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Body composition changes in females treated for breast cancer: a review of the evidence

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Abstract

Body composition changes cannot be precisely captured using body weight or body mass index measures. Therefore, the primary purpose of this review was to characterize the patterns of body composition change in females treated for breast cancer including only studies that utilize imaging technologies to quantify adipose tissue and lean body mass (LBM). We reviewed PubMed for studies published between 1971-2012 involving females diagnosed with breast cancer where computed axial tomography (CAT), dual energy x-ray absorptiometry (DXA) or magnetic resonance imaging (MRI) were employed for body composition assessment. Of the initial 440 studies, 106 papers were evaluated and 36 papers met all eligibility criteria (15 observational and 21 intervention trials). Results of these studies revealed that body weight did not consistently increase. Importantly, studies also showed that body weight did not accurately depict changes in lean or adipose tissues. Further findings included that sarcopenic obesity as a consequence of breast cancer treatment was not definitive, as menopausal status may be a substantial moderator of body composition. Overall, the behavioral interventions did not exhibit consistent or profound effects on body composition outcomes; approximately half showed favorable influence on adiposity while the effects on LBM were not apparent. The use of tamoxifen had a clear negative impact on body composition. The majority of studies were conducted in predominantly white survivors, highlighting the need for trials in minority populations. Collectively, these studies were limited by age, race and/or menopause status matched control groups, overall size and statistical power. Very few studies simultaneously collected diet and exercise data- two potential factors that impact body composition. Future

breast cancer trials should prioritize precise body composition methodologies to elucidate how these changes impact recurrence, prognosis and mortality, and to provide clinicians with appropriate advice regarding lifestyle recommendations in this growing sector of the population.

Body composition changes in females treated for breast cancer: a review of the evidence

Introduction

Approximately 230,000 women were diagnosed with invasive breast cancer in 2011 [1]. Death rates have decreased significantly over the past two decades, with 5 year survival rates of approximately 90% [2]. Although adjuvant combination chemotherapy has improved survival, weight gain and unfavorable changes in body composition are reported following its administration. Two prior reviews suggest that 50-96% of early stage breast cancer patients gained significant weight during adjuvant treatment, ranging from 2.5-6.2 kgs. However, weight gains of 10 kgs or more were not uncommon [3, 4]. Considering that elevations in body weight are frequent in the general population [5] and reportedly more prevalent for post-menopausal women prior to diagnosis, prevention of further weight gain is often targeted as a modifiable risk factor for overall health and long-term survivorship in this ever growing population.

The reasons behind post-diagnosis weight gain are not well understood. Although studies link weight gain with increased risk of recurrence and decreased survival [6, 7], the use of body weight as a prognostic indicator greatly limit these data. Obese women are known to underreport body weight [8] and self-reported measures are often used, which may lead to inaccuracies in weight pattern trajectories. More importantly, however, is the weight gain observed in women treated for breast cancer is distinctive, in that greater gains in fat mass relative to lean body mass (LBM) have been reported [9-12]; a concept known as *sarcopenic obesity*. These shifts in body composition cannot be captured using body weight or body mass index (BMI) measures. To further elucidate the relationships between body composition and breast cancer outcomes, more sophisticated and precise methodologies are required. Imaging

technologies, such as dual energy x-ray absorptiometry (DXA) and computed axial tomography (CAT), are being utilized with more frequency due to widespread availability and improved precision compared to bioelectrical impedance and skinfold anthropometry. The primary purpose of this review was to characterize the patterns of body composition changes that occur in females treated for breast cancer including only studies that utilize imaging technologies for fat and muscle mass quantification. A second purpose was to examine the influence of ethnicity on these changes.

Methodology

A comprehensive search of the literature was conducted using the PubMed (NIH) database (1971-2012). The search was limited to human studies. Keyword combinations of the medical subject headings (MeSH) included: “body composition,” “breast cancer,” “breast cancer survival,” “exercise,” “physical activity,” “adiposity,” “computed axial tomography,” “dual energy x-ray absorptiometry,” “magnetic resonance imaging,” “CAT,” “DEXA,” “DXA,” or “MRI.” A secondary search was conducted by manually reviewing references of relevant articles to identify further manuscripts for critical review.

Screening criteria

Papers were selected for review if they met the following inclusion criteria: 1) published in a peer reviewed journal; 2) included females diagnosed with breast cancer; and 3) employed CAT, DXA, or MRI for interpretable body composition assessment. Both observational and intervention studies were included. Papers were excluded if they: 1) assessed breast cancer risk; 2) reported outcomes for breast cancer patients intermixed with other cancer types; or 3) were literature reviews, commentaries or methods descriptions of on-going trials. The

preliminary computer-based literature search yielded 440 papers using keyword combinations. Titles and abstracts were reviewed for relevancy. If an abstract did not contain sufficient information to assess eligibility, the manuscript was accessed and reviewed.

Results

Initially, 106 papers were evaluated and 36 papers met all eligibility criteria. Only studies utilizing DXA and CAT scanning were included; MRI assessment of body composition was limited (**Figure 1**). The body of this review is organized by tissue (adipose or lean), study design (ie, observational or interventional) and time since treatment. Studies are of mixed menopausal status, unless otherwise noted. A summary of studies is provided in **Tables 1** and **2**, describing key characteristics of the population, the study design/purpose, the imaging technique and findings regarding body weight, adipose tissue and LBM, if specified.

Adiposity and observational studies

Excess adiposity is reportedly linked to poorer prognosis through increases in adipose derived circulating estrogens and via increased circulating levels of insulin, insulin-like growth factor and leptin [13]. Thus, body fat (BF) could serve as an important prognostic marker that is potentially modifiable. Of the observational studies included, 4 examined adiposity cross-sectionally. Using DXA, McTiernan et al [14] and Thomsom et al [15] reported that the average %BF in post-menopausal women was 38.3% and 46.9%, respectively, exceeding the current age-adjusted recommendations of 30-34% [16]. Ali [17] and Nguyen [18] examined the impact of tamoxifen on adiposity, utilizing DXA and CAT, respectively. Compared to controls, Ali et al reported significantly greater levels of BF in women taking tamoxifen and Nguyen et al found that fatty liver and intra-abdominal fat were more common among tamoxifen users.

Ten observational studies examined adiposity changes over time. The majority supported that an increase in %BF was common [9-11, 19-25]; however, the timing of these changes along the treatment continuum deserves elaboration. Six studies examined body composition changes over the course of first-line adjuvant chemotherapy with imaging obtained before and shortly after chemotherapy completion. Two studies reported no changes in %BF [10, 20], whereas four investigations found significant increases in %BF over the course of treatment [9, 11, 19, 23]. These differences could not be explained by stage of disease, chemotherapy regimen, duration of treatment, age or body weight patterns. In fact, of the three studies reporting increases in %BF, the associations with body weight were limited [11, 19, 23]. Further, using CAT, Cheney et al showed that the majority of women gained BF, particular visceral fat, irrespective of the direction of weight change [9].

Several of the observational studies examined body composition changes at later points of chemotherapy completion. Four studies followed women for 1 year (ie, before and ~6 months following chemotherapy treatment [11, 20, 21, 24]; three demonstrated significant gains in %BF over this time interval [11, 20, 21]. Interestingly, Nissen et al showed that women of normal weight at the time of diagnosis were more likely to experience increases in BF and body weight, whereas women who were overweight or obese at the time of diagnosis were more likely to experience decreases in BF and body weight. A weak association between increased BF and tamoxifen treatment was also reported ($p=0.15$) [24]. The investigation by Winters et al [25] examined body composition changes up to 2 years after chemotherapy in post-menopausal women; significant increases in %BF over time were reported. Irwin et al [22] investigated changes in %BF from diagnosis to 3 years post-diagnosis. Of the 132 women with

DXA results, 74% (n=98) experienced increases in %BF averaging $3.6\% \pm 3.0\%$. Interestingly, a significant trend of increasing gains in %BF with decreasing BMI category was reported; no significant associations were observed for treatment, menopause status or tamoxifen use, however.

Adiposity and intervention studies

Based on the observational findings of chemotherapy-associated weight gain, several behavioral intervention studies have been conducted. Six studies examined adiposity changes for interventions that promoted exercise during first-line adjuvant chemotherapy [26-31]; two of these reported results of the same trial [26, 27]. In all of these studies, participants were recruited prior to the second cycle of chemotherapy and the exercise intervention continued through chemotherapy completion. Demark-Wahnefried et al showed that both, diet and clinic-based aerobic and resistance exercise training (RET) led to decreases in BF in premenopausal women [29], while Courneya et al reported that aerobic exercise training (AET) prevented BF gains in a mixed menopausal population [27]. Additional analyses revealed that patients with stage IIB/IIIA disease experienced further declines in BF with exercise than women in the usual care group or with stage I/IIA disease [26]. Conversely, results from a home based diet and exercise study published subsequently by Demark-Wahnefried et al demonstrated increases in %BF in premenopausal women with Stage I-IIIa disease [28]. Djuric et al conducted a diet and exercise intervention using telephone counseling in pre- and postmenopausal women with Stage I-III disease. No significant changes in %BF were reported at the one year follow-up; however, intervention participants tended to experience decreases in %BF whereas controls tended to increase %BF [31]. Finally, DeNysschen et al found no differences

in %BF for women who participated in AET during the time of first-line chemotherapy administration [30]. Control participants in these interventions demonstrated consistent, positive gains in %BF, supporting the notion of early behavioral intervention initiation.

Two studies looked at adiposity changes for patients who had completed chemotherapy treatment within 12 months of study enrollment [30, 32]. Investigators recruited 30 women to start AET from the time of chemotherapy completion to 6 months post-treatment. Compared to women who had engaged in AET throughout chemotherapy and non-exercising controls, no differences were noted for changes in %BF at baseline or 6 month follow up. In fact, %BF trended upward in all groups throughout the 12 month trial [30]. Matthews et al conducted a walking intervention with women who had completed treatment within 1 year. Despite demonstrated differences in walking activity, no differences in %BF were detected; however, sample sizes were small [32].

Eleven behavioral interventions were conducted in women post-chemotherapy; the mean time from diagnosis to enrollment was 3-4 years [33-43]. Five studies showed that women engaging in exercise (eg, walking and/or weight training) 2-7 times/week had significant decreases in %BF when compared to baseline and/or non-exercising, controls [33, 35, 36, 39, 43]; three of these trials also advocated caloric reduction [35, 36, 43]. Thomson et al [41] reported significant decreases in %BF for women who followed one of two calorie-restricted diets - a low fat diet or a modified Atkins/reduced carbohydrate diet. In contrast, five trials failed to show differences in adiposity between intervention and control participants. Knobf et al [34] and Rogers et al [38] promoted weight training and walking several times/week over a 3-6 month timeframe; both reported null results post-intervention and at 3-month follow-up [37].

Winters-Stone et al tested the impact of 12 months of RET + impact exercise vs. stretching in post-menopausal survivors; no differences in adiposity were reported. Stendell-Hollis et al reported no significant reductions in %BF over a 6 month period for overweight breast cancer survivors consuming green tea [40]. Overall, 6 trials showed favorable results and 5 trials showed no differences in adiposity reduction.

Finally, three pharmacologically-based interventions examined the impact of adjuvant hormonal therapy on body composition [44-46]. Utilizing data from the REBBeca study, van Londen et al demonstrated significant decreases in %BF at 6, 12, 18 and 24 months among women on aromatase inhibitors (AIs) compared to women not prescribed AIs. The majority of these women were prescribed selective estrogen receptor modulators (SERMs), however. The two other trials showed that women switched to exemestane experienced favorable decreases in BF at 12 [44] and 24 months ($p < 0.05$) [45]; whereas women who stayed on tamoxifen demonstrated no changes.

Lean body mass and observational studies

Lean body mass encompasses metabolically demanding tissues including the liver, kidney, and muscle [47]. For purposes of this review, LBM is used synonymously with muscle and/or fat free mass. Three cross-sectional studies examined LBM in women with breast cancer. Ali et al [17] showed no differences in LBM between tamoxifen recipients vs. controls, whereas Prado et al [48] showed a 25% prevalence of sarcopenia (defined as muscle mass 2 standard deviations below sex-specific norms) in 55 women with Stage IV breast cancer. Chemotherapy toxicity was present in 50% of women with sarcopenia vs. 20% of nonsarcopenic women ($p = 0.03$); no associations were reported between sarcopenia and ER, human epidermal growth factor

receptor status (HER-2) or BMI. LBM findings by Winter-Stone et al [25] were stratified by low vs. normal bone mineral density (BMD) hampering extrapolation. However, the associations between low BMD, lower BMI ($24 \pm 3.1 \text{ kg/m}^2$) and lower levels of LBM in breast cancer survivors 12.6 months after chemotherapy completion are noteworthy.

Seven observational studies examined changes in LBM over time: six reported decreases [9-11, 21, 23, 24] and 1 reported no changes [19]. Two studies compared LBM in women who had received chemotherapy vs. radiation therapy (RT) [11, 23]. Kutynec et al observed declines in LBM for both treatment groups, yet losses were significantly greater in chemotherapy vs. RT recipients ($p=0.02$) [23]. Although not significant, the graphic depictions of LBM changes presented by Demark-Wahnefried et al clearly reveal that chemotherapy recipients exhibited decreases in LBM, whereas RT recipients showed increases [11], suggesting potential issues with statistical power. Two observational studies were completed over the course of chemotherapy. One [10] showed a trend toward decreasing LBM in 20 pre-menopausal women with Stage I or II disease ($p=0.10$), whereas the other reported no significant changes in LBM in 10 women with Stage I-III disease [19]. Three studies support LBM loss trajectories in 6-12 months following chemotherapy completion [9, 21, 24].

Lean body mass and intervention studies

Of the 21 interventional trials, 18 reported findings on LBM. Interpretations concerning LBM need to consider changes in body weight, since simultaneous loss of LBM can occur for participants who lose body weight - a frequent outcome of interest in these trials. Six studies examined changes in LBM for behavioral interventions that took place during first-line chemotherapy [26-31]. The START trial demonstrated that RET vs. usual care was associated

with significant increases in LBM ($p=0.004$), but also simultaneous gains in weight [27].

Stratified results revealed that women with Stage IIB/IIIA experienced greater gains in LBM using RET or AET vs. exercising women with Stage I/II disease who experienced no significant changes in LBM. A higher adherence rate of 8-10% was reported for women with Stage IIB/IIIA disease [26]. Four other trials failed to find significant changes in LBM for women participating in exercise interventions during chemotherapy [28-31]. However, retention of LBM could be viewed as a 'positive' vs. a 'null' finding in this context.

A total of nine trials examined LBM within 3-4 years of diagnosis and treatment. Five studies reported no changes in LBM [32, 34, 35, 40, 42]. The null findings of Mefford et al [35] are noteworthy given that intervention participants experienced no changes in LBM, despite losing body weight and fat mass. Conversely, in the 24-week dietary intervention trial by Thomson [41], participants lost an average of 6.1 kg of body weight, while simultaneously losing LBM. Strikingly, the prevalence of sarcopenic obesity increased from 10% at baseline to 18% at trial completion. Participants in the diet and exercise intervention conducted by Campbell et al experienced significant decreases in body weight ($p=0.04$), as well as a significant decreases in LBM ($p<0.001$) over the 24-week intervention period [43]. Two exercise interventions, one emphasizing AET and the other testing the effects of twice weekly weight training, both, demonstrated increases in LBM at 6 and 12 months follow up [33, 39]. When stratified by stage, hormone therapy, age and obesity, Irwin reported that women <56 years of age who exercised had the significantly greater gains in LBM vs. women >56 years or non-exercisers ($p<0.05$) [33]. The authors speculated that younger women may have more favorable

LBM responses to exercise in the setting of chemotherapy-induced menopause vs. natural menopause.

All three pharmacologically-based studies displayed favorable changes in LBM. Van Londen et al showed that post-menopausal women taking AIs exhibited significant increases in LBM at 12, 18 and 24 months post-AI initiation compared to baseline ($p \leq 0.05$) and to women not prescribed AIs at these same time points ($p \leq 0.05$); whereas no significant changes in LBM over time were observed for the non-AI recipients. Francini et al demonstrated that switching to exemestane from tamoxifen was associated with improved ratios of LBM to fat mass at 12 months compared to baseline ($p < 0.01$) and to women who stayed on tamoxifen ($p < 0.05$) [44]. Similar results were reported by Montagnani et al at up to 24 months after switching to exemestane from tamoxifen ($p < 0.05$ for baseline and between groups) [45].

Discussion

This paper summarizes the literature to date on body composition changes in women treated for breast cancer. This topic is particularly relevant given the health implications of weight gain, loss of LBM and increased adiposity for breast cancer survivors [49, 50]. Reviews of this nature are often difficult to synthesize since the inherent purpose is to streamline findings from studies that possess highly variable research purposes. As reflected in **Tables 1 and 2**, studies examined a variety of outcomes including fitness, quality of life, chemotherapy-associated symptoms, weight loss, bone health, and hormone levels, including some aspect of body composition. In spite of these diverging intentions, common themes emerge regarding findings and limitations.

First, body weight does not accurately depict potentially important changes in lean or adipose tissues. As LBM mass increases, fat mass can decrease, or vice versa, resulting in a net zero change in body weight or BMI. This phenomenon can be appreciated throughout **Tables 1 and 2**, as there is no consistent relationship between body weight and body composition changes. That said, BMI and body weight are easily obtained endpoints, and previous studies report an adverse relationship between higher body weight and BMI, and reduced survival and increased recurrence [51-57]. As a result, breast cancer survivors are currently advised to maintain a healthy body weight during and after treatment [58]. Interestingly, recent imaging studies in other cancer populations highlight the variability in LBM across the BMI spectrum [48, 59, 60]. Such studies are needed for women treated for breast cancer to understand the prognostic significance for a normal weight female with high levels of adiposity vs. an overweight female with lower levels of adiposity.

Second, the concept of sarcopenic obesity (ie, greater gains in BF relative to LBM) as a consequence of breast cancer treatment is not definitive, as menopausal status may be a substantial moderator of body composition. Studies in healthy female populations demonstrate that increases in BF and decreases in LBM coincide with aging and years since natural menopause ($p < 0.001$) [61], with the highest rates of LBM depletion occurring in the earliest postmenopausal years [62]. Therefore to decipher the consequential changes in body composition from breast cancer treatment, investigations need to account for these natural increases in adiposity and decreases in lean tissue that have yet to occur in premenopausal women or have already occurred in women diagnosed with post-menopausal breast cancer. Three observational studies were conducted exclusively in premenopausal women [10, 11, 21];

participants experienced increases in BF, especially trunkal fat, and trends toward decreased LBM within the first year following chemotherapy treatment. Considering that chemotherapy-induced ovarian failure (CIOF) occurs in 50-70% of premenopausal women who receive adjuvant chemotherapy [63], these post-treatment alterations in fat and LBM essentially mirror those observed for healthy women undergoing natural menopause. Perhaps these changes are a direct result of the relatively sudden immersion into menopause and not necessarily a mechanistic association with a particular chemotherapy treatment. Theoretically, studies involving women with post-menopausal breast cancer would shed further light on the sarcopenic obesity hypothesis. However, observational studies in exclusively post-menopausal women did not employ designs that would allow us to discern the natural patterns of body composition change after breast cancer treatment [14, 18, 25, 46]. Future studies that seek to understand the effects of breast cancer treatment on body composition should consider designs wherein the study recruitment or the statistical analyses stratify by menopausal status, or make comparisons to females without breast cancer.

Third, the effects of the behavioral interventions on body composition outcomes were not readily apparent, with only half of the exercise interventions showing declines in BF and the majority showing no improvements in LBM. While these findings are disappointing, we speculate there are several reasons for this occurrence. Nine of the interventions used women of mixed menopausal status; thus, the effects of the exercise intervention on adiposity and LBM were likely masked and biased toward the null since pre-menopausal women would have different trajectories and responses to exercise than post-menopausal women. To this end, when we restrict the interventions to post-menopausal women [32-34, 41, 42], the majority of

the exercise interventions do exhibit favorable decreases in %BF and gains or retention of LBM for previously inactive women [32-34]. Whereas, the only dietary intervention conducted in post-menopausal women showed significant decreases in %BF, but adverse responses to levels of LBM [41]. Conversely, only two studies have been conducted in women who were pre-menopausal at the time of treatment and recruitment [28, 29]. Although both studies reported LBM preservation, the results on adiposity were mixed. This underscores the need for larger trials in premenopausal women, especially considering this is when ~25% of breast cancer is diagnosed [64]. These studies also call attention to the limited number of interventions that combine both diet and exercise in women treated for breast cancer [28, 29, 35, 36]. The essential inclusion of increased physical activity with calorie restriction to facilitate weight loss while retaining muscle, was recently demonstrated in a study by Foster-Schubert et al [65] of overweight and obese women without a history of breast cancer. The diet + exercise group exhibited the greatest reductions in body weight (-12.4% between baseline and 12 months; $p=0.005$) and *gains* in LBM (+11.8% between baseline and 12 months; $p=0.008$) compared to the diet only, exercise only and control groups. Interestingly, none of the behavioral interventions that included both diet and exercise and imaging were conducted in post-menopausal women with breast cancer, the time when the predominant cases of breast cancer are diagnosed. This is not particularly surprising since the overall number of lifestyle intervention studies conducted in post-menopausal women without cancer is quite limited [66]. Finally, many of the behavioral interventions differed by type of exercise (ie, RET and AET), duration and intensity; all of which, have the potential to vary body composition outcomes. Although personal preference for type of exercise has been shown to be a significant

moderator of results [26], designing practical interventions for women at different stages of treatment and recovery remains challenging.

One further theme of this review relates to the use of SERMs and their clear impact on body composition. Previous studies reported inconsistent results for weight gain in women treated with tamoxifen [67, 68]. However, subgroup examination in the reviewed observational and interventional studies revealed higher overall BF, particularly trunkal fat for women prescribed SERMs [14, 17, 18, 24, 34] with inconsistent weight gain patterns. The pharmacologic trials that specifically examined body composition changes of women prescribed SERMs vs. AIs strongly supported these adiposity findings [44-46]; however, they provided additional, intriguing evidence regarding the favorable changes on LBM with AI vs. SERM therapy. It was speculated that the increases in LBM for women on AIs may have been due to a relative increase in male gonadal hormones [46]. Fortunately, Schmitz et al showed that women who exercised while on SERMs could achieve decreases in adiposity and gains in LBM, affording clinicians the opportunity to encourage exercise to combat the side effects of this treatment modality.

Limitations and Future considerations

Despite the methodological advantage that imaging technology affords, the limitations of these studies warrant consideration. Approximately half of the studies herein simultaneously collected dietary and exercise data using validated methods. Because of their confounding relationship, this underscores the need for future studies to comprehensively address these in the design and/or analyses. Additionally, control groups were often not matched for age, race, and/or menopause status and the statistical analyses often used group means versus individual

change, potentially masking important individual level data. Further, only 4 studies had >100 participants, limiting statistical power to stratify outcomes by important disease markers (eg, ER/PR or HER2 status) or treatments (eg, SERMs, AIs). Finally, findings reflect predominantly white survivors; a well-educated, highly motivated group of research participants. An original purpose of this review was to assess the influence of ethnicity on body composition in women treated for breast cancer. We were specifically interested in African-American women since they have a higher prevalence of overweight and obesity [5] and co-morbid conditions compared to other females [69, 70]; all of which are believed to contribute to survival disparities. However, of the studies included, none were conducted exclusively in these women, and 42% (n=15/36) of the studies failed to report the racial breakdown of their study population. Clearly, investigations in minority populations with different risk profiles are required.

We are amid an obesity epidemic and a concurrent rise in obesity-associated diseases, especially cardiovascular disease and diabetes. The definitive role of obesity in cancer development and recurrence has yet to be determined; however, the majority of women with breast cancer are overweight or obese at the time of diagnosis. Weight gain is considered a hallmark feature associated with breast cancer treatment, which only introduces or compounds this problem further. The cornerstone of therapeutic interventions is weight loss, which is most successfully achieved using diet, exercise and social support. This review highlighted potentially important changes in adiposity and LBM that occurred in this population, especially for women treated with SERMs. Future breast cancer trials should prioritize precise body composition methodologies to elucidate how these changes impact recurrence, prognosis and mortality, to

explore racial/ethnic differences, and to provide clinicians with appropriate advice regarding lifestyle recommendations in this growing sector of the population.

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