BODY WEIGHT AND PROGNOSIS IN CANCER SURVIVORS

This Guide had been provided by the Anticancer Fund, as a service to patients, to help them and their relatives better understand the influence of body weight on prognosis in cancer. We recommend patients to ask their doctors which treatments could be useful for their situation. The information described in this document is based on scientific research and has informative purposes only.

This guide summarizes the scientific evidence on the impact of body weight on the prognosis of a cancer patient after having been diagnosed and treated. Since most of the information on this subject derives from studies on breast cancer (BCa) patients with excess weight, the data presented here will mainly refer to this group of patients. Some specific aspects in prostate (PCa) and colorectal (CRC) cancer will also be shortly discussed.

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For words marked with an asterisk*, a definition is provided at the end of the document.
Body Weight and Prognosis in Cancer Survivors

A GUIDE FOR PATIENTS

Anticancer Fund

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Does being obese, overweight or underweight have an impact on my prognosis after completing my cancer treatment?

Overall, individuals with excess weight have a greater chance of dying from cancer than those with normal weight. Normal weight is defined as having a body mass index, or BMI*, between 18.5 and 24.9 kg/m². Above the level of 25, each 5 kg/m² increase in BMI* accounts for a 10% increase in deaths due to cancer (1;2). The morbidly obese (BMI* >40) have a more than 50% greater chance of dying because of cancer than individuals with normal weight (3).

Specifically for breast cancer (BCa), excess weight increases the risk of developing it (the incidence, which is not further discussed in this article) in post-menopausal* but not in premenopausal women. After the patient has been diagnosed and completed her anticancer treatment, excess weight worsens the prognosis* in both pre- and postmenopausal women. A worse prognosis* in these BCa survivors may refer to several different outcomes, such as for example, the breast cancer coming back (recurrence, relapse), or getting another cancer (second primary cancer), or getting another disease (co-morbidity), or dying from BCa (BCa specific mortality), or dying from any cause (overall mortality).

Regarding mortality, a meta-analysis* of 43 studies on BCa survivors concludes that being obese (BMI* > 30) when diagnosed increases the risk of dying from any cause, or from BCa specifically, by 33% (4). The higher BCa-specific mortality is partly due to more distant recurrences (metastases) appearing after 5 years or later (5;6).

A recent meta-analysis* of 21 studies concludes that being obese at diagnosis will worsen overall and BCa-specific mortality to the same extent in pre- and post-menopausal* BCa survivors. Likewise, having estrogen/progestin receptors* (receptor positive) or not (receptor negative) will not change the unfavorable impact of obesity (7). In the USA, the increase in mortality that is directly linked to obesity was the same in all races (8). However, African Americans have higher obesity rates and more aggressive BCa tumors; as a consequence their overall BCa burden is significantly heavier (9).
There are some studies suggesting that the unfavorable impact of obesity may be stronger (but more evidence is needed) in:

- **Node-positive** obese patients (who are more at risk of metastases) (5;10), but was not evident in studies on node-negative patients (11;12);
- **Aromatase inhibitor** treatment, but not with tamoxifen (13;14).
- **Hormone replacement therapy** use by postmenopausal* women (15)

Being **overweight** (BMI* 25.0 - 29.9) does not have a clear impact on mortality from BCa since the evidence from the different studies is not consistent. One study found a 26% increased risk (5), but others did not (10;15;16). We still do not have sufficient data to establish a clear-cut BMI* threshold value above which BCa prognosis* worsens significantly (4;17).

Being **underweight** (BMI* < 18.5) strongly increases overall mortality by 59% but this poorer survival was due to non-BCa causes (16).

It is important to note that overweight/obese cancer survivors have a four-fold greater risk of suffering and dying from other (co-morbid) diseases such as cardiovascular disease, diabetes mellitus type 2, asthma, osteoporosis* and back pain (18). Nowadays, survivors are equally likely to die from cardiovascular disease as from BCa (19). A **meta-analysis** of 23 studies shows that patients with diabetes before the diagnosis of BCa have a 61% higher overall mortality (20).

In summary, the relationship between BMI* and BCa prognosis* shows a U-shape with worse overall survival at both the extremes of BMI*, specifically those who are severely obese and those who are underweight (6). The 2014 Continuous Update Project (CUP) Report on “Diet, nutrition, physical activity and breast cancer survivors”, summarizing the evidence from 85 studies (on 164 416 women), concludes that in general there is consistent but still limited evidence that women with greater body fatness (higher BMI), in particular if postmenopausal, have higher overall and BCa specific mortality. More and better-designed studies are still needed to consolidate these findings and to gain more insight into the differences between pre- and postmenopausal women, having excess weight before or after diagnosis, tumor type, disease evolution and amount of treatment received. This information will improve the strength of the evidence from limited to convincing (21).
Does gaining weight after being diagnosed with breast cancer have an impact on my prognosis?

Breast cancer patients often gain weight (on average 2 to 4 kg) during and in the years after chemotherapy (22;23). Weight gain occurs more often in premenopausal* and in normal weight women (24;25). The gain is caused by an increase in fat mass generally and especially abdominal fat mass, but muscle mass is lost. These two changes constitute the so-called sarcopenic obesity (a fat belly with thin legs and arms). Several factors may be involved in these changes. Surprisingly, these patients do not eat more calories (intake) but they burn up less (expenditure). Not compensating for the drop in expenditure (by lowering their caloric intake) results in a positive energy balance; the excess of calories is transformed into body fat. Energy expenditure decreases because basal metabolism lowers during the chemotherapy, and patients do less physical exercise and sleep more (26;27). Part of the weight gain could also be explained by the premature menopause* caused by anticancer treatment (23).

Gaining weight after diagnosis worsens the prognosis*. For example, in the Nurses’ Health Study that followed 121 700 women for 9 years, an increase in BMI* of >2 kg/m² in the first year after diagnosis was associated with a 64% increase in BCa death and recurrence (28). In the Healthy Eating Activity Lifestyle study (HEAL), BCa survivors who had sarcopenia* within one year of diagnosis had a 2.86-fold higher overall mortality (29).

Why does being obese or gaining weight worsen breast cancer prognosis?

This worse prognosis* may be caused by a combination of several factors (30). Firstly, anticancer treatment and the response to it are often sub-optimal in obese women. A survey conducted in the USA showed that obese women underwent screening mammography* less often than normal weight women (31). This may result in delayed detection, and consequently, in a worse response to treatment. In addition, the dosage of chemotherapy administered is often not sufficient for their real body weight because of fears of toxicity at higher doses (32;33).

Secondly, excess body fat causes alterations that can result in the cancer being more aggressive and progressing faster even after treatment. Some well-identified alterations are the increases in hormones such as insulin* and leptin, circulating estrogens, growth factors* such as IGF-I, and inflammation (30;33;34).

Lastly and just as important, excess body fat increases co-morbid diseases (see above) which are nowadays an equally important cause of death as the cancer itself.
Does losing weight unintentionally after being diagnosed with breast cancer have an impact on my prognosis?

It is important to distinguish between weight loss that is intentional (by following a weight-losing diet after diagnosis) or unintentional (unplanned and caused by illness in general). Losing weight unintentionally worsens the prognosis*. For instance, in the Life After Cancer Epidemiology (LACE) study, obese women who had lost ≥ 10% of weight unintentionally in the period before the start of the study had a higher risk of recurrence and of death due to any cause (35). In the Shanghai cohort*, unintentional decreases in weight of > 1 kg also worsened prognosis* (36). In patients who are normal or underweight at diagnosis, further weight losses to BMI* levels < 18.5, together with the loss of muscle mass, can eventually lead to cachexia* that worsens prognosis* and survival considerably.

Can fasting during my chemotherapy improve the effectiveness of the anticancer treatment?

Novel research in laboratory cell cultures and animals indicates that fasting conditions by lowering the glucose* that is available to cells will improve antitoxic defenses in normal, but not in cancer cells. Through this process, the cell-killing effect of chemotherapy will be more effectively targeted to the cancer cells, and with less toxic side effects in non-cancerous tissues (37-39). Studies in human cancer patients investigating if the efficacy of chemotherapy improves during fasting are currently being conducted, but the results have not been published yet (40).
Can I benefit from following a diet to lose weight after being diagnosed with breast cancer?

**If I am obese/ overweight**

Numerous studies in both healthy and cancer patients have shown that restricting caloric intake to achieve even modest losses of weight and body fat can reverse the excessive production of insulin*, fat-tissue hormones such as leptin, growth factors* such as IGF-I, and inflammation. All these factors contribute to the worse prognosis* in obese BCa survivors (41-44).

As recommended for all individuals with excess weight, it has been suggested that an intentional weight loss of 5-10% would benefit BCa survivors by decreasing the risk of both BCa recurrences and co-morbidities (45). In practice, safe weight loss can be achieved by a typical hypo caloric diet (decrease daily caloric intake by 500 kcal) (46), or by following the recommendations of the Diabetes Prevention Program (DPP) (47). Even small decreases in caloric intake (by little more than 150 kcal/day), which is achieved by adapting the dietary pattern so that less energy-dense foods are consumed, could have significant beneficial benefits, as shown below, when discussing the various types of diets.

All guidelines emphasize the need to combine diet, physical exercise to maintain energy expenditure as well as bone and muscle mass (prevent sarcopenia*), and behavioral therapy (48). A reasonable goal is to reach a normal weight within 2 years.

However, we still need more evidence from randomized controlled trials* (RCT) that compare the effect of decreasing caloric intake (intervention) or not (control) on the progression or recurrence of BCa in survivors. These studies need to be conducted in sufficiently large and comparable groups of BCa survivors, and for sufficiently long periods of time.

Of importance, the degree of benefit achieved by such a dietary intervention will not be the same for all individuals. As suggested by the studies that follow survivors for years, those more liable to benefit from losing weight are:

- Patients with obesity (BMI* > 30) at diagnosis (4)
- Patients rapidly gaining weight and abdominal fat (48), especially if they are premenopausal* and with normal weight at diagnosis (24;28)
- Patients with alterations of the metabolic syndrome* such as abdominal obesity, high insulin* levels and insulin resistance*, high circulating inflammatory markers* (6;49-51)
If I have a normal weight
Current guidelines do not encourage weight loss if the BCa survivor has an ideal normal weight, but insist on avoiding weight gain (to levels of BMI* > 25) or weight loss (to levels of BMI* < 18.5), as well as preserving muscle and bone mass (45).

If I am underweight
In view of the significantly higher mortality of underweight BCa survivors (BMI* < 18.5), current guidelines advise an individual symptom-focused approach aimed at meeting nutritional needs, maintaining lean body mass (eventually with tailored physical exercise), and addressing the conditions causing unintentional weight loss such as vomiting and fatigue (45).

Which is the best way to achieve the most favorable weight to survive longer and with a better quality of life after being diagnosed with breast cancer?

Several RCT* have investigated how changing the diet can affect body weight, and if this approach can lower the chance of having a BCa recurrence and improve overall prognosis*. Various types of diet, all with the potential to lower body weight, have been investigated so far.

Diet with less fat
The Women’s Intervention Nutrition Study (WINS) showed that by decreasing fat intake from 30% to 20% of their total caloric intake (amounting to a decrease of 167 kcal per day) for 5 years, BCa survivors achieved an average loss of 2.7 kg of body weight. The risk of their BCa returning was decreased by 24%, and even more (by 42%) in the women who did not have estrogen receptors* in their tumor (53).

Diet with less carbohydrates
Several trials are currently investigating the effect of changing the proportion of carbohydrates in weight-losing diets. Usually, a decrease in carbohydrate implies a higher proportion of fats often accompanied by a moderate increase in protein intake. Such diets have proved effective to lose weight and normalize high insulin* levels, and could therefore improve prognosis* in cancer survivors (54). The CHOICE trial, conducted on overweight and obese BCa survivors, aims to reduce caloric intake and to increase physical exercise (to achieve a 700 kcal/day lowering of energy balance). It has so far shown that the loss of weight after 6 months was the same (6 kg) regardless of whether the diet contained 64% or 32% carbohydrate. The impact on BCa prognosis* is still being studied (46;55).
Diet with intermittent restriction
Recent trials have shown that hypo caloric diets with intermittent caloric and carbohydrate restriction (for example, by decreasing energy intake by 70% and limiting carbohydrate to 40 g two days per week), are more effective than daily caloric restriction, in improving prognostic factors such as insulin* function and body fat, as well as enjoying better adherence by the patients (56). Longer-term trials are needed to investigate if these dietary regimens are effective in improving BCa prognosis*.

Which dietary pattern is most appropriate to optimize my prognosis*?
The Women’s Healthy Eating and Living study (WHEL) reported that increasing the intake of fruits and vegetables from 6 to 9 servings per day for 7 years did not lower the risk of their BCa returning. (52;57).

Despite the disappointing results of the relatively short WHEL intervention, it should be noted that in this same group of BCa survivors, those who consumed more than 5 servings of vegetables and fruits daily all their life (demonstrated by their higher levels of carotenoids in blood) had a 31% lower risk of BCa recurrence. This observation reinforces the evidence that a lifelong consumption of a good quality diet improves overall survival (45).

The Healthy Eating Activity Lifestyle (HEAL) study on the habitual diet of BCa survivors also shows that those with higher intakes of fiber (more than 9 gram per day) had a 47% lower risk of dying from BCa (58). Likewise, those with the highest Healthy Eating Index-2005 score had an 88% reduced risk of death from BCa after 6 years of follow-up (60).

Finally, we are awaiting the results of the DIANA-5 trial investigating if consuming a Mediterranean diet will decrease BCa recurrences and improve survival (61).

The effect of alternative diets such as those named after Budwig, Buchinger, Gerson, Gonzalez and Breuss have not been investigated in randomized trials* involving BCa cancer survivors. Although the macrobiotic*, CRON (caloric restriction optimal nutrition) and the Ornish diets involve dietary changes (more fiber, less fat, less meat etc) similar to the dietary patterns that are associated with a lower cancer incidence, there is currently no evidence of any impact on BCa survival.
What should I take into account and be careful about when aiming to lose weight?

Excessive weight loss (to BMI* values < 20 kg/m²) can lead to loss of muscle and bone with an increased risk of fractures, especially with aromatase inhibitor treatment (62). Promoting physical activity to slow down loss of muscle and bone mass during weight loss regimens is thus indispensable to improve prognosis*. These measures are currently incorporated in all the lifestyle guidelines for cancer patients (48;63).

The 2014 CUP Report concludes that there is still insufficient evidence needed to make specific dietary recommendations for breast cancer survivors and gives the following general healthy lifestyle recommendations (21):

- maintain a healthy body weight
- be physically active
- eat foods containing fiber
- eat foods containing soy
- lower the intake of total fat and, in particular, saturated fat

Weight and prognosis in prostate and colorectal cancer survivors

Compared to BCa, the investigations on the effect of weight and weight-losing diets are scarcer for prostate (PCa) and colorectal (CRC) cancer. Unfortunately, not all the conclusions from the investigations on BCa survivors can be extrapolated to these other types of cancers (30). Some relevant differences are summarized here.

Obese men have a higher risk of advanced, more aggressive PCa when diagnosed (64-66), a higher risk of recurrence after treatment (67) and higher overall mortality (68). This fact has been recently confirmed by the 2014 Continuous Update Project Report on “Diet, nutrition, physical activity and prostate cancer” that updates the evidence on the risk of developing prostate cancer with data from 104 trials on 9 855 000 men (69). For example, gaining around 2 kg in the period 5 years before and 1 year after surgery increases the risk of recurrence by 94% (70).

In agreement with the BCa trials, decreasing fat intake to lose body weight seems to protect against PCa recurrence, but only at very low fat intakes. For example, after one year following an Ornish diet (10% fat intake), body weight decreased by 4.5 kg and recurrence decreased (71;72). More moderate decreases in fat intake (from 36 to 28% energy), however, did not influence tumor growth after 3 weeks (73).
For CRC, it is well known that being obese before diagnosis increases the incidence and mortality in men more than in women, and in colon more than in rectum (66). However, there is still not enough convincing evidence to conclude that excess body weight at and after diagnosis can influence prognosis* except in some sub-groups with a very specific molecular subtype of tumor (74;75). More evidence from RCT* investigating the impact of weight loss or control on the disease outcome of these cancer survivors is still warranted.

**Conclusions**

Breast cancer survivors who are obese or underweight at diagnosis, those rapidly gaining weight, and those with metabolic syndrome*, high circulating estrogens and inflammation have a worse prognosis* and are more likely to benefit from dietary measures to normalize their body weight. For this purpose, safe weight loss by restricting energy dense foods such as saturated fat and highly refined carbohydrates, and promoting nutrient-rich foods such as fruits and vegetables combined with physical exercise, is currently recommended for BCa survivors with a BMI* >25 kg/m². However, there is still no consensus on the “ideal” type of diet to achieve the best protection against a recurrence of BCa and against dying from it or other diseases. Although more trials are needed, there is some evidence that prognosis* is improved by the post-diagnosis diets that achieve reductions of at least 2 kg body weight in survivors with excess weight. Furthermore, the quality of the diet in terms of fruit and vegetable intake is important when consumed in high amounts for a lifetime, but has less impact when the improvement is limited to short periods as seen in some trials conducted after diagnosis. Changing the proportion of fat or carbohydrate does not seem to influence the degree of weight loss when caloric intake decreases equally, but we still do not have enough data to conclude if the influence on BCa-specific prognosis* is different. Finally, any strategy to optimize weight status in BCa survivors must combine dietary improvement with physical exercise (about 150 minutes moderate to intense activity per week), in order to improve hormone and metabolic function and prevent loss of bone and muscle mass.
Glossary

**Body Mass Index (BMI)**
The body mass index (BMI) is a statistical means of measuring body weight based on a person's weight and height. It can be calculated by dividing weight in kilograms by the square of the height in meters. It is used to calculate whether someone is overweight.

- BMI < 18.5 = underweight
- BMI between 18.5-24.9 = normal weight
- BMI between 25-29.9 = overweight
- BMI > 30 = obese
- BMI > 40 = morbid obese

**Cachexia**
A condition in which the patient loses weight and muscle tissue and is weak and tired. A loss of appetite is also associated.

**Cohort**
A group of people who will be followed-up for a certain period of time in a trial.

**Estrogen-/Progesterone receptors (receptor-positive or receptor-negative)**
The growth of normal breast cells is controlled by hormones, especially estrogen and progesterone. These hormones attach to special places reserved in the cell: the so-called "receptors". If the breast cancer cells also have similar receptors, they resemble normal breast cells. These cancer cells are called "estrogen-positive", "progesterone-positive" or, in general, "receptor-positive". If cancer cells are receptor-positive, they may be targeted with the aid of hormone therapy, in which medication is administered which blocks the action of the hormones. If cancer cells are receptor-negative, they do not respond to hormone therapy, which makes its use pointless.

**Glucose**
Glucose is a monosaccharide sugar that is very common in vegetal and animal tissue. It is the main energy source of the body.

**Growth Factor**
A natural substance that is made by certain cells in order to regulate the cellular processes, such as cell division, proliferation, and differentiation. They usually are proteins such as cytokines. Some growth factors are produced in the laboratory and used as a biological therapy.
Inflammatory markers
Inflammation markers or inflammatory markers are proteins whose quantity increases in case an infection occurs. They are measured in order to detect certain diseases. An example is CRP (or C-reactive protein); an increase of this protein can be a possible indication of, amongst other things, an infection after surgery.

Insulin
A hormone that is produced by the pancreas. It regulates the metabolism of sugar in the blood. A lack of insulin can lead to diabetes.

Insulin resistance
When the body does not respond properly to insulin*, it has become insensitive to it; this is called insulin resistance. Insulin is the hormone that lowers blood sugar levels. It thus balances the sugar in the blood. Once the body does not respond properly to insulin, too much sugar in the blood remains unused which may cause health problems such as diabetes.

Macrobiotic
The macrobiotic diet is mainly vegetarian and the products must in any case be organically grown, meaning that the fruit and vegetables are seasonal and originate as much as possible from the surrounding region. The products cannot be fertilized by animals, chemically treated or come from the greenhouse. Canned food or foods with color or flavor enhancers need to be avoided as well.

Mammography
A mammogram or mammography is an image of the breast gland taken by means of an X-ray. It is almost exclusively used for the early detection of breast cancer and monitoring breast cancers that have been declared as being “cured”.

Menopause/ menopausal
Refers to the time of life when a woman’s ovaries stop producing hormones and menstrual periods stop. Natural menopause usually occurs around age 50. A woman is said to be in menopause when she hasn’t had a period for 12 months in a row. Symptoms of menopause include hot flashes, mood swings, night sweats, vaginal dryness, trouble concentrating, and infertility.

Meta-analysis
A meta-analysis combines statistically the results of a number of similar clinical trials are combined and recalculated. This allows for a more reliable statement about the effect of an intervention or treatment.

Metabolic syndrome
It is a metabolic disorder, also called insulin resistance* syndrome, or syndrome X, which can be caused by an imbalance between food intake and physical activity. In other words, too much food and too little exercise. This causes a disturbance in the regulation of the metabolism by the brain. It is usually accompanied by high blood pressure, diabetes, obesity and a too high level of cholesterol. This disorder can lead to long-term cardiovascular disease, type 2 diabetes, and possibly some cancers.
Osteoporosis
A condition in which bone density or bone mineral density is reduced making the bone more fragile and vulnerable for fractures.

Prognosis
The likely outcome or course of a disease; the chance of recovery or recurrence.

Randomized clinical/controlled trial (RCT)
A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient’s choice to be in a randomized trial.

Sarcopenia
The loss of muscle mass and the associated reduction of muscle strength.
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