

## TOPICS

Cancers associated with obesity

Cancers likely to be associated with obesity

Cancers with insufficient evidence for a relationship with obesity

Cancers unlikely to be related to obesity

The impact of obesity on cancer

How obesity might lead to cancer

## *Obesity and Cancer Risk*

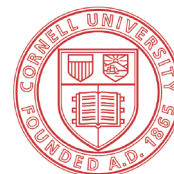
### **Summary**

Obesity has been associated with increased risk of a number of types of cancer. The risk of cancers of the colon and rectum, breast, body of the uterus (endometrium), kidney and esophagus have all been associated with obesity. Other cancers whose risk is likely to be related to obesity are cancers of the pancreas, liver, gall bladder and the cardia (uppermost region) of the stomach. The level of risk for most of these cancers is moderate, having relative risk values between 1.5 and 2.9. The contribution of obesity to the occurrence of cancer is considerable. In high income countries, such as the United States, obesity is considered to be the third largest contributor to cancer incidence behind smoking and alcohol use.

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## What types of cancer are associated with obesity?

### Introduction and Overview

The association between obesity and different types of cancer are described in the sections below. In this discussion, cancers are divided into four groups, based on the strength of the scientific evidence relating them to obesity. The four groups are: a) cancers associated with obesity; b) cancers likely to be associated with obesity; c) cancers for which there is insufficient evidence of an association with obesity; and d) cancers unlikely to be associated with obesity. There are two summary tables. Table 1 summarizes the strength of the obesity-related relative risk for the cancers associated with obesity. Table 2 summarizes the same information for cancers that are likely to be associated with obesity.

It is also important to note that most studies of obesity use a measure called body mass index (BMI). BMI is calculated by dividing weight in kilograms by height in meters squared ( $\text{kg}/\text{m}^2$ ). This calculation compensates for differences in body size between people and while it is not a direct measure of body fat, it is used as a gross indicator of body fat. The World Health Organization defines overweight as a BMI of 25 or greater and obesity as a BMI of 30 or greater. The National Heart, Lung and Blood Institute has a BMI calculator at their web site (<http://www.nhlbisupport.com/bmi/>).

These studies also use a measure of cancer risk called the relative risk. In the context of this discussion, relative risk would be the chance of obese people getting a certain type of cancer compared to the chance of normal weight people getting this type of cancer. For a more through discussion of cancer risk please see BCERF Fact Sheet # 49, *Understanding Breast Cancer Risk and Risk Factors Associated with Diet and Lifestyle*.

### 1. Cancers Associated with Obesity

There is sufficient evidence, for cancers within this group, to be assigned an association of increased risk with obesity. Cancers of the colon and rectum, breast, endometrium, kidney and esophagus make up this group. Each type of cancer is described separately below. Table 1 summarizes the risk levels and values reported for cancers associated with obesity.

**Table 1** Relative Risk Values of Cancers **ASSOCIATED** with Obesity

Type of Cancer	Relative Risk Range (Level of Risk)
Colon and Rectum, Men	1.5 – 2.0 (Moderate)
Colon and Rectum, Women	1.2 – 1.5 (Weak)
Postmenopausal Breast	1.5 – 2.5 (Moderate)
Endometrium (Body of the Uterus)	2.0 – 3.5 (Moderate to Strong)
Kidney	2.0 (Moderate)
Esophagus	2.0 – 3.0 (Moderate)

### A) Obesity and Risk of Cancer of the Colon and Rectum

#### Incidence of Cancer of the Colon and Rectum

Cancer of the colon and rectum is the third most common cancer in both men and women. It is estimated that there will be 112,340 new cases of colon cancer and 41,420 new cases of rectal cancer diagnosed in 2007. An estimated 52,180 deaths will occur from colorectal cancer in 2007; this is 10% of all cancer deaths for men and 11% for women. The incidence of these cancers has decreased over the last 20 years probably due at least in part to screening (colonoscopy) and early cancer (polyp) removal.

#### Effect of Obesity on the Risk of Cancer of the Colon and Rectum

An increase in the risk of colon and rectal cancer has been consistently associated with obesity. The obesity-related cancer risk has been found to be higher in men than in women. Obese men have a moderately increased risk of 1.5 to 2 times the risk of colon and rectal cancer compared to non-obese men. In women, obesity-related relative risk typically ranges from 1.2 to 1.5. Similar results have been reported for the association of obesity with the risk of early non-malignant colon tumors called adenomas. Waist-to-hip ratio, a measure of how fat is carried or body fat distribution also has a similar risk association. The reason for the difference in obesity-related risk between men and women is uncertain, but it may be at least partially explained by the inhibition of colon and rectum cancer growth by estrogen. The IARC (International Agency for Research on Cancer) working

group on cancer prevention has concluded that there is enough evidence to recommend prevention of weight gain to reduce the risk of colon and rectal cancer.

### **B) Obesity and Risk of Cancer of the Breast Incidence**

The American Cancer Society has estimated that there will be 180,510 cases of invasive breast cancer diagnosed in 2007. Of this total, 2,030 (1.1%) will be diagnosed in men. Breast cancer is the most commonly diagnosed cancer in women. There will be an estimated 40,910 breast cancer deaths in 2007. Breast cancer is, after lung cancer, the second largest source of cancer death for women. Fifteen percent of all deaths from cancer in women are due to cancer of the breast.

#### **Effect of Obesity on the Risk of Cancer of the Breast**

Obesity is a well established risk factor for postmenopausal breast cancer. 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 association between obesity and breast cancer is complex as reflected by the fact that the relationship with premenopausal breast cancer is the opposite of that seen postmenopausally. Obesity in postmenopausal women is associated with a moderate increase in breast cancer risk but obesity in premenopausal women is associated with a weak decrease in breast cancer risk. Obesity has also been well demonstrated to have negative effects on breast cancer diagnosis and survival. The relationship of obesity and breast cancer risk is discussed in more detail in BCERF Fact Sheet #56, *Obesity and Breast Cancer Risk*.

### **C) Obesity and Risk of Cancer of the Endometrium (Body of the Uterus)**

#### **Incidence**

It is estimated that 39,080 cases of endometrial cancer will be diagnosed in 2007. This makes it the fourth most common cancer in women. 7,400 women are predicted to die from this cancer in 2007. Endometrial cancer accounts for 3% of all cancer deaths.

#### **Effect of Obesity on the Risk of Cancer of the Endometrium**

There is convincing evidence from both case-control and cohort studies that adult obesity is associated with

an increase in endometrial cancer risk. Obese women are 2 to 3.5 times more likely to develop endometrial cancer than non-obese women. This is considered a moderate to strong association. Most studies have seen a gradual increase in the risk of getting endometrial cancer along with increases in BMI. This indicates that normal weight women have lower risk of getting endometrial cancer, overweight women have higher risk, and obese women have the highest level of risk. Some studies have examined premenopausal and postmenopausal women separately. Most, but not all, of these studies found increased risk of endometrial cancer among obese women in both age groups but with greater risk for older obese women.

### **D) Obesity and Risk of Cancer of the Kidney Incidence**

Kidney cancer makes up about 3.5% of all new cancers in the U.S. This is equal to 51,190 cases diagnosed in 2007. These cases are generally of two types, renal cell cancer and cancer of the renal pelvis. Approximately 85% of all kidney cancers are renal cell cancers, and this is the type of renal cancer that is associated with obesity. The incidence of renal cancer in men is about twice that in women. There are estimated to be 12,890 deaths from renal cancer in the U.S. in 2007.

#### **Effect of Obesity on the Risk of Cancer of the Kidney**

Almost all studies of the association of obesity and renal cell cancer have found that obesity is associated with more than a doubling of relative risk. These results are further strengthened by the consistency of results from studies conducted in a number of countries. Investigations have also reported similar dose response relationships between BMI and renal cell cancer; this indicates that heavier people have greater risk than lighter people. Some studies have reported a larger level of risk for women than men but these results need further study.

### **E) Obesity and Risk of Cancer of the Esophagus Incidence**

The incidence of cancer of the esophagus varies greatly throughout the world. It is uncommon in the U.S. but its prevalence is growing at a rapid rate in this and all developed countries. Studies of esophageal cancer in the U.S. have recently reported a 21% increase in the incidence of adenocarcinoma of the esophagus. In

contrast, the incidence of a second type of esophageal cancer, squamous-cell cancer, has remained stable. 15,560 new cases of cancer of the esophagus are predicted for 2007; this is not a very common cancer, as its incidence is 1% of all cancer cases. It is estimated that there will be 13,940 deaths in 2007 from this disease.

### Effect of Obesity on the Risk of Cancer of the Esophagus

Obesity has been linked to a 2 to 3 fold increase in the risk of adenocarcinoma occurring in the lower third of the esophagus, but it is unrelated to the risk of squamous-cell cancer of the esophagus. The increased risk of esophageal cancer associated with obesity is thought, by many investigators, to be linked to the effects of gastro-esophageal reflux disease (GERD).

In healthy people, the highly acidic contents of the stomach are separated from the esophagus by a valve-like closure known as the lower esophageal sphincter. However, for people with GERD, the sphincter does not close well and allows some of the stomach's contents to reach and damage the esophagus. GERD can be linked to obesity but the nature of this linkage is uncertain. Possible explanations include effects of fat-related hormones and increases in stomach pressure resulting from larger amounts of abdominal fat tissue. Even though the association of obesity and adenocarcinoma is well established, the role of GERD in the cancer formation is still uncertain. Two studies have not supported the relationship of GERD and esophageal cancer.

## 2. Cancers Likely to be Associated with Obesity

For cancers within this group there is insufficient evidence to indicate a definite association of their risk with obesity. However, there is sufficient evidence to indicate that, in all likelihood, their risk is associated with obesity. These cancers include cancer of the pancreas, liver, gall bladder, and gastric cardia. Each is described below. Table 2 summarizes the risk levels and values reported for these cancers.

### A) *Obesity and Risk of Cancer of the Pancreas* Incidence

The estimated number of new cases of cancer of the pancreas in the U.S., in 2007, is 37,170. This is not a common cancer as it makes up 2.6% of all new cases of

**Table 2** Relative Risk Values of Cancers **LIKELY TO BE** Associated with Obesity

Type of Cancer	Relative Risk Range (Level of Risk)
Pancreas	2.0 (Moderate)
Liver	1.5 – 4.0 (Moderate to Strong)
Gall Bladder	2.0 (Moderate)
Gastric Cardia	1.5 – 2.0 (Moderate)
Non-Hodgkin Lymphoma	1.4 – 2.0 (Moderate)

cancer for both men and women. In 2007, there are predicted to be 33,370 deaths from cancer of the pancreas.

### Effect of Obesity on the Risk of Cancer of the Pancreas

A number of recent studies have reported a doubling of the risk of cancer of the pancreas related to obesity. However, earlier, and smaller studies, have reported low risk and in some cases no association of obesity with pancreatic cancer risk. More study will be needed to sort out these different findings. However, there is a strong potential mechanism for a link between obesity and pancreatic cancer provided by diabetes. The risk of diabetes has been very strongly linked to obesity, and diabetes has a well established association with pancreatic cancer risk. Thus, obesity may be indirectly related to an increase in the risk of cancer of the pancreas by its very strong association with diabetes.

### B) *Obesity and Risk of Cancer of the Liver* Incidence

In 2007, it is predicted that there will be 19,160 new cases of cancer of the liver and bile duct. This is an uncommon cancer and its number of new cases is just over one percent of the predicted total number of new cancer cases, in general. 16,780 people are expected to die of this disease in 2007.

### Effect of Obesity on the Risk of Cancer of the Liver

Only five studies have examined the association between obesity and liver cancer. Four of these studies reported an increased risk of liver cancer but with

widely ranging levels of risk. The fifth study, in contrast, found no association. These results suggest that it is likely that liver cancer is associated with obesity, but more research will be needed to fully resolve this issue.

There have only been seven studies that evaluated the relationship between obesity and gall bladder cancer. Although these studies have been small, they have consistently reported a doubling of risk of gall bladder cancer among obese individuals.

### **C) Obesity and Risk of Cancer of the Gastric Cardia (Uppermost Region of the Stomach)**

#### **Incidence**

In 2007, an estimated 21,260 people (13,000 men and 8,260 women) are predicted to be diagnosed with stomach cancer. The number of deaths from stomach cancer in 2007 is estimated to be 11,210 with almost 60% of these deaths in men and the rest in women. While cancer occurs in other parts of the stomach, currently about half of all stomach cancers in the U.S. are in the gastric cardia region.

#### **Effect of Obesity on the Risk of Cancer of the Gastric Cardia**

A number of studies have reported an increase in the risk of cancer of the gastric cardia linked to obesity with weak to moderate levels of risk.

### **D) Obesity and Risk of Non-Hodgkin Lymphoma**

#### **Incidence**

In 2007, the number of new cases of non-Hodgkin lymphoma is forecasted to reach 63,190 (34,200 in men and 28,990 in women). During this year, the number of deaths from non-Hodgkin lymphoma is estimated to be 18,660; this accounts for 3% of all cancer deaths in men and women. The incidence of this disease in the U.S. has been stable for the past 5 years. This follows a period beginning in the early 70's which saw an unexplained near doubling of its incidence rate.

#### **Effect of Obesity on the Risk of Non-Hodgkin Lymphoma**

Sixteen case-control and cohort studies have examined the association of non-Hodgkin lymphoma and obesity. They have generally shown a moderate increase in the risk of this form of cancer related to obesity. A few of

these studies have reported a higher risk for women but more study will be required to resolve this concern.

### **3. Other Cancers for Which There is Insufficient Evidence for an Association with Obesity**

Studies of varying numbers and sizes have examined the relationship between obesity and the risk of: testicular cancer, thyroid cancer, cervical cancer, malignant melanoma, and cancers of the head and neck. There is currently insufficient evidence for any judgments to be made about the relationship of these cancers to obesity.

### **4. Cancers Which are Unlikely to be Associated with Obesity**

Cancers within this group have received sufficient study to determine that their risk has no association with obesity. They include lung cancer, ovarian cancer, and prostate cancer.

**Lung Cancer.** Smoking is the main cause of lung cancer and can affect body weight. Accordingly, the clearest way to examine a potential association between obesity and lung cancer is among groups of non-smokers. Three studies of nonsmokers have examined this relationship. The two larger studies found no association between obesity and lung cancer while the smaller study found that obesity was associated with decreased risk.

**Ovarian Cancer.** Most studies examining obesity and ovarian cancer risk have reported the lack of a risk association. An association would not be surprising. Ovarian cancer is considered a hormone related cancer and obesity can affect hormone levels. Nonetheless, existing studies indicate that there is no relationship between obesity and the risk of ovarian cancer.

**Prostate Cancer.** Three recent, large studies of obesity and prostate cancer have reported a weak (relative risk values of 1.09 to 1.27) but statistically supported (or significant) association. However, there are a large number of earlier studies that found no association between obesity and prostate cancer risk. In further support of a lack of an association, the earlier studies were carried out in a number of different countries, and evaluated a number of different aspects of this association. The IARC working group has concluded that it is unlikely that any important association between obesity and prostate cancer exists.

Recent studies have examined aggressive and non-aggressive prostate cancers separately. These studies have raised the possibility that obesity may increase the risk of aggressive prostate cancer yet decrease the risk of the non-aggressive form of this disease. More study will be required to resolve this issue.

### *Is there a way to estimate the impact of obesity on the incidence of different types of cancer?*

The impact of obesity on the incidence of various types of cancers can be estimated using an epidemiological statistic known as population attributable fraction. This statistic is calculated from the strength of the risk of each cancer's association with obesity and from how common obesity is in the population. The result is presented as a percentage. The population attributable fraction for obesity and different cancers is most easily understood as the percentage of all the cases of each type of cancer that would theoretically be eliminated if obesity was eliminated. An example can be made using the population attributable fraction value for endometrial cancer in Table 3. Its value is 57% and this indicates that if all obesity in the U.S. population was

eliminated 57% of all the cases of endometrial cancer in the population would also be theoretically eliminated.

The results in this table are dramatic. For the cancers which have been shown to be associated with obesity, the elimination of obesity would eliminate from one fifth to almost two thirds of these types of cancer. This is a considerable fraction of cases of these cancers within the population and indicates the large impact obesity has on these cancers.

### *How large is the effect of obesity on death from cancer, in general?*

A recent study of 900,000 U.S. residents examined the relationship of obesity to the risk of death from cancer. Since smoking is such a large contributor to cancer, the most relevant analyses examined nonsmokers only (383,594 participants). Among nonsmokers, the most obese women had a relative risk of death from cancer which was 1.9 times that of the normal weight women. The comparable value for men was 1.3.

The population attributable fraction for obesity and cancer death was also determined. The percentage of nonsmoking women's cancer deaths that were attributed to obesity was 20% and the value for men was 14%. As these values demonstrate, obesity has a considerable impact on death from all forms of cancer.

**Table 3** Population Attributable Fraction Values for Cancers Associated With Obesity

Type of Cancer	Population Attributable Fraction
Colon and Rectum, Men	35%
Colon and Rectum, Women	21%
Breast	23%
Endometrium (Body of the Uterus)	57%
Kidney	43%
Esophagus	52%

### *How is obesity thought to biologically influence the formation of cancer?*

How obesity might affect cancer risk is not clearly understood. Several interrelated explanations have been presented. Some of these explanations are discussed below.

Fat cells have been shown to produce substances that may increase cancer risk. A number of hormone-like substances are produced by fat cells. Some of these hormone-like substances have effects on the growth of cancer cells in the laboratory, and increases in these hormones could potentially increase cancer risk.

Obesity leads to other hormonal changes that can affect cancer risk. The two most studied hormonal pathways are the insulin-related pathways and the estrogen related pathways. Obesity can have effects on the levels of insulin in the body and of levels of a related hormone, insulin-like growth factor (IGF). Both insulin and IGF can increase the growth rate of cancer cells, and may also have effects on other hormones.

It is well established that the amount of estrogen in the body and the length of exposure to estrogen is linked to postmenopausal breast cancer and endometrial cancer risk in women. Studies have reported a direct relationship between body mass index and estrogen levels after, but not before, menopause. This effect has been reported in men as well. 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.

There is another way through which obesity may lead to a larger exposure to estrogen. This is through an obesity-related decrease in the levels of the protein in the blood that acts as a carrier for estrogen, the sex hormone binding globulin. The decrease in this carrier protein makes estrogen more available in the body and increases its activities, including those that are related to cancer formation.

Obesity has also been linked to the promotion of what has been called a low grade of chronic inflammation. This condition results in the formation of a number of cellular signaling agents (cytokines) which are potentially linked to cancer formation through several mechanisms including proliferation and genetic damage.

### *What can people do now?*

While sustained weight loss is difficult to achieve, preventing weight gain provides many health benefits, including decreased cancer risk. More importantly, it is something that most people can accomplish. Studies have shown that weight gain occurs gradually and results from as little as 100 excess Calories a day. This is not a large number of calories, 100 Calories is the equivalent of a 15 to 20 minute walk or one pat of butter. But the daily effect of these extra calories builds up over time leading to gradual but definite weight gain. Preventing this daily excess by adding a short walk or eliminating 100 extra calories from food can have a substantial effect when done on a daily basis. In addition to decreasing cancer risk, other substantial health benefits can be gained such as decreased risk of heart disease, diabetes and some forms of arthritis. ■

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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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