

ARTICLE TITLE: Obesity and Adverse Breast Cancer Risk and Outcome: Mechanistic Insights and Strategies for Intervention

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EDUCATIONAL OBJECTIVES:

After reading the article "Obesity and Adverse Breast Cancer Risk and Outcome: Mechanistic Insights and Strategies for Intervention," the learner should be able to:

1. Describe the relationship between obesity and breast cancer development and outcome in premenopausal and postmenopausal women and in hormone receptor positive and hormone receptor negative disease.
2. Appreciate some of the mechanisms that may explain how obesity promotes aggressive breast cancer behavior: obesity increases local and circulating proinflammatory cytokines, which promote tumor angiogenesis and stimulate the most malignant cancer stem cell population to drive cancer growth, invasion, and metastasis.
3. Discuss the implications of lifestyle interventions that could lower breast cancer risk and improve patient outcome.

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Obesity and Adverse Breast Cancer Risk and Outcome: Mechanistic Insights and Strategies for Intervention

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Abstract: Recent decades have seen an unprecedented rise in obesity, and the health impact thereof is increasingly evident. In 2014, worldwide, more than 1.9 billion adults were overweight (body mass index [BMI], 25-29.9 kg/m²), and of these, over 600 million were obese (BMI ≥30 kg/m²). Although the association between obesity and the risk of diabetes and coronary artery disease is widely known, the impact of obesity on cancer incidence, morbidity, and mortality is not fully appreciated. Obesity is associated both with a higher risk of developing breast cancer, particularly in postmenopausal women, and with worse disease outcome for women of all ages. The first part of this review summarizes the relationships between obesity and breast cancer development and outcomes in premenopausal and postmenopausal women and in those with hormone receptor-positive and -negative disease. The second part of this review addresses hypothesized molecular mechanistic insights that may underlie the effects of obesity to increase local and circulating proinflammatory cytokines, promote tumor angiogenesis and stimulate the most malignant cancer stem cell population to drive cancer growth, invasion, and metastasis. Finally, a review of observational studies demonstrates that increased physical activity is associated with lower breast cancer risk and better outcomes. The effects of recent lifestyle interventions to decrease sex steroids, insulin/insulin-like growth factor-1 pathway activation, and inflammatory biomarkers associated with worse breast cancer outcomes in obesity also are discussed. Although many observational studies indicate that exercise with weight loss is associated with improved breast cancer outcome, further prospective studies are needed to determine whether weight reduction will lead to improved patient outcomes. It is hoped that several ongoing lifestyle intervention trials, which are reviewed herein, will support the systematic incorporation of weight loss intervention strategies into care for patients with breast cancer. *CA Cancer J Clin* 2017;67:378-397. © 2017 The Authors. *CA A Cancer Journal for Clinicians* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Keywords: breast cancer, diet and exercise, hormone receptor, immunity, inflammatory cytokines, nuclear factor kappa B (NF-κB), obesity, postmenopausal and premenopausal, sex steroids, weight loss

Practical Implications for Continuing Education

- > Obesity increases postmenopausal ER positive breast cancer risk and mortality.
- > Increased estrogens and inflammatory mediators contribute to the aggressive breast cancer phenotype in obesity.
- > Observational studies support ongoing trials to test whether exercise/weight loss interventions will decrease breast cancer mortality.

Introduction

Obesity, defined as a body mass index (BMI) ≥30 kg/m², affects over 600 million adults worldwide, or 13% of the world population.¹ Obesity is a major health problem of particular importance in developed countries, such as the United States, where

obesity affects more than 36% of adults.² Whereas the impact of obesity on diabetes and heart disease is well known,^{3,4} our understanding of the impact of obesity on cancer is only beginning to change clinical practice. Although it has been known for several decades that obesity is associated with higher cancer mortality,^{5,6} studies that may establish a causal link are still ongoing, and efforts to intervene effectively with weight-reduction strategies in the cancer population have not yet entered routine clinical practice. Recent studies have demonstrated that overweight and obesity are associated with higher risks of adenocarcinoma of the esophagus, gastric cardia, thyroid, pancreas, colon, rectum, endometrium, prostate, gallbladder, ovary, and breast, in addition to multiple myeloma.⁷ Adipose tissue of obese individuals produces inflammatory cytokines and mediators, creating an environment that promotes cancer invasion and metastasis.⁸⁻¹⁰ Because breast cancer is the most common cancer and the second leading cause of cancer death among women in developed countries,¹¹ understanding how obesity impacts this disease has important public health implications. Here, we review how obesity is associated with breast cancer incidence and mortality. We also briefly review the molecular mechanisms in obese adipose tissue that increase inflammation, down-regulate antitumor immunity, and promote tumor angiogenesis, growth, and metastasis. Finally, we also review compelling evidence from observational studies indicating that exercise and weight loss are associated with lower disease risk and better survival, and ongoing studies designed to test whether weight loss intervention will ameliorate survival in patients with breast cancer.

Obesity and Breast Cancer Risk in Premenopausal Women

Overall Risk

Between 2011 and 2014, approximately 35% of premenopausal women ages 20 to 59 years in the United States were obese.² Approximately 20% of breast cancers are diagnosed in women younger than 50 years. An inverse association between obesity and premenopausal breast cancer risk has been reported.¹²⁻¹⁵ A pooled analysis of 7 studies, which included 337,819 women and 4385 invasive breast cancers, reported an inverse association between BMI and premenopausal breast cancer risk when comparing women who had a BMI >31 kg/m² versus those who had a BMI ≤21 kg/m² (risk ratio [RR], 0.54; 95% confidence interval [95% CI], 0.34-0.85).¹⁶ A 9-study meta-analysis also demonstrated an inverse correlation between premenopausal breast cancer risk and obesity (RR, 0.98; 95% CI, 0.97-0.99) per unit increase in BMI.¹⁷ Another large meta-analysis of 20 data sets, which included >2.5 million women and 7930 premenopausal breast cancers, demonstrated that premenopausal breast cancer risk is reduced by approximately 8% per 5 kg/m² BMI increase (RR,

0.92; 95% CI, 0.88-0.97 [$P = .001$]).¹⁸ That meta-analysis was comprised of prospective cohort studies, which provide a stronger study design than case-control studies.

The reduced premenopausal breast cancer risk with obesity is not observed in all studies. A case-control study demonstrated a modestly positive association between obesity and premenopausal breast cancer risk.¹⁹ Moreover, the Breast Cancer Prevention P-1 trial, which included 5864 premenopausal women, found that obesity was associated with higher premenopausal breast cancer risk (hazard ratio [HR], 1.70; 95% CI, 1.10-2.63).²⁰ Differences in the distribution of women with hormone receptor-positive and negative breast cancer in the studies described above might explain these differing results. Furthermore, 2 meta-analyses have reported differences between ethnicities, showing an inverse association between increased BMI and premenopausal breast cancer risk in most of groups, but a positive association in the Asian population.^{18,21}

Hormone Receptor-Positive Premenopausal Breast Cancer

The effect of obesity on premenopausal breast cancer risk differs across disease subtypes. Most studies report that obesity is associated with lower estrogen receptor (ER)-positive breast cancer risk before menopause,^{14,22-25} while others report no association.^{19,26} Two meta-analyses, which included 6106 and 2486 premenopausal women with ER-positive breast cancer, respectively, demonstrated an inverse association between BMI and ER-positive breast cancer before menopause.^{27,28} These observations appear to apply to both the Hispanic and non-Hispanic white populations in the United States.²⁴ Interestingly, a smaller study found that this inverse association between BMI and ER-positive or progesterone receptor (PR)-positive premenopausal breast cancer risk was restricted to white women ($n = 677$; $P = .02$), and there was a null association in African American women ($n = 884$; $P = .89$).²⁹ Figure 1A summarizes forest plots of these studies.^{14,19,22-28}

Hormone Receptor-Negative Premenopausal Breast Cancer

Triple-negative breast cancers (TNBCs) lack expression of ER, PR, and human epidermal growth factor receptor 2 (HER2) and have a very aggressive disease course. In contrast to ER-positive breast cancers, obesity is associated with a higher risk of premenopausal ER-negative breast cancer^{19,22-26} and TNBC in most studies.^{19,30-34} The Cancer and Steroid Hormone (CASH) population-based, case-control study, with 3432 breast cancers, reported a strong positive association between BMI and premenopausal TNBC risk.³⁵ In contrast, an Indian case-control study failed to associate premenopausal ER-negative/PR-negative breast cancer and TNBC with obesity but showed that greater waist circumference and waist-hip ratio was associated with an elevated risk

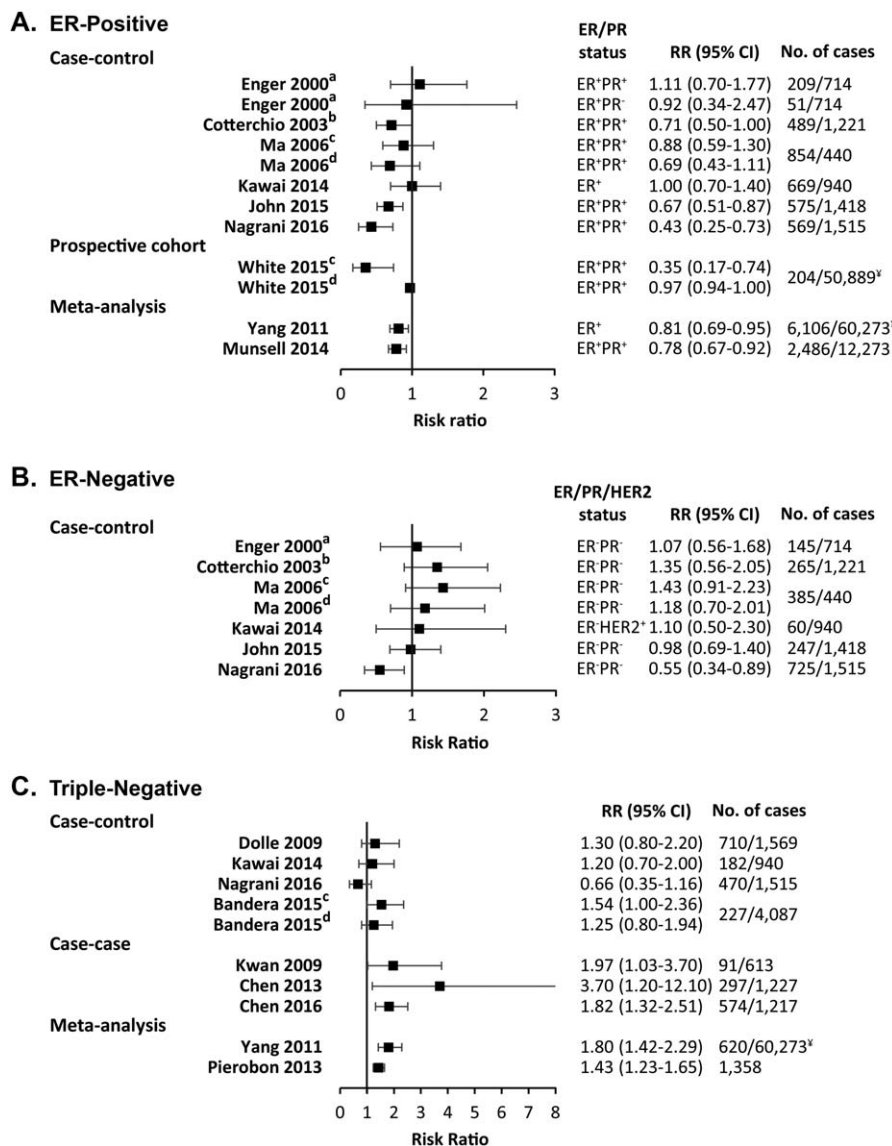


FIGURE 1. Forest Plots for the Association of Premenopausal Breast Cancer Risk and Body Mass Index. Body mass index (BMI) is compared between obese (BMI >30 kg/m²) and normal-weight (BMI <25 kg/m²) women for (A) estrogen receptor-positive (ER⁺) or/and progesterone receptor-positive (PR⁺) breast cancer from case-control studies (Kawai et al,¹⁹ Cotterchio et al,²² Ma et al,²³ John et al,²⁴ Nagrani et al,²⁵ and Enger et al²⁶), a prospective cohort study (White et al¹⁴), and meta-analyses (Yang et al²⁷ and Munsell et al²⁸); (B) ER-negative/PR-negative (ER⁻PR⁻) and human epidermal growth factor 2-positive (Her2⁺) or unknown breast cancer from case-control studies (Kawai et al,¹⁹ Cotterchio et al,²² Ma et al,²³ John et al,²⁴ Nagrani et al,²⁵ and Enger et al²⁶); and (C) triple-negative breast cancer from case-control studies (Kawai,¹⁹ Nagrani,²⁵ Dolle et al,³¹ and Bandera et al³³), case-case-studies (Kwan et al,³⁰ Chen et al,³² and Chen et al³⁴), and meta-analyses (Yang et al²⁷ and Pierobon et al³⁶). Risk ratio (RR) estimates include odds ratios, rate ratios, and hazard ratios. No. of cases indicates the number of premenopausal breast cancer cases/controls (for case-control studies) or premenopausal breast cancer cases/total population (prospective cohort, case-case studies, and meta-analyses). ¥ indicates the total number of women (not only premenopausal). Superscript letters indicate studies that compared: ^awomen with a BMI ≥27.1 kg/m² versus < 21.7 kg/m²; ^bwomen with a BMI >27 kg/m² versus ≤25 kg/m²; ^cwomen with grade I obesity (30-34.99 kg/m²) versus normal-weight women; and ^dwomen with grade II and III obesity (>35 kg/m²) versus normal-weight women. 95% CI indicates 95% confidence interval.

of premenopausal TNBC (*P* < .001).²⁵ Two meta-analyses of 620 women²⁷ and 1358 women³⁶ with TNBC reported an 80% and 43% higher risk of developing TNBC in obese premenopausal women, respectively. Figures 1B and 1C summarize forest plots of these studies.^{19,22,23,25-27,30-34,36}

Inflammatory Premenopausal Breast Cancer

Inflammatory breast cancer (IBC) has a rapid, aggressive disease course.³⁷ A recent case-control study from the

Breast Cancer Surveillance Consortium database (1994-2009) showed that obesity is associated with higher premenopausal IBC risk (RR, 3.62; 95% CI, 1.30-10.04) for all cases and for those with ER-positive (RR, 3.53; 95% CI, 1.20-10.39) and ER-negative (RR, 4.67; 95% CI, 1.45-15.02) IBC.³⁸ An older case-comparison study that included 68 IBCs also reported that a BMI > 26.65 kg/m² was associated with an up to 4-fold higher risk of premenopausal IBC.³⁹

Obesity and Breast Cancer Risk in Postmenopausal Women

Overall Risk

The prevalence of obesity among US women ages 60 years and older between 2011 and 2014 was approximately 39%.² Metabolic syndrome has increased with the rise of obesity⁴⁰ and is significantly associated with a higher postmenopausal breast cancer risk.⁴¹ Obesity consistently associates with higher postmenopausal breast cancer risk in many studies.^{14,16,22,42-45} The Million Women Study followed 1.2 million UK women ages 50 to 64 years for a mean of 5.4 years, including 45,037 with breast cancer, and identified a nearly 30% higher risk of developing postmenopausal breast cancer with obesity (RR, 1.29; 95% CI, 1.22-1.36).⁴⁶ Similarly, a meta-analysis of 34 studies comprising >2.5 million women, including 23,909 postmenopausal breast cancers, indicated that postmenopausal breast cancer risk was positively associated with each 5-kg/m² increase in BMI (RR, 1.12; 95% CI, 1.08-1.16 [$P < .0001$]).¹⁸ The association of obesity with a higher risk of postmenopausal breast cancer is greater in, and may be limited to, women who have not used menopausal hormone therapy (HT).⁴⁷⁻⁴⁹

Hormone Receptor-Positive Postmenopausal Breast Cancer

The association of postmenopausal breast cancer risk with obesity may be limited to ER-positive breast cancers. Obesity associates most strongly with postmenopausal hormone receptor-positive breast cancer risk in many prospective cohort studies and case-control studies.^{14,22,26,42,43,48-55} This association was stronger in women from Asia-Pacific than in those from North America, Europe, and Australia.¹⁸ Furthermore, an increase in BMI after age 18 years is associated with an elevated risk of postmenopausal ER-positive/PR-positive breast cancer.^{26,49,54} Weight gain was associated with a higher risk of ER-positive/PR-positive breast cancer after menopause only in Hispanics who did not receive HT and who had a normal BMI as young adults.⁵³ Notably, an Indian case-control study reported that obesity was associated with an elevated risk of ER-positive/PR-positive breast cancer only 10 years after menopause.²⁵ ER-positive/PR-positive postmenopausal breast cancer risk is also associated with higher waist circumference and waist-to-hip ratio.^{14,25,52,54} The higher ER-positive/PR-positive breast cancer risk with obesity is most notable among women who never used HT.^{42,49,56} A meta-analysis of 89 studies from 1980 to 2012, which included 59,185 women, demonstrated that the increment in postmenopausal ER-positive/PR-positive breast cancer risk with obesity (RR, 1.39; 95% CI, 1.14-1.70) was greater among HT never users (RR, 1.42; 95% CI, 1.30-1.55) than among

HT users (RR, 1.18; 95% CI, 0.98-1.42).²⁸ In contrast to ER-positive/PR-positive cancers, several studies indicate that the risk of ER-positive/PR-negative cancer is not higher with obesity.^{26,42,43,48-51,54} This subset of cancers has a more aggressive phenotype and more often has a luminal B than luminal A gene expression profile.⁵⁷

In summary, a large body of evidence indicates that, although obesity is inversely associated with receptor-positive breast cancer development before menopause, it is a risk factor for postmenopausal hormone receptor-positive breast cancer. Figures 2A and 2B presents forest plots of these studies.^{14,22,23,25,26,28,42,43,48-52,54,55}

Hormone Receptor-Negative Postmenopausal Breast Cancer

The association of obesity with the risk of ER-negative breast cancer and TNBC appears to differ before and after menopause. Although obesity is associated with higher risk before menopause, the risk of ER-negative breast cancer and TNBC is minimally or inversely associated with obesity after menopause. A Swedish mammography cohort of 51,823 postmenopausal women found an inverse association between obesity and hormone receptor-negative breast cancer,⁴⁸ as did other studies.^{25,33,48-50,53-55} In contrast, others reported a null or modest positive association,^{14,25,26,42,43,52,58} and few reports demonstrated a significant association between obesity and the risk of ER-negative/PR-negative breast cancer after menopause.^{22,51} Despite these conflicting reports, 2 large meta-analyses, including 2302 ER-negative/PR-negative breast cancers and 1883 TNBCs, respectively, both reported a null association between obesity and the risk of postmenopausal hormone receptor-negative breast cancer.^{28,36} Forest plots in Figures 3A and 3B summarize these studies.^{14,22,23,25,26,28,33,36,42,43,48-52,54,55,58}

Inflammatory Postmenopausal Breast Cancer

In premenopausal women, IBC risk after menopause is 3-fold to 5-fold higher with obesity.³⁹ A recent case-control study including 435 patients with IBC and 72,096 controls demonstrated that obesity was associated with a higher risk of IBC after menopause (RR, 3.75; 95% CI, 1.92-7.34).³⁸ Another case-control study reported that overweight and obesity were associated with higher IBC risk for premenopausal and postmenopausal women (odds ratio [OR], 3.77; 95% CI, 2.00-7.08).⁵⁹

Weight Loss and Breast Cancer Risk

Weight loss in adulthood has been associated with a lower breast cancer risk. Prospective cohort studies show that weight loss after age 18 years⁶⁰ or after menopause⁶¹ are both associated with a reduction in the risk of postmenopausal breast cancer, with stronger associations in women

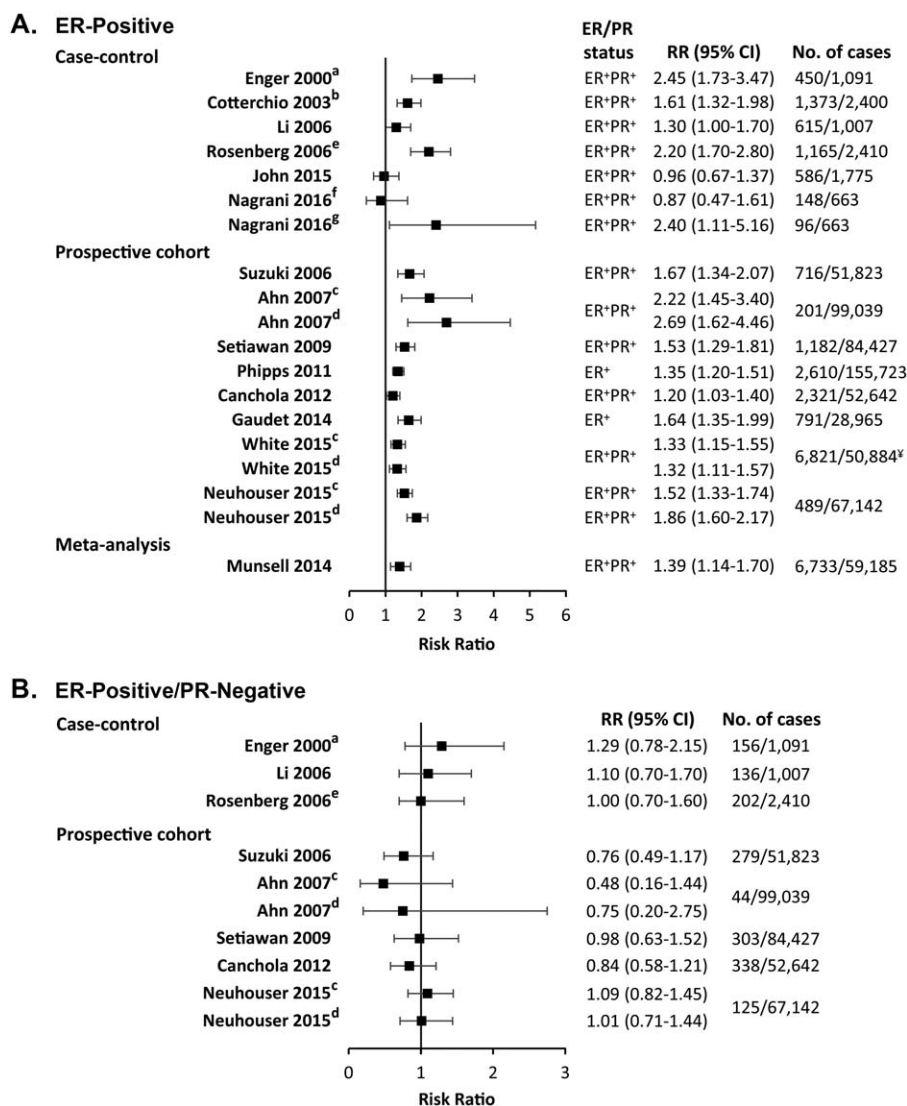


FIGURE 2. Forest Plots for the Association of Postmenopausal Breast Cancer Risk and Body Mass Index. Body mass index (BMI) is compared between obese (BMI > 30 kg/m²) and normal-weight (BMI < 25 kg/m²) women for (A) estrogen receptor-positive (ER⁺) and progesterone receptor-positive (PR⁺) or unknown breast cancer from case-control studies (Cotterchio et al,²² John et al,²³ Nagrani et al,²⁵ Enger et al,²⁶ Rosenberg et al⁵¹, and Li et al⁴²), prospective cohort studies (White et al,¹⁴ Neuhouser et al,⁴³ Suzuki et al,⁴⁸ Ahn et al,⁴⁹ Setiawan et al,⁵⁰ Phipps et al,⁵² Canchola et al,⁵⁴ and Gaudet et al⁵⁵), and a meta-analysis (Munsell²⁸); and (B) ER⁺ PR-negative (PR⁻) breast cancer from case-control studies (Enger et al,²⁶ Li et al,⁴² and Rosenberg et al⁵¹) and prospective cohort studies (Neuhouser et al,⁴³ Suzuki et al,⁴⁸ Ahn et al,⁴⁹ Setiawan et al,⁵⁰ and Canchola et al⁵⁴). Risk ratio (RR) estimates included odds ratios, rate ratios, and hazard ratios. No. of cases indicates the number of postmenopausal breast cancer cases/control (case-control studies) or postmenopausal breast cancer cases/total population (prospective cohort studies and meta-analysis). ¥ indicates the total number of women (not only premenopausal). Superscript letters indicate studies that compared: ^awomen with a BMI ≥ 27.1 kg/m² versus ≥ 21.7 kg/m²; ^bwomen with a BMI > 27 kg/m² versus ≤ 25 kg/m²; ^cwomen with grade I obesity (30-34.99 kg/m²) versus normal-weight women; ^dwomen with grade II and III obesity (>35 kg/m²) versus normal-weight women; ^ewomen with a BMI ≥ 28.3 kg/m² versus < 22.2 kg/m²; ^fwomen who were postmenopausal for less than 10 years; and ^gwomen who were postmenopausal for 10 years or more. 95% CI indicates 95% confidence interval.

who never used postmenopausal HT.⁶⁰ Two prospective cohort studies that included 4047 and 16,038 obese patients, respectively, reported that bariatric surgery resulted in a weight reduction and was associated with reduced all-cancer incidence in obese women but had no significant effects in men.^{62,63} Similarly, a prospective cohort study that included 1035 patients who underwent bariatric surgery and 5746 controls reported a reduced 5-year incidence of breast cancer after bariatric surgery⁶⁴

Weight Gain After Breast Cancer

From 50% up to 96% of women with breast cancer gain weight during treatment, and even those who do not usually gain weight over the next 3 years.^{65,66} Weight gain is greater in premenopausal women, those treated with chemotherapy, and women who are overweight at diagnosis.⁶⁷ Most large observational studies show that weight gain postdiagnosis is inversely associated with disease-free survival.⁶⁵⁻⁶⁹ Weight gain > 5.9 kg after diagnosis is associated with a 1.6-fold

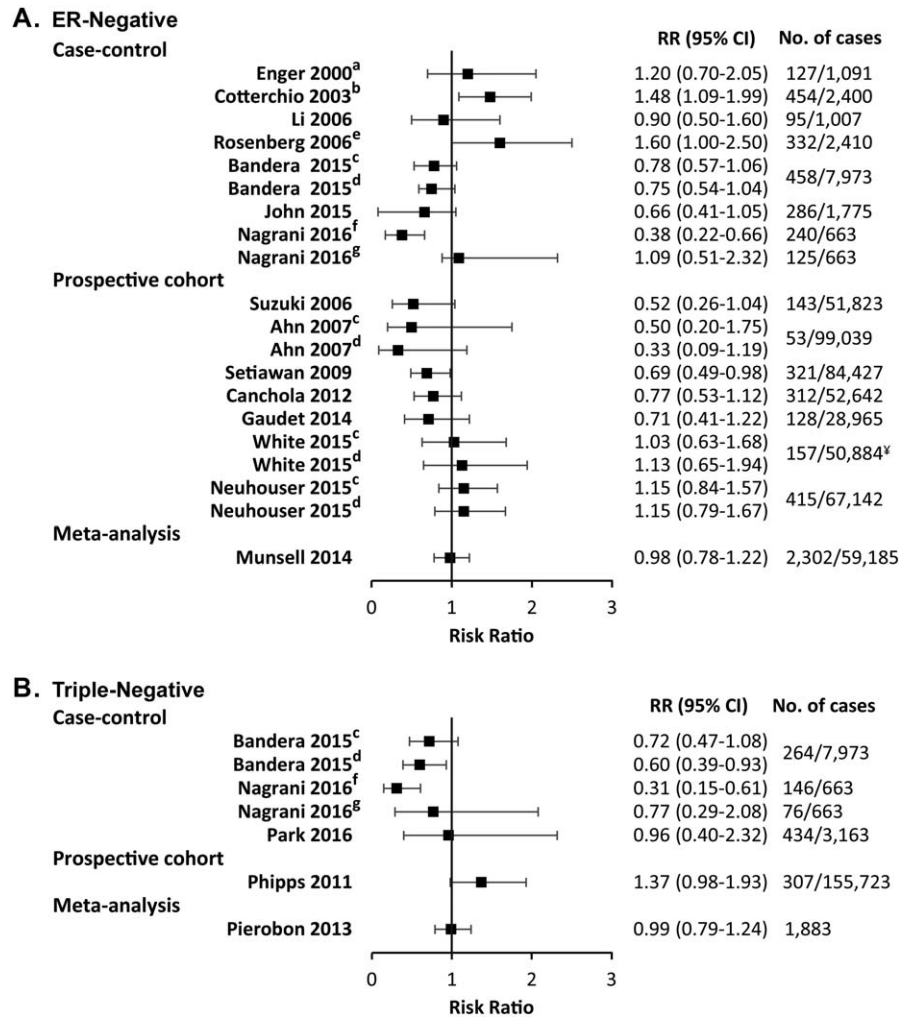


FIGURE 3. Forest Plots for the Association of Postmenopausal Breast Cancer Risk and Body Mass Index. Body mass index (BMI) is compared between obese (BMI > 30 kg/m²) and normal-weight (BMI < 25 kg/m²) women for (A) estrogen receptor-negative/progesterone receptor-negative and human epidermal growth factor receptor 2-unknown breast cancer from case-control studies (Cotterchio et al,²² John et al,²³ Nagrani et al,²⁵ Enger et al,²⁶ Rosenberg et al,⁵¹ Bandera et al,³³ and Li et al,⁴²), prospective cohort studies (White et al,¹⁴ Neuhouser et al,⁴³ Suzuki et al,⁴⁸ Ahn et al,⁴⁹ Setiawan et al,⁵⁰ Canchola et al,⁵⁴ and Gaudet et al,⁵⁵), and a meta-analysis (Munsell et al²⁸); and (B) triple-negative breast cancer from case-control studies (Nagrani et al,²⁵ Bandera et al,³³ and Park et al⁵⁸), a prospective cohort study (Phipps et al⁵²), and a meta-analysis (Pierobon et al⁵⁶). Risk ratio (RR) estimates included odds ratios, rate ratios, and hazard ratios. No. of cases indicates the number of postmenopausal breast cancer cases/control (case-control studies) or postmenopausal breast cancer cases/total population (prospective cohort studies and meta-analysis). † indicates the total number of women, not only those who were premenopausal. Superscript letters indicate studies that compared: ^awomen with a BMI ≥ 27.1 kg/m² versus <21.7 kg/m²; ^bwomen with a BMI > 27 kg/m² versus ≤ 25 kg/m²; ^cwomen with grade I obesity (30-34.99 kg/m²) versus normal-weight women; ^dwomen with grade II and III obesity (>35 kg/m²) versus normal-weight women; ^ewomen with a BMI ≥ 28.3 kg/m² versus <22.2 kg/m²; ^fwomen who were postmenopausal for less than 10 years; and ^gwomen who were postmenopausal for 10 years or more. 95% CI indicates 95% confidence interval.

higher risk of death.⁶⁸ Nichols et al reported that each 5-pound weight gain postdiagnosis was associated with a 13% increase in breast cancer-specific mortality and a 12% increase in all-cause mortality.⁶⁷ Weight gain after diagnosis is also associated with greater incidence and severity of complications after primary and reconstructive surgery, increased fatigue, more arthralgias, and up to twice the rate and severity of hot flashes.⁶⁶

Increased Breast Cancer Mortality in Obese Patients

Obesity is associated with a shorter time to disease recurrence and greater mortality for both premenopausal and

postmenopausal breast cancer. The American Cancer Society's Cancer Prevention Study II followed 495,477 women from 1982 to 1998 and reported a positive association between BMI and breast cancer mortality ($P < .001$): Women who had a BMI > 40 kg/m² had a greater than 2-fold higher risk of mortality compared with those who had a BMI from 18 to 24.9 kg/m² (RR, 2.12; 95% CI, 1.41-3.19).⁶ Other studies showed that obesity was associated with larger tumors, positive lymph node status, shorter distant disease-free interval and overall survival,⁷⁰⁻⁷² and triple-negative tumor subtype.⁷¹ A recent meta-analysis of 82 studies that included 213,075 breast cancer survivors confirmed that obesity was associated with greater breast cancer mortality (RR, 1.41; 95% CI, 1.29-1.53) in both

premenopausal (RR, 1.75; 95% CI, 1.26-2.41) and postmenopausal (RR, 1.34; 95% CI, 1.18-1.53) women.⁷³ In the Multiethnic Cohort Study, obesity was associated with higher all-cause and breast cancer-specific mortality irrespective of ethnicity in American women older than 50 years.⁷⁴ In contrast, the Contraceptive and Reproductive Experiences population-based, case-control study demonstrated that obesity was associated with increased breast cancer-specific mortality in white women, but not in African American women.⁷⁵

Outcome of Hormone Receptor-Positive Breast Cancer

Several studies have evaluated obesity and receptor-positive breast cancer outcome. Analyses of data from 3385 women with hormone receptor-positive breast cancers from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 Protocol indicated that obese women had greater all-cause mortality (HR, 1.31; 95% CI, 1.12-1.54).⁷⁶ Among 6885 women from 3 US clinical trials, a BMI ≥ 30 kg/m² was associated with decreased disease-free survival ($P = .008$) and overall survival ($P = .002$) in patients with hormone receptor-positive breast cancer.⁷⁷ A meta-analysis of 13 studies indicated that the adverse effects of obesity did not differ by hormone receptor or menopausal status. In that study, obesity was associated with increased breast cancer-specific mortality among women who had hormone receptor-positive breast cancer (HR, 1.36; 95% CI, 1.20-1.54), including both premenopausal (HR, 1.23; 95% CI, 1.07-1.42) and postmenopausal (HR, 1.15; 95% CI, 1.06-1.26) women.⁷⁸

Outcome of Hormone Receptor-Negative Breast Cancer

The 10% to 20% of women who have breast cancers of the TNBC subtype have a shorter survival than most other breast cancer subtypes.³⁶ Although several studies have demonstrated that the risk of TNBC is increased with obesity, particularly before menopause, the association of obesity with outcomes in women with TNBC is more controversial. Among patients with TNBC, obesity is associated with greater size ($P = .02$), stage ($P = .001$), and grade ($P = .01$).⁷⁹ In a retrospective study of 418 US patients with TNBC, 164 of whom were obese, no effect of obesity on disease-free or overall survival was observed.⁸⁰ In contrast, another study that included 107 patients with TNBC reported shorter disease-free survival ($P = .006$) and overall survival ($P = .015$) among obese patients.⁸¹ Given the small size of these studies, and because TNBC itself is associated with a shorter time to recurrence and death, larger studies or meta-analyses will be needed to determine whether obesity is associated with poorer survival in women with TNBC.

Outcome of IBC

IBC accounts for 2.5% of breast cancers and is characterized by rapid local and distant metastasis, younger age, and $<5\%$ long-term survival.³⁷ A study of 706 patients who had stage III locally advanced breast cancers, including 111 with IBC and 595 without IBC, showed that a BMI >25 kg/m² was associated with worse disease-free and overall survival ($P = .001$), but the difference did not reach significance in the IBC subset ($P = .45$).⁸² In contrast, another study of 177 patients with IBC showed that obesity was associated with worse survival only in the postmenopausal subgroup (HR, 1.86; 95% CI, 1.02-3.4).⁸³

The Influence of Obesity on Breast Cancer Response to Chemotherapy and Radiation Therapies

Chemotherapy and radiation doses in obese patients have been a matter of controversy. Comorbidities in obese patients with breast cancer have historically led to reduced chemotherapy dosing. Many centers routinely limit body surface area to 2 m² for calculations of chemotherapy dosing to reduce toxicity,⁸⁴ but decreased dose intensity of adjuvant chemotherapy has been associated with poorer outcomes.⁸⁵ A community oncology practice survey revealed consistent underdosing of obese patients for chemotherapy, and dose reductions in radiation therapy also limit treatment efficacy and outcome.⁸⁵ Notably, dosing chemotherapy in obese patients based on actual body weight does not increase adverse effects. A retrospective analysis identified no excess toxicity in obese patients with breast cancer who received full-dose adjuvant chemotherapy compared with nonobese patients. Obese women who received reduced chemotherapy doses had worse survival.⁸⁶ The American Society of Clinical Oncology guidelines recommend using actual body weight when calculating chemotherapy dosing regardless of BMI.⁸⁷

Obese Adipose Tissue

Hypoxia, Adipokines, and Inflammation in Obese Adipose Tissue

The adipose tissue is an endocrine organ that releases bioactive adipokines, including >50 different cytokines, chemokines, and hormone-like factors.⁸ In lean adipose tissue, mature adipocytes secrete mainly the antimitogenic hormone, adiponectin, and low levels of proangiogenic and promitogenic leptin.^{88,89} In obesity, preadipocyte to adipocyte maturation is decreased, yielding more preadipocytes,⁹⁰ which secrete high levels of leptin.^{88,89} As adipose tissue expands in obesity, oxygen demand exceeds supply, and hypoxia induces adipocyte gene expression changes, including those of inflammation-related adipokines.⁹¹

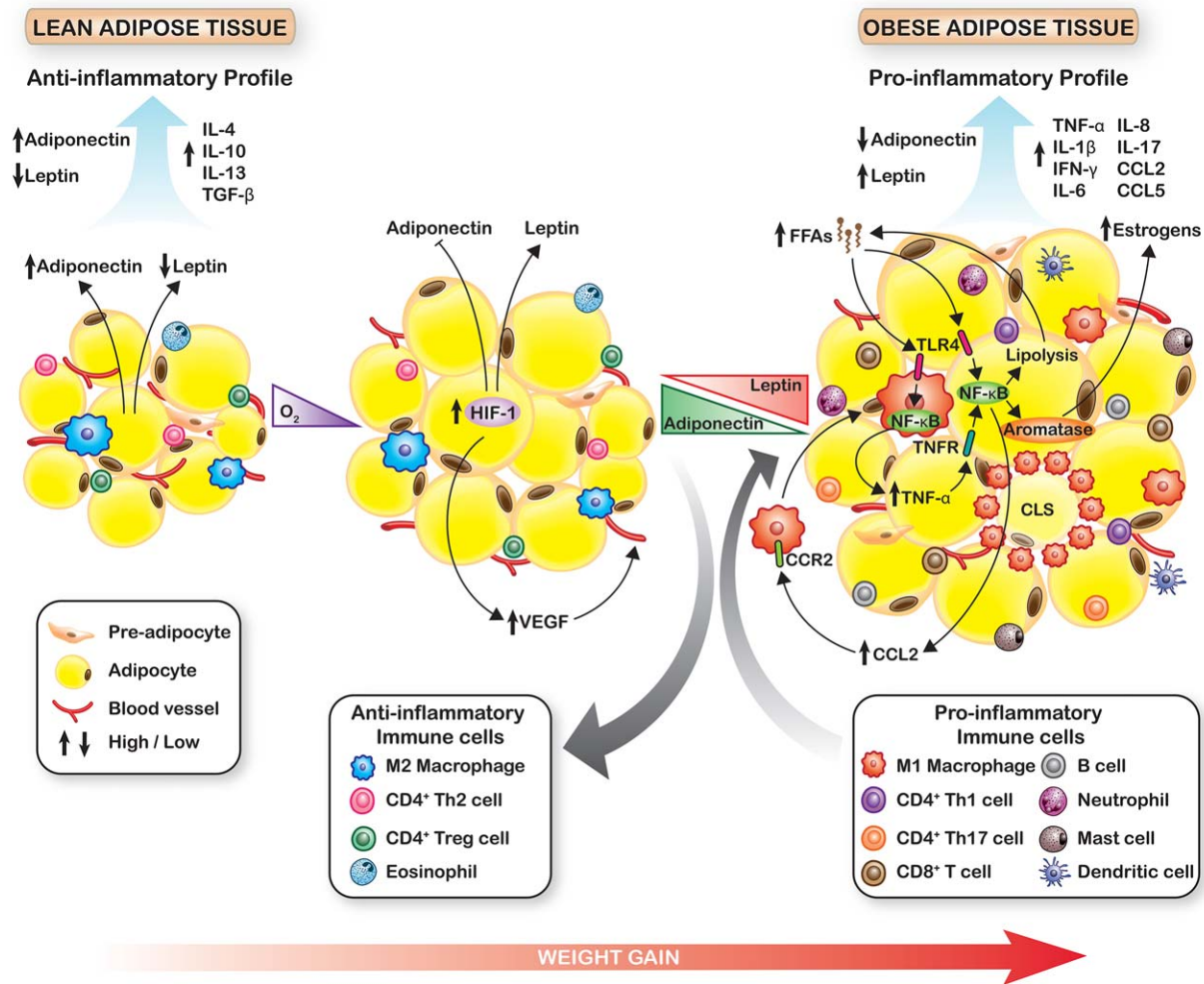


FIGURE 4. Changes in Adipose Tissue During Weight Gain. During obese adipose tissue expansion, preadipocyte differentiation is impaired, and hypoxia activates hypoxia-inducible factor 1 (HIF-1) to decrease adiponectin expression and upregulate leptin. HIF-1 also promotes angiogenesis by turning on vascular endothelial growth factor (VEGF). The altered leptin:adiponectin ratio promotes proinflammatory immune cell infiltration and the formation of crown-like structures (CLS). Dying adipocytes release free fatty acids (FFAs), which bind toll-like receptor 4 (TLR4) on macrophages and adipocytes to activate nuclear factor kappa B (NF- κ B) and upregulate secretion of inflammatory cytokines, including tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), IL-8, chemokine (C-C motif) ligand 5 (CCL5), and CCL2. These cytokines promote lipolysis and FFA release to further activate the NF- κ B pathway, which also increases aromatase expression and estrogen synthesis. CCL2 and other cytokines serve as chemoattractants to recruit monocytes/macrophages. These feed-forward loops establish a chronic inflammatory milieu in obese adipose tissue. IFN- γ indicates interferon gamma; TGF- β , transforming growth factor beta; TNFR, tumor necrosis factor receptor; Th1, T-helper 1 cells; Th17, T-helper 17 cells; Treg, T-regulatory cells.

Hypoxia-inducible factor-1 (HIF-1) acts as a molecular oxygen sensor to alter gene expression in hypoxia.⁹¹ HIF-1 directly upregulates expression of leptin and vascular endothelial growth factor (VEGF) and inhibits adiponectin expression (Fig. 4).⁹¹⁻⁹³

In lean adipose tissue, the anti-inflammatory cytokines interleukin 4 (IL-4), IL-10, IL-13, and transforming growth factor beta 1 (TGF- β 1) are produced by immune cells, including M2 macrophages, eosinophils, CD4-positive T helper 2 (Th2) cells, and regulatory T (Treg) cells (Fig. 4).⁹⁴⁻⁹⁶ Adipokines in obese adipose tissue, particularly leptin, alter the immune environment.^{94,97} Adipose tissue macrophages are increased and shift from the anti-inflammatory M2 subtype to proinflammatory M1 macrophages, which secrete tumor necrosis factor alpha (TNF- α),

IL-1 β , IL-6, IL-8, chemokine (C-C motif) ligand 2 (CCL2), and VEGF.^{94,95} T-lymphocyte populations change in obesity. Proinflammatory CD8-positive T cells and CD4-positive Th1 and Th17 cells, which produce interferon gamma (IFN- γ) and IL-17A, are increased, whereas anti-inflammatory CD4-positive Th2 and Treg cells are reduced.⁹⁴⁻⁹⁶ Infiltration of neutrophils, mast cells, mature B cells, and immature dendritic cells (DCs), which produce proinflammatory TNF- α , IL-6, and IL-8, increases, and eosinophils that release anti-inflammatory IL-4 and IL-13 are reduced (Fig. 4).⁹⁴⁻⁹⁶

Obesity, Inflammation, and the NF- κ B Pathway

Inflammation in obese adipose tissue is activated and maintained by the nuclear factor kappa B (NF- κ B) pathway.⁹⁸

The increased inflammatory cytokines in obese fat induce lipolysis, releasing free fatty acids (FFAs), which stimulate toll-like receptors (TLRs)⁹⁹ on adipocytes¹⁰⁰ and macrophages¹⁰¹ to turn on the NF- κ B pathway.¹⁰⁰ NF- κ B activates expression of genes encoding inflammatory cytokines, including TNF- α , IL-1 β , IL-6, IL-8 and CCL2,^{8,98} which, in turn, feed-forward to further activate NF- κ B.^{88,98,102} Circulating monocytes infiltrate adipose tissue, attracted by CCL2 via their surface receptor CCR2, and differentiate into macrophages (Fig. 4).¹⁰³

Estrogen Synthesis in Obese Adipose Tissue

Estrogen biosynthesis after menopause is catalyzed largely in adipose tissue, through the conversion of adrenal androgens into estrogens by aromatase.¹⁰⁴ Several cellular and molecular changes in obese adipose tissue alter estrogen biosynthesis and metabolism. NF- κ B pathway activation leads to an increase in aromatase expression in breast adipocytes and hence to greater estrogen synthesis (Fig. 4).^{8,105} Similarly, several cytokines that are upregulated in obese adipose tissue, such as TNF- α and IL-6, stimulate aromatase activity.¹⁰⁶ In obese mammary fat, microscopic foci of dying adipocytes surrounded by macrophages, called crown-like structures, exhibit increased aromatase activity.¹⁰⁷ In postmenopausal women, BMI correlates positively with serum estrone and estradiol levels and negatively with sex hormone-binding globulin levels, leading to an increase in total bioavailable estrogen.^{104,108} Compared with women who have a BMI <22.5 kg/m², obese women have an 86% increase in circulating estradiol, a 60% increase in estrone, and a 20% increase in testosterone.¹⁰⁸

Obese Adipose Tissue Creates a Pro-Oncogenic Environment

Obesity, Insulin, Insulin-Like Growth Factor-1, and the Leptin Adiponectin Reversal

Patients with the metabolic syndrome have increased levels of circulating insulin and insulin-like growth factor-1 (IGF-1) and a greater risk of breast cancer.¹⁰⁹ Elevated fasting insulin is associated with poor breast cancer outcome.¹¹⁰ Hyperinsulinemia reduces sex hormone-binding globulin levels and increases estrogen bioavailability, thereby increasing breast cancer risk.¹¹¹ These factors have been associated with poorer outcomes in patients with breast cancer.^{109,112} The high levels of TNF- α and IL-6 in obese fat impair insulin receptor β subunit activation and decrease glucose transport and fatty acid metabolism,^{113,114} mediating insulin resistance and upregulating insulin and IGF-1 levels. Because IGF-1 actions are mediated by IGF-1 receptor (IGF-1R), which is frequently overexpressed in breast cancers,¹¹⁵ and IGF-1 is a potent breast cancer mitogen, it has been posited that the

increased levels of circulating insulin and IGF-1 in obesity make an important contribution to the increased breast cancer risk and mortality in obese individuals.¹¹⁶

In obese adipose tissue, the adiponectin:leptin ratio is decreased. A recent case-control study showed that the highest serum leptin quartile was associated with a higher postmenopausal breast cancer risk relative to the lowest quartile (HR, 1.94; 95% CI, 1.37-2.17).¹¹⁷ This may relate to the effects of leptin to upregulate both the estrogen and insulin-signaling pathways.^{118,119} Leptin and leptin receptors are frequently increased in breast cancers and both are associated with poor outcome.¹²⁰⁻¹²² High serum and intra-tumor leptin levels are also associated with poor breast cancer outcome.¹²² In contrast, adiponectin is reduced in obesity, and this also constitutes a risk factor for postmenopausal breast cancer.^{123,124}

Inflammation and Cancer

Chronic NF- κ B activation in obese adipose tissue not only drives obesity-mediated inflammation but also stimulates antiapoptotic genes and breast cancer proliferation, invasion, angiogenesis, and metastasis.¹²⁵ Recent work suggests that NF- κ B mediates tumor progression through proinflammatory cytokines. Several proinflammatory/proangiogenic cytokines, including IL-6, IL-8, CCL2, CCL5, and VEGF, that are elevated in obese fat^{8,126} are associated with a poor prognosis when overexpressed in primary breast cancers and, with greater stage and grade, and with poor outcomes.¹²⁷⁻¹²⁹ Notably, IL-6 levels in peritumoral fat are higher than in all other breast quadrants¹⁰⁶ and increase with increasing tumor size and lymph node involvement.¹⁰ Recent work has shown that contact between breast cancer cells and adipocytes induces both cell types to secrete more IL-6, IL-8, CCL2, and CCL5 and the interaction of cancer cells with cancer-associated adipocytes promotes tumor invasion and metastasis.^{9,10} Adipose tissue contributes up to 35% of circulating IL-6,¹³⁰ and the increase in serum IL-6 after menopause^{131,132} may contribute to increased breast cancer risk and tumor progression. Elevated IL-8 from cancer cells, surrounding adipocytes, endothelial cells, infiltrating neutrophils, and tumor-associated macrophages (TAMs) promotes angiogenesis, tumor growth, metastasis, and chemotherapy resistance (Fig. 5).^{8,9,128} CCL2 and CCL5 also mediate tumor-promoting cross-talk between cancer cells and the microenvironment.^{127,129} Both chemokines are also expressed by tumor-invading mesenchymal stem cells, cancer-associated fibroblasts, and surrounding adipocytes to drive breast cancer cell motility and metastasis.^{8,9,133-136} In the inflammatory tumor microenvironment of obesity, TNF- α and IL-1 also enhance breast cancer growth and migration (Fig. 5).^{126,137}

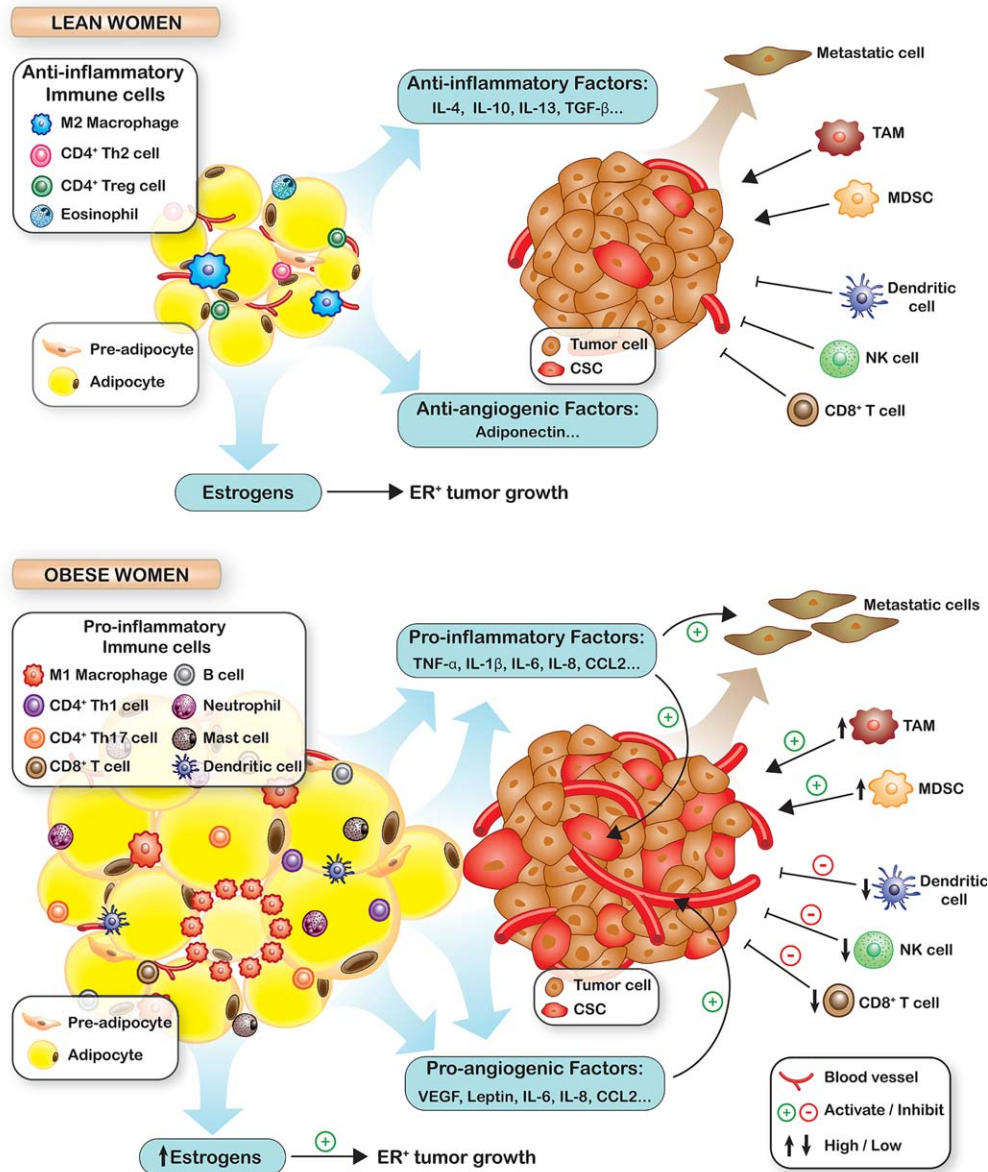


FIGURE 5. The Role of Obesity in Tumorigenesis. With obesity, secreted cytokines shift from an anti-inflammatory profile to a proinflammatory/proangiogenic profile. Proinflammatory and proangiogenic cytokine secretion also increases upon adipocyte:breast cancer cell contact to increase angiogenesis, cancer stem cell expansion, invasion, and metastasis. In obese adipose tissue, mediators of antitumor immunity, such as CD8-positive (CD8⁺) T cells, natural killer (NK) cells, and dendritic cells, decrease and myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) that suppress antitumor immunity accumulate. High aromatase levels drive higher estrogen synthesis to support estrogen receptor-positive (ER⁺) breast cancer growth. CCL indicates chemokine (C-C motif) ligand; IL, interleukin; TGF- β , transforming growth factor β ; TNF- α , tumor necrosis factor α ; VEGF, vascular endothelial growth factor.

Interaction of Adipocytes With Invading Breast Cancer Cells Upregulates Cancer Stem Cells

Most solid tumors appear to be generated and maintained by a stem-like population that can self-renew, give rise to heterogeneous tumor growth, and mediate drug resistance, tumor recurrence, and metastasis.¹³⁸⁻¹⁴⁰ TLR4 is expressed not only on adipocytes and immune cells, but many breast cancers also express this receptor.¹⁴¹ Free fatty acids (FFAs) produced by obese fat lipolysis stimulate TLR4 on the breast cancer cell surface to activate NF- κ B.¹⁴¹ This continuous NF- κ B activation leads to an increase in cancer stem

cells (CSCs).¹⁴² Moreover, cytokines synergistically upregulated by contact between breast cancer cells and adipocytes, as occurs early during breast cancer invasion, increase the abundance of stem-like cancer cells.⁹ Exposure of breast cancer cells to adipocytes, or to the cytokines they upregulate, led to evidence of CSC enrichment, including increased aldehyde dehydrogenase-1 (ALDH1) activity and mammosphere formation in vitro, and increased tumor-initiating cells and metastasis in mouse models.⁹ Adipocyte contact and proinflammatory cytokines CCL2, CCL5, IFN- γ -induced protein 10 (IP-10), IL-6, and IL-8

upregulated embryonic stem cell transcription factors, including c-Myc, sex-determining region Y box 2 (Sox2), and Nanog, to mediate CSC expansion⁹ (Fig. 5).

Others have also demonstrated that each of these cytokines individually promotes CSC expansion. IL-8 increased ALDH1 activity and mammosphere and breast cancer xenograft formation, and IL-8 blockade improved response to chemotherapy in mouse models.¹⁴³ IL-6,¹⁴⁴ CCL2,¹⁴⁵ and CCL5¹⁴⁶ have all been shown to stimulate CSCs. Because all of these cytokines are overexpressed in obese adipose tissue and are upregulated upon contact with invading breast cancer cells, breast CSC enrichment may underlie the worse prognosis of breast cancer in obese women (Fig. 5).

Changes in Antitumor Immunity Associated with Obesity

Obesity not only affects the profile of immune cells within adipose tissue but also modifies circulating and tumor-infiltrating immune cells and their functional activities. For example, obese individuals have decreased peripheral blood CD8-positive T cells, reduced lymphocyte proliferation in response to mitogens, and dysregulated cytokine expression.¹⁴⁷ Natural killer (NK) cells play an important role in the innate immune response against cancer. In obesity, both NK cell numbers and their cytotoxic activity are diminished.¹⁴⁷⁻¹⁴⁹ Dendritic cells (DCs) are antigen-presenting cells that activate the T cells essential for antitumor immunity.¹⁵⁰ Studies in diet-induced obese mice indicate that obesity impairs the efficacy of DC-dependent antitumor immunotherapies (Fig. 5).¹⁵¹

Tumor-associated macrophages (TAMs) actively promote all aspects of tumor initiation, growth, and development.¹⁵² TAMs derive from circulating monocytes in response to the chemokines produced by stromal and tumor cells, particularly CCL2. In obesity, circulating CCL2 is elevated, and high CCL2 levels are associated with increased TAMs and a poor prognosis in breast cancer.^{152,153} Myeloid-derived suppressor cells (MDSCs) home to human cancers and play a role in inhibiting antitumor responses and promoting tumor expansion and metastasis.^{154,155} Increased intratumor MDSC infiltration is associated with a poor prognosis (Fig. 5).^{94,156} In mice, obesity increases MDSC infiltration into the tumor microenvironment.⁹⁴

Obesity and Angiogenesis in Breast Cancer

Angiogenesis, which is the formation of new blood vessels from a preexisting vascular network, is required for tumor expansion and is an independent indicator of poor breast cancer prognosis.¹⁵⁷ VEGF is a potent proangiogenic growth factor that is essential for continued tumor growth, and elevated intratumor VEGF is associated with breast

cancer aggressiveness and a poor prognosis.^{157,158} In obesity, angiogenesis is driven by hypoxia-induced HIF-1 activation and VEGF induction.¹⁵⁹ Leptin¹⁶⁰⁻¹⁶² and several cytokines that are increased in obese adipose tissue, including IL-1 β , IL-6, IL-8, and TNF- α , upregulate VEGF to stimulate breast tumor angiogenesis.^{126,163} TNF- α and IL-1 β also activate leptin production through preadipocytes to further stimulate angiogenesis.⁹⁰ IL-8 increases the migration, proliferation, and survival of both endothelial cells and cancer cells.¹²⁸ The obese mammary gland may promote angiogenesis through a novel CCL2/IL-1 β /CXCL12 pathway that bypasses VEGF and its receptor. Infiltrating immune cells, cancer-associated adipocytes, and TAMs in the peritumoral microenvironment of obese fat promote tumor angiogenesis by upregulating the proangiogenic cytokines VEGF, IL-6, and IL-8, which support vessel growth in breast tumors (Fig. 5).¹⁶⁴

Obesity, Estrogens, and Breast Cancer

The stronger association between obesity and ER-positive, postmenopausal breast cancer risk, compared to that of ER-negative breast cancer after menopause, points to the importance of the estrogenic milieu of obesity.^{28,165,166} High postmenopausal BMI and recent or current postmenopausal hormone use, especially estrogen plus progestin, are associated with higher postmenopausal breast cancer risk.¹⁶⁷ In contrast, both tamoxifen and aromatase-inhibitor drugs, which block ER and prevent estrogen formation, respectively, decrease the risk of breast cancer.¹⁶⁷ Postmenopausal breast cancer risk in obesity is associated with elevated circulating free and total estradiol, estrone, and testosterone and decreased sex hormone-binding globulin (which increases free estrogens).^{108,168-174} Relative to women with the lowest quintile of circulating sex steroid levels, breast cancer risk is approximately double for those in the highest quintile, with an HR of 2.15 (95% CI, 1.87-2.46) for estradiol, 1.81 (95% CI, 1.5-2.10) for estrone, and 2.04 (95% CI, 1.76-2.37) for testosterone.¹⁰⁸ Elevated serum sex steroid levels account for a large component of the excess risk of postmenopausal breast cancer among obese women.¹⁷⁴ Estrogen levels are higher in the breast than in circulation and are higher in cancerous than benign breast tissue.¹⁷⁵ A recent study of paired serum and postmenopausal breast cancer tissue hormone levels concluded that tissue estradiol is associated with ER-positive breast cancer size and that BMI affects tissue levels of estradiol and its precursors.¹⁷⁶ The proestrogenic milieu in obese women is linked to inflammation in obese adipose tissue. Elevated IL-6 stimulates aromatase expression.¹⁰⁶ The resulting increased aromatization in breast cancer cells, cancer-associated fibroblasts, and cancer-associated adipocytes would increase local and circulating

estrogens, driving an obesity-inflammation-aromatase axis to promote local breast cancer development and growth.

Physical Activity and Breast Cancer Risk and Outcome

Physical Activity Associated With Reduced Breast Cancer Risk

In the Women's Health Initiative study of 155,723 women who were followed over a median of 7.3 years, the risk of breast cancer was lower by 15% to 23% in the tertile with the highest recreational physical activity (PA) relative to the lowest tertile.⁵² Similarly, among 25,624 Norwegian women, over 4 hours of leisure time PA per week was associated with a 37% lower risk (HR, 0.63; 95% CI, 0.42-0.95 [$P = .04$]), with an inverse dose response between PA and risk.¹⁷⁷ Two case-control studies also associated higher recreational PA versus none with a 30% to 60% lower breast cancer risk (most of borderline significance), with a significant decrease in premenopausal, receptor-negative cancers (HR, 0.46; 95% CI, 0.24-0.92).²⁶

Breast Cancer Mortality Is Inversely Associated With PA Before and After Breast Cancer Diagnosis

Many large, observational, prospective cohort studies have associated PA before and after a diagnosis of invasive breast cancer with better outcome. Recent meta-analyses indicate that, relative to sedentary women with breast cancer, those in the highest categories of activity *before* diagnosis have a 16% to 27% greater breast cancer-specific survival rate, and those in the highest PA category *after* diagnosis have 28% to 41% greater disease-specific survival.^{178,179} A meta-analysis of 22 prospective cohort studies that included 123,574 survivors of breast cancer who were followed for a mean of 4.3 to 12.7 years¹⁷⁹ showed that the highest categories of lifetime prediagnosis PA were associated with nearly 30% lower breast cancer-specific mortality (HR, 0.73; 95% CI, 0.54-0.98), and the HR for the highest recent prediagnosis PA was 0.84 (95% CI, 0.73-0.97) relative to the lowest category. The highest postdiagnosis PA category versus sedentary had an HR of 0.59 (95% CI, 0.45-0.78) for breast cancer-specific mortality, and those who met the recommended PA guideline of 8 or more metabolic equivalent of task (MET)-hours per week (approximately 2.5 hours of moderate activity per week) postdiagnosis had a 33% reduction in breast cancer mortality.¹⁷⁹ A pooled analysis of 4 studies that included 13,302 survivors associated PA of 10 MET-hours per week postdiagnosis with 27% lower all-cause mortality and 25% lower breast cancer-specific mortality.¹⁸⁰ It appears that all subgroups benefit regardless of age, BMI, race, stage, hormone receptor status, or menopausal status,^{178,179,181} with greater benefit seen in those who have higher initial BMI.¹⁷⁹ Most studies of PA

postdiagnosis show a dose-response effect.^{180,182-186} Notably, the Nurses' Health Study (NHS) showed a dose response for PA between 0 and 9 to 14.9 MET-hours per week, with an HR for breast cancer mortality of 0.50 (95% CI, 0.31-0.82).¹⁸⁴ Greater energy expenditure was not associated with greater risk reduction. Those spending 9 MET-hours per week (equivalent to walking 3-5 hours at average pace) in PA after diagnosis showed absolute, unadjusted mortality risk reductions of 4% at 5 years and 6% at 10 years versus women who had PA less than 3 MET-hours per week.¹⁸⁴ These risk reductions are similar to those derived from adjuvant chemotherapy.¹⁸⁷

Observational studies identify associations between factors and disease outcomes, but they do not establish causal links. To date, only a single large, randomized controlled trial (RCT) has reported an effect of diet and/or PA on breast cancer disease-free survival,¹⁸⁸ and none have yet reported a change in breast cancer-specific or all-cause mortality. Completed and ongoing lifestyle intervention trials of diet and/or exercise in breast cancer survivors are discussed below.

Ongoing Weight Loss Intervention Trials Will Test Effects on Breast Cancer Outcome

Several relatively small randomized and nonrandomized trials ($n = 10-103$ women) in breast cancer survivors have established that weight loss of up to 5% or more over 2 to 18 months is feasible.¹⁸⁹ In the prospective, randomized Women's Intervention Nutrition Study (WINS), a low-fat diet intervention yielded a mean 3.7% weight loss (mean, 2.3 kg at 1 year and 2.7 kg at 5 years; $P < .005$) and decreased the risk of recurrence (HR, 0.76; 95% CI, 0.60-0.98).¹⁸⁸ In contrast, in the Women's Healthy Eating and Living (WHEL) Study of a high-fiber, fruits and vegetables diet, women had a stable weight and showed no improvement in overall survival.¹⁹⁰

Ongoing, large, randomized trials aim to determine whether diet and exercise can improve breast cancer outcomes. The Canadian Life Style Intervention in Adjuvant Treatment of Early Breast Cancer (LISA) trial accrued 338 women with a BMI from 24 to 40 kg/m² to a 2-year, telephone-based, structured intervention aiming at a 500 to 100 kilocalorie per day deficit through diet and exercise. This yielded a weight loss of 5.3% at 6 months and 3.6% at 24 months versus 0.7% and 0.4% at these respective time points in controls ($P < .001$) over all BMI categories.¹⁹¹ Similarly, the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial¹⁹² randomized participants with BMI from 25 to 40 kg/m² to group-based interventions across 2 years with similar energy deficit goals and achieved a 6% mean weight loss at 12 months in the intervention group versus 1.5% in controls, with 26% of participants showing 10% or greater weight loss. Weight loss was lower

in younger patients and in those receiving chemotherapy.¹⁹² The ongoing German Docetaxel-Based Anthracycline-Free Adjuvant Treatment Evaluation as Well as Life Style Intervention (SUCCESS-C) trial will randomize 3547 women with lymph node-positive or high-risk, lymph node-negative cancers to 1 of 2 chemotherapy arms. A second randomization will compare disease-free survival in participants with a BMI from 24 to 40 kg/m² assigned to observation versus a telephone-based lifestyle intervention with diet and 150 to 200 minutes per week of moderate exercise. The Italian Diet and Androgens-5 (DIANA-5) trial accrued 1208 survivors of breast cancer between 2008 and 2010 to test the effects of an intensive group diet and exercise intervention over 5 years on patient outcome.¹⁹³ The ongoing Breast Cancer Weight Loss Study (BWEL) of the Alliance of Clinical Trials in Oncology will randomize more than 3000 overweight or obese, premenopausal and postmenopausal women with breast cancer to a health education program with or without weight loss intervention within 12 months of diagnosis and will follow effects on insulin resistance, biomarkers, and disease-free and overall survival over 10 years (clinicaltrials.gov identifier NCT02750826). Data on outcome benefits from these trials are not yet available.

Effects of Lifestyle Interventions on Biomarkers of Obesity

Several RCTs have indicated that exercise and diet interventions not only change biomarkers associated with poor outcome in obesity, including leptin,^{194,195} insulin,¹⁹¹ and estrogens,¹⁹⁴⁻¹⁹⁶ but that these effects are driven by weight loss.¹⁹⁷ Notably, in the absence of weight loss, diet and/or exercise appear to have little effect on these biomarkers. Because all of these factors are associated with poor breast cancer prognosis, it is speculated that they play causal roles in the adverse effect of obesity on outcome and that their downregulation through diet and PA predict a benefit on disease outcome.

Sex steroids

Circulating sex steroid levels increase with increasing BMI, and women with the highest quintiles of circulating estrogen, estrone, and testosterone have up to 2-fold higher breast cancer risk.¹⁰⁸ Elevated sex steroids account for most of the excess risk of postmenopausal breast cancer with obesity.¹⁷⁴ RCTs have shown that PA effectively reduces serum sex steroid levels in obese postmenopausal women without^{194,196} and with breast cancer.^{195,198} In postmenopausal women with a BMI >24 kg/m², a 3-month RCT of PA decreased estrone by 3.8% and estradiol by 7.7%. Estradiol decreased by 30% in those with a 10% weight loss.¹⁹⁶ Combining PA and diet yielded greater weight loss (-11.9%) than either diet (-10%) or PA (-3.3%) alone and even more striking

decreases in estrone, estradiol, and testosterone, indicating that weight loss is the driver linking PA to decreased sex steroids in postmenopausal women with BMI >25 kg/m².¹⁹⁴ Postmenopausal breast cancer survivors randomized in the Survivor's Health and Physical Exercise (SHAPE) RCT to increased PA and decreased energy intake showed a weight loss 5% or greater at 6 months, with decreased estradiol ($P = .002$), decreased estrone ($P = .02$), and increased sex hormone-binding globulin ($P < .01$).¹⁹⁵

Leptin

As noted previously, obese individuals have higher serum leptin levels,¹¹⁹ which are associated with higher postmenopausal breast cancer risk¹¹⁷ and a poor outcome.¹²² Aerobic exercise decreases leptin levels in association with weight loss.^{122,197} Invasive breast cancer survivors with the highest quartile of PA had lower serum leptin levels than sedentary patients ($P = .001$).¹⁹⁹ A PA intervention decreased serum leptin levels in postmenopausal women with a BMI >25 kg/m², and the decrease was most pronounced in the diet and exercise arm, which showed the greatest weight loss compared with either diet or exercise alone.¹⁹⁴ A 3-month PA intervention decreased leptin levels ($P = .031$) in patients with breast cancer²⁰⁰; and, in the SHAPE study of postmenopausal survivors of breast cancer, an intervention that yielded a mean weight loss of 5% or more (or 8.7 kg) decreased serum leptin levels ($P < .0001$).¹⁹⁵

Insulin, IGF-1, and glucose tolerance

Obesity is often associated with insulin resistance, leading to elevated levels of insulin and IGF-1, both of which are potent breast cancer growth factors.¹¹⁶ A decrease in fasting insulin levels is among the most consistent results of PA.¹¹⁹ The decrease in fasting glucose levels produced in PA intervention studies required weight loss.²⁰¹ In the DIANA RCT, a 4.06-kg mean weight loss in postmenopausal survivors of breast cancer decreased fasting glucose levels and improved glucose tolerance.²⁰² RCTs of PA in postmenopausal survivors of breast cancer have shown decreased insulin levels by 4% to 10.3% with little change in controls.^{186,203} Interestingly, although PA and weight loss interventions consistently improve glucose tolerance and insulin levels, reductions in serum IGF-1 and IGF-binding protein levels are variable and small.^{119,197,203}

Inflammatory biomarkers

Obese adipose tissue is a site of chronic inflammation. Numerous studies have shown that exercise with weight loss decreases inflammatory markers, including C-reactive protein, in postmenopausal women with or without breast cancer.¹⁹⁷ TNF- α decreases of 4% to 26% accompany weight loss of 6% to 26%, and reductions in IL-6 levels are decreased by 6% to 50%.¹⁹⁷ Several earlier small, short-term RCTs of exercise with minimal to no weight loss in

survivors of breast cancer failed to show decreases in IL-6.²⁰³ Chronic long-term PA is needed to significantly decrease IL-6.^{197,204} An intervention study in overweight and obese postmenopausal women who achieved an average of 7.3-kg weight loss showed that initial serum IL-6 levels strongly correlated with BMI and that IL-6 was decreased by diet and exercise.²⁰⁵ Similarly, a PA intervention RCT yielding a mean 5.7-kg weight loss in postmenopausal survivors of breast cancer showed a significant decrease in IL-6 levels, whereas the levels in sedentary controls were unchanged.²⁰⁶ The effect of weight loss to decrease IL-6 is greatest in obese individuals.²⁰³ Thus, the vicious cycle of inflammation, insulin resistance, and high estrogen levels, which are associated with and may be causally linked to the poor outcome of obese patients with breast cancer, can be interrupted by diet and exercise weight loss interventions.

Conclusions

The effects of obesity on the risk of breast cancer in premenopausal and postmenopausal women differ based on ER status. In premenopausal women, obesity is associated with a lower risk of ER-positive breast cancer and a higher risk of TNBC. However, in postmenopausal women, obesity is associated with a markedly higher risk of ER-positive breast cancer, particularly in nonusers of HT, but with only a modest or no effect on the risk of ER-negative breast cancer. In contrast, obesity increases the risk of death in both premenopausal and postmenopausal patients with breast cancer. Both biologic factors and undertreatment of obese patients appear to contribute to poor breast cancer outcomes in obesity.

The molecular mechanisms underlying the higher risk and poor breast cancer outcome with obesity are complex. Local hypoxia in obese adipose tissue upregulates the secretion of leptin, and VEGF and decreases adiponectin. High levels of certain cytokines and leptins secreted by the obese adipose tissue mediate infiltration of proinflammatory immune cells that increase preadipocyte numbers, increase the release of FFAs, and activate the NF- κ B pathway, in both adipocytes and immune cells, to sustain a chronic inflammatory milieu. Expansion of the preadipocyte population produces high levels of IL-6, IL-8, CCL2, CCL5, and VEGF to feed-forward and further upregulate NF- κ B and cytokine production.^{90,114} Furthermore, contact between

adipocytes and invading cancer cells would synergistically upregulate cytokine secretion.⁹ TNF- α and IL-6 impair insulin receptor activation^{113,114} to mediate insulin resistance and the high levels of insulin and IFG-1 that drive breast cancer growth. The NF- κ B pathway, TNF- α , and IL-6 also stimulate aromatase expression in breast stromal fibroblasts and adipocytes¹⁰⁶ to upregulate estrogen production in both cancer and stroma. These changes in the leptin:adiponectin ratio and the secretion of proinflammatory cytokines, IGF-1, and estrogen create a local microenvironment that is propitious for breast cancer development. Furthermore, proinflammatory and proangiogenic adipokines secreted by obese adipose tissue, together with impaired antitumor immunity in obesity, favor tumor progression, CSC expansion, and metastasis, leading to the poorer outcomes of obese patients with breast cancer.

A large body of observational studies has demonstrated that obesity, decreased PA, and weight gain all are associated with poor survival in patients with breast cancer. Exercise and weight loss decrease the inflammatory microenvironment in obese patients, improve antitumor immunity, decrease estrogen levels, and are associated with reduced breast cancer risk and better outcomes. Lifestyle intervention trials suggest that weight loss is feasible, and observational studies strongly suggest that it may indeed improve breast cancer survival. Long-term lifestyle changes, beyond a single year, may be required for sustained weight loss. Moreover, biomarker data suggest that there are plausible molecular mechanisms underlying these effects. Most patients with breast cancer are either overweight or obese at diagnosis.^{65,66} Practicing oncologists know that most women coping with new breast cancer therapy fail to lose weight on their own, and weight gain is very frequent.^{65,66} We have yet to fully realize the consequences of the recent rise of obesity prevalence on cancer incidence and outcomes. The time has come for systematic weight loss intervention through standardized diet and exercise programs during or after adjuvant therapy. One could argue, based on compelling data from observational studies, that the current state of knowledge supports the routine incorporation of weight loss intervention as part of management for patients with breast cancer. Ongoing lifestyle intervention trials should help to clarify this issue. ■

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