BODY COMPOSITION AND BREAST CANCER – THE ROLE OF LEAN BODY MASS

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Abstract

Breast cancer risk and outcomes for breast cancer survivors are known to be influenced by body composition. A wealth of literature surrounds the function and role of fat tissue, however considerably less is known regarding lean body mass and its functional role in immune, hormonal and metabolic regulation in breast cancer aetiology. This review outlines findings relevant to lean body mass before, and following breast cancer diagnosis. A paucity of research exists regarding lean body mass and breast cancer risk. However, post-diagnosis lean body mass losses are commonly reported and a concern for ongoing co-morbidity after treatment. A comprehensive mechanism for sarcopenic obesity in breast cancer survivors is currently unknown. However, findings from other disease states indicate that the effects of chronic inflammation and/or an increase in sedentary activity may partly explain the exaggerated losses of lean body mass. Exercise has been a successful intervention for attenuating lean body mass losses after treatment, while weight loss through energy restriction may exacerbate breast cancer related sarcopenia. Combining exercise with dietary intervention to optimise lean body mass may be ideal; however there is insufficient evidence for this at present. Similarly, the role of functional food supplements, such as omega-3 fatty acids and essential amino acids, may aid lean body mass maintenance through anti-inflammatory action and increased muscle protein synthesis.

There were 1.15 million new cases of breast cancer diagnosed worldwide in 2002,[1] while in Australia alone, 12,600 new cases are diagnosed each year and at the end of 2006 there were 144,000 breast cancer survivors country-wide.[2] Significant advances in research have increased our understanding of predisposing factors and improved the management of breast cancer, resulting in a five-year survival rate of 88% and a one-year survival of 97%.[2]

Over the last three decades, numerous studies and meta-analyses have established a relationship between body composition and breast cancer aetiology and prognosis.[3-6] Postmenopausal breast cancer risk has a positive correlation with body mass index (BMI),[3] while a lower BMI[3] but high waist to hip ratio (WHR) is associated with an increased risk of premenopausal breast cancer.[4,5] At the time of diagnosis, a higher BMI and WHR are both related to poorer prognosis, irrespective of menopausal status.[6]

Due to the strong correlation found between BMI, WHR and body fat mass, investigations have focused on the function of fat tissue in breast cancer aetiology with specific reference to its influence over sex hormone balance, endocrine function, insulin and insulin-like growth factors and adipokine expression.[7] More recently, better understanding of the function of lean body mass (LBM) indicates that it too exerts a powerful endocrine, immune and hormonal influence within the body.[8]

For breast cancer survivors, simultaneous LBM loss with fat tissue accumulation, known as sarcopenic obesity, is common.[9-11] The complete aetiology of LBM loss in this population is unclear, however it appears to be associated with poorer metabolic outcomes, such as earlier onset of cardiovascular disease and metabolic syndrome related diseases.[8,12,13] In addition, LBM has been shown to be a positive predictor of survival in chronic heart failure,[14] chronic kidney disease,[15] chronic obstructive pulmonary disease,[16] and cancer cachexia.[17] Evidence from these populations suggest that LBM loss may in part be related to inflammatory mediators present as a result of the disease state and treatment.[17,18]

The purpose of this review is: to provide a brief outline of findings related to LBM before and after breast cancer diagnosis; to explore the role of inflammation in LBM loss in breast cancer survivor populations; and review the established and potential roles of exercise and dietary intake in LBM maintenance specific to the breast cancer survivor population.

Search criteria

A literature search was carried out using MEDLINE and Pubmed databases. Selected studies and review articles were hand-searched for additional relevant references. Key terms used included: breast cancer (breast neoplasms, cancer of the breast, breast cancer survivor, breast neoplasm risk); body composition (percentage body fat, muscle mass, lean body mass, skeletal muscle, body composition); exercise (physical activity, resistance training, aerobic training); diet (energy intake, omega-3 fatty acids, diet therapy, caloric/energy restriction). Additional search criteria included, subjects >18 years of age, non-metastatic breast cancer survivors and articles published in English. Included articles were those that reported body fat composition and/or lean body mass in relation to: breast cancer risk (all study designs included); time after breast cancer diagnosis (all prospective and retrospective cohort studies, case series, non-randomised and randomised studies); and diet and exercise, or combined interventions post breast cancer diagnosis (all non-randomised and randomised control trials).

LBM prior to breast cancer diagnosis

There is a lack of studies prospectively assessing LBM in association with breast cancer risk using sensitive measures such as dual-energy X-ray absorptiometry, CT scanning, densitometry or bioelectrical impedance. Of the studies that could be located, two prospective cohorts consisting entirely of postmenopausal women, have reported mixed results for the effect of LBM on breast cancer risk as assessed by bioelectrical impedance.[19,20] In a Dutch postmenopausal population with a median of six years follow-up, each 1kg/m^2 increase in LBM-to-height ratio (LBM divided by height squared) was positively associated with breast cancer risk, with seemingly no effect from body fat to height ratio.[20] This differed somewhat to a postmenopausal Australian cohort measured at baseline and again after nine years.[19] Each 10kg increase in absolute lean body and fat mass, and 10cm increase in waist circumference, were associated with increased breast cancer risk. However, when results were stratified for time since onset of menopause and history of hormone replacement therapy (HRT), a significant effect was only found for those who had experienced menopause more than 15 years before assessment, and in never-users of HRT.[19-21]

These results are not surprising, as it is well established that adult weight increases and higher BMI values are significantly associated with postmenopausal breast cancer risk.[3,21] Considering normal weight gain in healthy adult populations involves a simultaneous increase in LBM and fat mass,[22] the association between breast cancer risk and absolute LBM in these studies may be secondary to the effects of significant long-term total body weight and fat mass gain during adulthood.

In contrast to the above findings, when the ratio of fat to skeletal muscle mass was measured at or shortly following diagnosis in a Uruguayan case-control study, a higher value for fat-to-muscle ratio was more indicative of a breast cancer diagnosis.[23] Compared to the lowest (1st) quartile of fat-to-muscle ratio, both 3rd and 4th quartiles had an odds risk of 4.86 and 6.09 ($p<0.0001$) independent of BMI and menopausal status. The authors noted that to maintain skeletal muscle mass at a level that was protective, regular exercise was mandatory. Alternatively, these results may indicate the importance of active lean tissue and its influence over immune and hormonal regulation.[24] Caution in interpretation of these data is required. Limitations regarding the body composition measurement methodology used, and the applicability of findings to populations in developed countries are not clear.

To date, few meaningful relationships between LBM and risk of breast cancer have been uncovered. Current evidence suggests that the effect of LBM may be secondary to total weight and fat mass gains prior to diagnosis. More prospective studies using accurate and repeated measures of body composition, along with markers of muscle function, are required to further elucidate the protective or predisposing effect of LBM and breast cancer risk.

Pattern of LBM changes after breast cancer treatment

Sarcopenic weight gains are common after treatment for breast cancer.[10] Over the five years following active treatment, 50-100% of survivors have been shown to increase total weight,[10,11] with the probability of re-attaining their pre-diagnosis weight being inversely associated with initial post-treatment weight gains.[12] LBM growth accounts for 20-40% of total weight gains in disease free populations.[22] Studies of breast cancer survivors have shown that more than one year after chemotherapy, total fat mass gains of 2.4kg to 6.7kg were accompanied by LBM losses of -0.4kg to -1.7kg, respectively.[9,25] Women who seemingly maintain their weight in the years after treatment still undergo these adverse changes, such that LBM losses match increases in adipose tissue.[26] Factors that are linked with more exaggerated changes include premenopausal status at diagnosis, experiencing treatment related menopause,[27] receiving chemotherapy compared to no chemotherapy, a lower BMI at diagnosis and those who are least physically active after treatment.[28] The sarcopenic pattern is still prevalent, albeit of smaller magnitude in postmenopausal breast cancer populations.[25, 29]

In regards to timing of LBM changes, the most significant changes are seen during adjuvant chemotherapy and in the 6 to 12 months following this.[9,25,29,30] By observing control groups in large randomised trials, the rate of sarcopenic weight gain seems to normalise two to four years post diagnosis,[31-34] however total weight increases can still occur after this point.[12]

LBM losses with concurrent fat and total weight gains are associated with metabolic dysfunction including impaired glucose metabolism,[13] high triglyceride levels,[35] and chronic inflammation in healthy and diseased populations.[8] While the function of fat tissue has been a focus of previous interventions aimed at breast cancer survivors, LBM should be evaluated more closely in future, as it is known to be a large contributor to glucose disposal,[8] triglyceride oxidation and, when stimulated through exercise, can exert systemic anti-inflammatory effects.[36]

Contributors to LBM losses

Studies assessing moderators of weight change during treatment (local surgery and radiotherapy, with or without chemotherapy) have not conclusively explained the reasons for the higher than expected total weight gains and the sarcopenic nature of the body composition changes.[9,25,27,37,38] The role of both resting metabolic rate and energy intake do not fully explain the magnitude of weight change after treatment.[9,27] It is thought that any increases in fat mass are sufficient to mask the resting metabolic rate reduction associated with LBM losses,[9] while weight gains have been observed even after a reduction in energy intake.[27] In contrast, lower levels of physical activity have been associated with increased weight,[38] however total weight gains still seem to be greater than predicted after accounting for the reduction in energy expenditure associated with decreased physical activity.[25] Therefore, auxiliary mechanisms other than those relating to

conventional energy balance, such as chronic inflammation metabolic disturbances related to sedentary activity, may partly explain the exaggerated changes in LBM.

Systemic inflammation has proven to be a strong inhibitor of muscle protein synthesis and increased muscle protein degradation in ovarian, gastroesophageal and pancreatic cancers.[39,40] A full review of these mechanisms can be found elsewhere.[40] In brief, increased circulating levels of inflammatory cytokines such as tumour necrosis factor (TNF-)alpha and interleukin-6 (IL-6), and increased genetic expression of inflammatory markers through nuclear factor-kappa B (Nf-ƙB), stimulate muscle degradation while inhibiting muscle protein synthesis.[40] At least one prospective study revealed that elevated levels of inflammatory markers have been positively associated with body mass accumulation in healthy populations.[41]

Direct associations between LBM changes and inflammatory markers have not yet been made in breast cancer survivor populations. Elevated levels of acute phase inflammatory markers, C-reactive protein and serum amyloid A, have been correlated with increased fatigue,[42] increased incidence of cardiovascular disease, insulin resistance,[43] and mortality independent of BMI, stage of disease and race.[44] Cytokines generated from active LBM (particularly skeletal muscle), known as myokines,[45] contribute to the anti/inflammatory balance of the body.[8] While the muscle-fat cytokine interplay has not been fully elucidated, numerous studies have confirmed that muscle activity has a significant anti-inflammatory influence on the systemic cytokine milieu, and further research may develop mechanisms that increase the importance of functional LBM in healthy and breast cancer populations.[24]

A reduction in physical activity and an increase in sedentary activity are common after breast cancer diagnosis.[28] Increased sedentary time, such as sitting or lying down, has been related to increased adiposity in breast cancer populations.[46] This phenomenon can be explained through an increase in abdominal fat deposition, decreased insulin sensitivity,[35] decreased triglyceride oxidation,[35] and an inhibition of muscle synthesis,[47] following muscle deactivation related to physical inactivity. Decreased energy expenditure plus the metabolic disturbances associated with physical inactivity, may partially explain discrepancies in predicted and actual weight gains found in breast cancer survivors.

Inflammation and sedentary activity related changes in metabolism have a significant role in LBM physiology. More research is needed to fully elucidate exact physiological mechanisms even in healthy populations, however compelling evidence indicates that regularly stimulated as opposed to dormant LBM may be closely related to LBM changes.[13, 48]

Influences of exercise and diet on LBM

Diet and physical activity interventions have had a significant impact on body composition changes in breast cancer survivors despite their disappointing influence on LBM following treatment.

Regular exercise in the well population has been shown to reduce breast cancer risk by 25-30%,[49] and after diagnosis, total mortality by ~40%, breast cancer mortality by 34%, and breast cancer recurrence by 24%.[50] Therefore, increased physical activity is recommended for healthy populations and breast cancer survivors alike.

With respect to LBM, randomised control trials that involved resistance training have shown 0.5 to 0.88kg LBM increases over 8 to 26 weeks.[51-53] In a population that typically loses muscle mass, aerobic exercise during and after treatment when compared to no intervention, has been shown to attenuate and sometimes reverse LBM losses.[32, 33] However, a recent meta-analysis of randomised control trials notes only body fat percentage is consistently improved by aerobic exercise in this population.[54] As well as absolute LBM growth, improvement of muscle function in conjunction with smaller absolute LBM growth is an important outcome in this population. A landmark randomised control trial by Schmitz et al (2009) investigated the effect of year long, twice weekly resistance training on outcomes relating to lymphoedema. The study did not detect a significant change in LBM compared to control. However upper and lower body strength increased by 29% and 32% respectively in the intervention group, compared to 4% and 8% respectively in the control.[31] Similarly, VO_2 max was disproportionately improved after aerobic exercise training compared to the relatively small improvements of body composition.[54,55] Considering the varying abilities of individuals of different body shapes and genetic predisposition to increasing absolute LBM, functional outcomes may give a more consistent insight into physiological improvement of LBM. Muscle strength has been shown to be a better predictor of mortality than muscle mass in ageing populations,[56] VO_2 max has long been an independent marker of mortality regardless of body composition in other populations,[57] and evidence shows that exercise training and muscle contraction exerts anti-inflammatory effects through myokine production.[24] While the data regarding outcomes and muscle function is lacking in breast cancer survivors, these consistent relationships in otherwise not dissimilar populations are suggestive of similar links in breast cancer populations.

Dietary interventions for breast cancer survivors have shown successful weight loss through energy restriction,[58-61] and with mixed results after low fat and high fruit and vegetable consumption.[62,63] Randomised control trials assessing weight loss through energy restriction in breast cancer survivors have resulted in 3.3 to 9.5kg weight loss over 6 to 12 months.[59-61] However, there has been little focus on lean mass maintenance in these studies. In otherwise healthy overweight and obese populations, weight loss through energy restriction without exercise inevitably results in losses of both fat and LBM.[60,64,65] A recent randomised control trial evaluated the efficacy of low carbohydrate or low fat diets for weight loss in breast cancer survivors and their potential hazard to LBM.[60] Similar weight loss was found for each group, however, while body fat percentage, metabolic markers and C-reactive protein decreased, a classification of sarcopenia categorised

by appendicular LBM (<5.67kg/m^2), measured by dual-energy X-ray absorptiometry, increased from 8% to 18% within the study cohort.[60] Considering the known link between breast cancer survival and the loss of LBM after treatment, this study is the first in this population that clearly indicates the need for additional interventions to attenuate LBM during weight loss.

Combining exercise and dietary restriction for breast cancer survivors has shown promise in attenuating LBM loss during total body weight loss.[66] Some studies have been underpowered or have failed to measure LBM,[67-69] leaving the need for more research into a model that has been useful in non-breast cancer populations.[65] Apart from exercise, anti-inflammatory nutrients may have utility in this population when addressing LBM maintenance. Long chain omega-3 fatty acids (LCn-3 FAs) through anti-inflammatory and mitochondrial influence, are associated with protein sparing and increased fat oxidation in overweight populations,[70-72] and LBM attenuation in cancer cachexia.[39,73] In conjunction with exercise, LCn-3FAs supplementation has shown to exert more powerful effects again on fat oxidation and LBM growth.[71] Substantial literature supports the ability of LCn-3FAs to reduce inflammation through many of the pathways associated with LBM loss.[74-76] An Australian study is currently underway investigating these relationships within a breast cancer survivor cohort. Another potential group of nutrients that show promise in LBM preservation are supplemented essential amino acids. Emerging findings indicate that essential amino acids, when dosed appropriately, may independently stimulate muscle protein synthesis.[77] Supplementation has improved LBM in both chronic heart failure and older female populations,[78,79] and has a theoretical potential in breast cancer populations.

Conclusions

Adipose tissue has long been a focus of breast cancer aetiology and management. While little published research exists, recent insights regarding the role of LBM in inflammatory, immune and hormonal balance indicate an intriguing avenue for improving breast cancer outcomes. Sarcopenic weight gains during and after breast cancer treatment are not fully understood, however inflammatory regulation, inactivation of muscle tissue through sedentary activity and muscle-fat communication via endocrine pathways may provide further explanation of these adverse changes. Regardless of the incomplete physiological understanding, exercise interventions during and after treatment are effective in attenuating and reversing LBM losses in breast cancer survivors. Perhaps more importantly, it has been shown to dramatically improve muscle function in breast cancer populations. In contrast, dietary energy restriction alone is effective in reducing weight, however, the concurrent loss of LBM during weight loss may expose survivors to more severe sarcopenic changes. Optimal management of body composition is still under investigation, however conclusions from other populations would indicate a combined diet and exercise approach is best. Finally, a potential role exists for specific dietary supplements that address chronic inflammation and inhibition of muscle protein synthesis likely present in breast cancer survivors.

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