

WJCO 5th Anniversary Special Issues (2): Breast cancer**Weight gain following breast cancer diagnosis: Implication and proposed mechanisms**

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Abstract

Weight gain occurs in the majority of women following breast cancer treatment. An overview of studies describing weight gain amongst women treated with early to modern chemotherapy regimens is included. Populations at higher risk include women who are younger, closer to ideal body weight and who have been treated with chemotherapy. Weight gain ranges between 1 to 5 kg, and may be associated with change in body composition with gain in fat mass and loss in lean body mass. Women are unlikely to return to pre-diagnosis weight. Possible mechanisms including inactivity and metabolic changes are explored. Potential interventions are reviewed including exercise, dietary changes and

pharmacologic agents. Although breast cancer prognosis does not appear to be significantly impacted, weight gain has negative consequences on quality of life and overall health. Future studies should explore change in body composition, metabolism and insulin resistance. Avoiding weight gain in breast cancer survivors following initial diagnosis and treatment should be encouraged.

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Key words: Breast cancer; Weight gain; Exercise; Survivorship; Insulin resistance

Core tip: Weight gain occurs in the majority of women following breast cancer treatment, especially those who are younger, closer to ideal body weight and who have been treated with chemotherapy. Although weight gain may be modest, changes are consistent with sarcopenic obesity. Women are unlikely to return to pre-diagnosis weight. Although the degree of weight gain does not appear to significantly alter prognosis, associated changes in metabolism and inactivity are of concern. Interventions should be promoted to avoid weight gain.

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INTRODUCTION

Weight gain following a diagnosis of breast cancer has been reported consistently in women treated for breast cancer, but was an unexpected finding when first described in women undergoing adjuvant chemotherapy by

Dixon and colleagues in 1978^[1]. After subsequent reports confirmed this observation, weight gain was included as a known side effect of adjuvant chemotherapy^[2]. Despite this, most women appear to be inadequately informed about this possibility, as demonstrated by one study reporting concern about treatment-associated weight gain in only 27% of survivors prior to therapy^[3].

WHY IS POST-TREATMENT WEIGHT GAIN OF CONCERN?

Obesity is a global issue associated with increased risk of developing post-menopausal breast cancer^[4] and a worse prognosis at the time of diagnosis^[5]. However, the effect of weight gain following a diagnosis of breast cancer is less well understood. While weight gain following diagnosis does not necessarily lead to obesity or its consequences, any impact on breast cancer prognosis and overall health, patient self-image, or quality of life (QoL) would be an undesirable outcome. These outcomes may be interrelated: weight gain can influence other medical conditions such as diabetes, heart disease, hypertension and hypercholesterolemia that may impact overall survival. For example, Erickson *et al*^[6] found associations between weight change and the incidence of developing diabetes in breast cancer patients in the Women's Healthy Eating and Living (WHEL) study. Perhaps most concerning, patients appear rarely to return to pre diagnosis weight^[7,8] which might be coupled with already well-described body image concerns (in 70% of women under age 50 in one study^[9]). Weight gain and receipt of mastectomy with or without reconstruction are two significant factors impacting body image and quality of life; weight gain following reconstruction can result in asymmetry in the reconstructed breast (autologous tissue) or in the contralateral breast in women who had implant surgery^[10,11]. McInnes *et al*^[12], in an early descriptive study of 50 women receiving chemotherapy, found weight gain of more than 2.5 kg in 62.5% and proposed a relationship between weight gain and QoL, while Ganz and associates identified the influence of weight problems after modern chemotherapy on QoL^[13]. Patients unaware of the possibility of weight gain exhibited distress about this unanticipated outcome^[14]; consequently post-treatment related weight gain is a serious source of concern and needs to be better understood.

DOES IT OCCUR, HOW MUCH, AND IN WHOM?

Weight gain following treatment for early stage breast cancer is a global concern with the phenomena described by investigators spanning the continents. Table 1 provides an overview of studies describing weight gain following a diagnosis of early stage breast cancer selected based on a focus on factors impacting weight gain after diagnosis rather than obesity at diagnosis and includes reports from

a diverse selection of nations. Studies focusing on prognosis related to weight gain are discussed later in the text.

Weight gain after chemotherapy was reported in France, a country that has the lowest rates of obesity in Europe^[15]. Obesity is less prevalent in Asian countries also, yet here too weight gain has been reported following diagnosis^[16,17]. In developing countries, such as Malaysia, 63% of women reported weight gain with a mean weight change of 2.73 kg^[18]. In the United States, weight gain is seen in different ethnic groups. In an exploratory assessment of weight change in a group of 37 African American breast cancer survivors, 47% reported weight gain after treatment^[19]. Vance and colleagues, in their 2011 review, noted that 50%-96% of breast cancer survivors reported weight gain with gains in the range of 2.5-6.2 kg^[20].

Early reports: Pre-anthracycline era

Initial reports describing weight gain in the 1990s described changes of up to 8-10 kg^[21]. The chemotherapy regimens used at the time included longer duration treatments of non-anthracycline containing regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF) and often use of up to one year of prednisone prescribed as an anticancer agent. (More recent steroid use has been limited to dexamethasone employed to avoid chemotherapy-induced emesis.)

Levine *et al*^[22] followed 32 women over a two-year period and reported in 1991 that 63% gained weight with an average gain at two years was of 6 kg. Subsequently Goodwin and colleagues, studying 535 patients treated between 1989 and 1996, determined that adjuvant chemotherapy treatment and onset of menopause were factors predicting weight gain one year after diagnosis^[23]. Most women in this study were treated with mostly non-anthracycline based chemotherapy, however some received anthracycline-containing cyclophosphamide, epirubicin, and fluorouracil (CEF) delivered for the same duration as CMF. Overall, the total group gained a mean of 1.6 kg at one year-84% of patients had gained weight-with no accompanying alteration in waist-hip ratio (WHR); however those receiving any type of chemotherapy gained 2.5 kg (95%CI: 1.8-3.2 kg).

More recent reports: Modern chemotherapy regimens

In more recent reports, covering a period of time during which adjuvant chemotherapy regimens incorporated anthracyclines and/or taxanes, weight gain is reported but generally to a lesser degree than earlier studies. In a prospective study from Turkey, Basaran *et al*^[24] reviewed weight change in 176 women receiving adjuvant chemotherapy between 2003 and 2007, 98% of whom received an anthracycline-based regimen, with or without a taxane; 72% had gained weight (median weight change: 3 kg) at end of year one. Age, menopausal status and comorbidities impacted the degree amount of weight gain.

Makari-Judson and associates conducted a retrospective review of 185 patients with early stage breast

Table 1 Overview of studies describing weight gain in women following a diagnosis of breast cancer

Ref.	Patient numbers	Average weight gain	Study type	Comment
Levine <i>et al</i> ^[22] , 1991	32	6.03 kg at 2 yr	Prospective	63% of women receiving chemotherapy gained weight
Goodwin <i>et al</i> ^[23] , 1999	535	1.6 kg at 1 yr	Prospective	Weight gain associated with chemotherapy and onset of menopause
Demark-Wahnefried <i>et al</i> ^[31] , 2001	53	2.5 kg at 1 yr with chemo 1 kg local rx at 1 yr 2.1 kg at 1 yr with chemo	Prospective	Study group premenopausal only Weight gain associated with chemotherapy Change in body composition (sarcopenic obesity)
Makari-Judson <i>et al</i> ^[8] , 2007	185	2.2 kg at 1 yr	Retrospective	Weight gain associated with chemotherapy Younger women closer to ideal BMI gained most Most received anthracycline chemotherapy
Saqui <i>et al</i> ^[25] , 2007	3088	Measured as relative weight gain > 5% on 65% of chemotherapy recipients	Prospective	Weight gain associated with chemotherapy Both anthracycline and non- anthracycline treatments similar
Heideman <i>et al</i> ^[26] , 2009	271	2 kg at one year	Retrospective	Younger, closer to ideal BMI more likely to gain Weight gain associated with chemotherapy and hormone therapy
Gu <i>et al</i> ^[16] , 2010	5014	2 kg at 18 mo	Prospective	Stage 0-III Weight gain associated with chemotherapy and younger, lower BMI, premenopausal women
Tredan <i>et al</i> ^[15] , 2010	272	3.9 kg at 1 yr	Prospective	All participants received chemotherapy Anthracycline 41%, anthracycline and taxane 58% Gained weight despite dietary counseling
Basaran <i>et al</i> ^[24] , 2011	176	3 kg at 1 yr	Prospective	Weight gain associated with chemotherapy Anthracycline/taxane chemotherapy
Chen <i>et al</i> ^[17] , 2011	4561	1.7 kg dx to 18 mo	Retrospective	Stage 0-IV, patient reported weights, Association of weight gain with younger age, premenopausal, and higher stage. Obese more likely to lose weight
Nissen <i>et al</i> ^[27] , 2011	49	1.95 kg at 1 yr	Prospective	All participants received chemotherapy Weight gain associated with being closer to ideal BMI Overweight/obese women lost weight
Yaw <i>et al</i> ^[18] , 2011	368	2.73 kg reported at study entry (treatment completion)	Retrospective	Patient reported weight gain one year prior to diagnosis and at study entry

BMI: Body mass index.

cancer and evaluated weight change at diagnosis, 1, 2 and 3 years^[8]. Ninety percent of this patient population received an anthracycline-containing regimen [most commonly doxorubicin and cyclophosphamide (AC) for four cycles]. Weight gain at 2 years was greater than one year, plateauing at year 3. Recursive partitioning analysis associated weight gain at year 1 with younger age, closer to ideal BMI and adjuvant chemotherapy. In fact, older and overweight patients receiving chemotherapy tended to lose weight, although these patients constituted a smaller subgroup. Length of chemotherapy, specific chemotherapy regimens, and hormonal therapy were not found to be significant predictors of weight gain. Of patients who had gained weight at year 1, only one in five had returned to baseline by year 3.

Similar results emerged from the WHEL study, which assessed the association between chemotherapy, and tamoxifen and weight gain in 2972 participants^[25]. Relative weight gain rather than an absolute number was reported because the authors considered it less likely to be confounded by initial body weight; a clinically meaningful gain was defined as a greater than 5% gain from baseline to year 1. Chemotherapy was significantly associated with weight gain while tamoxifen was not. Anthracycline *vs* non-anthracycline, or shorter duration of therapy (with

AC) compared with longer [six cycles of cyclophosphamide, doxorubicin and fluorouracil (CAF)] were not significant variables. Weight gain peaked at year 2, and then plateaued. After six years of follow up, only 10% returned to pre diagnosis weight.

Weight gain ranging from 1.95 kg to 4.5 kg has been described in the first year after chemotherapy. In a Dutch study of 271 women, the average gain at one year was 2 kg^[26]. Women who received both chemotherapy and hormonal treatments gained 4.5 kg at one year compared to 2 kg at five years. Nissen and co-investigators followed prospectively 49 chemotherapy-treated women ages 40-54 and found a mean gain of 1.95 kg accompanied by increased body fat; patients who were closer to ideal BMI at diagnosis experienced the greatest weight gains^[27]. In a prospective, observational study of 272 chemotherapy-treated women from France, weight change was reported at 6 and 12 mo post therapy^[15]. Approximately one third of the study population reported that they had experienced weight gain of unspecified amount in the year prior to diagnosis. At one year after diagnosis, 60% of women had gained weight (mean 3.9 kg) despite dietary counseling.

Gu *et al*^[16] reported findings from the Shanghai Breast Cancer Survival Study (SBCSS) of 5014 women with

stage 0-III breast cancer diagnosed between 2002 and 2006 and followed at 6, 18 and 36 mo after diagnosis and determined mean weight changes of 1, 2, and 1 kg respectively. Thirty-seven percent of survivors gained greater than 5% of their baseline body weight at 18 mo, a percentage similar to western studies despite the comparatively low obesity incidence in China. Younger age, premenopausal status, lower BMI at diagnosis, receipt of chemotherapy or radiation were significantly associated variables. In this study, women with co-morbidities and advanced stage were more likely to lose weight at 36 mo. In another report from SBCSS, Chen *et al.*^[17] described 4561 women with stage 0-IV breast cancer, measuring weight, height, and waist and hip circumference at study entry and again at 18 mo. Compared to patient reports from one year prior to diagnosis, there was a gain reported in 61% with a mean gain of 1.7 kg at 18 mo post diagnosis. Thirty-seven percent gained more than 5% of body weight, however 27% lost weight. An association with chemotherapy was found in univariate but not multivariate analyses however, 91% of this cohort received chemotherapy; multivariate analysis identified socio-demographics and lifestyle factors as significant. The inclusion of Stage IV patients in this study is more difficult to interpret since these women may have more comorbidities and poorer performance status.

Anti-estrogen therapy effect

Hormonal treatments, such as tamoxifen and aromatase inhibitors, are less frequently associated with significant weight gain. Tamoxifen use in the P1 prevention trial did not lead to a significant weight gain when compared to placebo^[28]; similarly, in the Women's Healthy Eating and Living (WHEL) study (see above), tamoxifen did not lead to significant changes in weight^[25]. Additionally, aromatase inhibitor usage did not lead to weight changes when compared to tamoxifen in the ATAC trial^[29].

Treatment with radiation does not appear to be an independent factor contributing to weight gain^[8]. Neither treatment with corticosteroids or adjuvant therapy with anti-estrogens appears to be strongly associated. Thus, when taking into consideration all breast cancer treatments, weight gain is most strongly correlated with use of cytotoxic therapies.

Menopause and age effect

Several studies describe an increased tendency toward weight gain in premenopausal women compared to postmenopausal women^[16,23,26]. However, inconsistencies in defining menopause in retrospective studies and the issue of chemotherapy-related amenorrhea complicate the interpretation of this effect on weight gain. Goodwin and colleagues identified the greatest weight gains (mean of 2.65 kg) in premenopausal women who experienced chemotherapy-associated amenorrhea (receiving either CMF or CEF, each delivering 6 mo of cyclophosphamide) and became postmenopausal^[23].

When weight gain is assessed following the use of

regimens less likely to cause chemotherapy-induced amenorrhea, younger age rather than menopausal status appears as a significant risk factor. Makari-Judson *et al.*^[8], employing recursive partitioning analysis found women younger than age 59 gained the most weight with no independent effect of menopausal status. Irwin and colleagues determined associations between weight gain and both younger age and postmenopausal status; this was further refined as younger post-menopausal women gaining significantly more than older post menopausal women and women who developed treatment-associated menopause after diagnosis^[30]. Tredan and associates found no influence of menopausal status on weight gain^[15].

Pre-treatment weight and BMI effect

Women of normal weight or women with closer to ideal BMI were found to be more likely to gain weight after diagnosis in several studies^[8,16,27]. Women with higher BMI ($> 30 \text{ kg/m}^2$) are less likely to gain weight, and some studies have demonstrated that these women are more likely to lose weight^[8,27]. Nissen *et al.*^[27] found women who were close to ideal BMI gained an average of 2 kg while overweight patients lost 1.4 kg, and those who were obese lost 1.9 kg. It is not clear why obese women may be more likely to lose weight following chemotherapy; although it is possible that this is related to co-morbidities, no studies have demonstrated decrease in energy intake however increased walking was identified as a factor favoring weight loss in the Nissen study.

IMPACT OF TREATMENT-ASSOCIATED WEIGHT GAIN

Body composition

Several authors have identified a change in body composition as well as weight gain. Nissen and colleagues conducted a longitudinal, randomized observational study of a physical activity intervention *vs* zoledronic acid and calcium^[27]. While the primary endpoints related to bone density, body composition measurements were made. Forty-nine women aged 40-55 were studied, all within 24 mo of their last menstrual period and all receiving chemotherapy. Chemotherapy included AC in 39%, and AC-T (doxorubicin and cyclophosphamide followed by paclitaxel for a total of 8 cycles of therapy) in 57%. There was no difference in weight gain between those receiving 4 compared with 8 cycles. Only normal ($< 25 \text{ kg/m}^2$) BMI at baseline was predictive of weight gain, with those having normal BMI gaining the most. Women of normal weight had an increase in fat mass in the torso and arms while younger subjects appeared to gain fat mass in arms. Weight gain in this study and in the Demark study is consistent with sarcopenic obesity, namely loss of lean body mass and gain in fat mass^[31].

Freedman and colleagues performed a prospective study of weight and body composition in 20 women with Stage I-III breast cancer receiving modern chemotherapy^[32]. Weight change and measurements of body

composition were compared with age and BMI-matched controls at the start of treatment, immediately after completion of chemotherapy and 6 mo later. Mean pre-treatment BMI was 24.1 kg/m². Six months after completion of chemotherapy, a statistically significant mean weight gain of 1.09 ± 2.46 kg was seen from the immediate post chemotherapy weight; however, this was not statistically significant when compared to the experience of controls. Strikingly, fat mass increased while lean body mass decreased in the women who received chemotherapy but not in the healthy controls. Using computed tomography, an unfavorable change of decrease in the ratio of visceral adipose tissue to subcutaneous fat was detected following chemotherapy. Although this small study did not demonstrate significant weight gain, the deleterious change in body composition is consistent with findings from others and raises concerns about metabolic function.

Cheney and associates, also using computerized tomography to measure changes in weight and abdominal and visceral subcutaneous adipose tissue, assessed 34 women prior to treatment and 6-12 mo later^[33]. Although the findings were not significant in terms of weight change, there was in this study similar to the Freedman study, a significant loss in lean body mass and gain in fat mass.

A small study by Campbell *et al*^[34] followed 10 women undergoing adjuvant chemotherapy and measured resting energy expenditure using dual energy x-ray absorptiometry across cycles of treatment. Although participants did not gain weight, and there was no change in resting energy expenditure, there was an increase in total fat mass. This was felt to be consistent with a decrease in physical activity.

Irwin *et al*^[30] reported results from the Health, Eating, Activity, and Lifestyle (HEAL) study concerning 514 women with stage 0-III breast cancers, almost half of whom used tamoxifen but only 27% received chemotherapy. Women, post treatment, increased their weight by a mean of 1.7 kg and their body fat by 2.1%. Weight increases were greatest for patients who were younger, postmenopausal, had a higher stage of disease, and who reported a decrease in their physical activity. Higher stage of disease may correspond to receipt of chemotherapy, longer duration of treatment and potential longer duration of de-conditioning.

Breast cancer prognosis

Speculation regarding the impact of treatment-related weight gain on breast cancer outcomes has been stimulated in part by the findings of increased incidence and poorer outcomes in patients with greater pretreatment weight or BMI^[35]. While minimizing weight gain is important, clarification of its impact on survival and recurrence outcomes is of critical importance.

The influence of weight gain on prognosis is inconsistent across studies. Camoriano and colleagues examined 646 lymph node-positive breast cancer patients treated prospectively in two clinical trials with extended non-anthracycline chemotherapy, chemo-hormonal

therapy, or observation, and found that premenopausal women who gained more than the median weight gain (of 5.9 kg) experienced significantly higher risk of death that persisted after controlling for other factors (multivariate hazard ratio 1.62); a similar trend in postmenopausal women (median weight gain for observed patients 1.8 kg, and for treated subjects 3.6 kg) was not statistically significant^[36]. Kroenke and associates, reporting results from the Nurses' Health Study (NHS), noted that patients with greater BMI before breast cancer diagnosis had a greater risk of breast cancer recurrence and death if a never-smoker or if premenopausal^[37]. In addition, patients who were never-smokers who gained weight after treatment had a higher risk of breast cancer recurrence and mortality, and all-cause mortality, than did never-smokers who had maintained their pre-treatment weight; significant covariates in the analysis included nodal status and tumor size (the effect of weight gain was more pronounced in patients with small tumors and negative lymph nodes) and baseline BMI [the effect on survival was seen in normal weight but not overweight (BMI ≥ 25 kg/m²) subjects].

In contrast, Caan *et al*^[38] evaluated a prospective cohort of women [1692 with complete data in the Life after Cancer Epidemiology (LACE) study] drawn from the Kaiser Permanente Northern California and Utah Cancer Registries. While similar findings as to patient characteristics associated with weight gain and pretreatment weight associations with mortality were found, no impact of treatment-associated weight gain with mortality was discovered.

A pooled analysis of the LACE, WHEL, NHS, and SBCSS studies was subsequently performed, incorporating 12915 patients with breast cancer diagnosed between 1990 and 2006^[39]. The analysis contained a mixture of patient-reported and measured outcomes. Weight gain after treatment tended to impact all-cause mortality in US but not Shanghai patients; overall there was no impact on breast cancer-specific mortality. However, overall mortality was increased in women who were normal weight who had gained 10% or more (mean 10.5 kg) of their pre-treatment weight when compared to overweight patients. The authors concluded that while evidence for poorer survival associated with weight gain was found, the relative weight gain was substantial. A higher mortality rate was found for patients who lost ≥ 10% of their pretreatment weight, particularly if they were smokers and were leaner prior to treatment. Similarly, Bradshaw and colleagues described a cohort of 1033 women from Long Island, NY, diagnosed with breast cancer between 1996 and 1997 for which complete data were available^[40]. Self-reported weights were employed at age 20, and one year prior to diagnosis, one year after, and at time of follow up questionnaire completion. Mortality-all cause and breast cancer-specific-was increased for women reporting a loss of > 5% or a gain of > 10% compared to pretreatment weight.

While the effect of weight gain on prognosis is vari-

able among studies, it appears to be significant in a subset of women. Investigations that linked obesity with metabolic outcomes and prognosis provide lessons and potential mechanisms. Goodwin and associates found that mean fasting insulin levels were higher in women diagnosed with breast cancer and that this negatively impacted prognosis in this subset^[41]. Similarly, Borugian *et al*^[42] determined that higher fasting insulin levels were associated with poorer prognosis.

Though the amount of weight gain observed as a consequence of chemotherapy regimens is modest on average, it may be sentinel of a more dramatic shift in body composition. Adipose tissue produces a variety of inflammatory cytokines, which may be directly responsible for altering risk^[43,44]. Some of these factors can act directly on the breast epithelium to stimulate the development and expansion of cancer cells. In particular, IL-6 was shown to expand substantially the population of cancer stem cells raising the prospect of recurrences with features of triple negative breast cancers (that is devoid of estrogen and progesterone receptors and HER2/*neu* overexpression) that have, stage for stage, poorer prognoses and fewer effective treatment options when compared to most other breast cancers. These effects may be magnified in the minority of women who suffer substantial weight gain.

PROPOSED MECHANISMS OF WEIGHT GAIN AND CHANGE IN BODY COMPOSITION

Weight gain is ultimately a result of energy surplus due to either increased intake or decreased energy expenditure. It is important to identify possible mechanisms of weight gain in order to advise women on how best to avoid it. While diagnosis- and treatment-related depression may alter eating patterns, most studies have demonstrated that caloric intake actually tends to decrease over the first year after breast cancer diagnosis, suggesting that weight gain is not likely a result of overeating^[45,46].

Decreased energy expenditure was demonstrated by Demark-Wahnefried *et al*^[51] in a study of 36 women receiving chemotherapy and 17 receiving only local treatment. Body composition, resting energy expenditure, dietary intake recalls and physical activity were recorded. Mean weight gain in the local treatment group was 1 kg compared to 2.1 kg in the chemotherapy group. Reduced activity and with no change in caloric intake was identified in the women who gained weight, who exhibited a body composition pattern consistent with sarcopenic obesity (loss of muscle mass and increase in body fat) that has also been suggested by other investigators^[27,47].

Decreased exercise and inactivity appeared to be linked to a higher risk of weight gain in the HEAL study^[48]. The activity levels of 812 patients were measured after diagnosis; chemotherapy patients' exercise time dropped by 3.6 h/wk compared to 1.6 h/wk for

surgery only patients. This was especially evident in patients with BMI > 30 kg/m² that lost 2.8 h of exercise compared to those with BMI < 25 kg/m² that lost only 1.7 h/wk. Women reported being less active 4-12 mo after diagnosis with an average 2-h drop in activity. A 50% reduction in activity level was noted in those treated with chemotherapy, surgery and radiation, compared to a drop of 24% in those treated with surgery alone. Broderick found weight gain and high levels of sedentary behavior in a study of 24 women at completion of chemotherapy with no improvement one year later^[49]. Patients may need encouragement to exercise since chemotherapy treatment may foster a more sedentary lifestyle.

In the study by Demark and colleagues, all of the women treated with chemotherapy experienced treatment-associated amenorrhea, leading to speculation about the role of hormones and menopause in a change of metabolism^[51]. Body composition and waist-hip ratio may change with the onset of menopause; as estrogen levels decrease, body composition changes and fat moves from hip to waist (*i.e.*, "pear-shaped" to "apple-shaped"). Weight gain was associated with increase in estrogen and insulin levels^[50]. Additionally, abdominal fat correlates with cortisol levels.

The results from Makari-Judson and colleagues suggest that insulin resistance may be a contributing factor^[50]. A prospective, observational study of 100 women receiving adjuvant therapy for early stage breast cancer measured BMI, waist hip ratio (WHR), fasting glucose and insulin at diagnosis, 6, 12 and 24 mo. Weight gain was associated with higher baseline WHR and homeostatic model assessment index (HOMA-IR), a measure of insulin resistance. In particular, women receiving chemotherapy had evidence of a deleterious effect on measures of insulin resistance at 6 mo and experienced weight gain. At 12 mo, although these measures had returned to baseline, participants continued to gain weight. By 24 mo, no further weight gain occurred and measures of insulin resistance were similar to baseline.

Even in the absence of weight gain, the change in metabolic profile may have negative implications. Increased adiposity in the abdominal region can be associated with insulin resistance; insulin and adiponectin may influence tumor growth pathways^[51]. Guinan *et al*^[52] described development of metabolic syndrome and insulin resistance in a population of 61 non-diabetic women at surgery and completion of chemotherapy and/or radiation (87% received chemotherapy and 84% radiation therapy). Although there was not a statistically significant gain in weight, percent body fat increased. There was a significant increase in fasting insulin and HOMA-IR which correlated with development of metabolic syndrome. Bell *et al*^[53] demonstrated impaired glucose metabolism in a small study of eight patients early on during chemotherapy and raised concerns about this when compared to non-malignant matched controls.

Genetic polymorphisms associated with obesity include the FTO, fat mass and obesity-associated protein.

These genetic predictors of weight gain were described by Reddy and colleagues in a retrospective analysis of 459 breast cancer patients^[54]. Blood samples were tested for single nucleotide polymorphisms in FTO and adiponectin pathway polymorphisms. In the general population, these genetic factors may contribute to weight gain: FTO decreases satiety and activity levels while adiponectin regulates insulin-like growth factor. The model was enhanced by incorporating environmental interactions demographic and clinical factors predictive for weight gain. Although limited by the fact that some of the weights were self-reported, this model is intriguing for combining genetic predisposition to obesity with the strongest clinical correlates for weight gain, namely, age and baseline BMI.

Weight gain may be a harbinger of more fundamental metabolic changes induced by chemotherapy. In addition to the direct DNA damage in tumor cells that are a result of chemotherapy agents such as anthracyclines, these drugs also interfere with mitochondrial function and ATP production which can have diverse effects^[55]. Cardiomyocytes derive as much as 90% of ATP from mitochondrial oxidative phosphorylation, and thus, are extremely sensitive to the effects of anthracyclines. In animal models, exercise has been shown to mitigate cardiotoxicity^[56] in part alleviating the effects on mitochondrial function^[57]. While overt toxicity may not be evident, other tissues may suffer from impairments. Insulin resistance could result from disruptions in glucose homeostasis in the muscle and liver providing a basis to propose a role for exercise in limiting weight gain.

POTENTIAL INTERVENTIONS TO AVOID WEIGHT GAIN

By identifying predictors of weight gain and populations at higher risk, we can target interventions specifically to those populations. Krogh-Madsen demonstrated in a general population that women who exercised regularly and then stopped for as little as two weeks, experienced a 7% increase in abdominal fat^[58]. There is consistent evidence that physical activity declines after diagnosis and that the reduced energy expenditure is associated with weight and fat gain. In addition to less energy expended for physical activity, more inactivity (*e.g.*, sitting) may contribute to a relative energy surplus and increased adiposity, even in the absence of higher energy intake. Paradoxically, the reduced energy intake observed in some prior studies also lowers daily energy expenditure due to less diet-induced thermogenesis (that is, the energy costs of digesting, absorbing and storing ingested nutrients). Finally, amenorrhea conserves energy output and can contribute to overall energy surplus and weight gain.

The “dose” of physical activity required to offset the deleterious effects of diagnosis and treatment on body weight and adiposity is not well characterized in cancer patients but evidence from the general population suggests it is not trivial. Women in the National Weight Con-

trol Registry^[59], a database of over 6000 people (mainly women who have lost weight and kept it off for more than 6 mo) report close to an hour of physical activity a day; an Institute of Medicine report generally concurred with that recommendation^[60]. A well-controlled study by Jakicic *et al.*^[61] demonstrated that women who performed less than 240 min of exercise per week slowly regained lost weight over the course of a year. An important consideration to prescribing an effective “dose” of exercise is the degree of compensatory behavior in terms of greater inactivity (hopefully minor) and increased energy intake.

Nissen and colleagues found that exercise was a stronger predictor of weight change during chemotherapy than energy intake^[27]. Goodwin and associates found that weight gain could be prevented in a group of 61 breast cancer patients with BMI of 20-35 kg/m² (OR 1.73 for each additional 30 min of exercise per week) however, weight loss required a combination of caloric reduction and exercise^[47].

Data from the SBCSS, demonstrated in a population of mostly normal BMI women at diagnosis (only 32% had BMI > 25 kg/m²) who exercised regularly, (65% reported exercise at baseline and 74% at 18 mo after diagnosis), that exercise did not prevent weight gain in the short run^[17]. The inability to identify a protective effect in this study may have been a consequence of the small numbers of non-exercisers, shorter follow up or because the exercise considered included such low to moderate intensity activities as walking and tai chi.

Exercise may improve metabolic profile and body composition without weight loss. Ligibel and co-investigators studied overweight (BMI > 25 kg/m²) but non-diabetic, breast cancer patients who were at least 3 mo beyond the completion of treatment^[62]. After 16 wk, fasting insulin levels decreased by 28% and hip circumference decreased in the exercise group compared to those receiving usual care, but there was not a significant decrease in WHR and no significant weight loss.

Kim and colleagues performed a meta-analysis of aerobic exercise on body composition in breast cancer patients and included ten trials of exercise interventions in women during (8 trials) or at completion (2 trials) of adjuvant treatment^[63]. The study groups participated in median of three sessions per week, 30-40 min each of moderate exercise and were found to have decreased percent body fat, without significant change in weight or lean body mass. De Backer carried out a review of twelve studies of resistance or resistance plus aerobic training. The studies had different endpoints: one study demonstrated a decrease in WHR, but of those that measured weight, BMI, or fat mass, there was no significant change^[64].

Loprinzi, in a narrative review, described the influence of physical activity, not only on weight gain, but also on other side effects of adjuvant treatment including fatigue, depression, and QoL^[65]. Participation in regular exercise contributed to weight loss and enhanced QoL, mood and energy level. In this review it was suggested, based on the

analyses by Kim and De Backer, that in order to decrease percent body fat, aerobic exercise would be favored over resistance training^[63,64].

Interventions for weight management or loss over the past twenty years were summarized by Demark-Wahnefried^[66]. Twelve studies were included consisting of exercise and dietary counseling. The interventions were not specifically directed towards women who had gained weight after treatment. The recommendation for weight to be an important outcome for overall health, functional status and quality of life was supported even if prognostic impact is inconclusive.

Regardless of whether or not exercise leads to avoiding weight gain after treatment, exercise improves breast cancer prognosis. Holmes found that 3 to 5 h walking per week at average pace (2-2.9 mph for one hour) reduced risk of death by 6% at ten years^[67]. Exercise has additional benefits on mood and QoL independent of weight loss and should be encouraged following recovery from surgery even in the midst of adjuvant treatment. A number of ongoing prospective, intervention trials will help further elucidate the contribution of physical activity to breast cancer prognosis.

In summary, breast cancer patients with a more normal BMI appear more likely to gain weight after treatment compared to overweight and obese survivors. This is in contrast to midlife women in the general population, in whom greater BMI is associated with weight gain^[68]. The weight gain and increase in waist circumference experienced over time in the general population may be prevented with increased participation in regular physical activity; similarly, evidence suggests that exercise has a role in avoiding weight gain in women after a diagnosis of breast cancer.

Obesity at the time of diagnosis is consistently correlated with a poorer prognosis^[5]. This same group of women appears to be more likely to experience unintentional weight loss following chemotherapy. It is not clear if intentional weight loss after a diagnosis of breast cancer affects prognosis. Interventions in addition to exercise may be necessary for obese women to reduce their BMI.

Patients frequently ask about diet alterations as a way of improving their cancer prognosis, but data are scant to make firm, evidence-based recommendations. The Women's Intervention Nutrition Study (WINS) study found that a low fat diet was associated with a 24% reduction in risk of relapse. Patients who were estrogen receptor-negative seemed to benefit more; this subgroup experienced a 42% reduction in relapse^[69]. However, some of this improved prognosis might be attributable to concurrent weight loss.

Goodwin *et al.*^[70] studied the impact of metformin in a group of non-diabetic breast cancer patients with fasting insulin levels at least 45 pmol/L and BMI at diagnosis of at least 28 kg/m². After treatment with metformin for 6 mo, fasting insulin levels decreased by 22%, insulin sensitivity improved by 25% and weight was reduced by

1.9 kg. Ongoing prospective trials are testing this further. Thus, in overweight and obese women, strategies to avoid weight gain may differ from those needed to achieve a healthy weight and may include diet, exercise and pharmacologic interventions.

CONCLUSION

Avoiding weight gain over time is challenging whether following a diagnosis of breast cancer or in the general population. Interventions during chemotherapy may prove especially difficult due to fatigue and other chemotherapy-associated symptoms, but may be necessary to avoid weight gain and improve QoL in both the short- and long-term and enhance prognosis. The two years after treatment may contain "teachable moments" when breast cancer survivors are open to lifestyle counseling. In their 2012 overview, Caan *et al.*^[39] conclude "prevention of weight gain appears to be an evidence based public health goal for breast cancer survivors."

Evidence suggests that following modern day chemotherapy, the modest weight gain experienced by breast cancer survivors does not impact on survival. However, a minority of breast cancer patients gains substantial weight, and further studies on the prognostic effect of change in body composition and measures of metabolism, including insulin resistance will be important. As the numbers of breast cancer survivors continue to grow, promoting strategies to avoid weight gain are supported by the literature and make sense to optimize overall health.

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