



## 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.

More information about the Anticancer Fund: [www.anticancerfund.org](http://www.anticancerfund.org)

*For words marked with an asterisk\*, a definition is provided at the end of the document.*



Table of Contents

Table of Contents.....2
Does being obese, overweight or underweight have an impact on my prognosis after completing my cancer treatment?.....3
Does gaining weight after being diagnosed with breast cancer have an impact on my prognosis? .....5
Why does being obese or gaining weight worsen breast cancer prognosis? .....5
Does losing weight unintentionally after being diagnosed with breast cancer have an impact on my prognosis? .....6
Can fasting during my chemotherapy improve the effectiveness of the anticancer treatment? .6
Can I benefit from following a diet to lose weight after being diagnosed with breast cancer? ....7
If I am obese/ overweight ..... 7
If I have a normal weight..... 8
If I am underweight ..... 8
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? .....8
Diet with less fat ..... 8
Diet with less carbohydrates ..... 8
Diet with intermittent restriction..... 9
Which dietary pattern is most appropriate to optimize my prognosis\*? ..... 9
What should I take into account and be careful about when aiming to lose weight?..... 10
Weight and prognosis in prostate and colorectal cancer survivors..... 10
Conclusions..... 11
Glossary..... 12
Reference List ..... 15

This guide has been written by Begoña Manuel-y-Keenoy, MD PhD, and reviewed by Michelle Harvie, Ph.D. and Lieve Vanschoubroek (Anticancer Fund). It was updated on 11/Dec/2014 to include the 2014 CUP reports on breast and prostate cancer.



## 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/m<sup>2</sup>. Above the level of 25, each 5 kg/m<sup>2</sup> 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 **rac**es (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  $>2 \text{ kg/m}^2$  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  $\geq 10\%$  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/m<sup>2</sup>) 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/m<sup>2</sup>.

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.



## Reference List

---

- (1) Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *The Lancet*. 2009;373(9669):1083-96.
- (2) Parr CL, Batty GD, Lam TH, Barzi F, Fang X, Ho SC, et al. Body-mass index and cancer mortality in the Asia-Pacific Studies Collaboration: pooled analyses of 424,519 participants. *Lancet Oncology*. 2010 Aug;11(8):741-52.
- (3) Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *New England Journal of Medicine*. 2003 Apr 24;348(17):1625-38.
- (4) Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Research and Treatment*. 2010 Oct;123(3):627-35.
- (5) Ewertz M, Jensen MB, Gunnarsdóttir KÁ, Højris I, Jakobsen EH, Nielsen D, et al. Effect of Obesity on Prognosis After Early-Stage Breast Cancer. *Journal of Clinical Oncology*. 2011 Jan 1;29(1):25-31.
- (6) Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting Insulin and Outcome in Early-Stage Breast Cancer: Results of a Prospective Cohort Study. *Journal of Clinical Oncology*. 2002 Jan 1;20(1):42-51.
- (7) Niraula S, Ocana A, Ennis M, Goodwin P. Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis. *Breast Cancer Research and Treatment*. 2012;134(2):769-81.
- (8) Conroy S, Maskarinec G, Wilkens L, White K, Henderson B, Kolonel L. Obesity and breast cancer survival in ethnically diverse postmenopausal women: the Multiethnic Cohort Study. *Breast Cancer Research and Treatment*. 2011;129(2):565-74.
- (9) American Cancer Society. Breast Cancer Facts & Figures 2011-2012. 2012 October 8 [Internet]. Available from: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-030975.pdf>.
- (10) de AE, McCaskill-Stevens W, Francis P, Quinaux E, Crown JP, Vicente M, et al. The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial. *Breast Cancer Research and Treatment*. 2010 Jan;119(1):145-53.
- (11) Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, Tamoxifen Use, and Outcomes in Women With Estrogen Receptor–Positive Early-Stage Breast Cancer. *Journal of the National Cancer Institute*. 2003 Oct 1;95(19):1467-76.



- (12) Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, Rudenstam CM, et al. Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. *Annals of Oncology*. 2004 Jun 1;15(6):875-84.
- (13) Sestak I, Distler W, Forbes JF, Dowsett M, Howell A, Cuzick J. Effect of Body Mass Index on Recurrences in Tamoxifen and Anastrozole Treated Women: An Exploratory Analysis From the ATAC Trial. *Journal of Clinical Oncology*. 2010 Jul 20;28(21):3411-5.
- (14) Goodwin PJ, Pritchard KI. Obesity and hormone therapy in breast cancer: an unfinished puzzle. *Journal of Clinical Oncology*. 2010 Jul 20;28(21):3405-7.
- (15) Rosenberg L, Czene K, Hall P. Obesity and poor breast cancer prognosis: an illusion because of hormone replacement therapy[quest]. *British Journal of Cancer*. 2009 Apr 14;100(9):1486-91.
- (16) Kwan ML, Chen WY, Kroenke CH, Weltzien EK, Beasley JM, Nechuta SJ, et al. Pre-diagnosis body mass index and survival after breast cancer in the After Breast Cancer Pooling Project. *Breast Cancer Research and Treatment*. 2012 Apr;132(2):729-39.
- (17) Goodwin PJ. Commentary on: "Effect of obesity on survival in women with breast cancer: systematic review and meta-analysis" (Melinda Protani, Michael Coory, Jennifer H. Martin). *Breast Cancer Research and Treatment*. 2010 Oct;123(3):637-40.
- (18) Guh D, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis A. The incidence of comorbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health*. 2009;9(1):88.
- (19) Demark-Wahnefried W, Platz EA, Ligibel JA, Blair CK, Courneya KS, Meyerhardt JA, et al. The role of obesity in cancer survival and recurrence. *Cancer Epidemiology, Biomarkers & Prevention*. 2012 Aug;21(8):1244-59.
- (20) Barone BB YH. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: A systematic review and meta-analysis. *JAMA: The Journal of the American Medical Association*. 2008 Dec 17;300(23):2754-64.
- (21) World Cancer Research Fund International, American Institute for Cancer Research, Continuous Update Project. Diet, Nutrition, Physical Activity, and Breast Cancer Survivors. 2014. Accessed 2014 November 28 [Internet]. Available from: <http://wcrf.org/sites/default/files/Breast-Cancer-Survivors-2014-Report.pdf>.
- (22) McTiernan A, Irwin M, VonGruenigen V. Weight, Physical Activity, Diet, and Prognosis in Breast and Gynecologic Cancers. *Journal of Clinical Oncology*. 2010 Sep 10;28(26):4074-80.
- (23) Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, et al. Changes in Weight, Body Composition, and Factors Influencing Energy Balance Among Premenopausal Breast Cancer Patients Receiving Adjuvant Chemotherapy. *Journal of Clinical Oncology*. 2001 May 1;19(9):2381-9.



- (24) Caan B, Sternfeld B, Gunderson E, Coates A, Quesenberry C, Slattery ML. Life After Cancer Epidemiology (LACE) Study: A cohort of early stage breast cancer survivors (United States). *Cancer Causes and Control*. 2005 Jun 1;16(5):545-56.
- (25) Nissen MJ, Shapiro A, Swenson KK. Changes in Weight and Body Composition in Women Receiving Chemotherapy for Breast Cancer. *Clinical Breast Cancer*. 2011 Feb;11(1):52-60.
- (26) Demark-Wahnefried W, Hars V, Conaway MR, Havlin K, Rimer BK, McElveen G, et al. Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. *American Journal of Clinical Nutrition*. 1997 May;65(5):1495-501.
- (27) Harvie MN, Campbell IT, Baildam A, Howell A. Energy Balance in Early Breast Cancer Patients Receiving Adjuvant Chemotherapy. *Breast Cancer Research and Treatment*. 2004 Feb 1;83(3):201-10.
- (28) Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, Weight Gain, and Survival After Breast Cancer Diagnosis. *Journal of Clinical Oncology*. 2005 Mar 1;23(7):1370-8.
- (29) Villasenor A, Ballard-Barbash R, Baumgartner K, Baumgartner R, Bernstein L, McTiernan A, et al. Prevalence and prognostic effect of sarcopenia in breast cancer survivors: the HEAL Study. *Journal of Cancer Survivorship*. 2012 Oct 4.
- (30) Parekh N, Chandran U, Bandera EV. Obesity in Cancer Survival. *Annual Review of Nutrition*. 2012 Jul 18;32(1):311-42.
- (31) Littman AJ, Koepsell TD, Forsberg CW, Boyko EJ, Yancy WS. Preventive Care in Relation to Obesity: An Analysis of a Large, National Survey. *American Journal of Preventive Medicine*. 2011 Nov 1;41(5):465-72.
- (32) Madarnas Y, Sawka CA, Franssen E, Bjarnason GA. Are medical oncologists biased in their treatment of the large woman with breast cancer? *Breast Cancer Research and Treatment*. 2001 Mar;66(2):123-33.
- (33) Sinicrope FA, Dannenberg AJ. Obesity and Breast Cancer Prognosis: Weight of the Evidence. *Journal of Clinical Oncology*. 2011 Jan 1;29(1):4-7.
- (34) Dee A, McKean-Cowdin R, Neuhouser ML, Ulrich C, Baumgartner RN, McTiernan A, et al. DEXA measures of body fat percentage and acute phase proteins among breast cancer survivors: a Cross-Sectional Analysis. *BMC Cancer*. 2012 Aug 8;12(1):343.
- (35) Caan BJ, Kwan ML, Hartzell G, Castillo A, Slattery ML, Sternfeld B, et al. Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. *Cancer Causes and Control*. 2008 Dec;19(10):1319-28.
- (36) Chen X, Lu W, Zheng W, Gu K, Chen Z, Zheng Y, et al. Obesity and weight change in relation to breast cancer survival. *Breast Cancer Research and Treatment*. 2010 Aug 1;122(3):823-33.



- (37) Raffaghello L, Lee C, Safdie FM, Wei M, Madia F, Bianchi G, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. *Proceedings of the National Academy of Sciences*. 2008 Jun 17;105(24):8215-20.
- (38) Raffaghello L, Safdie F, Bianchi G, Dorff T, Fontana L, Longo VD. Fasting and differential chemotherapy protection in patients. *Cell Cycle*. 2010 Nov 15;9(22):4474-6. Pubmed
- (39) Lee C, Raffaghello L, Longo VD. Starvation, detoxification, and multidrug resistance in cancer therapy. *Drug Resistance Updates*. 2012 Feb;15(1-2):114-22.
- (40) Clinical Trials NIH. Clinical Trials NIH. Registered trials on Short term fasting and Chemotherapy. 30-11-2012. [Internet] Available from: <http://www.nih.gov/health/clinicaltrials/>
- (41) Blackburn GL, Wang KA. Dietary fat reduction and breast cancer outcome: results from the Women's Intervention Nutrition Study (WINS). *The American Journal of Clinical Nutrition*. 2007 Sep;86(3):878S-81S.
- (42) Jen KL, Djuric Z, DiLaura NM, Buisson A, Redd JN, Maranci V, et al. Improvement of metabolism among obese breast cancer survivors in differing weight loss regimens. *Obesity Research*. 2004 Feb;12(2):306-12.
- (43) Pakiz B, Flatt SW, Bardwell WA, Rock CL, Mills PJ. Effects of a weight loss intervention on body mass, fitness, and inflammatory biomarkers in overweight or obese breast cancer survivors. *International Journal of Behavioral Medicine*. 2011 Dec;18(4):333-41.
- (44) Nørrelund H. The metabolic role of growth hormone in humans with particular reference to fasting. *Growth Hormone & IGF Research*. 2005 Apr;15(2):95-122.
- (45) Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. *Cancer Journal for Clinicians* 2012 Jul;62(4):242-74.
- (46) Thomson CA, Stopeck AT, Bea JW, Cussler E, Nardi E, Frey G, et al. Changes in Body Weight and Metabolic Indexes in Overweight Breast Cancer Survivors Enrolled in a Randomized Trial of Low-Fat vs. Reduced Carbohydrate Diets. *Nutrition and Cancer*. 2010 Nov 5;62(8):1142-52.
- (47) Campbell KL, Van Patten CL, Neil SE, Kirkham AA, Gotay CC, Gelmon KA, et al. Feasibility of a lifestyle intervention on body weight and serum biomarkers in breast cancer survivors with overweight and obesity. *Journal of the Academy of Nutrition and Dietetics*. 2012 Apr;112(4):559-67.
- (48) Demark-Wahnefried W, Campbell KL, Hayes SC. Weight management and its role in breast cancer rehabilitation. *Cancer*. 2012;118(S8):2277-87.



- (49) Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhouser ML, Wener MH, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *Journal of Clinical Oncology*. 2009 Jul 20;27(21):3437-44.
- (50) Goodwin PJ, Ennis M, Bahl M, Fantus IG, Pritchard KI, Trudeau ME, et al. High insulin levels in newly diagnosed breast cancer patients reflect underlying insulin resistance and are associated with components of the insulin resistance syndrome. *Breast Cancer Research and Treatment*. 2009 Apr;114(3):517-25.
- (51) Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Taylor SK, et al. Insulin- and Obesity-Related Variables in Early-Stage Breast Cancer: Correlations and Time Course of Prognostic Associations. *Journal of Clinical Oncology*. 2012 Jan 10;30(2):164-71.
- (52) Gold EB, Pierce JP, Natarajan L, Stefanick ML, Laughlin GA, Caan BJ, et al. Dietary Pattern Influences Breast Cancer Prognosis in Women Without Hot Flashes: The Women's Healthy Eating and Living Trial. *Journal of Clinical Oncology*. 2009 Jan 20;27(3):352-9.
- (53) Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, et al. Dietary Fat Reduction and Breast Cancer Outcome: Interim Efficacy Results From the Women's Intervention Nutrition Study. *Journal of the National Cancer Institute*. 2006 Dec 20;98(24):1767-76.
- (54) Champ CE, Volek JS, Siglin J, Jin L, Simone NL. Weight gain, metabolic syndrome, and breast cancer recurrence: are dietary recommendations supported by the data? *International Journal of Breast Cancer*. 2012;2012:506868.
- (55) Thompson H, Sedlacek S, Paul D, Wolfe P, McGinley J, Playdon M, et al. Effect of dietary patterns differing in carbohydrate and fat content on blood lipid and glucose profiles based on weight-loss success of breast-cancer survivors. *Breast Cancer Research*. 2012;14(1):R1.
- (56) Harvie M, Wright C, Pegington M, McMullan D, Mitchell E, Martin B, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. *British Journal of Nutrition*. 2013;FirstView:1-14.
- (57) Pierce JP NL. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: The women's healthy eating and living (whel) randomized trial. *JAMA: The Journal of the American Medical Association*. 2007 Jul 18;298(3):289-98.
- (58) Rock CL, Natarajan L, Pu M, Thomson CA, Flatt SW, Caan BJ, et al. Longitudinal Biological Exposure to Carotenoids Is Associated with Breast Cancer-Free Survival in the Women's Healthy Eating and Living Study. *Cancer Epidemiology Biomarkers & Prevention*. 2009 Feb 1;18(2):486-94.



- (59) Belle FN, Kampman E, McTiernan A, Bernstein L, Baumgartner K, Baumgartner R, et al. Dietary Fiber, Carbohydrates, Glycemic Index, and Glycemic Load in Relation to Breast Cancer Prognosis in the HEAL Cohort. *Cancer Epidemiology Biomarkers & Prevention*. 2011 May 1;20(5):890-9.
- (60) George SM, Irwin ML, Smith AW, Neuhouser ML, Reedy J, McTiernan A, et al. Postdiagnosis diet quality, the combination of diet quality and recreational physical activity, and prognosis after early-stage breast cancer. *Cancer Causes and Control*. 2011 Apr;22(4):589-98.
- (61) Villarini A, Pasanisi P, Traina A, Mano MP, Bonanni B, Panico S, et al. Lifestyle and breast cancer recurrences: the DIANA-5 trial. *Tumori*. 2012 Jan;98(1):1-18.
- (62) Hadji P, Body JJ, Aapro MS, Brufsky A, Coleman RE, Guise T, et al. Practical guidance for the management of aromatase inhibitor-associated bone loss. *Annals of Oncology*. 2008 Aug;19(8):1407-16.
- (63) Solti M, Webb T. Nutrition and exercise in cancer survivors. *Community Oncology*. 2012 Aug;9(8):266-8.
- (64) Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, et al. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiology, Biomarkers & Prevention*. 2007 Jan;16(1):63-9.
- (65) Discacciati A, Orsini N, Wolk A. Body mass index and incidence of localized and advanced prostate cancer--a dose-response meta-analysis of prospective studies. *Annals of Oncology*. 2012 Jul 1;23(7):1665-71.
- (66) World Cancer Research Fund. Continuous Update Project. Colorectal Cancer. 2012 April 16 [Internet]. Available from: [http://www.dietandcancerreport.org/cancer\\_resource\\_center/downloads/cu/Colorectal-Cancer-2011-Report.pdf](http://www.dietandcancerreport.org/cancer_resource_center/downloads/cu/Colorectal-Cancer-2011-Report.pdf).
- (67) Strom SS, Wang X, Pettaway CA, Logothetis CJ, Yamamura Y, Do KA, et al. Obesity, Weight Gain, and Risk of Biochemical Failure among Prostate Cancer Patients following Prostatectomy. *Clinical Cancer Research*. 2005 Oct 1;11(19):6889-94.
- (68) Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. *Cancer Prevention Research*. 2011 Apr 1;4(4):486-501. .
- (69) World Cancer Research Fund International, American Institute for Cancer Research, Continuous Update Project. Diet, Nutrition, Physical Activity, and Prostate Cancer. 2014. Accessed 2014 November 28 [Internet]. Available from: [www.wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf](http://www.wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf).
- (70) Joshu CE, Mondul AM, Menke A, Meinhold C, Han M, Humphreys EB, et al. Weight Gain Is Associated with an Increased Risk of Prostate Cancer Recurrence after Prostatectomy in the PSA Era. *Cancer Prevention Research*. 2011 Apr 1;4(4):544-51.



- (71) Ornish D, Wiedner G, Fair WR, Marlin R, Pettengil EB, Raisin CJ, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *The Journal of Urology*. 2005 Sep 1;174(3):1065-70.
- (72) Frattaroli J, Weidner G, Dnistrian AM, Kemp C, Daubenmier JJ, Marlin RO, et al. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology*. 2008 Dec;72(6):1319-23.
- (73) Demark-Wahnefried W, Polascik TJ, George SL, Switzer BR, Madden JF, Ruffin MT, et al. Flaxseed Supplementation (Not Dietary Fat Restriction) Reduces Prostate Cancer Proliferation Rates in Men Presurgery. *Cancer Epidemiology Biomarkers & Prevention*. 2008 Dec 1;17(12):3577-87.
- (74) Vrieling A, Kampman E. The role of body mass index, physical activity, and diet in colorectal cancer recurrence and survival: a review of the literature. *The American Journal of Clinical Nutrition*. 2010 Sep 1;92(3):471-90.
- (75) Campbell PT, Newton CC, Dehal AN, Jacobs EJ, Patel AV, Gapstur SM. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. *Journal of Clinical Oncology*. 2012 Jan 1;30(1):42-52.