RESTING METABOLIC RATE IN WOMEN 
WITH EARLY STAGE BREAST CANCER 

by 

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A thesis submitted in conformity with the requirements 
for the degree of M. Sc. 
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Women with breast cancer (BC) typically gain 2-6 kg of body weight following diagnosis. The reason for this is unclear. The objective of this study was to determine whether women with early-stage BC (EBC) experienced reduced resting metabolic rates (RMR). Comparisons were made to healthy women and women recovering from BC. No differences in measures of RMR relative to fat free mass (FFM) ($27\pm1$ kcal/kg/d); using bioelectrical impedance) were observed among the groups. Reassessment of RMR in EBC women 6 months after participating in a weight management program showed no RMR change. However, known predictors of RMR strongly correlated with RMRs of the Control group but not with those of EBC and the group recovering from breast cancer (RBC). This may suggest that unaccounted factors influenced RMR in BC. Moreover, despite reductions in dietary intake and maintenance of walking programs, EBC subjects only remained weight stable at 6 months.
TO ISABEL AND ETHAN
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TABLE OF CONTENTS

List of Tables ........................................................................................................... viii
List of Figures .......................................................................................................... ix
List of Appendices ................................................................................................... x
List of Abbreviations .............................................................................................. ix

CHAPTER 1. OUTLINE OF THESIS

1.1. Introduction 1
1.2. Hypothesis 1
1.3. Specific Objectives 1
1.4. Summary of Study Design 1

CHAPTER 2. REVIEW OF THE LITERATURE

2.1 Introduction 3
2.2. Breast Cancer Overview 3
   2.2.1. Definition of breast cancer 3
   2.2.2. Breast cancer statistics 4
   2.2.3. Staging of invasive breast cancer 4
   2.2.4. Treatment of the disease 5
      2.2.4.1. Local treatment 5
      2.2.4.2. Response to local treatment 6
      2.2.4.3. Systemic therapy 6
      2.2.4.4. Systemic treatment regimes and treatment responses 7
2.3. Body Size And Breast Cancer 8
   2.3.1. Body size at the time of diagnosis and prognosis 8
   2.3.2. Issues in body size and prognosis literature 9
      2.3.2.1. Body size measurements 9
      2.3.2.2. Classification and distribution 10
      2.3.2.3. Menopausal status as a potential confounder 11
      2.3.2.4. Hormonal receptor status as a potential confounder 12
2.3.2.6. Other prognostic factors as potential confounders 13

2.3.3. Potential mechanisms by which obesity influences prognosis 14
2.3.3.1. Estrogen 14
2.3.3.2. Sex-hormone-binding globulin (SHBG) 16
2.3.3.3. Testosterone 16
2.3.3.4 Progesterone 16
2.3.3.5. Insulin 16
2.3.3.6. Fat distribution 17
2.3.3.7. Dietary intake 17
2.3.3.7.1. Dietary fat 17
2.3.3.7.2. Dietary Fibre 19
2.3.3.7.3. Vitamins 19

2.3.4. Weight gain following diagnosis 20
2.3.4.1. Incidence and magnitude of weight gain 20
2.3.4.1.1. Factors influencing the magnitude of gain 20
2.3.4.2. Psychological impact of BC on weight gain 21
2.3.4.3. Effects of weight gain in BC prognosis 22

2.4. Nutrition Interventions In Breast Cancer 23
2.4.1. Studies on nutrition intervention in BC 23

2.5. Energy Imbalance In Women With BC 26
2.5.1. Dietary Intake 26
2.5.2. Physical activity 29
2.5.3. Metabolism 30
2.5.4. RMR in BC 33

2.6. Rationale And Summary 34

CHAPTER 3. MATERIALS AND PROCEDURE

3.1. Hypothesis 35
3.2. Specific Objectives 35
3.3. Design 35
CHAPTER 4. EXPERIMENTAL RESULTS

4.1. Population Assembly

4.2. Description Of The Study Population
   4.2.1. Age and anthropometric characteristics
   4.2.2. BMI and body fat distributions
   4.2.3. Menopausal status of study population
   4.2.4. Adjuvant therapy of BC population

4.3. RMR Analysis
   4.3.1. RMR data
   4.3.2. Body composition
   4.3.3. RMR relative to FFM
   4.3.4 Dietary intake
   4.3.5. Physical activity

4.4. The RMR Analysis of EBC Group
   4.4.1. Body size and composition
   4.4.2. RMR
   4.4.3. Dietary intakes
   4.4.4. Physical activity

4.5 Additional Analysis
4.5.2. Most recent body weights on BC subjects

CHAPTER 5. DISCUSSION

5.1. RMR

5.1.1. Comparison of RMR to existing BC study
5.1.2. Standard values of RMR in the literature

5.2. Predictive variables of RMR

5.2.1. FFM
5.2.2. Harris Benedict equation (HBE)
5.2.3. Other explanations for unaccounted variance in RMR

5.3. Study design

5.3.1. Selection of subjects
5.3.2. Sample size
5.3.3. Eligibility and exclusion criteria
5.3.4. Technical Error

5.4. External factors that may have influenced RMR

5.4.1. Accuracy of RMR measurement
5.4.2. Age
5.4.3. Ambient temperature
5.4.4. Diet-induced thermogenesis
5.4.5. Respiratory Quotient
5.4.6. Body size
5.4.7. Menopause status
5.4.8. Treatment

5.5. Dietary Intake
5.6. Exercise
5.7. Future Directions

CHAPTER 6.0. CONCLUSIONS
Figure 1. Protocol
Figure 2. Bar graphs of FFM and Fat Mass Among Groups
Figure 3. Daily Energy Intake of EBC at Baseline and 6 month
Figure 4. Mean Intake of Macronutrients of EBC at baseline and 6 month
Figure 5. Scatterplots for Regression of RMR of Indirect Calorimetry and HBE
Figure 6. Comparison of RMR for Indirect Calorimetry and HBE
Figure 7. Comparison of RMR of Indirect calorimetry and HBE Classified by Chemotherapy For EBC and RBC
Figure 8. Comparison of RMR of Indirect calorimetry and HBE Classified by Chemotherapy For BC
Figure 9. Baseline and Most Recent Body Weights of BC Subjects
Appendix 1. Eligibility Assessment 98
Appendix 2. Waist-to-hip circumference procedure 99
Appendix 3. BIS procedure and FFM prediction equation 100
Appendix 4. Harris Benedict Equation 101
Appendix 5. Classification for Intensity of Physical Activity 101
Appendix 6. Criteria for correlation coefficients 101
Appendix 7. Lusk Table: Analysis of the oxidation of carbohydrate and fat 102
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>BC</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>BIA</td>
<td>bioelectrical impedance analysis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BW</td>
<td>body weight</td>
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<tr>
<td>DIT</td>
<td>diet induced thermogenesis</td>
</tr>
<tr>
<td>DM</td>
<td>Demark-Wahanefried</td>
</tr>
<tr>
<td>EBC</td>
<td>Early Breast Cancer Group</td>
</tr>
<tr>
<td>ECF</td>
<td>extracellular fluids</td>
</tr>
<tr>
<td>EE</td>
<td>energy expenditure</td>
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<tr>
<td>ER</td>
<td>Estrogen receptor</td>
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<td>FFM</td>
<td>Fat free mass</td>
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<td>HBE</td>
<td>Harris Benedict Equation</td>
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<tr>
<td>ICF</td>
<td>intracellular fluids</td>
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<tr>
<td>PR</td>
<td>Progesterone receptor</td>
</tr>
<tr>
<td>R</td>
<td>resistance</td>
</tr>
<tr>
<td>RBC</td>
<td>Group of women recovering from breast cancer</td>
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<tr>
<td>RMR</td>
<td>Resing Metabolic Rate</td>
</tr>
<tr>
<td>RQ</td>
<td>( \text{VCO}_2/\text{VO}_2 ), carbon dioxide production/oxygen consumption</td>
</tr>
<tr>
<td>SHBG</td>
<td>sex-hormone binding globulin</td>
</tr>
<tr>
<td>TBW</td>
<td>total body water</td>
</tr>
<tr>
<td>TEE</td>
<td>thermic effect of exercise</td>
</tr>
<tr>
<td>VCO(_2)</td>
<td>carbon dioxide production</td>
</tr>
<tr>
<td>VO(_2)</td>
<td>oxygen consumption</td>
</tr>
<tr>
<td>WHR</td>
<td>Waist to Hip Circumference</td>
</tr>
<tr>
<td>WMI</td>
<td>Phase II Weight Management Intervention</td>
</tr>
<tr>
<td>X(_e)</td>
<td>reactance</td>
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<tr>
<td>Z</td>
<td>bioelectric impedance</td>
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Chapter 1. Outline of Thesis

1.1. Introduction

Independent of weight at diagnosis, the majority of females will gain 2 - 6 kilograms of body weight during the first 18 months following diagnosis of breast cancer (BC) [23]. While psychologically damaging in nature, more importantly, the body weight gain may be linked to a higher rate of cancer recurrence and therefore a poor prognosis. However, the mechanisms of weight gain are currently unknown.

Obviously an energy imbalance could cause weight gain. General cancer literature describes metabolic alterations in tumour-bearing hosts, but usually in the form of hypometabolism. There is a single cohort study on BC which suggested a reduction in resting metabolic rate (RMR) during BC treatment. However, this study was limited to premenopausal women undergoing chemotherapy [1]. The degree to which its findings can be extended to the entire BC cancer population is unknown. The focus of this thesis was to explore whether RMR was modified in women with BC.

1.2. Hypothesis

It is hypothesized that women recently diagnosed with early-stage BC have a lower RMR than their healthy controls or women recovering from BC. This postulated decline in RMR may then contribute to the weight gain in women following a diagnosis of BC.

1.3. Specific Objectives

To address this hypothesis, two separate objectives were considered: 1) to determine whether RMR differs in women with early-stage BC compared to healthy women or women recovering from early-stage BC and 2) to determine whether RMR changes over time during BC treatment.

1.4. Summary of study design

This study was designed to measure energy balance in women with and without BC in order to investigate potential mechanisms underlying the weight gain process. The
physical activity was also collected. Body composition and anthropometric measurements were taken in order to normalize RMR data for body size.

The study was comprised of three groups of subjects. Early BC group (EBC) consisted of women with newly-diagnosed, early-stage BC, Recovery group (RBC) consisted of women recovering from BC and Control group consisted of healthy women without breast cancer. Analyses were performed in two ways: a three group cross-sectional study and a within person analysis of the repeated measurements for EBC group (at baseline and at 6 months into the Phase II Multidisciplinary Weight Management in Primary Breast Cancer Study (WMI)) to examine changes in RMR over time. Repeated measurements did not include RBC, since their measurements were not obtained at the early stage of treatment, thereby eliminating the possibility of examining change through treatment in this group.
Chapter 2. Review of Literature

2.1 Introduction

Increased body weight appears to have both psychological and prognostic consequences for women with early-stage BC. The first section of this review provides an overview of the clinical aspects of this disease. The next section reviews available research on the effects of increased body weight (at the time of diagnosis and gained thereafter) in women with BC. It addresses the impact of increased weight on prognosis and psychological health. Special attention is made to appraise the quality of the work in this area and to speculate on potential mechanisms responsible for decreased disease-free survival in obese women. This section is then followed by a review of the nutritional intervention trials already performed in this area. The energy imbalance in weight-gaining women with BC is the focus of the final section with the possible components (dietary intake, physical activity and resting metabolic rate) at work in this process being considered.

2.2 Breast cancer overview

2.2.1. Definition of breast cancer

Invasive BC is a neoplastic disease of mammary epithelium and the etiology of BC is multifactorial. The nutrition-related etiology is unclear but obesity appears to be a major component, particularly postmenopausal women with its effect possibly mediated by the production and availability of extra-ovarian estrogen [2]. Dietary fat intake has also been shown to be a BC risk factor [3]. Although many researchers are convinced of the involvement of estrogen in the pathogenesis of BC, its precise role has yet to be elucidated [4]. BC is a heterogeneous disease with a natural history and prognosis that varies widely from patient to patient. Some patients experience a rapidly progressive disease which is refractory to any treatment while others experience a more indolent course with long periods of remission [5]. Disease spread beyond the local area (breast and axilla) is considered incurable.

In general, BC is considered a slow-growing tumour with a prolonged doubling time of cells compared to many other tumours [6]. Therefore, it may require many years
of tumour growth before detection is possible by palpation. The unfortunate truth, however, is that by the time a tumour is detected clinically it has often microscopically disseminated to other tissues [7]. The sites of predilection for distant metastases are lung, liver, bone, skin, brain and subcutaneous tissue [6].

2.2.2 Breast cancer statistics

Current statistics reveal that BC is the second leading cause of cancer deaths for women in Canada [8]. Statistics Canada estimated that 18,600 Canadian women would have been diagnosed with BC and another 5,300 would have died from the disease in 1996 [9]. The incidence of breast cancer is increasing in Canada, for reasons that remain uncertain [10]; although part of the increase may be due to early detection through mammography and identifying greater numbers of ductal carcinoma in situ cases. Overall mortality figures, conversely, have shown little change over the past three decades [11]. This stability is likely due to an improved ability to diagnose the disease in an earlier stage as well as improvements in treatments [10].

Incidence rates for breast cancer increase rapidly between the fourth and fifth decades of life and then continue to climb after this time, albeit at a less dramatic pace [12]. It is estimated that 5 per cent of cases occur before age 40; approximately two-thirds occur during and after menopause [13]. Once diagnosed, the chance of dying from the disease is largely dependent on the stage of the disease at detection.

2.2.3. Staging of invasive breast cancer

Cancer staging classifies a neoplasm on the basis of its progression at diagnosis [14]. The most important factors that influence disease progression are lymph node involvement, tumour size, histological type and histological differentiation [15, 16]. Of these, the presence and extent of lymph node involvement are the most significant [14, 17]. A metastatic spread to 4 or more nodes carries a relative risk of succumbing to the disease of 3.88 (relative to disease with no lymph node involvement) [18].

The TNM system developed by the International Union Against Cancer is an internationally recognized staging system to classify BC [6]. The components of the TNM system include: the extent of the primary tumour (T), involvement of the regional
This can then be supplemented with additional information related to cell biology and histology [19].

Steroid receptor status (i.e. estrogen receptor (ER)) also has strong prognostic value. This receptor appears to be responsible for the uptake of estrogen by normal mammary and some malignant breast tissues [6]. Estrogen is thought to act directly on breast tissue to promote growth and differentiation [6]. The level of ER in BC tumours inversely correlates with the chance of early recurrence in BC [19] and interestingly those tumours with high levels of receptors tend to have better treatment response as they may be more responsive to hormonal manipulations [17].

The women studied for this thesis were staged by TNM as T1-3, N0-1, M0 (which refers to all tumours less than 5cm with or without lymph node involvement and no evidence of distant metastases). ER status was not considered in the inclusion/exclusion criteria. The women could have any ER status. This is considered early-stage disease and is referred to as Stage I and II disease.

Unfortunately, early-stage disease is the most difficult stage in which to accurately predict outcome. A proportion of these women go on to develop metastatic disease despite the early recognition of the disease and favourable prognosis [15, 20, 21]. With our current knowledge of prognostic factors, the ability to correctly define a patient’s risk of recurrence in early-stage disease is limited [15]. There is a clear need to better identify prognostic factors to evaluate risk in this group. Body weight appears to have some potential as a useful prognostic indicator in this area.

2.2.4. Treatment of the disease

2.2.4.1. Local treatment
Management of invasive BC may involve both local and systemic treatment. The recommended local treatment of early-stage disease involves removal of the primary tumor with breast-conserving surgery (lumpectomy, quadrantectomy, subtotal mastectomy) followed by radiation [7]. Postoperative radiation may eradicate residual foci of microscopic tumour and decrease the likelihood of local recurrence [13]. A
modified radical mastectomy should be reserved for multiple lesions or large tumours (>4cm); situations which necessitate the removal of the entire breast [21].

A regional lymph node dissection is also performed and the subsequent histologic evaluation of the specimen determines the presence and extent of metastatic lymph nodal disease [14]. Local treatment alone is virtually a cure for women with tumours of 0.5 cm or less with negative nodes [16].

2.2.4.2. Response to local treatment

There are some adverse physical effects associated with both surgery and radiation therapy. Patients complain of tenderness, tightness, and pulling in the chest wall, breast and arm areas following surgery [22]. Women further report arm weakness, swelling and lymphedema with extensive nodal dissections; as well as fatigue, and soreness in areas that are radiated [22]. Although these physical side-effects are bothersome, the effects most distressing to women tend to be psychological in nature.

Psychiatric morbidity is thought to be related to the knowledge of receiving the diagnosis of a life-threatening illness as well as the loss or disfigurement of the breast [23]. Depression and anxiety presents in 20 to 30% of women diagnosed with the disease [23]. Women with BC also report feelings of unattractiveness, a loss of femininity and a radical change in body image following surgery [24]. It has been suggested that a woman’s positive image of her own body is strongly related to her concept of the ideal woman, which includes normal breasts [25]. Therefore, a mastectomy, which amputates the breast, may be more psychologically traumatic than breast-conserving surgery in some women [25, 26].

2.2.4.3. Systemic therapy

In the presence of positive lymph nodes, adjuvant systemic therapy is required to eradicate occult distant micrometastases [10]. To date, controlled clinical trials in early-stage disease have demonstrated improvement in disease-free survival with the use of cytotoxic polychemotherapy or endocrine therapy (i.e. tamoxifen) in node-positive women [10, 27-29].
The results suggest that chemotherapy has the most significant effect in women under 50 years, by reducing the annual odds of death during the first five years by about 25% [28]. Tamoxifen, on the other hand, has its greatest effect on women over 50 years by reducing those same odds by about 20% [28]. In 1985, the NIH Consensus Development Panel on Adjuvant Chemotherapy and Endocrine Therapy concluded that in the presence of positive nodes, chemotherapy should be administered to premenopausal women, and tamoxifen to postmenopausal women [30]. However approximately 60% of women diagnosed with invasive BC have no axillary node involvement at diagnosis (node-negative) [31]. Most of these women should be cured by local treatment alone, yet 10-40% develop distant metastatic disease [10, 15, 20, 21, 32]. Recent clinical trials in node-negative disease have demonstrated modest improvements in disease-free survival with the use of polychemotherapy and tamoxifen [21, 29, 30, 32-34]. However, the delivery of adjuvant therapy to all node-negative cases would result in exposing a large number of women to the unnecessary toxicity of treatment. Some researchers suggest adjuvant therapy be reserved for node-negative women of intermediate and high-risk [17, 21], but with our current understanding of prognostic factors it is difficult to determine this subgroup with certainty.

2.2.4.4. Systemic treatment regimes and treatment responses

Chemotherapeutic agents act by interfering with cell division [13]. They preferentially target and destroy rapidly dividing cells, like cancer cells. Standard chemotherapy in BC employs a multidrug regimen administered in six four-week cycles. The most common combination is cyclophosphamide, methotrexate, and fluorouracil (CMF) [28]. In some women, a more toxic (but more effective) drug, epirubicin is used in place of methotrexate (CEF).

The toxic effects of chemotherapy include nausea, vomiting, leukopenia, thrombocytopenia, alopecia, stomatitis, diarrhea, amenorrhea, fatigue [21] and weight gain [35-41]. Cyclophosphamide is able to suppress and in many cases permanently destroy ovarian function [27]. The ensuing hormonal changes are similar, but possibly more rapid to that observed in normal, healthy women naturally entering menopause
in premenopausal women [27, 42, 43]. Chemotherapy-induced amenorrhea and weight gain are predominant side effects in premenopausal women [27, 42, 43].

Breast tumours respond to manipulations of their hormonal milieu, hence endocrine therapy has been widely used in their management [13]. The most common hormone antagonist is tamoxifen. It acts as an antiestrogen and competes with estrogen for binding to steroid receptor sites of cancer cells [13]. Blockade of the ER sites is thought to inhibit estrogen-stimulated cell proliferation [44]. Tamoxifen may also effect other hormones for a beneficial treatment response [45-47].

Tamoxifen is delivered in oral tablet form and is generally taken for five years [28]. Tamoxifen therapy is well tolerated but adverse effects include hot flashes, anorexia, nausea, depression, vaginal discharge, irregular menses [21] and weight gain [39, 47, 48]. Tamoxifen does exhibit some beneficial effects on blood lipid concentration by decreasing total cholesterol and low-density lipoprotein concentrations in postmenopausal women [49]. It may also stabilize or increase bone mass.

2.3. Body Size and Breast Cancer

2.3.1. Body size at the time of diagnosis and prognosis

The studies that have examined the relationship of body size and prognosis in BC have concluded heavier patients were more likely to develop recurrent disease and to do so sooner than their nonobese counterparts [50-57]. However other studies were unable to confirm these findings [58-61]. A similar, but weaker trend exists when survival is the end-point of interest rather than recurrence. Some studies [50, 56, 62-68] have shown higher mortality from BC among heavier women while others have not confirmed these findings [58, 60, 69-71].

In one of these negative survival studies an insignificant linear correlation between body size and survival was reported but a significant quadratic one was found [69]. Therefore, women who were either over- or underweight were at increased risk of dying. Jain et al found an increased risk of dying from BC among women with increased pre-morbid tricep skinfold measurements but not with increased weight or BMI [70].
women (BMI >26 kg/m² [71] or > 27 [58]). Therefore, their groups may not have differed sufficiently in body size to detect an effect on survival. Another possible explanation for the weaker association in survival data is that obese women experienced higher mortality from other diseases than optimal-weight women, and therefore the association between body size and BC-related deaths was diminished [63].

The mechanism by which obesity worsens prognosis remains unknown, but the characteristic hormonal environment of increased bioavailable estrogens, hyperinsulinemia and insulin resistance among obese women may be involved. A critical review of fourteen studies published between 1975 to 1989, conducted by Goodwin and Boyd concluded that body size at diagnosis had modest prognostic value and that its effect was most marked in postmenopausal women [72]. Other researchers have also reported a more potent effect in postmenopausal rather than premenopausal women [51, 73]. The effect of body size on prognosis appears to be strongest among women with few known risk factors for recurrence (early-stage, node-negative disease) [18, 50, 53-55, 57, 67, 72]. It is conceivable that the effect of body size is more strongly expressed against the background of the relatively weaker risk factors of early stage disease [57]. Therefore the accurate determination of the prognostic value of body size in early-stage disease remains an important consideration.

2.3.2. Issues in body size and prognosis literature

The results described in section 2.3.1 Body size at the time of diagnosis and prognosis are somewhat confusing and inconclusive. However, some of the inconsistency may reflect the difficulty in properly studying body size in this cancer population. The following is a discussion of some of the specific issues relating to this area of research.

2.3.2.1. Body size measurements:

A consistent methodological shortcoming in these studies is body size measurement. Most studies retrieved these measurements from medical charts, registries or self-administered questionnaires. Therefore, the rigor of anthropometric
of comparability between studies. The studies used numerous body size indices (body weight, Body Mass Index (BMI) (also called Quetelet Index (QI)), body surface area (BSA), percentage of ideal body weight (%IBW), weight percentiles); and various definitions of overweight and obese weight, all of which compromises the validity of body size measurements.

The most commonly used measurement was body weight, but some researchers suspect that obesity [57] and body fat distribution [74-76], not increased body weight, more directly influence BC prognosis. Most body size measurements (including body weight) were only inaccurate proxies of obesity since they considered both lean body mass or fat-free mass (FFM) and fat mass [57] and afforded little relevance to the distribution of body fat [77, 78].

Tricep skinfold thickness has been recommended as the best single anthropometric measurement for assessing total body fat in adult women [79]. The only study to use tricep skinfold measurement found an inverse correlation between survival and tricep skinfold but not with weight, BMI, height, or weight to height ratio [70]. The ratio of waist to hip circumference (WHR) and waist circumference alone are both good measurements of body fat distribution and are more closely correlated to the metabolic consequences of excess adiposity [76, 80]. A waist circumference of >90cm in individuals under 40 years of age and >80cm individuals over 40 years of age has been associated with hyperlipidemia, insulin-resistance and increased risk of heart disease. Waist circumference and WHR are infrequently cited in BC literature. Therefore, inconsistent measurements and end-points may in part be responsible for the lack of consistent findings reported.

2.3.2.2. Classification and distribution

Even when comparable measurements of body size have been used, the methods of classifying women into body size groups and the prevalence of obesity have differed. For instance, studies have shown that results vary based on the designated cut-off point of the obese group. Reports in the literature found no association between BMI and
but a positive one if classified as >28 [54, 57] or >30 [63]. Researchers have also suggested that body size may not be strictly linearly related to prognosis [56, 69]. Their works suggest that both underweight and overweight women experienced inferior disease-free survival, and proposed that classifying the groups as nonobese (including normal and underweight) and obese could have underestimated the magnitude of difference between normal weight and obese patient. Unfortunately most studies grouped together women of normal and subnormal weight.

General prevalence of obesity in a population can influence a study’s ability to detect a relationship between body size and prognosis. This was nicely demonstrated by Zumoff and DasGupta whom sampled two different population (52% obesity vs 20% obesity) to investigate body weight and the incidence of positive nodes [67]. They found a significant relationship between weight and nodal status in the group with high prevalence of obesity, but no relation in that population that manifested no significant obesity. The high prevalence of obesity in the sample was required to produce significant results. In global terms, obesity figures vary drastically worldwide, which may result in a relationship between body size and BC that varies from country to country.

2.3.2.3. Menopausal status as a potential confounder

The influence of body size on BC prognosis may have also been modified by menopausal status, since estrogen levels are different in pre- and postmenopausal states [65]. The suspected effects of extra-ovarian estrogens from adipose tissue would be expected to be greater in postmenopausal women in whom over-all estrogen production is low [74]. However, many studies [52, 54, 55, 57, 61, 64, 68, 73] did not consider menopausal status in their statistical analysis.

In studies that stratified for menopausal status: three [51, 65, 77] found a stronger correlation between weight and prognosis in postmenopausal than in premenopausal women while one [63] found the opposite effect. One further study found no effect at all [70]. Studies that adjusted for menopausal status and other prognostic factors in multivariate analysis found that the relation between body size and prognosis remained
and prognosis requires further investigation.

2.3.2.4. Hormonal receptor status as a potential confounder

Obesity could possibly influence the level of receptor sites in BC; or likewise only be relevant in ER positive BC. Estrogens are thought to be growth stimulators of ER positive carcinomas [81] and obesity is associated with increased levels of extra-ovarian estrogen production (via aromatase activity in adipose tissue) [2]. Therefore, it is conceivable obesity could influence the hormonal milieu sufficiently to induce positive receptor tumours rather than negative ones [82]. Most studies [50-52, 59, 61, 63, 64, 66-68] have not stratified data based on ER status.

The results of studies that do stratify for ER status are conflicting; with both higher [2, 81] and lower levels of ER positive tumours in obese women have been reported [83]. Still other studies have shown no difference in levels from nonobese women [53-55, 74, 77, 84, 85]. There is some evidence that the influence of obesity on ER status may be age-specific [82]. Mehta et al found that obese women aged 60 or older had a higher incidence of ER+PR+ (PR-progesterone) tumours than nonobese women of the same age.

There has been some investigation of the interaction of receptor status on the relationship between body size and prognosis. Again the results are confusing, several studies [2, 74, 86, 87] have shown a stronger association between body size and poor prognosis in the obese ER positive women while others [57, 74] have not found this association. Verreault et al reported that the relationship between obesity and advanced disease was more potent in ER positive rather than ER negative tumours [87]. Thus, the relationship between receptor status, body size and BC prognosis remains undefined. However many researchers hypothesize that the most significant effect of obesity should be in ER-positive, postmenopausal women since they are most sensitive to extra-ovarian estrogen [88].
It is possible that a delayed diagnosis may explain, at least in part, the inferior prognosis observed in heavier [2, 74, 89]. The discovery of tumours may be more difficult in overweight women with larger breasts [63]. It is possible that obese individuals were less likely to seek medical attention. However, studies that have attempted to control for the ‘delayed diagnosis’ factor by sampling tumours that are nonpalable in size and detected only by mammography, concluded the deleterious effect of body size on prognosis was unlikely to be an artifact of delayed diagnosis among heavier women [74, 87].

2.3.2.6. Other prognostic factors as potential confounders

It has been suggested that increased body size influences the course of hormone-responsive BCs by promoting more rapidly progressive primary tumours [2, 74]. Therefore heavier women present with larger tumours and more extensive lymph node involvement [89]. Although some studies have found a relationship between body size and tumour stage [56, 90], tumour size [54-56, 58, 59, 87], and axillary nodal status [53, 55, 58, 59, 66, 67, 77, 87, 89]; others have found no relationship between body size and stage [50-52, 74], tumour size [50, 55, 59, 74], nodal status [51, 59, 65, 74], or histological grade [87]. The conflicting results may reflect the different study designs as well as the various methods of body size measurements.

Studies on body size and prognosis that adjusted for the stage of disease in multivariate analysis can be summarized as follows: twelve [50-53, 55-57, 63, 65, 66, 68, 69] found the relationship of body size and prognosis to be independent of other prognostic factors and seven [35, 58-60, 70, 91] did not. Therefore, the higher rate of recurrence in obese women can not be entirely explained due to advanced BC presentation at the time of diagnosis [51, 66].

To conclude, clear interpretation of the literature on body size and breast cancer is difficult due to the lack of consistency and quality of some study designs. Future prospective trials are needed with improved measurement techniques for body fat composition and distribution to better define the relationship between obesity and
to exhibit the strongest correlation, that is postmenopausal women with early-stage, ER-positive, nonpalable tumours. A more homogenous sample could be acquired if eligibility criteria included guidelines for tumour stage, menopausal status, hormone receptor status, and method of detection. Data analysis in future studies should be adjusted for factors (i.e. treatment regime) not controlled for in eligibility criteria but may confound the results. However, in reviewing the existing literature, it would appear that the majority of studies suggest a negative linear relationship between body size and prognosis. The relationship appears to be strongest in studies which involved women with early-stage, node-negative disease, especially those who are postmenopausal. The strength of the association is dependent upon how the groups were classified. Studies demonstrated stronger associations when the obese group had higher cut-off points and/or the nonobese groups excluded underweight women. Finally, no other variables (i.e. delayed detection or advanced disease presentation in heavier women) reviewed for this paper could entirely account for the observed association between body size and prognosis.

2.3.3. Potential mechanisms by which obesity influences prognosis

Many physical alterations in the host may affect the rapidity of breast cancer growth. To date, the mechanism by which obesity influences BC prognosis is unclear. However, it may relate to the hormonal consequences of obesity. The following is a review of some of the potential mechanisms by which obesity could influence BC prognosis as cited in the literature.

2.3.3.1. Estrogens

Estrogens have been classically implicated in breast tumorigenesis [92]; although other hormones are also actively under investigation. Estrogens are thought to be critical in the growth of duct epithelium, and the normal development of the breast during puberty [93]. However, the nature of its role in the neoplastic process has not been precisely defined. The possible effects of estrogen in BC include: 1) acting as a true carcinogen by directly initiating malignant transformation of cells, 2) promoting tumour
agent by allowing a carcinogen to initiate neoplastic transformation in its presence”[4].

Most researchers agree that if estrogen indeed has a role in BC, it is likely a promoter of cell proliferation [80, 88, 94-96].

Studies which have measured the estrogen levels of women with and without BC have observed no consistent differences between the groups [97-99]. However, many studies have shown that women with BC have higher levels of non-protein-bound estradiol [98-100], higher levels of albumin-bound estradiol [100-102] and lower levels of sex-hormone-binding protein(SHBG)-bound estradiol than controls [99-102]. Estradiol is generally regarded as the most important estrogen in the development of BC [103]. Circulating estradiol is predominantly bound to a protein with only a small percentage (1 to 3%) that is non-protein bound [100, 104]. The unbound fraction of estradiol is biologically active in breast tissue [95]; although some researchers consider the active component to also include that portion bound to albumin [105]. Bound estradiol is bound with high affinity to SHBG and with low affinity but at an enormous capacity to albumin [99]. The current research suggests that breast tissue of those women with BC may have greater exposure to unbound biologically active estrogen than women without the disease.

The physiologic state of obesity can alter hormone production and metabolism [106]. Increased body fat results in an elevation of androstenedione production, increased conversion of androstenedione to estrone, and increased production of other estrogens (i.e. estradiol) [102]. Estrone accounts for the majority of estrogens produced in postmenopausal women and for a significant proportion in menstruating women [107]. Estrone can be metabolized to estradiol [95].

Studies have shown significant correlation between plasma levels of estrone [98] as well as estradiol [98, 107] and body weight, with one exception [104]. Several studies [99-101], again with one exception [98], have shown that obesity was strongly associated with increased levels of non-protein bound estradiol. Therefore, obesity may promote an estrogenic environment which is more favourable for tumour growth. The increased
levels of unbound circulating estrogen could enhance tumour proliferation and therefore promote advanced disease among overweight women [83].

2.3.3.2. Sex-hormone-binding globulin (SHBG)

SHBG, as previously discussed, is a specific plasma protein which binds and transports sex-hormones like estradiol and testosterone with high affinity [57]. Low levels of this globulin increases the availability of estradiol to peripheral tissues for biological interactions [77]. Research has shown that obesity results in depressed level of sex hormone-binding globulin and therefore contributes to increased levels of free estradiol [101, 105].

2.3.3.3. Testosterone

Testosterone can be aromatized into estrogens in ovaries, fat and other tissues [105]. Increased circulating levels of testosterone and other androgens (androstenedione, dihydrotestosterone, and dehydroepiandrosterone sulfate) have been implicated as promoters of BC development [108] in a manner that is independent of body weight and body fat distribution [108]. Obesity is associated with normal production of testosterone but with increased metabolic clearance [106]. The role of testosterone in BC prognosis is unclear.

2.3.3.4. Progesterone

Women who are obese have been shown to have lower than normal levels of progesterone [101, 109]. Progesterone is an estrogen antagonist; and therefore lower levels of progesterone could allow for greater unopposed estrogen stimulation of the mammary tissues [4, 105]. Progestrogens also suppress SHBG production [105].

2.3.3.5. Insulin

Insulin is a potent anabolic hormone, and has been investigated for its potential role in tumour stimulation [106]. Insulin appears to exhibit a synergistic potentiation effect on estrogen-induced growth of BC cells [81]. It may down-regulate SHBG [80]. Hyperinsulinemia, a typical characteristic of obesity, may be involved in tumorigenesis
2.3.3.6. Fat distribution

Some researchers have suggested that levels of biologically active estrogens may be influenced by body fat distribution [55]. Women tend to gain weight either in areas of the upper body such as the abdomen, shoulders, and the nape of the neck (android obesity) or in the lower body region including the buttocks and thighs (gynoid obesity) [75]. Hormonal and metabolic abnormalities are more pronounced in women with android obesity [76, 104]. One study reported that BC patients with android obesity had lower levels of SHBG than those with gynoid obesity [104]. A reduction in available binding proteins could have conceivably resulted in higher levels of unbound estradiol.

Body fat distribution has also been investigated in relation to other BC prognostic factors. One study reported that an increasing waist to hip ratio had a stronger correlation to the degree of nodal involvement than either weight or BMI [77]. Therefore, it appears that the distribution of body fat rather than obesity per se may be responsible for the favourable hormonal environment for BC growth, although further research is required.

2.3.3.7. Dietary intake

Dietary constituents may have a role in the development of BC. Although not the focus of this thesis, the following section briefly highlights some of the current research.

2.3.3.7.1 Dietary Fat

It is difficult to determine whether it is obesity or the diet leading to obesity or both that contributes to poor prognosis among heavy women [53]. Some studies [62, 91, 111] have observed an increased risk of dying, albeit not statistically significant, associated with increased total dietary fat while others [5, 18, 68] have not observed any association. An additional study reported a significant relationship between disease-free
In all but one of these studies [111], there was no dose-response relationship between the intake of total dietary fat and BC prognosis. Only two of the studies adjusted for energy intake as a possible confounder [62, 111]; both of which found a positive association. Two studies [61, 111] observed that increased levels of saturated fat negatively affected prognosis. The Rohan study was not able to show this [62]. Verreault et al reported that increased intake of saturated fat was associated with greater lymph node involvement [87].

In animal work, Sprague-Dawley rats, injected with a chemical carcinogen, had increased mammary tumour proliferation when placed on a high fat diet [112]. They also experienced a reduction in tumour growth when switched from high- to low-fat chow. However, another study using the same type of rat, treated with a different carcinogen, demonstrated an inhibition of mammary tumour growth with a calorie reduction diet (by 30%), irrespective of the fat level [113].

Various types of dietary fat have been investigated for their role in BC. For instance, linoleic acid intake is thought to influence the metastatic spread of BC disease [114, 115]. Both in vitro and in vivo studies suggested that levels of non-protein bound- and albumin bound-estradiol were increased by the presence of free fatty acids, in particular polyunsaturated fatty acids [93]. Free fatty acids, which are released from adipose tissue, increase the levels of biologically active estradiol by acting as a competitive inhibitor with estradiol for SHBG and albumin [80].

The effect of dietary fats on levels of serum estradiol has also been considered a possible mechanism for poor BC prognosis [113]. Postmenopausal women with BC placed on a low fat diet (20%) experienced a reduction in serum estradiol [47, 116].

Taken together, many studies support the hypothesis that dietary fat intake influences the progression of breast tumours although the evidence is inconclusive at this time. The evidence also does not demonstrate a relationship between a high fat diet and a worsened prognosis in obese women.
Other constituents of the diet have also been investigated for possible roles in BC prognosis. Holm et al found that low fibre intake was associated with larger tumours; and that low carbohydrate and retinol intake was more common among women with ER-negative tumours [117]. A nutrition intervention study in BC reported increased fibre consumption in women following a low fat diet and a significant reduction in serum estradiol in this group [116]. Dietary fibres are thought to increase fecal weight and decrease the enterohepatic circulation of estrogens [105]. Two studies have shown an inverse relationship between estradiol concentration and the amount of fibre in the diet [105, 116]. However the effect of dietary fibre on survival has not been demonstrated in other studies [5, 62, 70].

2.3.3.7.3 Vitamins

A study by Ingram and colleagues did show an improved survival in women with high consumption of fruits, beta-carotene or vitamin C [5]. Howe et al performed a combined analysis of 12 case-control studies on breast cancer risk and determined a protective effect of beta-carotene, vitamin C and vitamin A intake [3]. The precise role of these dietary constituents (such as fibre, carotenoids, vitamins) in BC prognosis awaits further study, particularly in studies which compare obese and nonobese women with BC.

In conclusion, most of the reviewed literature suggests that biologically active estrogen could enhance the disease process of obese women with BC. The exact reason that obese women have heightened exposure to biologically active estrogen remains unknown. Increased production of estrogen in adipose tissue, decreased levels of bound estrogen through the down regulation of SHBG, or decreased levels of estrogen antagonists (i.e. progesterone) are all possibilities.
2.3.4.1. Incidence and magnitude of weight gain

Weight change in cancer populations is typically weight loss or cancer cachexia [118]. DeWys and co-workers determined that weight loss was present in more than 50% of cancer patients at the time of diagnosis and that weight loss was an independent predictor of survival [119]. Therefore, the commonly reported weight gain in 50 to 100% of women with early-stage BC is curious [35-41].

The magnitude of weight gain has been shown to be between 2 and 6 kilograms within eighteen months of diagnosis [35-40, 120], although gains of 10 kilograms or more are not unusual [35-37, 121]. This weight gain is thought to be predominately body fat rather than lean mass [120, 122]. Studies have observed increased skinfold and decreased lean muscle mass measurements relative to normal standards in women with BC [120, 122].

2.3.4.1.1. Factors influencing magnitude of gain

Various characteristics can influence the magnitude of weight gain. There appears to be striking variability in the amount of weight gained based on the type of treatment received [35]. The typical gain for a woman of early-stage BC appears to be greatest in those undergoing multi-agent chemotherapy [35, 38, 39], intermediate in single-agent chemotherapy [35, 38] or tamoxifen therapy [39, 48]; and relatively small in those having surgery alone [123] or in combination with radiation [39]. However, Camoriano and one other author observed no weight gain associated with tamoxifen [32, 123].

Some researchers have suspected that weight gain may be particularly problematic in women treated with multi-agent chemotherapy in combination with prednisone or ovarian ablation by radiation [35, 60]. However, others have observed no heightened effect of weight gain with the addition of prednisone [27, 36] or in chemotherapy-induced amenorrhea [39, 123]. Women with late-stage disease, in contrast to early-stage BC generally experience weight loss when treated with the CMF chemotherapy regimen [124]; although weight gain in late-stage BC has been well-
medroxyprogesterone [125, 126]. Heasman suggested that following the same chemotherapy (CMF), women with early-stage disease have an increased appetite while those with metastatic disease have a decreased appetite [35].

The duration of adjuvant chemotherapy may have also influenced the magnitude of weight gain. Bonnadonna et al found that women treated with 12 months of therapy versus 6 months experienced an additional 2 kg weight gain [27]. Body weight when tracked over time tends to peak at the end of adjuvant chemotherapy treatment [36, 39, 123]. Two studies reported that changes in body weights following treatment for BC were independent of body size at the time of diagnosis [35, 60]. An additional study confirmed this finding in postmenopausal women but observed greater gains in premenopausal women who were heavier at the time of initial treatment than in their lighter counterparts [123].

Menopausal state of a woman also appears to influence the degree of weight gain. A review of several studies [35, 36, 40, 60, 121, 123] found that premenopausal women gain more weight than postmenopausal women.

Overall, the literature suggests that the choice of treatment affects the magnitude of the gain. Chemotherapy likely has a major effect, either directly or indirectly, on body weight. However, it is likely not the only contributing factor since BC women without chemotherapy also gain weight. Menopausal status, either natural or artificial, may influence the propensity of weight gain in a woman with BC.

2.3.4.2. Psychological impact of BC on weight gain

It has been estimated that more than half of the women with newly diagnosed BC experience considerable psycho-social distress within the first year of treatment [22, 127]. Most commonly affected areas were: body image; self-esteem; mood; sexuality; marital and interpersonal relations; and coping ability [22, 24, 39, 127, 128]. Depression is not unusual [25]. Distress is long-term, probably due to the chronic nature of the disease and to potentially disfiguring, and lengthy treatments [127, 128].
those receiving adjuvant chemotherapy [22, 127]. It has been suggested that patients treated with chemotherapy tend to worry more about treatment success than those treated with other therapies [128]. Chemotherapy may also have a strong psychological impact due to the length of treatment and the large number of physical side-effects [128].

The physical side-effect of weight gain has been frequently reported as a concern by highly distressed women with BC [22]. In fact, one study found that weight gain was more distressing to women than any other component of BC treatment [121]. The emotions associated with being overweight would obviously further compromise the psychological health of these women. Increased body weight has been shown to intensify the feelings of inadequacy, loneliness, and the threat of social rejection that often accompanies a cancer diagnosis [122]. An increase in body weight also negatively affects self-esteem, body image and the sexuality of women with BC [22].

2.3.4.3. Effects of weight gain on BC prognosis

It is conceivable that weight gain following the diagnosis could influence BC outcome given the association between weight at diagnosis and prognosis. The relationship between weight gain and prognosis has not been well defined, but some investigators have found a decrease in disease-free survival with weight gain that is independent of weight at diagnosis [38, 41, 123]. However others have found no association [35, 60].

The lack of consistent findings could be due to a number of factors. Perhaps the observation periods were too short to observe the influence of increased weight on the natural history of the disease [35]. Sample sizes were small in several of the studies [36, 38, 41] and may therefore lack sufficient power to detect an effect. One study with a relatively long follow-up period and large sample size (median F/U of 6.6 years, N=646) showed that patients gaining more than the median amount of weight (>5.9 kg) had a greater chance of relapse and dying from the disease than those who gained less than the median weight [123]. These trends existed for both pre and postmenopausal women. However in multivariate analysis, only the premenopausal women with above the median
times more likely to relapse and 1.6 times more likely to die from their disease than their leaner counterparts when other prognostic factors were considered (p = .04). The lack of consistent findings may also result from the inclusion of women with advanced disease. Two studies [35, 38] included women with greater than 4 positive nodes. These women were already at high risk of recurrence and therefore their inclusion may have diminished the modest impact of weight gain on disease outcome.

The weight gain and prognosis issue is compelling, albeit unconfirmed at this time. Further work is required to determine the prognostic effect of weight gain and the degree to which prevention of weight gain can improve overall prognosis. If weight gain has a negative impact on disease outcome, it likely operates through similar mechanisms as discussed previously in section 2.3.3. Potential mechanisms by which obesity influences prognosis and the prevention of this gain would likely improve the overall disease-free survival.

2.4. Nutrition interventions in breast cancer:

The majority of women diagnosed with early-stage breast cancer go on to lead long and productive lives. Yet, obesity in any woman increases her overall mortality rate from other causes [64]. Therefore, an excessive weight gain during treatment of BC is undesirable from a general health perspective. The literature also suggests that increased body weight (either at diagnosis or gained thereafter) is extremely distressing for women with BC [36, 121] and may negatively impact on their disease-free survival [38, 41, 123]. The development of effective weight management interventions to minimize weight gain may have considerable health benefits to these women.

2.4.1. Studies on nutritional intervention in BC

The Phase II Multidisciplinary Weight Management in Primary Breast Cancer (WMI), along with several feasibility studies have demonstrated that women undergoing early-stage BC treatment were able to successfully adhere to weight management
programs with fat intake reduction (to approximately 20-25% of total energy) and improved carbohydrate intake [116, 124, 129, 130].

In the WMI, there was no change in caloric intake (baseline, 1530 kcal ± 412; 1 year, 1515 ± 293; mean ± SD), but significant changes in the nutrient composition of diet with reduced percent of calories from fat (31 to 26.5% p=0.003), increased from carbohydrate (52.0 to 57.2%, p=0.006) as well as increased fibre intake (16.4 to 20.3 gm/d, p=0.004) [130]. In the Nutrition Adjuvant Study, postmenopausal women with BC experienced a reduction in the percent energy intake derived from fat (37.6 ± 2.1 to 23.1% ± 4%, mean ± SD, baseline to 3-months) but also a 25% reduction in total energy intake (from 1789 ± 99 to 1326 kcal/day ± 76 kcal/day, mean ± SD, baseline to 3-months) after three months of observation [124].

Another low-fat feasibility study with postmenopausal women reported decreased fat intake (56 ± 16 to 32g/day ± 13 g/day, mean ± SD, baseline to 6-months) and total energy intake (1504 ± 420 to 1324kcal/day ± 475 kcal/day, mean ± SD, baseline to 6-months) after six months of observation [116]. After the fifth month, the women also had a significant reduction in their serum concentrations of cholesterol, HDL cholesterol and estradiol.

A later Swedish feasibility trial to assess long-term adherence to dietary intervention recruited women with BC aged 50-65 receiving adjuvant therapy [129]. It reported a significant change in the consumption of total energy (1850 to 1700 kcal/day, mean, baseline to 2-years), fat calories (37 to 24% of total energy, mean, baseline to 2-years) and carbohydrate calories (46 to 57% of total energy, mean, baseline to 2-years) after two years. The intervention group had a mean body weight reduction of 1.4 kg in the first year but with a increase of 1.0 kg during the second year. The non-intervention group (observed women with BC) had gained 1.3 kg at two-year follow-up. The Women’s Intervention Nutrition Study (WINS) also evaluated long-term adherence to a dietary fat reduction program in postmenopausal BC women treated with adjuvant therapy [11]. It reported a significant reduction in the percent energy intake derived from fat in the intervention versus control group at 3 months (20.3 ± 2% versus 31.5% ± 2%, mean ± SD, respectively) which was maintained throughout 24 months of observation.
kcal/day ± 395 kcal/day, mean ± SD, baseline to 6-months) after six months of observation. The weight difference between the intervention and control group was 3.3 kg after 18 months of observation (1.5 ± 5 kg loss compared to 1.8 ± 6 kg weight gain, mean ± SD, intervention versus control group, P < .001).

A BC prevention trial involving free-living healthy women aged 45 to 69 years also demonstrated a reduced consumption of fat calories (to 20% of total energy) and increased consumption of fruits and grains after two years [131]. The average weight loss in this study was 3.1 kg of body weight after 12 months of observation. Change in body weight over time was also recorded in one study that looked at the effects of low-fat diet (20% fat) and tamoxifen on hormone levels [47]. Their results suggest that tamoxifen partially suppressed the weight loss of the diet-intervention group (1.5 kg with tamoxifen versus 4 kg without any adjuvant therapy, mean loss of body weight) at one-year. During the same time, women in the non-intervention group treated with tamoxifen gained weight.

An intervention by Winningham et al successfully showed that an aerobic interval-training exercise program could help stabilize body weight and reduce body fat deposition in women with BC undergoing chemotherapy [122]. In this study, lean muscle mass was maintained, if not increased in some women, thereby possibly improving metabolic rate. Unfortunately, dietary intake records were not obtained in this study.

The trials outlined above support the addition of nutrition therapy in adjuvant BC treatment to promote improved nutritional intake and modest weight reduction. However, the literature also indicated that women with BC lost fewer kilograms of body weight than their healthy counterparts, despite comparable effort in weight management programs. This suggests that perhaps a physiologic influence may be at work in women with BC.

The women recruited for our study had also reported difficulty in maintaining body weight. Our sample was recruited from the Phase II Multidisciplinary Weight Management in Primary Breast Cancer (WMI) conducted by Dr. Goodwin and colleagues
of a multi-disciplinary weight management approach to influence the psychological response to BC in women with recent diagnosis, and thereby normalize eating behavior and enhance physical activity. The primary goal of weight maintenance was successfully achieved with minimal weight change (0.5 kg); although overweight subjects had significantly higher losses (1.6 kg). However, as previously stated, subjects commonly reported that this weight maintenance, or energy balance was difficult to maintained despite their best efforts to reduce dietary intake and improve physical activity. Since our study measured components of energy balance, we were able to explore this claim at a mechanistic level.

2.5. Energy Imbalance in Women with BC

Energy balance of the body is maintained through the incredibly tight coupling of energy intake and output over time [132]. Long term maintenance of a stable body weights reflects minimal changes in the amount of stored energy [133]. A positive energy balance sufficiently sustained will promote tissue accretion; often in the form of body fat [134]. A variety of hypotheses for positive energy balance or weight gain observed in women with BC have been proposed.

2.5.1. Dietary intake

Oxidation of nutrients (fat, carbohydrate and protein) contained in the diet provides the necessary energy to maintain normal body function activity. A surplus of these nutrients beyond our needs can result in energy storage. It is possible that women with BC experience weight gain due to a dietary intake beyond their bodily needs. Psychological distress of the disease may have a tremendous impact on eating behavior. The concept of restrained eating first introduced by Herman and Mack has been investigated in relationship to women with BC. Restrained eating is thought to be a person’s conscious control of eating in an effort to lose weight or maintain an acceptable weight [135]. In theory, individuals who are restrained eaters, in the presence of stress, are more likely to adopt disinhibition with bingeing eating behavior than those who are unrestrained eaters [136].
Binge eating behavior is thought to be a potential outlet for the distress of BC [39]. A small, retrospective study by DeGeorge et al investigated these concepts but failed to show an association between restrained eaters and increased weight gain [39]. However, she found an association between high levels of disinhibition as well as perceived hunger and weight gain. The type of BC treatment did not impact on the results.

Levine et al, measured self-reported eating and exercise behavior in women on chemotherapy and found no association between either overeating or inactivity and weight gain [37]. The study also measured psychological adjustment to BC illness and the variables that were consistent with high psychological distress significantly correlated with weight gain. Furthermore, women with repressive coping strategies experienced higher gains than those who openly expressed emotions. Unfortunately, the self-reports of eating and exercise behavior were not included in the analysis of weight gain based on psychological factors. It has also been suspected by other authors that increased dietary intake may be a method to combat chemotherapy-induced nausea. Women who experienced this mild nausea often report an improvement in nausea with frequent snacking [35].

Although the above studies suggest weight gain results from increased intake, none have validated their findings against dietary intake records. Several other studies have attempted to quantify the dietary intake of women treated for BC. Goodwin et al used a food frequency questionnaire and found the intake of 101 premenopausal women with node-negative invasive BC was 1772 ± 64 kcal/day [137]. In this study, the mean total caloric intake of these women was no different than those women classified as low BC risk (similar risk of BC development to the general population). Another recent study noted a reduction of energy intake (1296 ± 212 kcal) in 20 premenopausal, early stage BC women during chemotherapy [1]. However, most of women (16/20) received doxorubicin which was not a typical treatment reported in the weight gain literature. This drug is now sometimes offered to women with node-positive disease and is associated with a higher incidence of mouth sores and severe nausea than standard treatment (CMF).
randomly selected days during the first 14 days of chemotherapy treatment and another three during the last 14 days [40]. She reported no difference in the intakes of weight gainers and non-gainers. Another group administered a set of nutritional records (3-day food record, 56-item questionnaire, 56-item dietary preference questionnaire) on five occasions within the first six months of chemotherapy [138]. They compared energy intake, food preferences and food servings between a small group of women with BC and healthy controls. They concluded that BC patients consumed a greater number of calories and food servings than their healthy controls. The higher intake was primarily from the breads/cereals and meat/fish categories. There was no difference in snack and dessert consumption between the groups. Unfortunately, the food frequency questionnaires did not highly correlate with the 3-day food records and therefore weakens the validity of results. No consistent changes in taste or appetite were reported within the BC group.

In a nutrition feasibility study, women over age 50 receiving chemotherapy and/or hormonal therapy were randomized to a nonintervention arm (standard nutritional counseling for nutritional adequacy) or intervention arm (counseling for nutritional adequacy plus a reduction of fat intake to 20% of calories) [124]. Since the nonintervention group received standard therapy, their intakes should be reflective of the average woman receiving BC treatment. The total energy intake of this group was 1621 kcal/day ± 93 kcal/day (36.8% ± 1.6% derived from fat, mean ± SD, baseline) at baseline and remained relatively unchanged three months later. These intakes were similar to Goodwin’s results and to typical intakes of North American women of their age [131, 137].

A later report, by Chlebowski with an enlarged sample found that the control arm had a mean total energy intake of 1544 kcal/day ± 369 (32.1% ± 7.3% derived from fat, mean ± SD, at 6-months) after six months of observation [11]. The nonintervention BC group in a Swedish feasibility study, with a similar design to Chlebowski, reported a mean energy intake of 1800 kcal/day (37% derived from fat) at baseline which remained
stable for two years. In the same study the percent contribution of energy from fat decreased to 34% at two years.

The current literature does not support the notion that women with early-stage breast cancer increase their energy intake after detection of the disease. However, the interpretations of these results are limited by the accuracy of the applied dietary assessment methods. In general, it is very difficult to measure energy intake accurately without influencing the subject's eating behavior [133]. In this thesis, we measured the dietary intake of women in our study by dietary records. These women were experienced at maintaining diet records for the WMI and this would have hopefully improved the quality of our results.

2.5.2. Physical activity

The thermic effect of exercise (TEE) accounts for 15% to 20% of the total energy expenditure in ambulatory, working sedentary adults [43, 139]. A decline in physical activity could promote a positive energy balance. The impact of psycho-social distress and treatments of BC on activity levels have both been studied. A study by Ganz et al found that at least 50% of women, irrespective of whether or not adjuvant treatment was given, reported physical problems with arm tightness and numbness, limited mobility, fatigue, lifting, sleeping and sports [128]. A further study, by this group, showed that women reported a significant impairment in their ability to perform both daily and recreational activities [22]. Other studies described fatigue and decline in activity associated with chemotherapy [36, 128, 138] and radiation treatment [128].

WMI and three other studies have compared the level of activity and change of body weight [1, 37, 39, 130]. One found that women who reported a general decrease in their level of activity while on treatment gained significantly more weight than those who maintained or increased their level of activity [39]. Levine et al found no association between self-reported exercise and weight gain [37]. Demark-Wahnefried used a self-administered weekly activity questionnaire in women on chemotherapy and observed a small decrease in energy expended in physical activity, but no change in body weight [1].
weight maintenance (p=0.003) [130].

There were a few studies which suggested that women undergoing treatment for BC have impaired physical performance but only one study found a correlation between exercise and weight change. Although exciting, these findings were preliminary and therefore more quantitative testing is required to explore this relationship.

2.5.3. Metabolism:

Energy generated from the oxidative metabolism of food is expended on major body processes thereby sustaining life. The processes of energy expenditure (EE) include: RMR, diet-induced thermogenesis (DIT), environment thermogenesis and the thermic effect of exercise/work (TEE) [140]. RMR is the sum of all energy-requiring processes of the body while in a restful, postabsorptive state [141]. It accounts for 75% to 90% of the total EE in healthy individuals, the remainder of which results from the thermogenesis of dietary intake (DIT; which is typically 7 to 10% of total EE [139]), environment (shivering/nonshivering thermogenesis) and TEE [142].

However, the health and nutritional status of an individual are major determinants of EE and the magnitude of their influence should be defined. For instance, the need of medications may influence the level of EE (i.e. catecholamines, nicotine, caffeine and aspirin increase EE; whilst narcotic analgesics, sedatives, beta blockers and general anesthesia all decrease EE) [139]. A prolonged fast or severe hypocaloric diet could result in decreased EE as a response to lean muscle mass depletion and metabolic alterations (which favors energy conservation of body stores) [141]. With various disease states a wide range of EEs exist. Many disease states and injury (burns, trauma, sepsis) produce undisputed increases in EE [143] but interestingly, the impact of cancer on EE in the human body is inconsistent [118].

Early work on EE in cancer focused on hypermetabolism and the development of cancer cachexia [144, 145]. In a case-control study, Warnold and co-workers investigated the body composition and energy balance of ten cancer patients (none of whom had BC) prior to surgical treatment and nine hospitalized age-matched controls
Energy expenditure (expressed as kcal/day; calculated by a method using heart rate and oxygen consumption measurements) was elevated in cancer patients, but not in controls, while energy intake was not significantly different between groups. They concluded that the weight loss associated with cancer was due, at least in part, to hypermetabolism. The presence of cancer-induced hypermetabolism gained further support by Bozetti and co-workers when 60% of their subjects with locally advanced or disseminated cancers (5 of 65 subjects had BC) had at least a 20% increase in RMR (expressed as kcal/day, measured by closed circuit metabolic measurement cart) [145].

However, Knox et al measured RMR of 200 nutritionally depleted cancer patients (<10 patients had BC of unknown stage) and suggested that hypermetabolism was not a consistent manifestation of the disease process [146]. They compared observed RMR (expressed as kcal/kg body weight/day, measured by metabolic cart) to estimated RMR (by Harris-Benedict Equation, HBE) [147] (Appendix 4). A classic method for RMR estimation is the HBE, which uses the variables of age, height, weight and sex, was developed in 1919 but remains the premier equation today [148]. HBE correctly predicts RMR in 80 -90% of normal individuals; although routinely overestimating it within 10-14 % of measured value [134, 142, 149].

Knox et al found that 41% of subjects had normal RMR when measured RMR was compared to RMR of HBE (99.5% of HBE), 25% had increased RMR (121.9%) and 33% had decreased RMR (79.2%) [146]. Subjects with hypermetabolism had a longer duration of disease than either the normo- or hypometabolic groups (32.8 vs. 12.8 vs. 21.0 months, respectively). This suggests that the tumour-bearing state may influence energy metabolism differently during various phases of the tumour life cycle. The mechanism for the hypometabolic response to illness was unclear.

Others have suggested that hypermetabolism was more predominant in large bulky tumours [150], or in metastatic rather than early stage, local disease [151, 152]. However, the concept of elevated metabolism secondary to tumour burden or stage has not gained unanimous support. Two additional studies compared cancer patients (with and without weight loss) to hospitalized noncancer patients (with and without weight loss) [153, 154]. The first study did observe an elevated RMR in weight losing cancer
expressed as kcal/kg BW/day) and to weight stable cancer patients (RMR expressed as kcal/mmol total body potassium/day). The second study, using a similar study design observed no detectable difference in RMR (expressed as kcal/kg FFM/day) between groups (cancer vs noncancer) [154]. However there was a significant difference in RMR between weight losing patients and weight stable patients, irrespective of the presence of tumour.

A third study compared RMR in fifteen patients with esophageal carcinoma and in an age-, sex-, and race-matched control group [155]. This study found no difference in RMR (kcal/kg BW/day and kcal/kg FFM/day) between groups. Researchers have also investigated whether RMR differs with different tumour types. Hansell et al observed no significant difference between RMR (expressed as kcal/kg FFM/day) in three different tumours (colorectal, gastric, and bronchial cancer) [156] whilst Dempsey and colleagues did observe differences in RMR between tumour types in their study [157]. The latter study found elevated RMR (expressed as observed/estimated RMR based on Harris-Benedict Equation) in gastric cancers, normal RMR in colorectal or esophageal cancers, and decreased RMR in pancreatic and hepatobiliary cancers.

In conclusion, several studies support the existence of metabolic alteration in cancers; although it is not a general finding throughout the literature. The literature has not presented consistent findings of metabolic abnormality in cancer-bearing patients. Furthermore, there is little in the way of data that is specific to BC. Therefore, there may be true variability in RMR based on the stage, type, and development of the tumour. However, some of the variability may also be due to the various methods employed to measure energy expenditure and to normalize RMR data for differences in body size. Moreover, the majority of studies have been on heterogeneous groups of cancer patients which may be inappropriate if RMR varies based on tumour site or histological type. There is little information specific to BC. Most studies have made little attempt to evaluate tumour burden or treatment regime which may also significantly impact on host metabolism. Future research with better study designs may offer greater insight to the metabolic state of cancer-bearing patients.
There is little information on the RMR of women with early-stage BC in the literature. The weight gain noted in women with early-stage BC is not consistent with the metabolic outcomes described in the general cancer literature. If weight gain was truly a metabolic phenomenon, a reduction in RMR and/or thermogenesis would need to be sufficient to promote energy storage. RMR is directly related to the body compartment called lean body mass or fat-free mass (FFM) [158], which consist of skeletal muscle, nonskeletal muscle, skin and bone [159]. This compartment contains most of the metabolically active tissue in the body and is reduced during prolonged inactivity or insufficient energy intake. Hypocaloric dieting, if sustained, forces the body to utilize FFM as a source of protein for energy utilization [160].

Unfortunately, the research is limited on this topic and only recently has a study published data using the open-circuit, ventilated hood system on premenopausal women with BC [1]. It reported a significant reduction in RMR in these women whilst on chemotherapy and a re-establishment of RMR similar to baseline levels after chemotherapy completion. A reduction in RMR did not translate into weight gain; although the concurrent reduction of energy intake may have influenced the results. The few other studies that do exist have study design limitations which preclude their interpretation. For instance, one study fails to restrict RMR measurements to the fasting state [40]. Therefore, it is impossible to distinguish between RMR and thermogenesis, thus it is not surprising that this study failed to show any associations. Unfortunately, the other two studies involved both BC and other tumour patients (discussed previously in section 2.5.3. Metabolism) but they failed to describe the stage of the BC disease and to perform subgroup analysis on BC tumours alone [145, 146]. The RMR specifically relating to women with early-stage BC was undetermined in these latter studies. Therefore, at the present time there is only one study which has measured RMR in early-stage BC in a reliable fashion but only in premenopausal women.

The literature also supports a reduced lean muscle mass in women with early stage disease [120, 122]. A reduction in metabolically active tissue could contribute to lower metabolic rates which could promote weight gain [161]. Further quantitative data
2.6. Rationale and Summary

This review of the literature has hopefully captured the difficulties in investigating body weight and energy imbalance in women with BC. Given the study design limitations, the research does suggest that increased body weight (at diagnosis and gained thereafter) has a negative impact on disease-free survival. The exact mechanism remains unknown.

It is also evident that women with BC are under tremendous psychological distress which is only exacerbated by weight gain. It is clear that the majority of women treated for early-stage BC gain weight. The literature has not precisely determined the factors at work in the weight gain process. To date, the literature does not provide consistent evidence that increased body weight results from overeating, inactivity or reduced RMR. However, there is a suggestion that women with BC have reduced lean muscle mass, and a few studies have reported overeating and/or inactivity. The literature also reports hyper-, normo-, and hypometabolism in cancer-bearing patients and suggests that metabolic alterations may be tumour site and stage specific. Only one study has measured RMR in women with early-stage BC with a reliable technique and it has reported a reduction in RMR during chemotherapy that reverts to normal when treatment is completed. The most persuasive evidence remains the common frustrations of women with BC with their inability to maintain or lose body weight despite best efforts.

Women with BC often want to know how best to help themselves. Determination of the mechanism behind weight gain will likely help women better cope with this undesirable consequence of the disease. Further research should begin with the investigation of RMR in women with early-stage BC using a valid technique, since 1) a study has already confirmed a reduced RMR in a subset of these women (premenopausal women on chemotherapy) and 2) given that a prolonged reduction in RMR could translate into weight gain.
Chapter 3. Materials and Procedure

3.1. Hypothesis
It is hypothesized that women recently diagnosed with early-stage BC have a lower resting metabolic rate than their healthy controls or women recovering from BC and it is RMR which contributes to the difficulty women have remaining weight stable following diagnosis.

3.2. Specific Objectives
To address this hypothesis, two separate objectives were considered: 1) to determine whether RMR differs in women with early-stage BC compared to healthy women or women recovering from early-stage BC and 2) to determine whether RMR changes over time during treatment for BC.

3.3. Design
This comparative study was designed to measure energy balance in women with and without BC in order to investigate potential mechanisms underlying the weight gain process. The two components of energy balance considered were dietary intake and RMR. Body composition and anthropometric measurements were also used in order to normalize RMR data for body size.

The study comprised of 3 groups of women: Early BC group (EBC; n=10) consisted of women with newly-diagnosed, early-staged BC, Recovery group (RBC; n=9) consisted of women recovering from BC and Control group (n=11) consisted of healthy women without breast cancer.

3.4 Analyses
1) The mean RMRs of the 3 groups were compared by two-way analysis of variance (ANOVA) using PROC GLM followed by a post hoc test (Student-Newman-Keuls test). When appropriate, covariates (FFM, weight, height, age) were included in analysis. Potential differences in body composition, physical activity and dietary intake between the groups were investigated in a similar manner.
2) The RMR of EBC subjects at baseline and 6 month follow up were compared using paired t-test analysis. Similar analyses were conducted to investigate body composition, physical activity and dietary intake over time. All statistical analyses were performed using Statistical Analysis System (SAS) software (SAS Institute, Cary NC).

3.5. Subject and Group Characteristics:

EBC consisted of ten women with newly-diagnosed (within 6 months of diagnosis), early-stage (T1-3,N0-1, M0) BC who had primary surgery and were receiving adjuvant therapy during the time of our study. These women were entered into the WMI, therefore they were actively attempting to prevent weight gain.

RBC was comprised of nine women recovering from early-stage BC who had previously participated in the WMI. All these women were without recurrence of the disease at the time of study (between 15 and 28 months since initial diagnosis), and had completed BC therapy (with exception of ongoing tamoxifen treatment for some).

Control group consisted of eleven healthy, age-and weight-matched women without BC and were recruited through advertisement at several hospitals throughout Toronto. Exclusion criteria for all groups included BMI (BMI kg/m²) <20 or >35 and the presence of other major diseases (see appendix 1 for complete eligibility assessment).

3.6. Sample Size:

Using a power analysis based on preliminary data, 9 women per group were necessary to achieve an acceptable 0.8 power to detect a significant level of difference in RMR when using an alpha of 0.05 and an effect size of 15%. The effect size is based on the RMR data from our preliminary study in women with BC (EBC) and their healthy controls, thus we assumed that the data reflected true population means and variances.

3.7. Methods

3.7.1. Dietary Records

Subjects were instructed to maintain three detailed 24 hour diet records. The women recorded dietary intake on a randomly assigned week- and weekend day
(except for those women tested on Monday who were assigned to two weekdays); as well they recorded their intake on the day prior to test day. Three days of record-keeping was chosen as it is thought to be the minimum number of days required to adequately reflect long-term usual intake of macronutrients and yet more cost-effective than a larger record collection [162]. The women were instructed to weigh (by food scale) and measure foods; and to provide detailed information (i.e. brand names, recipes, %MF).

These records were later entered into the Minnesota Nutrient Database System (NDS) software program developed by the University of Minnesota, St. Paul [163]. Each record was reviewed by a registered dietitian (the author) for completeness. The records were then analyzed by NDS program for energy content (kcal/day), and the contribution of protein, fat and carbohydrate (grams/day and % of total energy for each) to diet.

3.7.2. Body Composition

Fat mass and FFM were determined using the bioelectrical impedance technique (BIA). This technique involves applying a weak alternating electrical current to the body and measuring the opposition of body tissues to that charge. This measured opposition is known as bioelectric impedance (Z) and comprises two forms of opposition. The two forms of opposition are: resistance (R) which is pure opposition to the flow of the electrical current and reactance (Xc) which is the capacitance of membranes and nonionic tissues; although reactance is very small in most biologic conductors and often ignored in prediction equations [164]. By calculation, Z is the square root of the sum of R and Xc, or

\[ Z^2 = R^2 + Xc^2 \]

and is frequency dependent [164]. In the human body, the electrical circuit generally runs via aqueous ionic tissue and the Z value can generate an estimate of total body water (TBW). Moreover given that FFM is high water/electrolyte material and fat mass is low, the body can be separated into these two compartments using this technique [165].

The theoretical background of body composition determination is based on Ohm’s Law which relates bioelectrical impedance to the square of the length of the conductor (e.g. body height) divided by its volume (e.g. TBW or FFM which contains
linearly related to body height (cm)$^2$/body resistance (ohms) [167] and prediction equations for FFM, using BIA, have been well-validated at a single frequency of 50 kHz [168-170]. These equations and others [166, 171] have also been validated as reliable predictors of FFM during periods of change in body weight.

Errors of FFM estimation could occur in situations of abnormal hydration and/or electrolyte status [167], or insufficient penetration through both extracellular (ECF) and intracellular fluid (ICF) compartments. A single frequency of 50 kHz should pass through both ECF and ICF, although the proportion of penetration into the ICF may vary based on the capacitance of various tissues [172]. In some situations, insufficient penetration occurs resulting in the underestimation of fluid in the intracellular compartment.

Population-derived predictive equations for FFM have been developed, in part, to address the hydration, electrolyte and fluid shift characteristics of specific populations. To our knowledge, a specific regression equation for FFM in the BC population does not exist.

The instrument used in our study was a bioelectrical impedance spectroscopy, (4000B, Xitron, San Diego) which can apply more than a single frequency in a given test. In the interest of cost, our instrument was validated against a BIA instrument (model Spectrum II, RJL Systems, Detroit) which had been previously validated for TBW with $\text{H}_2^{18}$O isotope dilution [173]. The advantage of multifrequency BIA is the ability to measure resistance and reactance through a spectrum of frequencies. It can discriminate between ICF and ECF, since low frequency currents (1 to 5 kHz) are unable to penetrate cell membranes and thus reflect only ECF, whilst high frequency currents (>100 kHz) penetrate cell membranes with zero capacitance and reflects TBW; (ICF = TBW - ECF) [174]. Moreover multifrequency BIA does not rely on population-derived prediction equations, since complete measurement of ECF and ICF compartments (at high frequencies) account for fluid shifts. The 4000B BIA software performs a least squares
Regression analysis to fit all the resistance and reactance data to estimate ECF resistance (RECF) and ICF resistance (RICF, which includes the capacitance of the cell membrane). TBW was derived from RECF, RICF, height, weight and gender. FFM was then derived from TBW data.

All weight and height measurements were performed by the Health-O-Metre balance beam scale (Continental Scale Corporation; Bridgeview, Illinois, USA) in the Taste Panel Room (Fitzgerald Bldg., rm 334). Waist and hip circumferences were measured with a flexible measuring tape.

3.7.3. Indirect calorimetry

The term “indirect” calorimetry refers to a method of energy expenditure determination by which oxygen consumption (VO₂) and carbon dioxide production (VCO₂) are measured rather than a direct measure of heat transfer [132]. In a healthy individual, there is a direct relationship between energy generated and the volume of oxygen consumed [149]. In an alert, restful postabsorptive state, the measurement of gas exchange (VO₂ and VCO₂) is thought to estimate RMR [149]. A common indirect calorimetry instrument to measure gas exchange and calculate RMR is the metabolic cart [175].

We used an open circuit ventilated-hood system (Enhanced Metabolic System, Life Energy Systems Inc., Salt Lake City, Utah). The clear plexiglass hood (20L capacity) placed over the subject’s head allowed free and normal breathing by the subject, and for sampling of enclosed air by connective tubing from hood to cart. A study investigating the reproducibility of EE using hooded open calorimetry suggested that best results with this method were achieved when subjects 1) fast overnight 2) are resting 3) not distracted or hearing loud noises 4) spend an initial period of ten minutes to acclimatize the hood [176]. These suggestions were been incorporated into our protocol. A constant rate of air entered the hood to maintain a continuous flow of fresh room air. Alternating samples of expired gases (air in hood) and inspired gases (room air) were taken every 10 seconds. O₂ and CO₂ concentrations were directly measured from these samples by means of a zirconium dioxide sensor and an infrared energy absorption CO₂
output from these sensors could be directly read from the instrument as well as presented in computer printout form. All calculations for VO₂ (ml/min.), VCO₂ (ml/min.), respiratory quotient (RQ, VCO₂/VO₂) and RMR (kcal/24 hours) were made by the Life Energy Systems onboard. For our study, RMR was also expressed relative to FFM (kcal/kg FFM), since FFM is a better estimator of metabolically active tissue, (the component responsible for all the VO₂, VCO₂ and the work performed by the body), than total body weight [158]. FFM was determined as described above by BIA.
Diagram of Study Protocol

Test day

3-day diet record

pretest day 12H fast

baseline questionnaire

bioelectrical impedance

anthropometric measurements

open circuit calorimetry

EBC Only

Repeat Test 6 months later

Figure 1
3.8.1 Baseline Information

There were three components to the study: analysis of dietary intake, body composition and RMR. Upon recruitment, the women were assigned the three days for dietary record keeping. A test day was scheduled and only one woman was measured per day. For the test, the women were requested to fast (except water) from 8 PM in the evening prior to the test day. They were also requested to maintain good hydration by consuming a minimal amount of caffeine-containing products (<3 servings) and to avoid alcohol and excessive exercise in the previous 24 hours to the test. Those women receiving chemotherapy were to be free of any intravenous fluids for 72 hours prior to the test.

Information on each subject was obtained from data records of the WMT. This included information on: subject’s breast disease (initial date of diagnosis, side of breast involved, tumour stage, tumour size, nodal status and hormonal receptor status) and treatment (type of definitive surgery, radiation, tamoxifen and/or chemotherapy). On the day of the test, the subject arrived at the Department of Nutritional Sciences, University of Toronto (Fitzgerald Bldg., 150 College St., rm 334) at the University of Toronto at 8:00 am.

The Baseline Information questionnaire collected the subjects’ name, address, age, menopausal status, weight history (usual body weight, weight change), as well as medical history and medications. At this time, records were reviewed for detail with the subject. Clarification of the record was made if required. The subjects were also interviewed about current BC treatment, physical activity practices, and any side-effects from treatment.

3.8.2 Anthropometric and Body Composition Measurements

Following the review of the dietary records, the subject was weighed and height measured using the Health-o-metre balance beam scale (Continental Scale Corporation; Bridgeview, Illinois, USA) in the Taste Panel Room (Fitzgerald Bldg., rm 334). Weight and height were measured (in lightweight street clothes, without coats, or
were taken over the undergarments of the women with a flexible measurement tape. These measurements were taken three times at each site and an average for each was calculated. The waist-hip circumference procedure was in accordance to the method described by Dr. R. Gibson [79] (appendix 2 for waist and hip circumference procedure).

The subject then redressed except for her shoes and socks and was then rested in a semi-recumbent position with arms and legs comfortably positioned and slightly apart for the BIS measurement. All jewelry was removed by subjects. Two pairs of BIS electrodes were placed on the dorsal side of left hand and foot according to previously established electrode placement guidelines [168] (appendix 3 for BIS procedure). Applied excitation current delivered 50 frequencies between 5 kHz to 500kHz. Three separate measurements were taken and the average was calculated. Readings of $R_{FCF}$ and $R_{ICF}$ were recorded directly from the instrument. This procedure was non-invasive, comfortable and ten minutes in duration.

3.8.3. Resting Metabolic Rate Measurement

RMR was estimated by indirect calorimetry with a ventilated-hood system. It was our intention to place the RMR measurement last, to allow all subjects to have minimal activity for at least sixty minutes (the duration of experiment 1 and 2 plus acclimatization period) prior to the metabolic cart test. Subjects were settled in a semi-recumbent position and the hood was gently placed over the head. Flow rate was monitored to ensure adequate air exchange and the subject questioned regarding her comfort level. Once the subject was comfortable, a television was turned on and a twenty minute acclimatization period was initiated. This allowed the subject to become accustomed to the procedure and to develop a normal pattern of breathing. The subject was requested not to speak and to have minimal movement. She was allowed to close her eyes, but not fall asleep.

Acclimatization was followed by a forty-minute test period. The $O_2$ and $CO_2$ concentrations of this period were used to determine $VO_2$ (ml/min.), $VCO_2$ (ml/min.), respiratory quotient ($RQ, VCO_2/VO_2$) and to estimate RMR (kcal/24 hours). The entire
person analysis to allow us to examine possible changes in dietary intake, body composition and RMR over time.
Chapter 4. Experimental Results

4.1. Population Assembly

Thirty-six subjects were recruited for the study of which thirty went onto data analysis. Reasons for ineligibility included nonfasting for study, history of hypothyroidism, previous history of BC, BMI <20, and age >70. Ineligibles were equally distributed amongst groups. Of the eligible candidates, nineteen recruits had a history of BC and eleven did not.

4.2. Description of the Study Population

4.2.1 Age and Anthropometric Characteristics

The subjects ranged in age from 32 to 68 and had a mean BMI of 26.5 kg/m². The women with BC, despite their illness have similar anthropometric measurements to our sample of a healthy population of women (Table 1). No woman was grossly under or overweight (BMI <20 or >35) which was reflective our entry criteria. Controls were aged-matched (± 5 years) to EBC subjects and the mean age of RBC was 5 years older than EBC or Control. EBC and RBC data were also collapsed into a single BC group and compared to healthy controls in some comparisons. Age and anthropometric characteristics of these two latter groups were not statistically different.

Table 1. Age and Anthropometric Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs. (range)</td>
<td>49.4 ± 4.0 (32-67)</td>
<td>55.0 ± 2.3 (45-65)</td>
<td>49.7 ± 2.9 (37-68)</td>
</tr>
<tr>
<td>Weight, kg (range)</td>
<td>67.0 ± 2.1 (61-79)</td>
<td>67.7 ± 1.9 (60-76)</td>
<td>68.0 ± 2.3 (60-81)</td>
</tr>
<tr>
<td>Height, cm (range)</td>
<td>161.5 ± 1.6 (155-170)</td>
<td>158.7 ± 1.6 (150-166)</td>
<td>159.6 ± 2.5 (150-171)</td>
</tr>
<tr>
<td>Waist, cm (range)</td>
<td>83.0 ± 3.1 (73-99)</td>
<td>84.1 ± 3.8 (70-104)</td>
<td>78.1 ± 2.5 (74-92)</td>
</tr>
<tr>
<td>Waist to Hip Ratio (range)</td>
<td>0.80 ± 0.03 (.70-.98)</td>
<td>0.78 ± 0.03 (.72-.93)</td>
<td>0.75 ± 0.02 (.61-.83)</td>
</tr>
<tr>
<td>BMI, kg/m² (range)</td>
<td>25.9 ± 1.1 (22-32)</td>
<td>26.9 ± 0.9 (23-31)</td>
<td>26.9 ± 1.3 (24-34)</td>
</tr>
</tbody>
</table>

a: values are means ± SEM. All statistical comparisons have p>0.05 by ANOVA.
4.22 BMI and Body Fat Distributions

Table 2 illustrates that the EBC and Controls had similar BMI distributions, although the Control group had a higher proportion of women with BMI >31.

Table 2. Body Mass Index Of Study Women

<table>
<thead>
<tr>
<th>Body Mass Index</th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>26-31</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>&gt;31</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

In Table 3., the women were placed into tertiles based on their percent body fat mass. Interestingly, twelve of thirty study subjects had a BMI within an ideal range, yet only three women were less than thirty-five percent body fat. Also, BC (EBC and RBC) had a greater proportion of women with >43% body fat than Control group.

Table 3. Percent Body Fat Of Study Women

<table>
<thead>
<tr>
<th>Percent Body Fat</th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>35-43</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>&gt;43</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Body fat distribution based on waist circumference suggested that EBC and Control groups were similar(Table 4). Waist circumference also suggests no woman <40 years of age had android obesity.

Table 4 Distribution of Study Sample by Age and Waist Circumference

<table>
<thead>
<tr>
<th>Age (yrs.) and Waist Circumference (cm)</th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 and under; &lt;90cm</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>40 and under; &gt;90cm</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>over 40; &lt;80cm</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>over 40; &gt;80cm</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
Menopause status can be affected by BC treatment and the majority of women in this study were postmenopausal at the time of test (Table 5). Those controls classified as peri/postmenopausal were all without a menstrual period for over a year except one subject who was perimenopausal. In the EBC group, one of the seven peri/postmenopause women had a regular menstrual cycle at diagnosis which stopped with chemotherapy. Four of the nine peri/postmenopause women in the RBC group had regular menstrual cycles at the start of BC treatment and all entered menopause during chemotherapy.

<table>
<thead>
<tr>
<th>Menopausal Status</th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>premenopause&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>peri and postmenopausal&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup>: regular menstrual cycle

<sup>b</sup>: perimenopausal, irregular menstrual cycle with skipped periods but at least one cycle during the previous year; postmenopausal, no menstruation in past year

**4.24 Adjuvant Therapy of BC Population**

The medical management of the study women with BC was surgical removal of BC tumour and lymph node dissection combined with adjuvant therapy (Table 6). In the EBC group, only one of six women had completed a full course of chemotherapy (6 cycles) at the time of baseline measurement; four received CMF and two CEF. Epirubicin (E) was considered a more potent chemotherapeutic agent than methotrexate (M). Epirubicin was administered to two of the three positive node women in the group, and the third (postmenopause) received tamoxifen.

All those RBC subjects treated with chemotherapy had completed a full course at the time of measurement. Three received CMF and two had CEF; all of these women had positive nodes. The women treated with CEF had more advanced disease (greater
than three positive nodes) than the rest of the RBC group. One postmenopausal woman had one node positive and was treated with tamoxifen.

All women scheduled to receive radiation had completed a full 25 day course at the time of measurement (except 4 women in EBC at baseline measurement only) and those placed on tamoxifen were still taking the drug once daily (20mg/d) at the time of measurement.

Table 6. Adjuvant Treatment Received By Study Women

<table>
<thead>
<tr>
<th></th>
<th>EBC</th>
<th>RBC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=10)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Radiation</td>
<td>10a</td>
<td>7</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

a: 4 of 10 received radiation between baseline and follow up measurement

4.3. RMR Analysis

4.3.1. RMR Data

The objective was to determine the RMRs of women receiving treatment for early stage BC and to compare them to RMRs of women recovering from BC and healthy controls (Table 7). RMR were determined by indirect calorimetry. The mean RMRs were not statistically different among the groups.

Table 7. Mean RMRs Of Study Women

<table>
<thead>
<tr>
<th></th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMR(kcal/d)</td>
<td>1134.0 ± 47.2</td>
<td>1132.0 ± 41.3</td>
<td>1183.9 ± 27.2</td>
</tr>
<tr>
<td>95%CI (kcal/d)</td>
<td>1042 - 1227</td>
<td>1051 - 1213</td>
<td>1131 - 1237</td>
</tr>
</tbody>
</table>

a: values are expressed as means ± SEM. All statistical comparisons have p>0.05 by ANOVA.

4.3.2. Body Compositions

Body compositions (FFM; fat mass; total body fluids, TBF; extracellular fluids, ECF; intracellular fluids, ICL) were determined by multifrequency BIA for each group.
inclusion of weight and height as covariates resulted in significant differences in these body compartments (FFM \( p < 0.03 \); fat mass, \( p < 0.04 \)) with lower FFM and higher fat mass in EBC and RBC patients (Figure 2). The observed differences were stronger for the two group comparison of EBC to Control (FFM, \( p < 0.009 \); fat mass, \( p < 0.01 \)).

Table 8. Body Composition Of Study Women

<table>
<thead>
<tr>
<th></th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (kg)</td>
<td>38.24 ± .86(^b)</td>
<td>38.00 ± .97(^b)</td>
<td>41.14 ± 1.3(^c)</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>28.66 ± 2.1(^b)</td>
<td>29.70 ± 1.6(^b)</td>
<td>27.84 ± 1.6(^c)</td>
</tr>
<tr>
<td>Fat Mass (% BW)</td>
<td>42.53 ± 1.9(^b)</td>
<td>43.73 ± 1.4(^b)</td>
<td>40.30 ± 1.5(^c)</td>
</tr>
<tr>
<td>ICF (L)</td>
<td>12.4 ± .29(^b)</td>
<td>12.13 ± .45(^b)</td>
<td>13.85 ± .56(^c)</td>
</tr>
<tr>
<td>ECF (L)</td>
<td>15.48 ± .39(^b)</td>
<td>15.58 ± .34</td>
<td>16.16 ± .47(^c)</td>
</tr>
<tr>
<td>TBF (L)</td>
<td>27.94 ± .62(^b)</td>
<td>27.94 ± .63(^b)</td>
<td>30.14 ± .97(^c)</td>
</tr>
</tbody>
</table>

\(^a\): values are expressed as means ± SEM using ANOVA. 
\(^b,c\): statistical group differences were determined by post hoc test, Student-Newman-Kuels and identified by different superscripts in same row, \( p < 0.05 \): all other comparisons, \( p > 0.05 \)
Figure 2. Bar graph presents mean and SEM for fat mass and FFM determined by bioelectrical impedance. Control groups had significantly higher amounts of FFM and lower fat mass compared to other groups using ANOVA with p<0.05.
4.3.3. RMR Relative to FFM

RMRs were then compared relative to FFM to standardized the data for differences in body composition. FFM was also used in analysis of covariance. No statistical differences were observed in RMR among groups. (Table 9).

Table 9. Mean RMR Relative To FFM Of Study Women

<table>
<thead>
<tr>
<th></th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMR/FFM(^a) (kcal/kg/d)</td>
<td>29.63 ± .95</td>
<td>29.85 ± .97</td>
<td>28.91 ± .71</td>
</tr>
<tr>
<td>95% CI</td>
<td>27.77 - 31.49</td>
<td>27.95 - 31.75</td>
<td>27.52 - 30.30</td>
</tr>
</tbody>
</table>

\(^a\): values are expressed as means ± SEM. All statistical comparisons have p > 0.05 by ANOVA.

4.3.4. Dietary Intake

Mean energy intake and the contributions from protein, fat and carbohydrate were compared between groups (Table 10). No statistical differences were observed in dietary intakes between groups.

Table 10. Mean Dietary Intakes \(^ab\)

<table>
<thead>
<tr>
<th></th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Energy (kcal/d)</td>
<td>1627.6 ± 87.3</td>
<td>1501.14 ± 118.3</td>
<td>1530.3 ± 135.0</td>
</tr>
<tr>
<td>Protein, grams/d (% of total energy)</td>
<td>66.3 ± 4.2 (16.4 ± 1.0)</td>
<td>64.6 ± 5.7 (17.3 ± 1.1)</td>
<td>58.8 ± 6.1 (17.0 ± 1.0)</td>
</tr>
<tr>
<td>Fat, grams/d (% of total energy)</td>
<td>55.6 ± 3.8 (29.5 ± 1.3)</td>
<td>44.7 ± 5.8 (26.2 ± 3.0)</td>
<td>48.1 ± 5.2 (28.7 ± 1.1)</td>
</tr>
<tr>
<td>Carbohydrate, g/d (% of total energy)</td>
<td>220.7 ± 15.4 (54.2 ± 1.8)</td>
<td>213.3 ± 23.1 (56.5 ± 2.8)</td>
<td>196.1 ± 21.7 (55.5 ± 1.1)</td>
</tr>
</tbody>
</table>

\(^a\): values are expressed as means ± SEM. All statistical comparisons have p > .05 by ANOVA.

\(^b\): percent of total energy has been adjusted to ensure the sum of protein, fat and carbohydrate = 100%
dietary fibre contents (total, soluble and insoluble) were higher in RBC compared to EBC or Control, although the insoluble comparisons was the only statistically significant one (p<.05) (Table 11).

Table 11. Dietary Fibres

<table>
<thead>
<tr>
<th></th>
<th>EBC</th>
<th>RBC</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=10)</td>
<td>(n=9)</td>
<td>(n=11)</td>
</tr>
<tr>
<td>Total Fibre, grams</td>
<td>17.3 ± 2.0</td>
<td>22.2 ± 3.2</td>
<td>16.3 ± 2.0</td>
</tr>
<tr>
<td>Soluble Fibre, grams</td>
<td>6.1 ± .8</td>
<td>6.6 ± 1.0</td>
<td>5.8 ± 0.7</td>
</tr>
<tr>
<td>Insoluble Fibre, grams</td>
<td>11.2 ± 1.3</td>
<td>15.5 ± 2.3</td>
<td>10.48 ± 1.1</td>
</tr>
</tbody>
</table>

α: values are expressed as means ± SEM, using ANOVA

β: significant difference among groups determined by post hoc test, Student-Newman-Kuels p<.05; all other comparisons, p >.05

4.3.5. Physical Activity

All subjects were asked about their current exercise practices in terms of the frequency and duration of exercise each week. The types of activity were also recorded. A level of intensity was assigned to every activity event by this author (appendix 5). Physical activity data were compared by total minutes of exercise per week and then weighted for level of intensity (Table 12). The time spent in physical activity was not significantly different among groups but the level of intensity was significantly lower in EBC compared to RBC or Control.

Table 12. Exercise per Week of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>EBC</th>
<th>RBC</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>128 ± 46</td>
<td>208 ± 48</td>
<td>177 ± 41</td>
</tr>
<tr>
<td>95% CL</td>
<td>39 - 218</td>
<td>114 - 303</td>
<td>99 - 258</td>
</tr>
<tr>
<td>Weighted Exercise</td>
<td>129 ± 46</td>
<td>222 ± 51</td>
<td>232 ± 60</td>
</tr>
<tr>
<td>95% CI</td>
<td>39 - 218</td>
<td>121 - 317</td>
<td>114 - 350</td>
</tr>
<tr>
<td>Exercise Intensity</td>
<td>.67 ± .2</td>
<td>1.1 ± 1.1</td>
<td>1.3 ± .3</td>
</tr>
</tbody>
</table>

α: values are expressed as means ± SEM. Exercise intensity was significantly different at p<0.05 with all other statistical comparisons having p>0.05 by ANOVA.

β: Weighted exercise = minutes of exercise x intensity
### 4.4 Analysis of the EBC Group

#### 4.4.1. Body Size and Compositions

The second objective was to investigate potential changes in RMR during BC treatment. For this purpose, EBC group was tested again six months after the initial measurements. No significant changes in body size and composition characteristics were revealed by paired t-test analysis over this time in EBC subjects (Table 13).

| Table 13. Body size and Composition Measurements$^{a,b}$ |
|-----------------|-----------------|
|                | Baseline        | Follow Up    |
| Weight, kg     | 67.0 ± 2.1      | 67.7 ± 2.0   |
| Waist, cm      | 83.0 ± 3.1      | 81.5 ± 3.2   |
| Waist to Hip Ratio | 0.80 ± .03       | 0.78± .03   |
| BMI, kg/m$^2$  | 25.9 ± 1.1      | 26.1 ±1.0    |
| FFM (kg)       | 38.24 ± .86     | 37.79 ± 1.4  |
| FM (kg)        | 28.66 ± 2.1     | 29.93 ± 1.8  |
| FM (% BW)      | 42.53 ± 1.9     | 44.1 ± 2.0   |

$^a$: values are means ± SEM. No significant differences using paired t-test, p>0.05.  
$^b$: Baseline (time 0); Follow up (6 months)

#### 4.4.2. RMR

There were also no significant differences in RMR of the EBC group between the baseline and follow up measurements.

| Table 14. RMR Of EBC Women$^a$ |
|-----------------|-----------------|
|                | Baseline        | Follow-Up    |
| RMR (kcal/d)   | 1134.0 ± 47     | 1117.4 ± 51  |
| RMR/FFM (kcal/d/kg) | 29.6 ± 1         | 29.7 ± 1    |

$^a$: values are expressed as means ± SEM. No significant differences using paired t-test, p>0.05

#### 4.4.3. Dietary Intakes

Although mean body weight and RMR remained relatively stable at 6 months, there was significant reductions in dietary intakes by EBC women. Figures 3 and 4 illustrates these changes in nutrient intakes.
Figure 3. Mean Energy Intake of EBC at Baseline and Six Month. Data based on results of three 24-hour diet records at baseline and 6 month test for each subject. Records were analyzed by NDS (nutrient data system) for total energy intake (kcal/d) and presented as mean ± SEM. EBC subjects had a significant reduction in energy intake from baseline to 6 months.
Three-day diet records at baseline and 6 month were analyzed by NDS (nutrient data system). EBC subjects had a significant reduction in protein, fat and carbohydrate from baseline to 6 month using paired t-test analyses.

* Statistically different, p<0.05
All the women in EBC group were encouraged to become physically active as part of the WMI program. Most members of this group walked for exercise at the time of the baseline measurement. Follow up measurements suggested that the women continued to maintain their walking programs six months later and even had an improvement in the number of minutes walked each week, although this was not statistically significant (Table 15).

Table 15 Mean Minutes of Exercise per Week of EBC

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>128.8 ± 45.8</td>
<td>169.4 ± 43.4</td>
</tr>
<tr>
<td>95% CL</td>
<td>39 - 218</td>
<td>84 - 255</td>
</tr>
</tbody>
</table>

*a:* values are expressed as means ± SEM. Statistical comparison had p>0.05 by ANOVA.

4.5. Additional Analysis

This section contains analyses that do not directly answer the specific objectives of this study. However, they provide useful information regarding the RMRs and body weights of this sample of BC patients and therefore are presented for purpose of discussion.

4.5.1. Predictors of RMR

Additional analyses were performed to determine whether conventional variables (FFM, weight, height, age, and HBE) which typically describe RMR data could predict the RMRs of this study within reasonable limits.

Correlation analysis between FFM and RMR for each group were conducted to performed the magnitude of the relation between FFM and RMR. Pearson’s Correlation Coefficients suggested a substantial relation between FFM and RMR for the study sample (r=0.58, p=0.001). When groups were examined separately, the correlation coefficient suggested a high relationship between FFM and RMR for EBC (r=0.65, p<.04) and Control (r=0.62, p<.05) and a substantial but non significant one for RBC (r=0.50, p<.17). These interpretations were based on criteria established by Burnand, Kernan and Feinstein for quantitative significant of correlation (appendix 6) [177]. In regression analysis, close to forty percent of the variability in the RMR data was explained by FFM.
in EBC and Control ($r^2 = 0.42$ and 0.38 respectively); although the RMR data was not as well described by FFM in RBC group ($r^2 = 0.25$).

A forward stepwise multiple regression model was used to describe the RMR data in relationship to conventional predictive variables (FFM, weight, height and age). With this model, the variables of FFM, weight and age explained 0.49 of the variance in RMR of our entire study sample. The regression analysis was also conducted on each group separately and the best model for EBC was comprised of two variables (FFM and weight) with a $r^2$ value of 0.57. The inclusion of the other variables did not improve the model. The best model of RBC was described by variables weight and height at a $r^2$ value of 0.44. In Controls, a three-variable model (FFM, weight and age) best explained RMR variance with a collective $r^2$ value of 0.95.

Regression analyses were conducted to examine the association of RMR values from indirect calorimetry and those by HBE for each group (Figure 5). In all groups, HBE overestimated RMR, albeit most consistently for Controls (Figure 6). When chemotherapy was considered, there appeared to be no discernible patterns based on the presence of chemotherapy (Figures 7 and 8).
Figure 5. Scatterplots of RMR of Indirect Calorimetry and HBE of Each Group. The regression of data for RMR measured by indirect calorimetry and estimated by HBE were plotted for each group. This illustrates a strong correlation between RMR of indirect calorimetry and HBE for Control group, but poor relationships of these for both BC groups, particularly EBC.
Figure 6. RMR Values Of Harris Benedict Equation Plotted In Descending Order Against RMR Values by Indirect Calorimetry For Each Subject in the EBC, RBC and Control Groups. This figure illustrated that HBE overestimated RMR measured by the indirect calorimetry method for all subjects. However, HBE appeared to overestimate RMR more consistently in Controls than in either BC groups.
Figure 7. Plotted RMR Obtained By Indirect Calorimetry and HBE in EBC and RBC Groups. Subjects were classified based on whether they did or did not receive chemotherapy. It is difficult to describe results due to small sample size, although HBE appears to be a poor predictor of RMR measured by metabolic cart.
Figure 8. Plotted Data of RMRs Obtained By Indirect Calorimetry and HBE of BC Subjects. EBC and RBC were collapsed and subjects were grouped based on whether they did or did not receive chemotherapy. This illustrates that HBE poorly estimated RMR by metabolic cart in BC. It does not demonstrate a discernable difference between chemotherapy and nonchemotherapy subjects.
Another way to compare results from indirect calorimetry and HBE was to compare the difference between their RMR results. This difference was investigated by analyzing the absolute RMR difference (RMR difference=indirect calorimetry-HBE, (O-E)) and percent RMR difference (percent RMR difference=indirect calorimetry/HBE, (O/E)) among the groups. The findings revealed no statistical differences between the difference of RMR among groups (Table 16).

Table 16. RMR Obtained From Indirect calorimetry and HBE of Study Women

<table>
<thead>
<tr>
<th></th>
<th>EBC (n=10)</th>
<th>RBC (n=9)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-E, kcal/d</td>
<td>-229 ± 44</td>
<td>-207 ± 34</td>
<td>-184 ± 13</td>
</tr>
<tr>
<td>95% CI</td>
<td>143 - 314</td>
<td>143 - 273</td>
<td>159 - 209</td>
</tr>
<tr>
<td>O/E, %</td>
<td>17 ± 3</td>
<td>15 ± 3</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>95% CI</td>
<td>10-23</td>
<td>10-21</td>
<td>12-15</td>
</tr>
</tbody>
</table>

*a: values are expressed as means ± SEM. All statistical comparisons have p>0.05 by ANOVA.

b: O-E = observed RMR (indirect calorimetry) - expected RMR (HBE)

c: O/E = observed/expected RMR

Taken together, the striking findings of these analyses were that conventional predictors of RMR were able to estimate RMR with reasonable accuracy for the Control group but not BC groups. This may suggest that other factors not accounted for by these conventional factors had substantially contributed to RMR of BC subjects.

4.5.2. Most Recent Body Weight on BC Subjects

A recent medical chart review (1997) for recorded body weights on all BC subjects indicated that body weight had not significantly changed from baseline body weights to most recent charted weight (2 1/2 to 3 year period) (Figure 8). This review also reported that 14 of the 19 women were in good health without recurrence; two have been lost in follow up (1 EBC, 1 RBC); two have died from BC (brain metastases; leptomeningeal metastases) (1 EBC, 1 RBC) and one had terminal disease with BC spread to skin, liver and bone (EBC). Only one of these three women with known metastatic spread was node positive (3 nodes) at the time of diagnosis.
Figure 9. Baseline and Most Recent Body Weights in BC Subjects. A medical chart review was recently conducted on subjects with BC. Thirty to thirty-six months had elapsed since baseline measurement and 14 of 19 subjects were included in analysis (excluded: 2 lost to F/U; 2 died; 1 metastatic disease). No significant change in body weight was found by paired t-test; p>0.05.
Chapter 5. Discussion

The main objective of this research was to measure RMR using a reliable technique in women with BC and to investigate whether it was lower in these women compared to healthy controls. Another goal was to determine whether RMR changed over time. Dietary intake, body composition and physical activity were also investigated for their roles in energy balance. The current literature suggests that weight gain occurs in the majority of women with BC, but has been unable to precisely determine its cause. Dietary intake, physical activity and RMR have all been implicated but results have been inconsistent. However, one study found reduced RMR in premenopausal women during chemotherapy and two others reported reduced lean body mass in women with BC. Given that lean FFM is a known determinant of RMR, a reduced lean body mass in BC women could potentially lower RMR and promote weight gain.

5.1. RMR

The results comparing EBC, RBC, and Controls do not support the hypothesis of lower RMR among women with early-stage BC. Subgroup analysis of the EBC subjects revealed no change in RMR over time. These results departed from the earlier findings of reduced RMR in the study by Demark-Wahnefried et al [1]. Nevertheless on further analysis, it was found that conventional variables could account for > 90% of variance in RMR data of controls but < 45% in those with BC. Thus, it would appear that an unaccounted for variable(s) was playing a major role in women with BC.

5.1.1. Comparison of RMR to Existing BC Study

While Demark-Wahnefried’s study design was different, a comparison of this study to theirs is worthwhile. Demark-Wahnefried et al measured RMR by indirect calorimetry in 18 early-stage BC premenopausal women on chemotherapy and did not include healthy controls. The RMR taken at midpoint of chemotherapy was most comparable to baseline RMR of EBC in this study. The baseline measurement of EBC was scheduled approximately six month post-diagnosis, although the phase of medical management was variable (all completed surgical intervention while 6 had ongoing
Mean RMR of EBC was 1134 kcal/d compared to 1296 kcal/d reported by Demark-Wahnefried. Results were more similar when RMR was expressed relative to FFM (29.63 kcal/kg, EBC at baseline; 30.77 kcal/kg, Demark-Wahnefried study). Demark-Wahnefried et al described its RMR as reduced, but they were similar to RMRs of the current study which showed no difference in RMRs between BC and Controls.

Interestingly, the Demark-Wahnefried study reported decreased RMR at the midpoint of chemotherapy from pretreatment (p= 0.02) and then a rebound in RMR at the completion of chemotherapy to levels similar to their pre-chemotherapy measurements. This current study did not identify a change in RMR following completion of chemotherapy (from 1134 kcal/d to 1117 kcal/d for EBC) based on 6 month measurements when all chemotherapy was finished. However, these studies likely differed in their abilities to detect a change in RMR since EBC was smaller, and more heterogeneous than Demark-Wahnefried’s sample (n=9 EBC; n=18 in Demark-Wahnefried study)

The current study also did not have pretreatment RMR measurements, therefore a full determination of the effect of treatment on RMR was not possible. Demark-Wahnefried et al had younger group of women (49.4 EBC vs 39.9 D-W) which may contribute to the differences in findings. Other possible explanations for differences include: body weight (67.0 EBC vs 64.5 kg D-W), treatment (chemotherapy and/or hormonal therapy (EBC) vs chemotherapy alone (D-W)) and menopausal status (pre and postmenopausal (EBC) vs premenopausal alone(D-W)) and thereby limits the value of further comparison. Therefore, one cannot necessarily conclude that the two sets of results are contradictory.

5.1.2. Standard Values of RMR in the Literature

The evaluation of the RMR of any individual requires comparison with previously established values. Standard values of metabolic rate (expressed kcal/m² body surface area) in a healthy population of women as cited in the literature were used to evaluate the quality of the present RMR data (Table 17). The current study had an average RMR of
below published standards, the difference could be accounted for by the fact that the accepted values are typically measured with mouthpieces, noseclips or face masks as opposed to the noninvasive hood method of the current study (which is likely more comfortable). Greater comfort may result in less spontaneous movement by subjects and thereby reduce measured RMR [178]. From this it would appear that the RMR data is reasonably consistent with standard measurements.

Table 17 Standard Resting Metabolic Rate in Women

<table>
<thead>
<tr>
<th>Study</th>
<th>50 years</th>
<th>55 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleisch</td>
<td>33.9</td>
<td>33.3</td>
</tr>
<tr>
<td>Robertson and Reid</td>
<td>31.9</td>
<td>31.6</td>
</tr>
<tr>
<td>Boothby et al.</td>
<td>34.4</td>
<td>33.4</td>
</tr>
<tr>
<td>Aub and Du Bois</td>
<td>36.0</td>
<td>-</td>
</tr>
</tbody>
</table>

Metabolic Rates expressed as kcal per body surface area per hour; kcal m$^{-2}$ hour$^{-1}$


5.2. Predictive Variables of RMR

Known predictive variables (FFM, weight, height, age, and HBE) of RMR were used to describe RMR data and to determine whether they could predict RMR within adequate limits. A major finding of this study was that conventional variables strongly described control subjects but were poor predictors of RMR in BC groups. In stepwise regression analysis, combinations of these variables explained a remarkable 95% of the variance in RMR data in Control (FFM, weight, height); yet only 57% in EBC (FFM, weight) and 44% in RBC (weight, height). This inability to tightly correlate conventional variables to RMR in BC subjects perhaps offers a clue as to why the etiology of weight-gain factors in BC has evaded researchers. It may well be that these contributing factors are unique to situations of BC and cannot be described by classical methods. The following section explores the predictive value of FFM and HBE in RMR and offers possible explanations for the unaccounted variance in BC groups.
The amount of FFM a woman carries strongly influences her rate of metabolism, and therefore analysis of this association should demonstrate a sizable linear relation. It was anticipated that correlation analysis would show substantial relationship between FFM and RMR for all groups. The results of this analysis supported this opinion and had an r value of 0.58 (p=0.01) with all subjects analyzed. Regression analysis between FFM and RMR showed that nearly forty percent of the variance in RMR data could be attributed to the amount of FFM carried in EBC and control subjects, but not to those of RBC ($r^2 = 0.25$).

These results suggested that FFM had similar predictive value for EBC and Control but not RBC. Since the RBC was comprised of an older group of women, age may have decreased the predictive strength of FFM in this group [149]. Components of FFM such as skeletal muscle mass and total bone mass can decline at varying rates with aging. Moreover, the rate of loss in each compartment per subject may be affected by her level of physical activity and menopause status [179]. These changes diminish the linear association between the size of FFM and the amount of metabolic work. Therefore, age could account for a reduced correlation between FFM and RMR in RBC but it is difficult to speculate as to the extent.

After univariable regression analysis, additional variables were added to FFM in stepwise fashion to attempt to further explain the RMR data. These additions, as previously mentioned, improved the regression model in controls such that 95% of RMR variance could be explained on the basis of those variables. However, only modest improvement was shown in the model for EBC with 57% explained variance and little change in RBC with 44%. Therefore when the best model of each group, using a combination of individual factors known to influence RMR, was compared appreciable differences in RMR between BC groups and Controls became apparent.

5.2.2 HBE

Striking RMR differences between groups were also evident when RMR values from indirect calorimetry were compared to those of HBE. This was a useful comparison
since published reports do exist on the expected relationship between the two. That is, HBE should predict RMR within 10-14% of measured value in 80-90% of normal weight healthy individuals. In the current study, HBE did correctly predict RMR within 14% of RMR by indirect calorimetry in 80% of control subjects. However, only 45% of EBC and 75% of RBC subjects were predicted within 14% of measured RMR. In fact, RMR was overestimated by HBE in up to 23% in these latter two groups. Therefore, similar to multiple regression data, HBE failed to consistently predict RMR in BC subjects. HBE, in contrast to the multiple regression results, had better correlation with RBC than EBC.

Figure 5, depicting scatterplots of the association between RMR values from indirect calorimetry and HBE for each group, convincingly displays the strong evidence regarding HBE. An almost random scatter of datapoints for EBC ($r^2=0.16$), an improved correlation for the group recovering from BC ($r^2=0.33$) and a chiefly linear relationship for Controls ($r^2=0.80$) can clearly be seen.

One interpretation of the discrepancy between RMR of HBE and indirect calorimetry is that differences in body compositions of groups may have influenced results. A comprehensive review of indirect calorimetry by McClave and Snider suggested that the predictability of HBE diminished to only 40 to 65% in obese individuals [142]. Despite a similar body weight BC subjects had statistically higher body fat than Control (42.5% Body Fat, EBC; 43.7%, RBC; 40.3%, Controls) and this extra fat mass of BC subjects groups could possibly have diminished the accuracy of HBE. However it is unlikely that high body fat accounts for all the variation since RBC and EBC had similar body fats but different HBE precision. An alternative, and perhaps more compelling explanation is that other unidentified factors had greater influence on RMR in BC groups and thereby diminished the strength of the predictive equation.

Taken collectively, it would appear that the classic predictive variables of RMR do not strongly correlate with RMR of BC subjects. Two variables, age and body fat have been identified as potential confounders but it is unlikely that they account for all of the disparity between BC and control subjects.
Chemotherapy

Chemically-induced menopause is a profound physiologic side-effect of chemotherapy and occurs in the majority of premenopausal women treated with cyclophosphamide-based therapy (CEF or CMF) [27, 42]. In the current study, 63% of women treated with chemotherapy entered menopause during treatment. A report on the endocrine profile of women undergoing chemotherapy found that 77% of patients in that series became amenorrheic within a mean of <3 months after initiating chemotherapy [42]. Changes in plasma hormone levels appeared to be abrupt and dramatic with levels of estrone, estradiol, and progestrone reduced by half and a more than doubling of luteinizing hormone by the fourth cycle of chemotherapy. Following these initial changes, only estrone and estradiol continued slow and gradual declines. This report suggested that changes in hormones were consistent with those observed in normal, healthy women as they enter menopause. Nevertheless these changes occurred in a matter of months rather than the years that typify a natural course of menopause and it may be that this abrupt transition into menopause had an impact on RMR.

A review on natural menopause suggested that body composition changes as menopause approaches and that these changes arise partly from a deficit of estrogen [179]. This period is characterized by an initial phase of rapid decline in bone mineral mass and total body potassium followed by a slow, more gradual decline thereafter. Body fat mass is also increased. These changes can influence RMR as total body potassium reflects skeletal and body cell masses. Therefore, the steep decline in estrogens during chemotherapy may hasten the natural compositional changes observed in women which favour lower RMRs. Data from this thesis observed higher fat mass and lower fat-free mass in BC women; although subgroup analysis on chemotherapy-induced menopause subjects was not performed due to small numbers.

It can also be postulated that the mere presence of a menstrual cycle has energetic consequences and therefore its absence would equate to an energy loss. Studies have shown that the maintenance of the menstrual cycle affords a small baseline increase in energy expenditure above that of postmenopausal women [179]. Moreover, there are
The luteal phase of the menstrual cycle [180]. Therefore, the premature destruction of ovarian function by chemotherapy would result in a loss of both energetic processes and thereby reduce RMR. Interestingly, predictive RMR variables (FFM, HBE, height, weight and age) would have little relevance in this type of RMR alteration.

**Tamoxifen Therapy**

The classical action of tamoxifen is the inhibition of estrogen-stimulated tumor growth by the blockade of ER sites on BC cells. However, common side-effects of this therapy relate to ovarian dysfunction (hot flashes, vaginal discharge, irregular menses) which suggests that other, non-mammary ER sites may be affected. Researchers have also suggested that tamoxifen blocks ER sites in the hypothalamic-pituitary axis, thereby interfering with growth hormone (GH) release [45]. It is this action by tamoxifen that may contribute to the alterations in RMR.

Estrogens have a permissive role in the release of GH by the pituitary gland which then stimulates the synthesis of insulin-like growth factor-I (IGF-I) in the liver [45]. It is possible that this cascade can be blunted with the blockade of estrogen by tamoxifen at the hypothalamic-pituitary axis. The literature on GH-deficient adults has offered excellent insight on the widespread physiological implications of GH and IGF-I, including their effects on body composition, substrate oxidation and energy expenditure. From this body of work, the following observations can be made: a) GH-deficient adults have excess adiposity with reduced FFM, b) treatment with either hormone is followed by enhanced FFM and RMR as well as reduced fat mass and protein oxidation, c) both GH and IGF-I promote lipolysis and lipid oxidation and d) IGF-I reverses the insulin resistance induced by GH [181-183]. Furthermore, other studies with normal subjects and obese women have shown increased RMR in response to the administration of GH [183]. Therefore, there exists the precedent of reduced RMR secondary to deficient levels of GH, but whether reduced GH and/or IGF-I levels associated with tamoxifen are sufficient to explain the observed similar RMR effects has yet to be examined.
There may be several reasons why observed RMRs were not statistically different among the study groups. Obviously, the first is that RMR of groups were truly different but this study was unable to detect the significant difference. The following section evaluates the study design and potential sources of error with respect to design and analysis.

5.3.1. Selection of Subjects

A heterogeneous sample of BC subjects for this study was thought to be important since the weight gain phenomenon had been reported in all groups of BC (pre and postmenopausal; chemotherapy and no chemotherapy) [35, 38, 39, 48, 123]. However by recruiting in this manner, the study may have reduced its' ability to detect a true effect on RMR, particularly if that effect was experienced only in a subgroup of the sample (i.e. premenopausal or multi-agent chemotherapy). Furthermore, as already discussed, the sample recruited from the WMI may be biased towards more healthy individuals and not representative of the general BC population.

5.3.2. Sample Size

To accept the conclusion that no significant difference in RMR existed between groups, the sample size had to be sufficiently large to provide the necessary power to observe the difference, if it was there. A sample size of 9 subjects per group was calculated based on preliminary data which had an effect size of 15% difference (or 150 kcal). Actual group size at the time of analysis was 10, 9 and 11 for EBC, RBC and Controls, respectively. Given the observed difference of RMR (49.9 kcal/d between EBC and Control) along with the combined standard deviations (149 kcal, EBC; 90 kcal, Control), there was only 15% power to detect a difference in two-tailed analysis and 36% for one-tailed test. All RMR analysis were two-tailed tests. Therefore the differences may have existed, but with insufficient power remained undetectable.
Subjects for this study were recruited from the WMI trial and therefore had to also meet the criteria for that trial. One criteria was the absence of psychiatric illness (i.e. depression, major psychiatric disorders, eating disorders) as determined by a psychological assessment. Obviously the rationale of the criteria is reasonable. Individuals with psychiatric illness may be harmed by nonspecific psychological support, or in the case of eating disorders, by information regarding diet records, indirect calorimetry and anthropometry. Unfortunately it has been suggested that more than half of the women diagnosed with BC will experience psycho-social distress within the first year of treatment [22, 127] and many will go onto clinical depression [25]. It is also clear that mental well-being influences physical activity and dietary intake. Therefore the exclusion of those women with psychiatric illness from the sample may have unwittingly excluded the major weight-gainers.

A similar argument can be made for the exclusion of women based on health reasons. Again, the restriction of those women with “concurrent medical problems that require a special diet that influences weight directly or through medical use ...or unable to participate in physical activity because of physical disability (e.g. paraplegia, severe arthritis)” forms a potential selection bias towards healthy women. Fortunately, this was unlikely as only two subjects had been excluded from the WMI based on the health criteria.

**5.3.4. Technical Error**

The technical component of this study involved the measurement of anthropometrics, body composition and resting metabolic rate of each subject. A technical error at any of these points could easily introduce error. Quality assurance was practiced with the metabolic cart and BIA with each being calibrated prior to use. The metabolic cart was routinely checked for leaks, since volume losses of both oxygen and carbon dioxide could artifactually lower RMR. For both the indirect calorimetry and BIA measurement, subjects were placed in a reclined position during measurements. Readings may have varied due to this position as some studies have shown more
5.4. External Factors That May Have Influenced RMR Measurement

The following section will consider other major determinants and confounders of RMR and their role in the present study.

5.4.1. Accuracy Of RMR Measurement

Indirect calorimetry has some methodological limitations which may influence the accuracy of the RMR measurement. First, there is significant within and between person variability in RMR. Within person variation of day-to-day of RMR has been estimated to be anywhere from 4% [134] to 15% [184]. Moreover, there is within day fluctuations in RMR due to variety of influences i.e. changes in body temperature, movement, circadian rhythm [185]. This current study performed a single, forty minute baseline measurement on each subject and a 24 hour RMR was extrapolated from that test. Intermittent metabolic recordings may provide better estimations of 24 hour RMR [185] but given laboratory constraints and the time already invested by BC subjects in their medical treatment, intermittent measurements were considered impractical.

5.4.2. Age

Increased age is associated with reduced RMR primarily due to decreased FFM and increased fat mass [139]. Aging is also associated with hormonal changes that may decrease RMR (↓ Growth hormone) [186]. There are some suggestions that the tight association between FFM and RMR may decline with aging. This study matched Control subjects with EBC subjects for age (± 5 years). The point estimate of age between groups was not statistically different, but RBC was 5 years older on average and had less spread in subject ages (45 -65) than the other two groups (EBC, 32-67; Control, 37 -68). Age as well as body composition (FFM, fat mass) variables were included in analysis of covariance. Other possible age-related RMR changes (hormonal influences) were not directly controlled for but hopefully adjusted with the analysis of covariance (covariate
5.4.3. Ambient Temperature

The uncontrolled ambient temperature of the test room may have resulted in some variation in metabolic rate. Ambient temperature is known to directly affect energy expenditure by influencing the body's ability to maintain a core temperature of 37°C. The ambient temperature at which there is a minimum energy expenditure is termed the zone of neutrality. This temperature is dependent on the warmth of clothing and individual variation in thermoregulation, but generally thought to be around 27°C in nude, normal subjects [134]. Cold-induced thermogenesis is a response to an ambient temperature above or below the zone of the thermal neutrality and could increase energy expenditure.

Subjects were all tested in the same room and an attempt was made to keep the subject comfortable but room temperature was not strictly controlled. Subjects were measured in street clothing and they were provided a blanket in conditions of cold temperature. No subject was visibly shivering during measurement; but the presence of nonshivering thermogenesis was not determined. Having said that, nonshivering thermogenesis, unlike shivering, is thought to have minimal effect on RMR [187].

5.4.4. Diet-Induced Thermogenesis

Indirect calorimetry was performed on subjects in the postabsorptive state to minimize the effect of DIT. What constitutes the postabsorptive state, which describes a state at which the digestive process of food is terminally complete, is a matter of some debate ranging anywhere from 8 to 18 hours following the last meal [134]. Moreover, the magnitude of DIT is dependent on other factors such as the type of ingested food and size of meal. Therefore, it is conceivable that some subjects were not truly postabsorptive when measured by indirect calorimetry. The protocol involved a 12-13 hour fast period to render a postabsorptive state at the time of measurement. However, it was possible that an extremely large meal the night before, particularly one high in
5.4.5. Respiratory Quotient

The respiratory quotient (RQ, VCO₂/VO₂) is helpful in evaluating whether subjects were truly fasting, since it reflects net substrate oxidation at the time of measurement. The normal physiological range of this constant in humans is between 0.67 and 1.3 [188]; although higher values can be seen in excessive lipogenesis [134]. RQ values indicate the following: 0.7, complete fat oxidation; 0.8, protein oxidation; 1.0, carbohydrate oxidation; and >1.0 up to 8.67, lipogenesis [143].

Nonprotein RQ is a term used for an RQ that is adjusted for the protein used in energy metabolism and therefore only reflects carbohydrate and fat oxidation. With nonprotein RQ; 0.7 indicates 100% fat oxidation with negligible use of carbohydrate fuel, whereas 1.0 indicates the opposite (100% carbohydrate oxidation and negligible fat). A nonprotein RQ of 0.85 would therefore reflect a half and half fuel mixture of carbohydrate and fat [139]. Certain metabolic criteria must be present in order to use the nonprotein RQ: 1) that the amount of protein utilized in energy metabolism is small or corrected for (from nitrogen excretion in urine and sweat) and 2) that other metabolic processes which involve the production and/or utilization of O₂ and/or CO₂ (i.e. gluconeogenesis from proteins, ketones body formation, and lipogenesis) are quantitatively negligible compared to glucose and fatty acid oxidation [189].

In the current study mean RQ were 0.89, 0.87 and 0.87 for EBC, RBC, and Control respectively. These were within a normal physiological range for humans (0.67 to 1.3) and if the above criteria is assumed then the predominant oxidized fuel was carbohydrate. According to Lusk, a nonprotein RQ of 0.87 indicates, that 55.6% of the oxygen was consumed by carbohydrate and 44.4% by fat; and likewise a nonprotein RQ of 0.89 indicates that 62.5% carbohydrate and 37.5% fat oxidation (Appendix 7. Lusk Table) [189].

Subjects were measured after a short-term fast (>12 hours), and therefore energy needs were met by stored fuels. In theory, the body should be conserving liver glycogen
A maximum of 20 hours. Oxidized fatty acids from stored triacylglycerol would then be used for fuel for the rest of the body [160]. This mixed fuel combination, as described should carry lower RQ values than observed in current study (i.e. RQ≈0.82-3) [134]. The most obvious reason for higher RQs was that a fasted, postabsorptive state had not been achieved. However other explanations were possible: 1) some subjects were hyperventilating and artificially influencing RQ (↑VCO₂); 2) some subjects were moving excessively or 3) that either the O₂ or CO₂ analyzers were out of calibration. However in this study all subjects were acclimatized to the hood before test period in order to reduce potential hyperventilation, and the technician requested subjects to remain as still as possible. Finally, the metabolic cart was calibrated before each test. Moreover, VCO₂ and VO₂ for each group were monitored to ensure that they were within reasonable physiological limits during the test. Thus, the exact explanation for the higher than anticipated RQ values was difficult to determine. It was unlikely that all women were nonfasted or hyperventilated, but unfortunately individual variation can greatly influence mean estimate of groups with small numbers. Fortunately, the RQ values were consistent across groups which facilitates relative comparison. Furthermore, RMR values which were calculated from VCO₂ and VO₂ were comparable to published standards in healthy women and previously reported RMR in BC subjects.

5.4.6. Body Size

The overall size of an individual will help to determine RMR, since it relates to the amount of metabolically active tissue. The sample for this present study had similar characteristics of body size (height, weight, BMI) among the groups and was also reflective of the Canadian population. A recent survey reported the average BMI for Canadian women as 25.8 kg/m² between the age of 45 to 54 years [190] and the average BMI of this sample was 26.5 kg/m² (average age of 51.4). Since there were no substantial differences of body size among the groups, it like had a similar influence on RMR for all.
However, BC subjects had significantly reduced FFM and higher amounts of body fat compared to Controls regardless of similar body size (height, weight, BMI). These findings agreed with existing reports of higher body fat and lower lean muscle mass measurements in women with BC relative to normal standards [120, 122]. With reduced FFM, one may expect lower RMR but on the contrary no statistically significant difference of RMR was observed.

It may be postulated that the variation in body composition was reflecting general differences in lifestyles between groups. After all, lifestyle choices in physical activity could influence body composition and energy balance. Research supports preservation of FFM and reduced body fat in women who chronically participate in endurance exercise [191]. Physical activity was measured through self-report in this study and time spent by EBC women in exercise was not statistically different than by other groups; although it was considerably lower (129 min./week, EBC; 208, RBC; 179 Control) and the intensity of the performed exercise was significantly lower in EBC. Again, the lack of significant findings for time spent exercising may be due to insufficient power.

Results of EBC suggested that body size and composition did not significantly change over time. The body weight results were similar to those of the larger sample from WMI (mean change of -0.53 kg body weight over 16 months following diagnosis; n=55) from which EBC was recruited [130] as well as to the Demark-Wahnefried study (no change in body composition or weight) [1], but were in contrast to most of the existing literature which reports 2-6 kg body weight gain in 18 months [35, 38, 39, 48, 123].

There were several explanations for the lack of gain in the present study. First, the follow up measurement was performed 10 to 12 months after diagnosis and perhaps insufficient time elapsed to observe the change in weight. While this may be, a recent retrospective chart review (approximately 2 1/2 to 3 years after diagnosis) on 14 of the 19 BC subjects observed no significant difference between baseline and last reported weight.

Second, several subjects received epirubicin, a relatively recent addition to BC chemotherapy which might not have the same effect on body weight [43]. If the 2 of
BC subjects who received epirubicin had a different weight experience (weight stability or loss), that may have been sufficient to influence the overall point estimates of body composition and weight. On inspection of data, one subject treated with epirubicin had 2.2 kg gain and the other had a 0.1 loss. Therefore it would seem unlikely that epirubicin skewed results.

Third, the recruited BC subjects, unlike the general BC population had the advantage of the WMI and therefore had received psychological, nutrition and exercise education about potential weight gain. The presence of WMI could have introduced a steady state into the typical energy imbalance observed in BC. It might be argued that the participants of WMI may have also been characteristically unique from their BC counterparts. For instance, they may be more health conscious based on their willingness to participate in this type of study. At the outset of this study, the WMI study seemed like a logical place to recruit weight stable BC to compare to weight stable controls to ensure that weight change did not impede the comparison of RMR data. However in doing so, it may have altered the environment that favored weight gain.

5.4.7. Menopause Status

The menopausal state of the woman with BC has been identified in earlier BC work to influence the degree of weight gain. A review of several studies [35, 36, 40, 60, 121, 123] found that premenopausal women gained more weight than postmenopausal women. At the outset, it was realized that many BC subjects could have a change of menstrual status during this study, and therefore control subjects were not matched to BC ones. It was not possible to predict which BC subjects would become amenorrheic and as it turned out, 5 of 8 subjects treated with chemotherapy stopped menstruating at some point in the study. Therefore menopause status was recognized as an important factor since alterations in ovarian function may have influenced RMR and this factor was not possible to control aprior.
It was important to select BC subjects, irrespective of their treatment regime, since weight gain was a general finding in all groups; although the magnitude of gain may vary with treatment. Currently the only descriptive data for RMR is a single cohort of premenopause women on chemotherapy; therefore this study provided essential descriptive information on RMR in pre- and postmenopausal women treated with various adjuvant therapies. Unfortunately, the sample size of this study was too small to perform treatment subgroup analysis but data was descriptive presented by treatment and/or menopause when appropriate.

5.5. Dietary intake

Dietary intakes were not significantly different between groups; although EBC did reduced total energy intake from baseline to follow up measurement. The pattern of dietary intakes of EBC and RBC were consistent with WMI findings which reported a reduction in dietary intake during the treatment with a restoration by year end. Baseline and year end measurements of WMI (baseline, 1530 kcal/d ± 412; 1 year, 1515 ± 293; mean ± SD) were very comparable to baseline measurements of RBC, RBC and Controls (1627 kcal/d ± 87, 1501 ± 118, 1530 ± 135; mean ± SEM respectively).

There was a dramatic reduction in total calories from baseline to 6 month measurements (1627 kcal/d ± 87, baseline; 1298 kcal/d ± 74 follow up; mean ± SEM). Reductions were achieved across all nutrients with the percent contribution of fat, carbohydrate and protein to total energy intake remaining relatively stable (approximately 16% protein, 29% fat and 55% carbohydrate).

RBC subjects who were further along in BC recovery had levels of caloric intake, not dissimilar to Controls or EBC at baseline. Therefore, there appeared to be a return to typical energy intakes following the WMI. That been said, these subjects did have higher levels of insoluble fibre intake which may reflect more healthful eating.
It is possible that BC treatment is indirectly affecting energy expenditure through a reduction in physical activity. Many women with BC have described a tremendous fatigue associated with radiation or chemotherapy. Moreover, side-effects of treatments often leave women feeling unwell and/or uncomfortable. In addition to these direct physical effects, time spent receiving and recovering from treatment often reduces leisure time or temporally removes women from the workplace. Therefore, an energetic performance at work or play may be replaced with a less energetic sedentary pace. It is possible that women with BC were spending less time engaged in physical activity. Physical inactivity results in an absolute loss of expended calories and when chronic, a secondary reduction in RMR though diminished lean body mass.

In the present study, the time spent in exercise by EBC subjects (129 min., EBC; 208 min., RBC; 179 min., Control) was less but not statistically different than other groups. The lack of significant findings may be due to insufficient power due to small sample size. The level of intensity of physical activities were significantly lower in EBC compared to other groups. Despite increased time spent in physical activity by RBC, FFM (38 kg, EBC; 38 kg, RBC) and fat mass (29 kg, EBC; 30 kg RBC) were comparable to EBC and statistically different from control (41 kg FFM; 28 kg fat mass). The exercise of choice for most EBC subjects throughout the study was walking; although time spent in activity increased at follow-up measurement.

5.7. Future Direction

EBC subjects maintained exercise and reduced caloric intake, yet experienced no change in body composition or weight at 6 month follow up. This group had similar mean RMR to other groups; although RMRs were not well-described by classical predictive variables. Taken collectively, this present study has offered a potential direction for future efforts which depart from the traditional route of binge or overeating theorem. Based on the findings of this study, the mechanism of weight gain in BC is most likely related to energy expenditure and that weight gain can be offset with the addition of exercise and dietary management. Alteration in energy expenditure in
women with BC is unlikely the result of the BC per se but rather from the direct and indirect (reduced physical activity) effect of BC treatment. It is plausible that the change in RMR is a response to hormone manipulation of treatment and is unrelated to FFM. Therefore conventional predictive methods, such as HBE, would be poor estimators of RMR in women with BC.

In the future, one could design a study that measures RMR prior to treatment, at 4 months (to allow for potential changes in hormones) and post-treatment (6 months) in premenopausal women. A similar sequence of RMR measurements could be obtained in postmenopausal women, even though their treatment may extend beyond 6 months. In addition to RMR and FFM, this study could include measurements of estradiol and GH. Moreover, a more precise attempt to quantify exercise would be needed, perhaps with a valid questionnaire. Sample size should be sufficient to perform subgroup analysis by: 1) chemotherapy vs hormonal therapy and 2) chemotherapy-induced menopause vs chemotherapy treated women who have menstrual cycles.
Chapter 6. Conclusions

The results of this study do not support the hypothesis that RMR is lower in women recently diagnosed with BC. However the following statements can be made:

1) Body compositions were different in women with BC. BC women had higher body fat (43% EBC, 44% RBC, and 40% Control) and lower FFM (38kg EBC, 38kg RBC and 41kg Control) compared to healthy controls.

2) Classic predictive variables of RMR (including weight, height, age and FFM) accounted for >95% of the variance in RMR in the Control group, but <45% of RMR in women on BC treatment, thereby suggesting that other variables are playing an important role in RMR in BC.

3) This study confirms the difficulty women with BC have with weight management. Despite EBC reduction in dietary intake and maintenance of a walking program at 6 months they did not lose body weight.


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84. **Daniell, H.W.** The Influence Of Obesity And Age At Diagnosis On The Estrogen Receptors And Weight In Women With Breast Cancer. 61: 1237-1240, 1988.


123. 

124. 

125. 

126. 

127. 

128. 

129. 

130. 

131. 

132. 

133. 


The Influence of Different Methods On Basal Metabolic Rate Measurements in Human Subjects. 50: 731-6, 1989.


Healthy Sedentary And Trained, Young And Old Men And Women. 24: 832-837, 1992.
Appendices

Appendix 1: Eligibility Assessment

a. Breast Cancer Group (EBC and RBC)

The eligibility assessment for the women with BC was developed for the WMI by Dr. Goodwin and was a two step procedure with an initial medical assessment followed by a psychological assessment. Some additional criteria was developed specifically for this thesis study. Women for our study were identified by Dr. Goodwin and members of her research group. All women met the following eligibility criteria:

i. They have recent (within 9 months when accepted into WMI) diagnosis of histologically confirmed, surgically resected invasive BC (T1-3, N0-1, M0).

ii. They have a BMI (BMI kg/m$^2$) not less than 20 or greater than 35.

iii. They are less than or equal to 70 years of age.

iv. They reside close enough to the treatment centre to participate in the study.

v. They are known to maintain good dietary records during the WMI.*

vi. They have or presently are participating in the WMI.*

Women were excluded from the study if they met any of the following criteria:

i. They have concurrent medical problems that require a special diet or that influence weight directly or through medical use (e.g. untreated hypothyroidism, sprue, inflammatory bowel disease, illnesses requiring corticosteroid use).

ii. They were unable to participate in physical activity because of physical disability (e.g. paraplegia, severe arthritis).

iii. They were unable to write English sufficiently well to complete dietary records.

iv. They had BC recurrence during WMI.*

v. They failed to maintain dietary records during WMI.*

vi. They were determined ineligible by psychiatrist due to psychiatric illness (e.g. major psychiatric disorders, eating disorders).

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* criteria developed specifically for this study
b. Healthy Controls

The eligibility for the healthy control group were as follows:

i. They have a BMI (BMI kg/m²) not less than 20 or greater than 35.

ii. They are matched in age (± 5 years) to a participant in EBC and have a similar body weight (± 2.5 kg).

iii. They reside close enough to the treatment centre to participate in the study.

Women were excluded from the healthy control group if they met any of the following criteria:

i. They had previous breast cancer.

ii. They have medical problems that require a special diet or that influence weight directly or through medical use (e.g. untreated hypothyroidism, sprue, inflammatory bowel disease, illnesses requiring corticosteroid use).

iii. They were unable to participate in physical activity because of physical disability (e.g. paraplegia, severe arthritis).

iv. They were unable to write English sufficiently well to complete dietary records.

v. They reported a history of major psychiatric illness or eating disorder.

vi. They were following hypocaloric or other weight-loss diets (e.g. macrobiotic diets).

vii. They were not weight stable.

vii. They were unwilling to participate in any of the three experiments involved in this study.

Appendix 2: Waist-hip circumference

Procedure

1. Ask the subject to remove clothing except undergarments.

2. Ask the subject to stand erect with the abdomen relaxed, arms at the sides, feet together and with weight equally divided over both legs.
4. Apply horizontally the measuring tape midway between the lowest rib and the iliac crest.
5. Measure the waist circumference to the nearest millimetre. The subject should be breathing normally.
6. Measure the hip circumference at the point yielding the maximum circumference over the buttocks, with the tape held in a horizontal plane, touching the skin but not indenting it [79].

**Appendix 3: BIS procedure**

**Procedure**

1. Place subject in reclined position with arms and legs slightly abducted from the midline of the body.
2. Clean all skin contact areas with alcohol.
3. ECG gum electrodes are placed as follows: one electrode is placed on the dorsum of the left wrist between the styloid processes of the radium and ulna; and the second electrode is placed on the dorsum of the left hand centred over the metacarpal proximal to the metacarpal-phalangeal joint; the third electrode is placed on the dorsum of the left foot between the malleoli of the tibia and fibula; and the fourth electrode is placed on the dorsum of the left foot centred over the third metatarsal proximal to the metatarsal-phalangeal joint.
4. Hand and foot leads are connected to the electrode tabs with the red clip on the proximal electrode (which introduced the current) and the black clips on the distal electrodes (which detected the current).
5. An excitation current is introduced.
6. Resistance and reactance are read directly from the instrument [168].
7. Estimates of FFM, fat weight, total body water and % body fat are derived using height, weight, gender, resistance and reactance with onboard computer software equations.
Appendix 4 Harris Benedict Equations

For Males: RMR (kcal/24h) = 66.5 + (13.75 x BW) + (5.003 x H) - (6.775 x A),
For Females: RMR (kcal/24h) = 655.1 + (9.563 x BW) + (1.850 x H) - (4.676 x A),
where BW = body weight in kilograms, H = height in centimetres, and A = age in years.

Appendix 5 Classification of Intensity of Physical Activity

<table>
<thead>
<tr>
<th>Activity</th>
<th>Weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>0</td>
</tr>
<tr>
<td>Light</td>
<td>0.5</td>
</tr>
<tr>
<td>(light), aquafitness, line dancing, bowling</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.0</td>
</tr>
<tr>
<td>brisk walking (level ground), leisure cycling, dancing, swimming laps (easy), weight training (moderate)</td>
<td></td>
</tr>
<tr>
<td>Hard</td>
<td>1.5</td>
</tr>
<tr>
<td>jogging, brisk walking (hills), cycling, aerobic classes, tennis, skiing, backpacking</td>
<td></td>
</tr>
</tbody>
</table>

Appendix 6 Criteria for Correlation Coefficients

Criteria for the quantitative significance of statistical correlations

- < 0.30 insignificant
- 0.30 - 0.45 moderate
- 0.45 - 0.60 substantial
- > 0.6 high
## Appendix 7 Lusk Table on the Analysis of the Oxidation of Carbohydrate and Fat

### Percentage of Total Oxygen Consumed

<table>
<thead>
<tr>
<th>RQ</th>
<th>Carbohydrate (1)</th>
<th>Fat (2)</th>
<th>Carbohydrate (3)</th>
<th>Fat (4)</th>
<th>Calories per Liter (5)</th>
<th>CO₂ (6)</th>
</tr>
</thead>
<tbody>
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<td>100.0</td>
<td>0</td>
<td>100.0</td>
<td>4.886</td>
<td>6.629</td>
</tr>
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<td>1.02</td>
<td>99.0</td>
<td>1.10</td>
<td>98.9</td>
<td>4.890</td>
<td>6.605</td>
</tr>
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<td>4.44</td>
<td>95.6</td>
<td>4.76</td>
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