to the thyroid gland .....	70
3.6 <i>Missing data</i> .....	72
3.7 <i>Data analysis</i> .....	74
3.7.1 Recruitment.....	74

3.7.2	Reliability studies .....	75
3.7.3	Aim 1 – fatigue level and prevalence .....	75
3.7.4	Aim 2 – cortisol rhythm and thyroid function indices.....	76
3.7.5	Aims 3 and 4 – Radiation dose to the thyroid gland.....	78
<b>4</b>	<b>Results.....</b>	<b>80</b>
4.1	<i>Introduction</i> .....	80
4.2	<i>Recruitment</i> .....	81
4.2.1	Overall summary.....	81
4.2.2	Participant characteristics .....	83
4.2.3	Differences between consenting and declining patients.....	85
4.3	<i>Reliability studies</i> .....	87
4.3.1	Questionnaire psychometric analyses.....	87
4.3.2	Intra-observer reliability of waist and hip circumference measurements.....	88
4.3.3	Coefficients of variation in salivary cortisol assays .....	88
4.4	<i>Aim 1 – Fatigue level and prevalence</i> .....	89
4.4.1	Descriptive summary of fatigue dimensions and fatigue prevalence .....	89
4.4.2	Fatigue level and prevalence over time – longitudinal analyses (Hypothesis 1)..	92
4.4.3	Demographic variables, quality of life and fatigue.....	95
4.4.4	Aim 1 conclusions .....	102
4.5	<i>Aim 2 – Cortisol rhythm and thyroid function indices</i> .....	103
4.5.1	Salivary cortisol rhythm overview.....	103
4.5.2	Descriptive summary of salivary cortisol indices.....	103
4.5.3	Salivary cortisol and fatigue (Hypothesis 2).....	106
4.5.4	Thyroid function indices overview .....	117
4.5.5	Descriptive summary of thyroid function indices.....	117
4.5.6	Thyroid function and fatigue (Hypothesis 3).....	119
4.5.7	Aim 2 conclusions .....	125
4.6	<i>Aim 3 – Radiation dose to the thyroid gland</i> .....	126
4.6.1	Overview of available data .....	126
4.6.2	Descriptive summary of age, thyroid size, thyroid function and radiation dose	126
4.6.3	Changes in radiation dose, thyroid function and fatigue between treatment groups (Hypotheses 4 and 5) .....	128
4.6.4	Radiation dose received by the thyroid gland in supraclavicular fossa RT.....	128
4.6.5	Aim 3 conclusions .....	131
4.7	<i>Aim 4 – Relationships between radiation dose, thyroid function and fatigue</i> .....	132
4.7.1	Correlations summary (Hypothesis 6) .....	132
4.7.2	Aim 4 conclusions .....	133
<b>5</b>	<b>Discussion .....</b>	<b>134</b>
5.1	<i>Introduction</i> .....	134
5.2	<i>Recruitment and attrition</i> .....	135
5.2.1	Recruitment process.....	135
5.2.2	Attrition.....	135
5.3	<i>Fatigue level and prevalence</i> .....	138
5.3.1	Introduction.....	138
5.3.2	Fatigue before adjuvant RT .....	139
5.3.3	Fatigue at six months after RT.....	142



5.3.4	Fatigue at 12 months after RT .....	148
5.4	<i>Cortisol rhythm and thyroid function indices</i> .....	150
5.4.1	Salivary cortisol indices .....	150
5.4.2	Cortisol and fatigue .....	157
5.4.3	Thyroid function indices .....	160
5.4.4	Thyroid function and fatigue .....	163
5.5	<i>Radiation dose to the thyroid and fatigue</i> .....	165
5.5.1	Thyroid gland tolerance doses .....	165
5.5.2	Mean thyroid dose and thyroid function .....	168
5.5.3	Radiation dose and fatigue .....	170
5.6	<i>Limitations of research</i> .....	172
<b>6</b>	<b>Conclusion</b> .....	<b>178</b>
	<b>Appendices</b> .....	<b>181</b>
	<b><i>Appendix A. Ethics approval, consent forms and funding approval</i></b> .....	<b>181</b>
A.1	NSCCH Ethics Committee approval – 29 November 2007 .....	182
A.2	The University of Sydney Ethics Committee approval – 21 January 2008 .....	185
A.3	NSCCH Ethics Committee amendment approval – 8 May 2008 .....	186
A.4	The University of Sydney Ethics Committee amendment approval .....	189
A.5	Participant consent form – General .....	190
A.6	Participant consent form – Tissue .....	194
A.7	Cancer Institute NSW funding approval – 1 December 2006 .....	195
	<b><i>Appendix B. Demographics and fatigue questionnaires</i></b> .....	<b>196</b>
B.1	Demographics questionnaire .....	196
B.2	Multidimensional Fatigue Symptom Inventory–Short Form .....	197
B.3	Somatic and Psychological HEalth REport–12 .....	198
B.4	EORTC Quality of Life Questionnaire–C30 .....	199
B.5	Fatigue Impact Scale .....	201
	<b><i>Appendix C. Instructions for saliva collection</i></b> .....	<b>203</b>
	<b><i>Appendix D. DSL-10-67100i ACTIVE® Cortisol EIA kit package insert</i></b> .....	<b>206</b>
	<b>References</b> .....	<b>213</b>

## List of Figures

<b>Figure 2.1</b> Fatigue Adaptation Model (Olson 2007).....	14
<b>Figure 2.2</b> The adrenal gland, adapted from Nussey & Whitehead (2001).....	31
<b>Figure 2.3</b> Thyroid gland (Nussey & Whitehead 2001) .....	37
<b>Figure 2.4</b> Feedback control of cortisol and thyroid hormones .....	45
<b>Figure 3.1</b> Assessment timepoints .....	51
<b>Figure 3.2</b> Salivette saliva collection tube .....	64
<b>Figure 3.3</b> Difference between $AUC_g$ and $AUC_i$ .....	77
<b>Figure 4.1</b> Cohort 1 recruitment summary.....	82
<b>Figure 4.2</b> Cohort 2 recruitment summary.....	82
<b>Figure 4.3</b> Fatigue dimensions at each timepoint: MFSI-SF .....	89
<b>Figure 4.4</b> Fatigue impact on function: FIS .....	89
<b>Figure 4.5</b> Total fatigue impact: FIS.....	89
<b>Figure 4.6</b> Functioning and quality of life at each timepoint: EORTC QLQ-C30.....	90
<b>Figure 4.7</b> Symptoms experienced at each timepoint: EORTC QLQ-C30.....	90
<b>Figure 4.8</b> Salivary cortisol rhythm; Cohort 1 $n = 21$ .....	105
<b>Figure 4.9</b> Salivary cortisol rhythm; Cohort 2 $n = 10$ .....	105
<b>Figure 4.10</b> Correlation between $T_0$ general fatigue and $T_0$ awakening time .....	111
<b>Figure 4.11</b> Correlation between $T_0$ physical fatigue and $T_0$ 30 minutes cortisol .....	111
<b>Figure 4.12</b> Correlation between $T_0$ physical fatigue and $T_0$ $AUC_i$ .....	112
<b>Figure 4.13</b> Correlation between $T_1$ vigor and $T_1$ awakening cortisol .....	112
<b>Figure 4.14</b> Correlation between $T_1$ vigor and $T_1$ $AUC_i$ .....	112
<b>Figure 4.15</b> Correlation between $T_1$ vigor and $T_1$ cortisol slope .....	113
<b>Figure 4.16</b> Correlation between $T_1$ mental fatigue and $T_1$ cortisol slope.....	113
<b>Figure 4.17</b> Correlation between $T_1$ vigor and $T_1$ awakening cortisol – minus outlier .....	113
<b>Figure 4.18</b> Correlation between $T_1$ vigor and $T_1$ $AUC_i$ – minus outlier .....	113
<b>Figure 4.19</b> Correlation between $T_1$ vigor and $T_1$ cortisol slope – minus outlier .....	114
<b>Figure 4.20</b> Correlation between $T_1$ mental fatigue and $T_1$ cortisol slope – minus outlier....	114
<b>Figure 4.21</b> Correlation between $T_2$ mental fatigue and $T_2$ ACR .....	115
<b>Figure 4.22</b> Correlation between $T_2$ vigor and $T_2$ ACR.....	115
<b>Figure 4.23</b> Percentage change in cortisol levels from baseline to $T_1$ .....	115

<b>Figure 4.24</b> Percentage change in cortisol levels from T <sub>1</sub> to T <sub>2</sub> .....	115
<b>Figure 4.25</b> Correlation between % change in evening cortisol from baseline and T <sub>1</sub> physical fatigue .....	116
<b>Figure 4.26</b> Correlation between % change in evening cortisol from baseline and T <sub>1</sub> general fatigue.....	116
<b>Figure 4.27</b> TSH; Cohort 1 <i>n</i> = 25 .....	119
<b>Figure 4.28</b> TSH; Cohort 2 <i>n</i> = 10 .....	119
<b>Figure 4.29</b> Free T4 and free T3; .....	119
<b>Figure 4.30</b> Free T4 and free T3; Cohort 2 <i>n</i> = 10.....	119
<b>Figure 4.31</b> Percentage change in thyroid function from baseline to T <sub>1</sub> .....	123
<b>Figure 4.32</b> Percentage change in thyroid function from T <sub>1</sub> to T <sub>2</sub> .....	123
<b>Figure 4.33</b> Correlation between % change in free T4 from T <sub>1</sub> to T <sub>2</sub> and T <sub>2</sub> physical fatigue .....	124
<b>Figure 4.34</b> Correlation between % change in free T4 from T <sub>1</sub> to T <sub>2</sub> and T <sub>2</sub> emotional fatigue .....	124
<b>Figure 4.35</b> DVH of participants in the ‘tangents + SCF’ RT treatment; <i>n</i> = 9.....	129
<b>Figure 4.36</b> BEV of participant with lowest radiation dose to the thyroid gland .....	130
<b>Figure 4.37</b> BEV of participant with highest radiation dose to the thyroid gland.....	130
<b>Figure 4.38</b> Correlation between percentage change in TSH and mean thyroid gland dose .	132
<b>Figure 4.39</b> Correlation between T <sub>1</sub> free T3 and mean thyroid gland dose.....	133
<b>Figure 4.40</b> Correlation between percentage change in free T3 and mean thyroid dose.....	133
<b>Figure 5.1</b> Superior border placement of the SCF field.....	167
<b>Figure 5.2</b> Medial border placement of the SCF field .....	167

## List of Tables

<b>Table 2.1</b> Studies comparing QoL in breast cancer survivors and controls.....	9
<b>Table 2.2</b> Fatigue development during Radiation Therapy.....	21
<b>Table 2.3</b> Studies of cortisol and fatigue relationships in breast cancer patients.....	35
<b>Table 2.4</b> Studies showing radiation dose to the thyroid during breast cancer RT.....	43
<b>Table 3.1</b> Links between aims and hypotheses .....	49
<b>Table 3.2</b> Citations using the Fatigue Impact Scale.....	61
<b>Table 3.3</b> Population reference values for salivary cortisol.....	68
<b>Table 3.4</b> PaLMS laboratory reference values.....	69
<b>Table 4.1</b> Reasons for non-participation and exclusion.....	81
<b>Table 4.2</b> Demographics of Cohort 1 and Cohort 2.....	84
<b>Table 4.3</b> Results of the Chi-Square ( $\chi^2$ ) test between consenting and declining patients .....	86
<b>Table 4.4</b> Internal consistency reliability of questionnaires.....	87
<b>Table 4.5</b> SPHERE–12 category membership in Cohort 1 and 2 at each timepoint.....	91
<b>Table 4.6</b> Current fatigue compared to fatigue pre-diagnosis.....	91
<b>Table 4.7</b> Differences in fatigue, functioning and quality of life over time.....	93
<b>Table 4.8</b> SPHERE–12 classifications at T <sub>0</sub> and T <sub>1</sub> ; <i>n</i> (%).....	94
<b>Table 4.9</b> SPHERE–12 classifications at T <sub>1</sub> and T <sub>2</sub> ; <i>n</i> (%).....	95
<b>Table 4.10</b> Significant correlates of multidimensional fatigue (MFSI–SF).....	96
<b>Table 4.11</b> Significant correlates of fatigue (EORTC QLQ–C30) at each timepoint.....	97
<b>Table 4.12</b> Quality of life predictors of T <sub>1</sub> and T <sub>2</sub> fatigue .....	98
<b>Table 4.13</b> Significant differences in MFSI–SF fatigue between demographic categories...	100
<b>Table 4.14</b> Descriptive summary of salivary cortisol indices .....	104
<b>Table 4.15</b> Salivary cortisol indices; changes over time for each cohort.....	104
<b>Table 4.16</b> Descriptive statistics of salivary cortisol indices for SPHERE–12 categories ....	107
<b>Table 4.17</b> Differences in salivary cortisol indices between fatigued and non-fatigued participants.....	109
<b>Table 4.18</b> Spearman's Rho coefficients for T <sub>1</sub> MFSI–SF subscales and salivary cortisol; Cohort 1 <i>n</i> = 18 .....	116
<b>Table 4.19</b> Spearman's Rho coefficients for T <sub>2</sub> MFSI–SF subscales and salivary cortisol; Cohort 2 <i>n</i> = 7 .....	117
<b>Table 4.20</b> Descriptive summary of thyroid function indices.....	118

<b>Table 4.21</b> Thyroid function indices; changes over time for each cohort.....	118
<b>Table 4.22</b> Descriptive statistics of thyroid function indices for SPHERE–12 categories ....	120
<b>Table 4.23</b> Differences in thyroid function between fatigued and non-fatigued participants	122
<b>Table 4.24</b> Spearman's Rho coefficients for T <sub>1</sub> MFSI–SF subscales and thyroid function; Cohort 1 <i>n</i> = 21 .....	123
<b>Table 4.25</b> Spearman's Rho coefficients for T <sub>2</sub> MFSI–SF subscales and thyroid function; Cohort 2 <i>n</i> = 6 .....	124
<b>Table 4.26</b> Differences in thyroid function from T <sub>0</sub> to T <sub>1</sub> between different breast RT techniques .....	127
<b>Table 4.27</b> Differences in age, thyroid gland size, thyroid function and radiation dose between different breast RT techniques.....	128
<b>Table 5.1</b> MFSI–SF subscale means in participants, breast cancer and healthy adults .....	140
<b>Table 5.2</b> Salivary cortisol levels in the current study compared to previous research.....	152
<b>Table 5.3</b> Cortisol AUC parameters in the current study compared to previous research.....	155
<b>Table 5.4</b> Thyroid function indices in the current study compared to previous research .....	162

## Abbreviations

#	Radiation treatment fraction
3D CRT	3-Dimensional Conformal Radiation Therapy
ACR	Awakening Cortisol Response
ACTH	Adrenocorticotrophic Hormone
ADP	Adenosine Diphosphate
AP	Anterio-Posterior
APBI	Accelerated Partial Breast Irradiation
ATP	Adenosine Triphosphate
AUC	Area Under Curve
AUC <sub>i</sub>	Area Under Curve with respect to increase
AUC <sub>g</sub>	Area Under Curve with respect to ground
BEV	Beam's Eye View
BMI	Body Mass Index
BMRI	Brain and Mind Research Institute
CAR	Cortisol Awakening Response
CFS	Chronic Fatigue Syndrome
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRH	Corticotropin-Releasing Hormone
CT	Chemotherapy
CV	Coefficient of Variation
DCIS	Ductal Carcinoma In Situ
DRR	Digitally Reconstructed Radiograph
DVH	Dose-Volume Histogram
EIA	Enzyme Immunoassay
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
ER	Oestrogen Receptor
FIS	Fatigue Impact Scale
ft3	Free triiodothyronine
ft4	Free thyroxine

GAS	General Adaptation Syndrome
Gy	Gray
HER-2	Human Epidermal growth factor Receptor 2
HH:MM	Hours:Minutes
HPA axis	Hypothalamic-Pituitary-Adrenal axis
HPT axis	Hypothalamic-Pituitary-Thyroidal axis
HRT	Hormone Replacement Therapy
IBS	Irritable Bowel Syndrome
IMRT	Intensity Modulated Radiation Therapy
M/F	Male/Female
MFSI–SF	Multidimensional Fatigue Symptom Inventory–Short Form
MV	Megavoltage
nd	No data
NSCCH	Northern Sydney Central Coast Health
NSW	New South Wales
OCP	Oral Contraceptive Pill
PA	Posterior-Anterior
QoL	Quality of Life
RIA	Radioimmunoassay
RNSH	Royal North Shore Hospital
$r_s$	Spearman’s correlation coefficient Rho
RT	Radiation Therapy
SCF	Supraclavicular Fossa
SF–36	Short Form–36 questionnaire
SPHERE–12	Somatic and Psychological HEalth REport–12
TLD	Thermoluminescent Device
T <sub>0</sub>	Baseline measure, pre-RT
T <sub>1</sub>	Six months post-RT measure
T <sub>2</sub>	12 months post-RT measure
TRH	Thyrotropin-Releasing Hormone
TSH	Thyroid-Stimulating Hormone
WHO	World Health Organisation
WHR	Waist to Hip Ratio