

## TOPICS

Measurement of obesity

BMI and breast cancer risk

Weight gain and loss and breast cancer risk

Body fat distribution and the risk of breast cancer

Modifiers of the relationship of obesity and breast cancer

## *Obesity and Breast Cancer Risk*

Obesity is well established as a risk factor for postmenopausal breast cancer. Studies of body mass index (BMI) and breast cancer risk have found that postmenopausal women whose BMI falls in the obese category have about twice the breast cancer risk of women with a BMI in the normal weight category. The relationship of obesity to breast cancer may be modified by several other risk factors including menopausal status, use of hormone therapy after menopause, drinking alcohol, age, genetics, and physical activity.

The connection between obesity and breast cancer is complex. The relationship of obesity to premenopausal breast cancer may be opposite that seen with postmenopausal breast cancer. This is to say, obesity before menopause has been related to a weak decrease in premenopausal breast cancer risk while obesity after menopause has been related to a moderate increase in postmenopausal breast cancer.

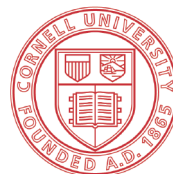
Other measures of body weight and the amount of body fat have also been linked to an increase in the risk of postmenopausal breast cancer. These include excess weight gain during adulthood, abdominal body fat distribution, and adult weight. While weight gained during adulthood has been consistently associated with increased risk of breast cancer, less consistency has been reported for abdominal body fat distribution and adult weight. On the whole, studies suggest that the underlying characteristic linking obesity to postmenopausal breast cancer is the amount of body fat.

Obesity is an important breast cancer risk factor. It is one of few breast cancer risk factors that women can modify. Obesity makes a substantial contribution to the incidence of breast cancer in the U.S. because it is common among U.S. women, and it is associated with a moderate level of breast cancer risk.

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### What is obesity?

Obesity is defined as having too much body fat. The health effects related to obesity are largely determined by body fat. As such, obesity research is concerned with the amount of fat itself, not body weight. Variation in peoples' body weight arises not from fat alone but from differences in the relative amounts of bone, muscle, fat, water, and other tissue types within the body.

### How is obesity measured?

Obesity is typically measured by the size of a person's BMI which stands for Body Mass Index. BMI accounts for differences in individual height and weight. One's BMI is calculated by dividing one's weight (in kilograms) by height (in meters) squared ( $\text{kg}/\text{m}^2$ ). The World Health Organization defines overweight as a BMI greater than 25 and obesity as a BMI greater than 30. Although BMI is not a direct measure of body fat, it is used as a rough indicator of body fat. However, BMI is not a good indicator of body fat in a number of subgroups of people such as adolescents, the elderly and some racial groups. Thus, BMI values must be adjusted for use in these populations. A BMI calculator is available at the web site of the National Heart, Lung and Blood Institute: <http://www.nhlbisupport.com/bmi/bmicalc.htm>.

### Which aspects of obesity are important for breast cancer risk?

Several aspects of obesity are important because of their effect on health, including breast cancer risk. These include the time of life when a weight gain occurred, the life period when a person becomes overweight or obese, and where the weight is carried on the individual's body (body fat distribution). All of these aspects of obesity are discussed in more detail below.

### Is body weight related to breast cancer risk?

The vast majority of studies have found that greater body weight is associated with a decrease in breast cancer risk *before* menopause (*premenopause*) and an increase in breast cancer risk *after* menopause (*postmenopause*). This relationship was also supported by an important study which combined the data from seven major cohort studies of breast cancer risk. The combined data made it possible for researchers to analyze information from a total of 337,819 women with 4,385 cases of breast cancer. These seven studies

were all cohort studies which measured body size before women were diagnosed with breast cancer. Cohort studies are considered more precise. The results of this large analysis were in general agreement with several earlier studies. *Postmenopausal* women weighing more than 176 pounds had a weak increase in breast cancer risk (relative risk = 1.25) compared to women weighing less than 132 pounds. *Premenopausal* women weighing more than 176 pounds had a moderate decrease in breast cancer risk (relative risk = 0.58) compared to women weighing less than 132 pounds.

### Is body mass index (BMI) related to breast cancer risk?

More recent studies have focused on BMI as it is considered a better measure of obesity than body weight. The relationship between BMI and breast cancer risk is similar to that seen for body weight. In the same combined analysis of seven cohort studies described above, *postmenopausal* women with a BMI greater than 33 had an weak increase in the risk of breast cancer (relative risk = 1.27) compared to women with a BMI less than 21. A BMI greater than 33 was associated with a moderate decrease in breast cancer risk (relative risk = 0.58) among *premenopausal* women with a BMI greater than 33 compared to lighter women.

Some epidemiologic studies have failed to find a relationship between BMI and breast cancer risk among *postmenopausal* women who used hormone therapy. This effect is due to a masking of the effect of obesity by hormone therapy which also increases breast cancer risk. (see *Are there factors that may modify the relationship between obesity and breast cancer risk?* below). Some studies also examined risk among the subgroup of women who had never used hormone therapy after menopause, to estimate more accurately the effects of obesity alone on breast cancer risk. Five cohort studies used this approach. These reports found about a doubling of *postmenopausal* breast cancer risk associated with BMI values above 30 among women who had never used hormone therapy. This is considered a moderate increase in risk. These are important results as cohort studies are considered most reliable, and all five studies reported a statistically significant increase in risk. They also reported a statistically reliable dose-response relationship for risk.

This means that normal weight women had the lowest risk, overweight women had higher risk, and obese women had the highest risk.

### **Is weight gain related to breast cancer risk?**

Since weight gained during adulthood is believed to be largely fat tissue, a number of studies have examined the effect of weight gain on breast cancer risk. Most studies focused on adult weight gain (after age 18 or 20), but more recent studies have tried to determine if there is a particular life period when weight change affects breast cancer risk to the greatest extent.

The relationship of weight gain to breast cancer risk is similar to that of body weight and BMI. Weight gain is related to an increase in the risk of breast cancer among postmenopausal women and a decrease in breast cancer risk among premenopausal women. Among premenopausal women who gained weight in adulthood, there is a moderate decrease in premenopausal breast cancer risk (relative risk of about 0.7), but there is a moderate increase in postmenopausal breast cancer risk with adult weight gain (relative risk of about 2.0). The relationship of weight gain to postmenopausal breast cancer has been highly consistent, even for studies with quite different designs. The relationship between weight gain and breast cancer risk is also stronger among women who did not use hormone therapy after menopause. (See *Are there factors that may modify the relationship between obesity and breast cancer risk?* below)

There are biological reasons to expect that weight gain during certain life periods would be important, and almost all studies have found that weight gain during adulthood, in general, is most important. An important implication of these findings is that maintenance of adult weight, not necessarily weight loss, is a viable goal for health.

More study is needed of this potentially significant aspect of the relationship between obesity of obesity and breast cancer.

### **Does losing weight decrease breast cancer risk?**

Because obesity has been linked to increased risk of postmenopausal breast cancer, researchers have tried to discover whether weight loss in adulthood is linked to decreases in breast cancer risk. However, adult weight loss is much less common than weight gain. Because of

this these studies are difficult to conduct and few studies have examined this question. All the studies that have examined weight loss and postmenopausal breast cancer risk found a weak, statistically uncertain association between breast cancer and adult weight loss. The modifying effect of hormone therapy after menopause was accounted for in two cohort studies which examined non-users separately. One of these studies of non-users of hormones found a weak association between weight loss and decreased risk of breast cancer (Parker and Folsom, 2003), the other found a moderate to strong association between weight loss and breast cancer risk.

One of these studies also examined weight loss during two life periods, loss after age 18 and loss since menopause. Weight loss at both of these life periods was associated with a decrease in postmenopausal breast cancer risk but weight loss after age 18 had a greater effect. More study will be required to establish the extent of the decrease in breast cancer risk associated with weight loss. Nonetheless, the results of these studies and their biological foundation suggest that weight loss may be a sensible, albeit difficult, way to decrease the risk of postmenopausal breast cancer.

### **Is body fat distribution related to breast cancer risk?**

How weight is carried on the body, called body fat distribution, may be a modifier of the relationship between obesity and breast cancer risk. Fat carried in the abdominal (tummy) area may be linked to breast cancer risk. Abdominal body fat distribution is usually measured by waist measurement alone or waist measurement divided by hip measurement (known as waist to hip ratio). Individuals with abdominal body fat distribution have large waists and large waist to hip ratios. This type of stature has been called an apple shaped body. Fat which is carried in the abdominal areas is considered metabolically more active, and this type of fat distribution has also been linked to an increase in the risk of cardiovascular disease and diabetes.

The results of studies that have examined the relationship between waist or waist to hip ratio and premenopausal breast cancer risk have been inconsistent so no firm conclusions can be made about this relationship.

Studies examining waist size or waist to hip ratio and *postmenopausal* breast cancer risk have also been inconsistent. This relationship is also modified by the use of hormone therapy after menopause. Studies that have analyzed groups of women who have never taken hormones have been more consistent and have demonstrated an increase in breast cancer risk among women with a high waist to hip ratio. One of the larger cohort studies reported a moderate increase in breast cancer risk (relative risk value of 1.9) for non-users of hormones with waists 36 to 55 inches around compared to women with waists up to 28 inches; the relative risk reported for all the women (hormone users and non-users together) was 1.2 .

There may be a genetic component to this effect. One large study has reported that a family history of breast cancer may be an important modifier of waist to hip ratio and *postmenopausal* breast cancer risk. When women with a first degree relative with breast cancer (mother or sister) were examined separately, there was a moderate increase in breast cancer risk among women with the highest waist to hip ratio compared to women with the lowest waist to hip ratio. But surprisingly, no association was observed between waist to hip ratio and *postmenopausal* breast cancer risk for women without a family history of breast cancer. More study is need before there will be a clear understanding of these relationships.

### **Does being overweight but not obese increase women's breast cancer risk?**

A number of studies have demonstrated that there is a progressive increase in breast cancer risk with BMI. This indicates that being overweight is associated with increased breast cancer risk. However, the level of risk associated with overweight is less than that associated with obesity.

### **What is the biological explanation for the relationship between obesity and *postmenopausal* breast cancer risk?**

The biological relationship between obesity and breast cancer risk is not clearly understood but a number of hypotheses have been proposed. Three of the major hypotheses are discussed below.

1) *Obesity leads to a larger exposure to estrogen.* It is well established that the amount of estrogen in the

body and the length of lifetime exposure to estrogen is linked to breast cancer risk. Women who are exposed to more estrogen due to a longer period of reproductive capacity or who have higher levels of naturally produced estrogen within their bodies are at higher risk of getting breast cancer. Studies have reported a direct relationship between body mass index and estrogen levels after, but not before, menopause. *Postmenopausal* women with higher BMI values have increased estrogen exposure. In addition, several studies have shown that the breast tumors diagnosed in obese women are more likely to be estrogen receptor and progesterone receptor positive. The increased estrogen exposure is thought to arise from the activity of a key enzyme found in fat cells. This enzyme, aromatase, is able to produce estrogen from other hormones. After menopause the ovaries are no longer producing estrogen and the production of estrogen by this pathway has an important effect on estrogen exposure.

There is another avenue by which obesity may lead to a larger exposure to estrogen. This is through obesity-related decreases in the levels of the proteins in the blood that act as carriers for estrogen, the steroid hormone binding globulins. The obesity-related loss of these carrier proteins makes estrogen more available in the body and increases its activities. This likely includes activities that are related to breast cancer formation.

2) *Fat cells produce substances that could possibly increase breast cancer risk.* A number of hormone-like substances are produced by fat cells. Some of these are leptin, adiponectin, resistin, and tumor necrosis factor-alpha. A number of these substances have been shown to have effects on breast cells in the laboratory and increases in these hormones could potentially increase breast cancer risk although very few studies have been conducted in women.

3) *Obesity leads to other hormonal changes that might affect breast cancer risk: Insulin Related Pathways.* Obesity can also have effects on the levels of insulin and a related hormone, insulin like growth factor (IGF) levels. Both insulin and IGF can increase the growth rate of breast cells, and may also have effects on estrogen and its carrier proteins.

*Why are there differences in obesity-related breast cancer risk for pre- and postmenopausal women?* Our discussion of the effects of obesity on estrogen and

**Table 1** Menopausal status modifies the association of obesity and the risk of breast cancer

	Risk Of <u>Premenopausal</u> Breast Cancer	Risk Of <u>Postmenopausal</u> Breast Cancer
Women Who Are Obese Before Menopause	Moderate Decrease	Moderate Increase (if weight is retained)
Women Who Are Obese After Menopause	(Does not apply)	Moderate Increase
Women Who Gain Weight During Adulthood	Moderate Decrease	Moderate Increase

other hormone levels following menopause raises the question as to how obesity can have the opposite effects on breast cancer risk before and after menopause. The most favored hypothesis for this paradox is built around levels of proliferation, or cell multiplication, in the breast. Cancer risk can, in general, be related to how rapidly cells are multiplying or proliferating within a tissue such as the breast. Thus, the cells that have the highest risk of becoming cancerous are those that have the highest levels of proliferation. Estrogen and progesterone are considered the main hormones that affect proliferation in the breast. The production of estrogen by fat cells in postmenopausal women is thought to be a likely mechanism for the association of obesity and postmenopausal breast cancer risk. Obese postmenopausal women are exposed to more estrogen and would be likely to have higher levels of breast proliferation (and breast cancer risk) than women with normal weight.

The opposite is the case for obese premenopausal women. Obese premenopausal women commonly have irregular menstrual cycles and less frequent ovulation. This disorder leads to disturbances in the production of one of the hormones linked to breast proliferation, progesterone. Thus, the breast cells of obese premenopausal women may undergo less overall proliferation, an effect which would be associated with a decrease in breast cancer risk. Most women, who are obese before menopause, are also obese after menopause, and they likely lose the protective effect after menopause.

### Are there factors that may modify the relationship between obesity and breast cancer risk?

Several factors have been identified that may be able to modify the relationship between breast cancer risk and obesity. These modifying factors have been used to identify groups of women for whom the relationship is particularly strong or weak.

**Menopausal Status** As described in the previous sections, the relationship of obesity and breast cancer risk differs by the menopausal status of the women being studied. Obesity during the life period before menopause is associated with a decrease in breast cancer risk. On the other hand, obesity after menopause is associated with an increase in breast cancer risk. In this context, it is important to realize that in the United States about 80% of all breast cancer cases occur after menopause. (See Table 1)

**Hormone Therapy After Menopause**, commercially known as hormone replacement therapy, is another established modifier of the relationship between obesity and breast cancer risk. This treatment contains estrogen and progesterone and users of hormone therapy after menopause have consistently been shown to have an increased risk of breast cancer.

Early studies of obesity and breast cancer risk did not account for use of hormone therapy after menopause. More recent studies have examined separately those women who used hormone therapy and those who never used hormone therapy. These more careful evaluations have reported a moderate association of obesity and breast cancer risk among

women who did not take hormone therapy after menopause but no association among women who were hormone therapy users. Studies of this type are thought to more accurately reflect the true association of obesity and breast cancer risk. Use of hormones after menopause is thought to mask the effect of obesity on breast cancer risk because of the greater risk conferred by hormone use. In fact, some study cohorts have reported that as many as 50% of the women under study were using hormone therapy. In addition, use of hormone therapy after menopause has also been reported to be higher for normal weight women than for heavier women, further complicating the analysis.

Much less well established are modifications in risk related to the use of alcohol, women's age and a family history of breast cancer.

**Alcohol Intake** is linked to a moderate increase in breast cancer risk. A number of studies have reported increases in estrogens associated with alcohol drinking. Thus, like hormone therapy after menopause, alcohol drinking could potentially modify the association of obesity and breast cancer risk by increasing estrogen exposure. But the effect of alcohol would be expected to be much less than that seen with hormone therapy.

A woman's **age**, especially following menopause, may also be an important modifier of the risk of breast cancer associated with obesity. Some studies have examined the relationship of obesity and breast cancer risk for postmenopausal women grouped by their age of diagnosis. These examinations have reported a progressive increase in risk for groups of increasingly older women. However, this effect was not clearly observed in all studies and more research is required for a resolution of this issue.

**Genetics** may also have a modifying effect on the relationship between obesity and breast cancer risk. As was discussed in an earlier section (see *Is how weight is carried on the body related to breast cancer risk?*), a large cohort study reported an association between obesity, as measured by waist to hip ratio, and breast cancer risk only among women with a family history of breast cancer. Another smaller study reported that women with a family history of breast cancer who had gained more than 37.5 pounds since age 18 had increased risk of breast cancer compared to women who gained 9 or less pounds. More research will be necessary to define these relationships.

**Physical Activity** may modify the association between obesity and breast cancer risk. This is an area which has been studied very little but which holds promise. One large case control study of women in China found a multiplicative interaction between BMI and physical activity. In this study both pre- and post-menopausal women with a high BMI who had little physical activity had a moderate to strong increase in their breast cancer risk relative to women who were most active and lean. In contrast, women in the same BMI category with high levels of physical activity potentially had a weak decrease in breast cancer risk. This is an area of high potential consequence and is one that should be studied in more detail.

### **How important is the association between obesity and breast cancer?**

Obesity is one of the most important breast cancer risk factors for several reasons. First, when compared to most breast cancer risk factors, obesity is associated with a substantial level of risk. A BMI of 30 or more is associated with about a doubling of the risk of the most common form of breast cancer, postmenopausal breast cancer. While this is considered only a moderate level of risk, most of the other established breast cancer risk factors fall into the weak risk category. Second, unlike almost all of the other breast cancer risk factors, obesity can be modified by both weight loss and prevention of weight gain. Although it has not been firmly established that weight loss decreases the risk of breast cancer, prevention of weight gain is the critical first step toward dealing with overweight and obesity. Third, overweight and obesity make a substantial contribution to the incidence of breast cancer in the U.S. These conditions are common among U.S. women; the best estimates indicate that one third of American women are obese and two thirds are overweight or obese. One theoretical estimate, of the size of this problem suggested that, if obesity could somehow be eliminated, there would be a 30% to 50% decrease in the number of cases of breast cancer. This indicates a substantial contribution of obesity to breast cancer incidence.

### **What other health disturbances are associated with obesity?**

Obesity is linked with a number of health problems other than breast cancer. Obesity, is associated with

increases in the risk of cancer of the colon and rectum, uterus, kidney, and esophagus (in men and possibly women). It is also likely to be associated with cancers of the pancreas, liver, gall bladder, and the uppermost (cardia) region of the stomach (in men and possibly women). Additionally, obesity is associated with a moderate increase in the risk of cardiovascular disease, and a strong increase in the risk of both diabetes and arthritis of the knee.

### **Does obesity affect survival from breast cancer?**

Both premenopausal and postmenopausal women who are overweight or obese at the time of cancer diagnosis have lower predicted rates of survival. Obese women are diagnosed at more advanced stages of breast cancer. Recurrence of breast cancer is also more frequent in obese women. Further, survival time has been shown to be shorter for obese women.

A few studies have examined weight gain after diagnosis in relation to breast cancer survival. This is an important issue as weight gain is reported in most women who receive adjuvant treatment following breast cancer diagnosis. The results of these studies have been mixed but the two largest studies both reported increased risk of relapse and death for women who gained the most weight. In accordance, with this, the guidelines provided by the American Cancer Society suggest that women take steps to maintain their weight after breast cancer diagnosis.

### **What can women do now?**

BMI and weight gain are breast cancer risk factors over which women have some control. Epidemiological studies have most consistently associated these measures of obesity with increased breast cancer risk. Prevention of weight gain is a critical first step toward dealing with overweight and obesity. Preventing weight gain is also a very good target for breast cancer risk reduction. Studies have shown that weight gain occurs gradually with most people gaining 2 to 4 pounds a year during adulthood. On a daily basis, this is equivalent to an excess of 50 to 100 calories each day. Using a daily approach, women could eliminate this excess by adding to their schedule as little as a 15 to 20 minute walk each day (2000 steps) or by substituting a mini (2 oz) for a full size whole grain bagel. These small daily changes add up and can counteract the gradual upward weight drift which has led to the current high levels of overweight and obesity. Other examples of activities and substitutions that could cause similar savings are available at America on the Move's website located at: <http://aom.americaonthemove.org/atf/cf/{6F63DF36-03B7-43FC-ACB6-0C930C220704}/100Ways toDecrease100Calories.pdf> and <http://www.activatechestercounty.org/pdf/Tip%20Sheet%201.pdf>. ■

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A complete bibliography of references used in the preparation of this fact sheet is available on the BCERF web site at <http://envirocancer.cornell.edu>

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