BODY WEIGHT AND PROGNOSIS IN CANCER SURVIVORS

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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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TABLE OF CONTENTS

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Highlights

What are the goals of "Body Weight and Prognosis in Cancer Survivors"?

- Cover scientific evidence about the impact of weight management on overall survival, cancer-free survival and risk of recurrence in cancer survivors
- Give some evidence-based answers to this frequently asked question
- Does losing weight by restricting caloric intake and changing dietary pattern help a cancer patient to survive longer and better?

Please note that the influence of weight on cancer incidence and primary prevention are not discussed here.

Which cancer types are covered?

- 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 these patients.
- Some specific aspects in prostate (PCa) and colorectal (CRC) cancer survivors will also be shortly discussed.

Summary

Excess body weight is associated with a higher rate of death from many cancers. In breast cancer (BCa) the higher mortality is not only due to a higher incidence (in postmenopausal women), but also to a poorer survival after diagnosis. Being obese (body mass index BMI >30 kg/m2) at diagnosis increases all-cause and BCa mortality by 33%. Being overweight or obese (ov/ob, BMI ≥ 25 kg/m2) at diagnosis increases the risk of distant BCa recurrence (metastases, appearing later than 5 years after diagnosis) but not of locorregional recurrences. Being underweight (BMI < 18.5 kg/m2) at diagnosis also increases all-cause mortality by 59% in BCa patients.

Weight gain (2 to 4 kg) after diagnosis of BCa is frequent and associated with a higher mortality. It is caused by a decrease in energy expenditure and results in sarcopenic obesity (increase in abdominal fat mass and decrease in the lean muscle mass). Weight gain tends to be more pronounced in younger (premenopausal) and in normal weight patients.
Unintentional weight loss of more than 10% (in a period of about 7 years after diagnosis) was also associated with higher BCa recurrence and mortality in the LACE (Life After Cancer Epidemiology) study. Unintentional weight loss is caused by the disease itself and can eventually lead to cachexia, especially in normal and underweight survivors, and can worsen prognosis and survival significantly.
The poorer survival associated with obesity and weight gain can in part be explained by an insufficient dosage of adjuvant therapy, in addition to alterations directly due to high adiposity such as insulin resistance, hyperinsulinism, higher bioavailability of IGF-I and estrogens, as well as inflammation.

Fasting or caloric restriction modulates the cellular detoxification and antioxidant response to improve the resistance to the toxic effects of chemotherapy in normal, but not in cancerous cells. In addition, by lowering blood glucose, insulin and IGF-I levels, cancerous growth signals will be down regulated.

Controlled dietary intervention trials investigating the impact of controlling weight on BCa prognosis give inconclusive results. In the WINS (Women's Intervention Nutrition Study), a moderate lowering of caloric intake by restricting dietary fat resulted in a 24% lower BCa relapse after 5 years of follow-up. The effect was more pronounced in estrogen receptor negative women. In the WHEL (Women's Healthy Eating and Living) trial, in contrast, a similar lowering of caloric intake achieved by increasing fruits and vegetable intakes did not lead to any difference in survival or BCa events after 7 years. However, in conditions associated with high circulating estrogens (postmenopausal hot flushes-negative women), the WHEL intervention decreased BCa recurrences by 47%.

The impact of body weight and of weight-losing diets is less well studied in prostate (PCa) and colorectal (CRC) cancer. Obesity at diagnosis is associated with a higher risk of advanced, more aggressive forms and a higher risk of recurrence after treatment. Weight gain at the time and after diagnosis also increases the risk of PCa recurrence. Intentional weight loss in obese patients may protect against PCa recurrence by following a diet very low in fat but more evidence is needed. Current guidelines for cancer survivors uphold the same lifestyle advice given to all individuals with excess weight. Decreasing caloric intake in order to reach or maintain a BMI between 18.5 and 25 kg/m2 and physical activity to prevent bone and muscle loss are strongly indicated in survivors with obesity at diagnosis, those rapidly gaining weight, and those with metabolic syndrome, high circulating estrogens (for BCa) and inflammation.

Why is weight management important for cancer survivors?

Population studies have shown that morbid obesity (BMI > 40 kg/m2) is associated with a 52% and 62% higher rate of death from all cancers for men and women respectively (1) and that each 5 kg/m2 increase of BMI above 25 kg/m2 accounts for a 10% increase in the mortality due to cancer (2;3). These data, however, do not specify whether the impact of excess body weight and body fat is solely on the risk of developing cancer (incidence) or also on the prognosis after diagnosis. The information emerging from the cohorts of cancer survivors who are being followed up since the moment of diagnosis can give more insight into this question. A cancer survivor is defined by the Center for Disease Control (CDC) as “anyone diagnosed with cancer from the time of diagnosis through the rest of their life”. The National Cancer Survivorship Initiative (NCSI) includes those undergoing primary treatment, in remission following treatment, cured (disease-free), disease-stable and those with active or advanced disease (4;5).

These follow-up studies will also enable us to differentiate between deaths caused by the cancer specifically or by co-morbidities. Cancer patients are more prone to suffer from co-morbid diseases such as type 2 diabetes mellitus, asthma, back pain, osteoporosis and cardiovascular disease, and conditions more specifically linked to the cancer and its treatment such as lymphedema, fatigue, arthralgias and cardiotoxicity (6).

EVIDENCE FROM PROSPECTIVE OBSERVATIONAL STUDIES IN BREAST CANCER SURVIVORS

- Impact of Body Weight & Composition at the time of diagnosis

A meta-analysis of 43 studies (with a median of 1192 subjects per study) showed that women who were obese (BMI > 30 kg/m2) when diagnosed with BCa after a median follow-up of 14 years had a 33% higher death rate due to any cause or due specifically to BCa compared to the non-obese (BMI < 25 kg/m2). This worse survival was still significant after adjustment for age, menopausal status, hormone receptor status, and cancer stage (7). A more recent systematic review encompassing 33 BCa studies highlights the methodological issues that make it difficult to integrate all these results into clear-cut conclusions and recommendations for all cancer survivors (8).

Overall versus Breast Cancer-specific outcomes: In contrast to the clear independent impact of obesity on overall mortality, there is less consistent evidence (from more highly powered recent studies) of an independent effect of obesity on outcomes specifically related to BCa such as disease-free survival, BCa mortality or BCa recurrence. In the most recent systematic review, out of 32 studies reporting BCa recurrence or specific mortality, 22 consistently reported that obesity before or at the time of diagnosis has an unfavorable effect on BCa prognosis (8). As illustrated in the following studies, the impact of excess weight differs depending on which type of outcome is monitored and which cut-offs are used to define excess and normal weight.

The Danish Breast Cancer Cooperative Group (DBCG) followed 18 967 patients with early-stage BCa for more than 10 years. After adjusting for known negative prognostic factors such as tumor size, grade and nodes, DBCG found that the risk of dying from BCa increased by 26% in overweight patients (BMI: 25.0 - 29.9 kg/m2) and by 38% in the obese when compared to normal weight (BMI < 25 kg/m2). Whereas there was no impact on locoregional recurrences, the risk of distant metastasis increased significantly with increasing BMI. For instance, the ov/ob patients (BMI ≥ 25 kg/m2) had a 42-46% increased risk in the period of time 5-10 years after diagnosis, but not in the first 5 years (9). This finding confirms earlier data which detected risk increases of 72% for distant BCa recurrences and of 78% for BCa death in patients with excessive weight (BMI > 27.8 kg/m2 compared to normal weight BMI 21.9 - 24.5 kg/m2) (10). Overall, these findings suggest that adjuvant treatment is less effective in women with excessive weight. As a consequence, they will suffer from more long-term recurrences such as metastasis appearing later than 5 years after diagnosis (11).

In contrast, the After Breast Cancer Pooling Project (ABCPP) that followed 14 938 BCa patients for a median of 7.8 years after diagnosis observed a U-shaped association between the BMI at diagnosis and overall mortality with a 81% increased risk in survivors who were morbidly obese and a 59% increased risk in those who were underweight (BMI < 18.5 kg/m2). However, the patients who were overweight, obese and even the severely obese had no statistically significant increased mortality risk after adjustment for the above-mentioned risk factors. Moreover, the risk of BCa recurrence and BCa –specific mortality was not related to BMI, which indicates the poorer survival in the two extreme ranges of BMI was mainly due to non-cancer causes (12).

The few studies using waist-hip ratio to define abdominal obesity or suprailiac/thigh ratio to define android obesity confirm the poorer prognosis in patients with high central adiposity at the time of cancer diagnosis (7;8;13).
Most studies reveal a U- or J-shaped relationship between BMI and BCa prognosis with clearly worse outcomes at both the extremes of BMI who are either the severely obese or the underweight. However, for the middle and overweight range of BMI there is no or inconsistent evidence of increased risk (10;12;14) in contrast to the above-mentioned DBDG study (9). These inconsistencies may in part be due to differences in the definition of "non-obese" (15). Some studies pool various degrees of obesity as "obese" (BMI > 30 kg/m2) and do not distinguish between underweight, normal weight or overweight subjects within the group defined as "non-obese" (BMI < 30 kg/m2). Indeed, there is still not enough evidence to set a BMI threshold value above which the risk of recurrence and mortality increases significantly.

In the 2014 Continuous Update Project (CUP) Report on "Diet, nutrition, physical activity and breast cancer survivors", the evidence from 85 studies (on 164 416 women) investigating the relationship between body fatness, BCa and mortalitywas analyzed taking into account the timing of assessment of body fatness. By making a distinction between three periods (before diagnosis, < 12 months after diagnosis and ≥ 12 months after diagnosis) the impact of body fatness on either incidence of the primary breast cancer or on prognosis after diagnosis could be separately assessed. It concluded that the evidence was limited but generally consistent of a positive association between greater body fatness (which the CUP Panel interprets to be marked by BMI) and all-cause mortality, breast cancer mortality in postmenopausal women, and development of second primary breast cancer (16).

- Change in weight and body composition during treatment and after

Weight gain during and after systemic adjuvant chemotherapy has been described since the early days of cancer treatment (17). This unbalanced increase in weight results in a change in body composition with a relative increase of central (abdominal) fat mass, and decrease in lean mass especially in legs and lower trunk (sarcopenic obesity). With the improvement of therapy regimens and better evidence-based dietary and lifestyle advice, the large gains of up to 7 kg body fat that were seen in the first 6 months after diagnosis in the earlier studies (18) have gradually been reduced. Now more recently, typical increases of 2-4 kg in body weight and of 2% in body fat mass are being reported (17;19). This is equivalent to an additional 2.89 kg gain in weight when compared to the same age group in the general population (20). In the Life After Cancer Epidemiology (LACE) study, the gain in weight was more pronounced in the younger (premenopausal) patients. For example, in the period encompassing the year before and the year after diagnosis, the proportion of women who gained > 8 kg was 20% in the group less than 50 years old and 6% in those older than 70 years (20). In a group of 72 patients aged 40-55 years and receiving chemotherapy, the increase in weight and in fat mass in torso and extremities was evident in patients with normal weight at diagnosis, but not in ov/ob patients (21).

Several studies reported that a gain in weight during and after cancer treatment was associated with a higher mortality. In the Nurses' Health Study (NHS) that followed 121 700 women for a median of 9 years, an increase in BMI of > 2kg/m2 in the first year after diagnosis was associated with a 64% increase in BCa death and recurrence in patients with normal weight at diagnosis, but not in ov/ob women (22). In the Shanghai cohort (n 5 042) followed for 46 months, increases of ≥5 kg in the 6 months after diagnosis worsened survival by 31%, and by 90% if the weight gain was extended for 18 months (23).

Furthermore, in the Healthy Eating Activity Lifestyle study (HEAL, n 471), BCa survivors with sarcopenia within one year of diagnosis had a 2.86-fold higher overall mortality. The risk of BCa-specific mortality was also 95% higher, but not statistically significant (24).

It should be noted that decreases in weight of more than 1 kg also worsened prognosis in the Shanghai cohort (23). Similarly, in the 7-year follow-up of the LACE study, obese women who lost ≥ 10% of weight unintentionally in the period between pre-diagnosis and study-entry had a 2.5 and 2.8-fold higher risk of recurrence and overall mortality respectively, whereas weight gain did not confer any additional risk (25). However, there is still not enough evidence discriminating between the impact of intentional (weight-losing diets) and unintentional (caused by disease in general) weight loss.

WHICH FACTORS CAN MODULATE THE IMPACT OF EXCESS WEIGHT ON BREAST CANCER PROGNOSIS?

- Menopausal status/Hormone replacement therapy/Hormone receptor status

The latest World Cancer Research Fund (WCRF) update reports that in postmenopausal women there is convincing evidence that excess weight increases the incidence of BCa. In premenopausal women, in contrast, BCa incidence decreases with excess weight, but the evidence is weaker and designated as probable by the WCRF (26). In contrast, for cancer survivors, it is uncertain how menopausal status affects the impact of obesity on prognosis. For instance, in the Nurses' Health Study (NHS), the impact of a high BMI at diagnosis and of increasing weight after diagnosis was stronger in premenopausal women (22). Among Japanese BCa survivors, obesity (Asians are classified as obese when BMI > 25.8 kg/m2 and have normal weight when BMI 21.2-23.3 kg/m2) increased overall and BCa-specific mortality only in premenopausal women (27). Premenopausal women also gained more weight in the LACE study (19). In the meta-analysis by Protani, obesity tended to have a more pronounced impact in pre-menopausal women (47% versus 22% in postmenopausal). Yet due to the heterogeneity of the participants in the different studies, this meta-analysis was underpowered to detect a statistical difference (7). However, a more recent meta-analysis of 21 studies shows that the impact of obesity on overall or BCa-specific survival does not differ significantly by menopausal status (28).

Interestingly, a 10-year follow-up of 2 640 postmenopausal patients in the Swedish Breast Cancer Study found that obesity doubled BCa mortality only in those who had ever used estrogen-progestin therapy (29).
Among obese BCa patients in China, those who were estrogen/progestin receptor negative had a fourfold higher risk of relapse and mortality from BCa than the receptor-positive obese patients (23). Correspondingly, the impact of a >10% weight loss on mortality and recurrence was more pronounced in estrogen and progestin receptor negative patients (25). However, the most recent meta-analysis did not find any significant differences between obese survivors who were either hormone receptor positive or negative (28).

- AJCC Stage/Tumor grade/ Nodal status

At diagnosis, overweight and obese patients have a more unfavorable prognostic profile in terms of older age, more menopause, larger tumors, more ductal grade 3 histology and more positive nodes (9).
The impact of obesity on BrCA-specific mortality and recurrences was seen in node-positive patients (who are more at risk of metastases) (9) (14), but was not evident in node-negative study populations in the National Surgery Adjuvant Breast and Bowel Project (NSABP B14) trial (30) nor in the International Breast Cancer Study Group (IBCSG) (31).

- Type of adjuvant Chemo-Hormonal therapy/ Surgery/Radiation

In the Arimidex Tamoxifen Alone or in Combination (ATAC) trial the increased mortality and recurrence associated with obesity (BMI > 35 kg/m2compared normal weight: BMI <23 kg/m2) was found with aromatase inhibitor treatment (a 53% higher risk), whereas with tamoxifen the 18% higher risk was not statistically significant (32). Similar results were observed in the Austrian Br Ca trial (ABCSG-12) (33). Likewise, the impact of Tamoxifen on prognosis was not affected by the degree of ov/ob or underweight (30).

- Diabetes/Co-Morbidities

Part of the increased overall mortality in ov/ob cancer survivors is explained by their fourfold increased risk of co-morbidities (type 2 diabetes mellitus, asthma, back pain, osteoporosis and cardiovascular disease) (6). In the ABCPP, co-morbidities were already present in 44% of the overweight, and in 60% of the obese at the time of diagnosis (12). In fact, cancer survivors are equally likely to die from cardiovascular disease as from BCa (34). A meta-analysis involving 13 019 patients shows that suffering from diabetes at diagnosis increases the all-cause mortality of BCa patients by 61% (35).

- Smoking/Alcohol/ Physical activity

Few studies adjust for lifestyle factors, which could modulate the pathophysiologic changes that are induced by an increase in adiposity. In the Nurses' Health Study (NHS), the unfavorable impact of ov/ob at diagnosis on BCa recurrence and death was only seen in never smokers (22).

- Race /Socio-economic factors

There is little data from non- Caucasian cancer survivors, despite the well-known fact that African Americans have higher BCa mortality and obesity rates as well as lower socio-economic status (36). Data from the Multiethnic Cohort (MEC) study on 3842 ethnically diverse postmenopausal BCa survivors in the USA did not find any significant evidence of between- race differences in the impact of obesity on overall or BCa-specific mortality (37). Since the African Americans have higher obesity rates and more aggressive BCa tumors, they suffer from a heavier BCa burden with more serious overall health implications (36).

PREVALENCE OF CANCER SURVIVORS AFFECTED BY EXCESS WEIGHT

Survival rates have gradually improved since 1975. The most recent 5-year relative survival rate for all cancers in the US is 67% (38) and for BCa specifically 89% (ranging from 99% for localized disease to 23% for distant-stage disease (36). This means that the population of cancer survivors is steadily increasing.
In the USA, there were 11.9 million survivors in 2008 (39), 13.7 million in 2012 and there will be an estimated 18 million in 2022 (40). Twenty-two percent of these are BCa survivors (36) (39). Therefore, the current 2.97 million BCa survivors in the USA in 2012 will increase to an estimated 3.79 million in 2022 (40).

Worldwide, the number of cancer survivors within five years of diagnosis has been estimated to be almost 28.7 million for 2008 with over 5 million BCa survivors (41).
In the USA about 50% are ov/ob at diagnosis and 20% are obese, as reported in LACE study (20). Therefore in 2012, in the USA alone, more than 600 000 obese BCa survivors could have a worse prognosis as a direct consequence of their excessive adiposity. As for the overweight survivors, there is still no consensus on the BMI threshold value above which BCa prognosis worsens significantly. Nevertheless, the pooled data allows us to estimate that maintaining a BMI of < 25 kg/m2 could prevent 11 to 18 thousand BCa deaths per year in the USA (11).

Mechanisms of action

WHY/HOW DO BREAST CANCER SURVIVORS GAIN WEIGHT DURING AND AFTER TREATMENT?

Caloric intake does not increase significantly, and cannot explain the weight gain seen in the first year after diagnosis. For example, in the HEAL (Healthy Eating Activity and Lifestyle) cohort, patients even decreased daily caloric intake by 137kcal, but still gained 1.5 kg in body weight in the first year after diagnosis (42). Pioneering work by Demark-Wahnefried showed that during adjuvant BCa chemotherapy, weight gain was mainly due to reduced energy expenditure. At the mid-point of a chemotherapy cycle, resting metabolic rate decreased by 322 kJoules /day, and by the end of the cycle returned to pre-treatment levels (43) or remained lower (18). Addition of chemotherapy to local treatment such as radiation and surgery also decreased the energy expended in physical activity during the first year after diagnosis. This is possibly related to the more sedentary lifestyle and longer sleeping hours during treatment (17;18).

During the first year of adjuvant treatment body fat mass increased from 33.5% to 35.8%. This increase is in the same range as the difference between an average pre-menopausal 40 year-old and a menopausal 50-year old. This suggests that therapy-induced premature amenorrhea can also play a role in weight and body fat gain in BCa survivors (17).

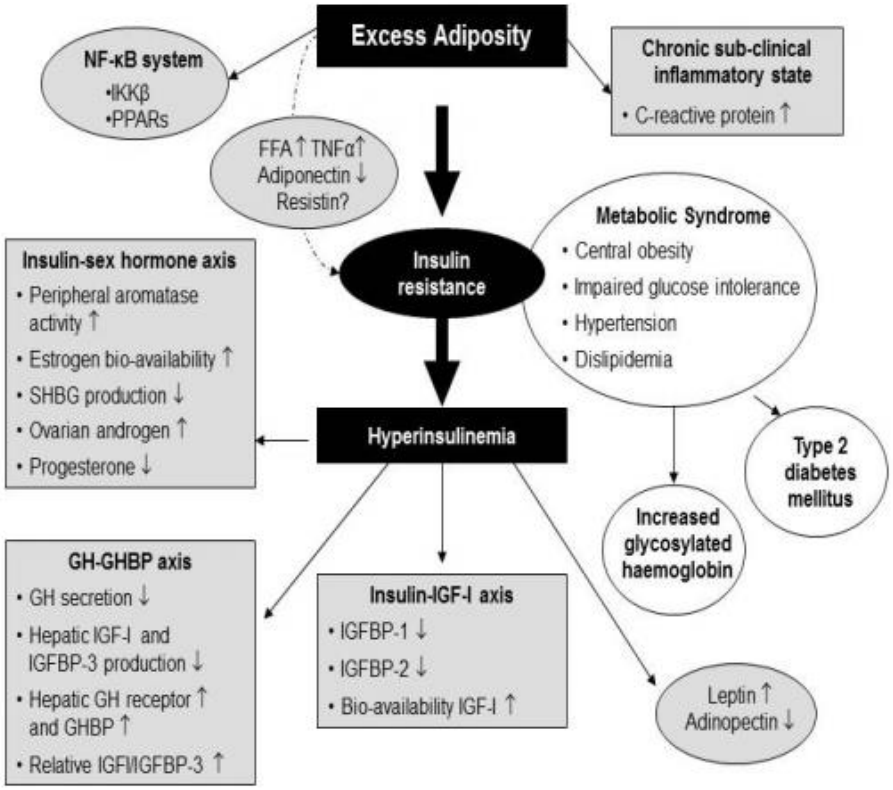
HOW DOES EXCESS WEIGHT AND AN INCREASE IN ADIPOSE TISSUE WORSEN PROGNOSIS?

Several potential pathophysiologic alterations have been proposed to explain how the poorer BCa prognosis in obesity and weight gain is associated with both more biologically aggressive tumors that progress more rapidly, as well as a poorer response to cancer treatment.

- Regarding cancer progression

As summarized in a recent overview by Patterson and illustrated in Figure 1, the mechanisms linking excess adiposity to cancer risk and progression are based on the following evidence (44).

Figure 1:



The presence of the metabolic syndrome in patients undergoing chemotherapy is an unfavorable prognostic factor and high blood glucose predicts more rapid disease progression (45). The underlying insulin resistance reflected by the high insulin (Highest quartile >51.9 pmol/L compared to the lowest quartile <27 pmol/L plasma insulin) at diagnosis increased the risk of BCa recurrence two-fold and the risk of death due to BCa three-fold in a cohort of 512 patients followed up for 7 years (10;46). This unfavorable impact of high insulin is strong in the first 5 years after diagnosis and decreases progressively in the next 6 to 12 years of follow-up (47). These findings suggest that patients with high insulin levels should be preferably targeted for more aggressive anti-cancer treatment (46).

The pro-mitogenic effects of insulin are amplified by the (over)expression in cancer cells of receptors to insulin (in particular the more sensitive isoform A) and to other growth factors such as IGF-I and II, as well as hybrid Insulin/IGF-I receptors. In addition, high insulin levels by occupying the binding sites in circulating hormone binding globulins will increase the bioavailability of IGF-I and estrogens, thus further stimulating growth and proliferation in the tumor (11). Furthermore, in postmenopausal BCa patients with obesity there is a higher synthesis of estrogens in the expanded adipose tissue, including the breast tissue. This is mainly due to up-regulation and higher activity of the enzyme aromatase, which transforms androgens into estrogens. The impact of higher estrogen levels in obesity is especially relevant in estrogen receptor positive tumors of postmenopausal patients.

Breast cancer survivors with body fat mass ≥ 35% in the first year post-diagnosis and those who gain ≥ 5% in weight have higher acute phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA) that are biomarkers of low-grade chronic inflammation (48). The higher adiposity causes an imbalance of adipokines (lower adiponectin, higher leptin) and a pathologic expansion of macrophages in the adipose tissue, including the cancerous breast tissue of obese women. This leads to an excess of pro-inflammatory cytokines (prostaglandin PGE2, interleukins IL-6, IL-1ß, IL-8 and IL-10, tumor necrosis factor TNFα and macrophage inflammatory, monocyte chemo attractant protein 1)(8;49). These will further aggravate the prognosis by cross-talking with the hormonal alterations. For example, they will synergistically enhance VEGF (vascular endothelial growth factor) production in the adipose tissue, and thus promote angiogenesis (50). In fact, elevated inflammation markers (CRP and SAA) 31 months after diagnosis, predicted a 2 to 3-fold increase in overall mortality (51).

- Regarding the response to cancer treatment

Higher BMI is associated to a poorer histopathological response to neoadjuvant chemotherapy before surgery (52). There are several potential explanations. A survey conducted in the USA showed that mammography screening is less frequent in obese than in normal weight women (53). This may result in delayed detection, and consequently in a worse response to therapy. Moreover, overweight and obese women can be under-dosed in case chemotherapy dosages are calculated based on ideal weight instead of on actual body weight for fear of toxicity (54). Under-dosing of adjuvant hormonal treatment may also be inadequate to suppress the enhanced aromatase activity and excess production of estrogens completely (11).

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How could intermittent fasting, caloric restriction or voluntary weight loss after diagnosis improve cancer prognosis?

In view of the clear harmful consequences of a weight gain before and/or after diagnosis, one would expect that dietary interventions limiting caloric intake with the purpose of losing or preventing weight gain would have a favorable impact on BCa prognosis. The rationale underlying the potential beneficial effects of caloric restriction or fasting is based on several experimentally proven mechanisms.

MODULATION OF THE TOXICITY OF ANTI-CANCER DRUGS BY FASTING

Cell cultures exposed to fasting conditions (such as lowering glucose and serum concentration in the culture medium) and mice exposed to short-term starvation (48 hours) develop a so-called "differential stress resistance" that protects normal, but not cancer cells, against the toxic and oxidant effects of drugs such as cyclophosphamide, doxorubicin and etoposide (55;56). Fasting or dietary restriction can modulate the Keap-Nrf2 (Kelch like ECH associated protein-Nuclear related factor E2) pathways, and thus enhance transcription of phase II detoxification and antioxidant enzymes. As a result, the resistance of non-cancerous cells to the toxic effects of chemotherapy improves (57).

IMPROVEMENT OF CELLULAR ENERGY SIGNALING BY FASTING

The longer survival and protection against the toxicity of chemotherapy observed after a 72-hour fast in mice was associated to a 70% decrease in IGF-I with a concomitant increase in its binding protein IGFBP-1 (58). This leads to a downstream down-regulation of mitogenic signaling pathways mediated by the insulin/IGF-I-axis such as MAPK/Ras, PI3K/AKT /mTOR and other proto-oncogenes (57). A 36-120 hour fast in humans also results in decreases of blood glucose and IGF-1 (59). But so far, there are no human studies reporting an enhanced efficacy of chemotherapy in response to fasting.

Known as the Warburg effect, cancerous cells are extremely avid for glucose that is channeled towards the biosynthesis of cell components for the proliferating cells. Restricting glucose availability leads to a shift in nutrient signaling in non-cancerous cells, which involves activation of the "cellular energy sensor" AMPK (adenosine 5-monophosphateactivated kinase) and SIRT1 (sirtuin 1). These enhance PGC1α (peroxisome proliferator-activated receptor-γ-coactivator)-dependent transcription. PGC1α activation protects the cell by shutting down growth signals while maintaining repair mechanisms and conserving mitochondrial function (60). Malignant cells are unable to block the growth signals in response to glucose restriction and as a result remain or become even more vulnerable to chemotherapy (57).

HORMONAL AND METABOLIC EFFECTS OF CALORIC RESTRICTION

Even modest weight and body fat losses -achieved by restricting caloric intake in various dietary regimens- lead to an improvement in insulin sensitivity and a lowering of insulin and leptin levels, which reverses the growth -factor imbalances that worsen prognosis in BCa survivors (61;62). Restricting caloric intake by modifying the dietary pattern, for example by increasing fiber intake, can also affect the bioavailability of estrogens and other growth factors, as well as improve insulin sensitivity (63). In addition, an intervention resulting in a 7% in weight loss in CA survivors lowered pro-inflammatory cytokines (64).

Does it work? What is the quality of the evidence that dietary interventions to maintain or lose weight have an impact on breast cancer prognosis?

Neither the data on the impact of increased adiposity from the prospective observational studies nor the pathophysiological mechanisms described above provide enough evidence to prove that a loss in weight or preventing weight gain after diagnosis improves the prognosis of BCa patients. In order to address this question, several intervention trials have been set up and are summarized here. The 2011 updated systematic review by Davies on nutritional interventions specifically for cancer survivors (65;66) and the evidence-based nutritional guidelines compiled by Robien (67) and the ACS (68), noted that there is a high heterogeneity with regard to the type of dietary intervention, combination with or without other lifestyle changes such as physical activity, and the baseline characteristics and tumor status of the patients enrolled. Notably, the different outcomes investigated to determine the prognosis of cancer survivors ranged from overall or all-cause mortality or survival, cancer-specific mortality, disease-free survival (referring to any cancer or specifically to BCa), recurrence, relapse, second primary cancer, contralateral or ipsilateral BCa and recurrence-free or relapse-free survival.

Apart from the review by Patterson that reports on the effect of dietary patterns and macronutrients in both observational and intervention studies (69), there is at the present no meta-analysis focusing specifically on dietary interventions that involve a change in caloric intake in cancer survivors. Therefore, it is relevant to describe the individual trials separately. They all address weight management but target different aspects of the diet. These trials are summarized in Table 1.

TYPE OF CONTROLLED DIETARY INTERVENTIONS AFFECTING CALORIC INTAKE IN BREAST CANCER SURVIVORS:

- Caloric restriction by short-term fasting during & after treatment

In a case series report, 10 patients fasting for 48-140 hours prior to and for 5-56 hours following chemotherapy reported fewer side effects but no differences in tumor reduction markers (70). Current ongoing trials are summarized in the section Perspectives.

- By restricting fat intake

In the Women's Intervention Nutrition Study (WINS, n=2437), the intervention group succeeded in decreasing fat intake (from a baseline 30% to 20% of total energy intake) and maintaining it for 5 years. This was accompanied by a slightly lower caloric intake (a difference of 167 kcal/day) and resulted in a loss of 2.7 kg (4%) of body weight and a 1.1 kg/m2 reduction in BMI. After 5 years, the risk of a BCa relapse was 24% lower (borderline statistical significance) in the whole intervention group and 42% significantly lower in the subgroup who were estrogen receptor negative (71).

- By changing the proportion of dietary carbohydrates and fat

Several trials are currently investigating the effect of changing the proportion carbohydrates in weight-losing diets. Usually, a decrease in carbohydrate implies a higher proportion of fats, which is often accompanied by a moderate increase in protein intake. Such diets have proved effective to lose weight and normalize high insulin levels and could thus improve prognosis in cancer survivors (72). In the ongoing CHOICE trial the impact of a negative energy balance (700 kcal/day), achieved by caloric restriction in combination with increasing physical activity, is being studied in postmenopausal ov/ob BCa patients (n=370). The diets are balanced in protein (20% of energy), but contain either low fat (16% with 64% carbohydrate) or high fat (48% with 32% carbohydrate). After 6 months, the loss of weight (by 6 kg) and body-fat (by 2.4%) was similar in both groups and associated to beneficial changes in serum lipids and glucose (73;74). It also remains to be seen if the type of regimen to restrict carbohydrate and energy intake also influences prognosis.

- By intermittent restriction

Current trials have shown that hypocaloric diets where the caloric restriction is intermittent (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 (75). Longer-term trials are needed to investigate if these different dietary regimens are effective in improving BCa prognosis in the long-term.

- By changing dietary pattern: Increasing intake of fruits and vegetables, fiber, Mediterranean diet

In the Women's Healthy Eating and Living study (WHEL, n=3088), the intervention group (9.2 servings of fruits and vegetables per day versus 6.2 in the control group) achieved 65%, 25% and 30% higher intakes of vegetables, fruit and fiber respectively, as well as a 13% lower intake of fat. However, after 7 years of follow-up, body weight had not changed significantly in either group and the survival curves and BCa events were identical (76). Subgroup post-hoc analyses revealed that hot flushes negative women (associated with higher circulating estrogens and with an overall worse prognosis) were significantly protected by the WHEL intervention (31% fewer BCa recurrences). Protection by the WHEL diet was even more pronounced in the postmenopausal hot flushes negative sub- group (47% fewer BCa recurrences) (77).

Interestingly in this study, among the 1765 tamoxifen users and irrespective of the study group, those with high intakes of vegetables before the intervention (> 4 servings per day) had a 44% reduced risk of BCa recurrences (78). Similarly, the patients with the highest average plasma carotenoid concentration over time (before and during the 7 years of the trial) had a 33% reduced risk of BCa recurrence. Their better prognosis was not influenced by the changes in fruit and vegetable intake during the relatively short trial period of 7 years (79). Both these observations support the claim that a lifelong consumption of a good quality diet, even before diagnosis, improves overall survival (68).

The protective effect of fiber is also supported by the results of the Healthy Eating Activity Lifestyle (HEAL, n=688) study where intakes above 9 gram per day conferred a 47% lower risk of BCa mortality (80). In this prospective observational study, the women with the highest quartile of the Healthy Eating Index-2005 score had an 88% reduced risk of death from BCa after 6 years of follow-up (81). The potential benefit of a Mediterranean diet on BCa recurrences and survival is currently being investigated in the ongoing DIANA-5 multicenter randomized controlled intervention trial (n 1208) (82).

- Alternative hypocaloric "anti-cancer" diets

The effect of alternative diets such as those named after Budwig, Buchinger, Gerson, Gonzalez and Breuss have not been investigated in randomized trials involving cancer survivors. Likewise, although the macrobiotic, CRON (caloric restriction optimal nutrition) and the Ornish diets involve dietary modifications that resemble dietary patterns associated with a lower cancer incidence, there is currently no evidence of any impact on BCa survival.

Guidelines

WHEN & HOW SHOULD THE DIETARY INTERVENTION START?

During the initial stage of diagnosis and treatment, current guidelines advise an individual symptom-focused approach aimed at meeting nutritional needs, maintaining lean body mass and addressing conditions such as vomiting and fatigue (68).
During the early post-treatment stage, enrollment of eligible patients in a nutritional intervention program occurs while they are more compliant for long-term dietary adaptation (67). For the long-term management of weight in the disease-free or stable disease phase, current guidelines encourage a 3-part approach consisting of dietary changes to maintain or reach a normal weight within 2 years, exercise to maintain energy expenditure as well as bone and muscle mass (prevent sarcopenia), and behavioral therapy (83). Safe weight loss should be achieved by caloric restriction by reducing energy dense foods (saturated fat and refined carbohydrates) while maintaining adequate intakes of all essential nutrients (68).

Subgroups at high-risk/ liable to benefit from dietary interventions involving caloric restriction

- Patients with obesity (BMI > 30 kg/m2) at diagnosis (7)
- Patients rapidly gaining weight and abdominal fat (83), especially if they are premenopausal and with normal weight at diagnosis (20;22)
- Patients with alterations of the metabolic syndrome such as abdominal obesity, high insulin levels and insulin resistance, high circulating inflammatory markers (10;46;47;51).
- Patients with conditions associated with high circulating estrogens, such as in the hot flushes-negative postmenopausal subgroup in the WHEL trial, might benefit more from a dietary increase in fruits and vegetables (77). (These conclusions from post-hoc analyses need to be confirmed by specific intervention trials).
- Estrogen receptor negative patients who benefited more from a reduction in dietary fat in the WINS trial (71). (These conclusions from post-hoc analyses need to be confirmed by specific intervention trials).

DOSE RESPONSE TO DIETARY INTERVENTIONS

Most authors agree that in all individuals with excess weight, an intentional weight loss of 5-10% achieved by healthy eating, caloric restriction and physical exercise, and maintaining a BMI between 18.5 and 25 kg/m2 is likely to have significant health benefits. This approach also applies to cancer survivors who would benefit from the decrease in the risk of both BCa recurrences and of co-morbidities (68). In practice this can be achieved by a typical hypocaloric diet (decrease daily caloric intake by 500 kcal) (73) or by following the recommendations of the Diabetes Prevention Program (DPP) that also stressed moderate to intense physical exercise (at least 150 minutes/week) (84). Even small decreases in caloric intake (by little more than 150 kcal/day), achieved by adapting the dietary pattern, have significant beneficial benefits. The WINS data suggests that for every 38 patients with BCa who change their diet by eating less fat, one additional BCa recurrence would be prevented (71). However, in order to retard cancer growth significantly, the mice studies indicate that substantial weight losses (for example a 30% lowering of body fat) are needed (56).

Is it safe? Potential adverse effects

LEAN & BONE MASS

Excessive weight loss with a drop in BMI values to less than 20 kg/m2 is a well-known risk factor for fractures especially if associated with aromatase inhibitor treatment (85). In overweight postmenopausal BCa survivors undergoing weight loss diets, a weight loss of 6 kg was achieved at the expense of a significant 0.7 kg loss of lean mass (73). Promoting physical activity to slow down loss of muscle and bone mass during weight loss regimens is thus indispensable to improve prognosis. It is currently incorporated in all the lifestyle guidelines for cancer patients (83;86).

Perspectives

LIMITATIONS OF THE INTERVENTION TRIALS

In order to propose clear guidelines to BCa patients, future trials will need to address the limitations found in the afore-mentioned trials. Some study design issues are small participant numbers and multiple interventions, heterogeneity and imbalance in the comparison groups in relation to confounding and other prognostic factors, lack of biomarkers of dietary compliance/adherence, drop-in in the control groups, short duration and variable time-frames and inconsistent definition of the endpoints. Moreover, It is not clear to what extent individual studies fully adjusted for potential confounders such as the tumour type, type of treatment, amount of treatment received, and the dissemination of the disease (16). Unbalanced quoting of study results, for example, by giving too much weight to non-RCT studies or not taking into account unpublished results, can also distort conclusions (65).
It should be stressed that any strategy derived from the conclusions of dietary intervention studies on cancer survivors will need to take into account that cancer is not a static disease and that the nutritional needs of each individual-and thus the impact of any diet change- can evolve in the course of the various phases of survivorship.

Moreover, dietary advice to manage weight -and thus influence prognosis -will be inadequate if not combined with appropriate recommendations on physical exercise.
And finally, though this is not the subject of this article, primary prevention to stop the incidence of cancer is still the best recommendation to improve the prognosis of individuals at risk. This implies that an optimal diet and lifestyle should be adopted since pregnancy and early age.

The 2014 CUP Report concludes that the above-mentioned limitations in study design reduce the strength of the evidence needed to make specific dietary recommendations for breast cancer survivors. Nevertheless, the following healthy lifestyle recommendations are given (16):

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

ONGOING TRIALS ON BREAST CANCER PATIENTS

There are 3 ongoing Phase I trials on the safety and feasibility of short term fasting just before and/or during chemotherapy in several types of cancer, but no results are available yet (87). Another, potentially promising approach, is the use of energy-restriction mimetics, such as metformin, that activate the same metabolic pathways as during the cellular energy stress caused by glucose deprivation (88). As for interventions to control weight in BCa survivors, there are 28 trials currently registered in the NIH Clinical Trials website (89). Three relevant trials still underway are the Exercise and Nutrition to Enhance Recovery and Good Health in You (ENERGY) trial (90), the Lifestyle Intervention Study in Adjuvant Treatment of Early Breast Cancer (LISA)(91) and the lifestyle intervention arm of the European SUCCESS C trial (92) (the protocols are shown in Table 1). Several important considerations for the design of these trials were outlined in a 2006 NCI workshop. For example, in a 5-year diet and physical activity controlled intervention trial -to achieve a 10% reduction of body weight in BCa survivors with BMI> 25 kg/m2, or to avoid weight gain in those with BMI≤ 25 kg/m2- an estimated sample size of 4400 to 5100 would be needed in order to investigate the impact of weight control on disease-free and BCa recurrence-free survival with sufficient power (93).

Addenda

SUMMARY OF THE EVIDENCE ON THE IMPACT OF WEIGHT ON PROGNOSIS IN PROSTATE CANCER SURVIVORS

Obesity is associated with a higher risk of dying from prostate cancer (PCa), but it is not clear whether this is the result of increased incidence, faster progression after diagnosis, or both (8). Regarding incidence, the data from the Cancer Prevention Study II Nutrition Cohort (n=69 991 subjects followed for 11 years) reveals that obese patients have a higher risk of advanced PCa forms, but a lower risk of localized forms (94). A recent meta-analysis of prospective studies on more than a million subjects has confirmed this finding. It indicates that excess adiposity has an opposing etiologic impact depending on the PCa subtype (95;96). These conclusions are further supported 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 (97). By discriminating between the different types of prostate cancer (fatal, advanced and early non-advanced) it can now conclude with that there is strong evidence that being overweight or obese increases the risk of advanced cancer.

It is important to note that no conclusion could be drawn for total or non-advanced prostate cancer and that no distinction could be made between the periods before and after diagnosis. These findings have obvious implications on the prognosis of these patients.

In addition, obesity at diagnosis and weight gain in the 25 years before diagnosis both increase the risk of biochemical recurrence (PSA increase) after prostatectomy or radiotherapy (98). More specifically, an increase in weight of more than 2.2 kg in the period encompassing 5 years before diagnosis and 1 year after radical prostatectomy is associated with a 94% increase in the risk of recurrence (99).

Overall, a meta-analysis indicates that each 5 kg/m2 increase in BMI increases the risk of biochemical recurrence by 21% in treated PCa patients (n= 26 479), the risk of of PCa mortality by 20% in PCa survivors (n= 18 203) and by 15% in a population that was initially cancer-free (n=1 263 483) (100). Dietary intervention trials with an impact on weight show that decreasing fat intake to 15% of total energy intake (with or without supplementation with fish oil) in newly diagnosed PCa patients resulted in the loss of around 2.5 kg in body weight after 4-6 weeks even though the intervention was designed to maintain body weight. Compared to the habitual Western diet (40% energy from fat), the low fat diet led to significant decreases in serum lipids and proliferation indexes in the prostate cancer cells, but no change in PSA or hormonal status (101;102). In PCa patients awaiting prostatectomy, a more moderate lowering of dietary fat intake (from 36 to 28% energy) resulted in a slight but significant decrease in BMI (from 29 to 28 kg/m2) after 3 weeks, but no effect on tumor proliferation rates (103). A more drastic lowering of fat intake to 10% energy by adhering to a vegan Ornish diet led to a decrease of 4.5 kg body weight, as well as a significant lowering of PSA levels after one year. There was also less recourse to conventional cancer therapy after two years (104;105).

The current guidelines on weight management in PCa patients do not differ from those for BCa survivors. The 2014 CUP recommendations stress the importance of maintaining a healthy weight, eating a healthy diet and being physically active (97). Since these patients are likely to lose bone and muscle mass as a result of androgen deprivation therapy, special emphasis is given to adequate exercise (68).

SUMMARY OF THE EVIDENCE ON THE IMPACT OF WEIGHT ON PROGNOSIS IN COLORECTAL CANCER SURVIVORS

There is convincing evidence that obesity increases the risk of developing colorectal cancer (CRC), more in men than women (96;106). In contrast, there are not enough studies investigating the impact of excess body weight and adiposity at and after diagnosis on CRC recurrence and survival (8). A systematic review of 20 observational studies reports a weak but inconsistent association between obesity and high visceral fat before/at diagnosis and mortality (all-cause and colorectal specific), and more in women than men and depending on the molecular subtype of tumor (107). The follow-up study of the Cancer Prevention Study II Nutrition Cohort (n= 184 000) demonstrated a significant association between mortality and high pre-diagnosis BMI in both men and women, but not with post-diagnosis BMI. Again, this association was stronger in the localized than in the regional tumors (108).

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Table 1: Dietary intervention trials affecting weight control in breast cancer survivors

Author Year (Ref.)	Study	Subject characteristics	Study Design Intervention target dietary intake	Achieved dietary intake Int. *minus* Co.	Duration (drop-out Int./Co.)	Impact on adiposity Int. *minus* Co.	Clinical Outcome
Chlebowski 2006 (71)	WINS (2437)	48-79 y <1 yr post-surgery Conventional Ca Therapy 65% menopausal HRT 27/27/46% Ob/ov/nl	Multicenter RCT ↓ Fat to 15%En (from baseline 29.6 %) Weight maintenance (baseline≈1600 kcal/d)	– 8 %En Fat – 167 kcal/d + 2.4 g/d Fiber	5 y (61/56%)	– 2.7 kg body weight – 1.1 kg/m^2 BMI	HR Relapse-free survival **0.76 (0.60-0.98)** **0.58 (0.37-0.91) in ER–subgroup** HR Disease-free survival 0.81 (0.65-0.99) HR overall survival 0.89 (0.65-1.21), ns
Pierce 2007 (76;77)	WHEL (3088)	18-70 y <23 mo after diagnosis ≈48% menopausal HRT 26/31/43% Ob/ov/nl	Multicenter RCT ↑ Fruits to 3/d ↑ Vegetable servings to 5/d ↑ Fiber to 30g/d ↓ Fat to 15-20%En (from baseline 28.6 %) Weight maintenance (baseline≈1700 kcal/d)	+ 1 Fruit/d + 2 Veg./d same ↓ 170 kcal/d in both groups - 3.5% En Fat + 5.3 g/d Fiber	7 y (15/15%)	Body Weight unchanged in both Int. and Co.	HR Disease-free survival 0,90 (0.80-1.14), ns 0,69 (0.51-0.93) in hot flushes - subgroup HR overall survival 0,91 (0.72-1.15), ns
Thompson 2012 (74)	CHOICE (142)	56 ± 8 y > 4 mo after completion treatment All postmenopausal Ob class I/ov	Non-random CT ↓ to 1200 Kcal/d + ↑ PA = weight losing (↓ 700 kcal/d) *Either* low CH (32/fat 46/prot 22%) *or* low fat (17/CH 62/prot 20%)		6 mo. (13/11/9%)	↓ 10 kg body weight in both intervention groups	Beneficial effect on blood glucose and lipids in both intervention groups.

Author Year (Ref.)	Study	Subject characteristics	Study Design Intervention target dietary intake	Achieved dietary intake Int. *minus* Co.	Duration (drop-out Int./Co.)	Impact on adiposity Int. *minus* Co.	Clinical Outcome
Scott 2013 (109)	(90)	36-77 y 3-18 mo after completion treatment 68% postmenopausal Ob/ov	RCT ↓ by 600 Kcal/d + ↑ PA Individualized weight losing healthy eating & exercise	Same intake energy, CH, protein in Int. and Co. – 9 g/d fat	6 mo. (13/12%)	– 0.69 kg body weight – 0.30 kg/m^2 BMI – 3.32 cm WC	Significant improvement in Int. for cholesterol, leptin, diastolic blood pressure, cardiopulmonary fitness and quality of life.
Villarini 2012 (82;110)	DIANA-5 (96)	53±11 y (Int.) 48±9 y (Co.) During adjuvant chemotherapy	RCT ↓ by 250 Kcal/d Mediterranean macrobiotic diet	+ 1.4 whole cereal/d + 0.2 legume/d – 0.5 sugar/d – 1 refined cereal/d – 0.4 dairy/d Similar consumption meat, vegetables, fruit	≈3 mo.(1st cycle) (1%)	– 1.3 kg body weight – 0.50 kg/m^2 BMI – 1.2 cm WC	Feasible lifestyle improvement in BCa patients under treatment Follow-up trial (n 1208) investigating BCa recurrence is still ongoing
Campbell 2012 (111)	(14)	55 ± 8 y ≥ 3 mo after completion treatment 85% postmenopausal Ob/ov	Single group pre-post test ↓ dietary calories + ↑ PA= Weight losing (↓ 7% body weight: DPP guidelines) ↓ Fat to 20%En (baseline 31.8 %)	Unchanged kcal/d ↓ 5.3%En fat ↑ 13.1 Met equiv. h/week	6 mo. (follow-up 36 mo.)	↓ 3.8 kg body weight ↓ 1.4 kg/m^2 BMI ↓ 4.2 cm WC	Feasible lifestyle improvement in BCa survivors. Trend for improvement in LDL cholesterol A similar 1 y -intervention (NEW trial. 439 at risk postmenopausal) resulted in beneficial changes in steroid and metabolic hormones (109).
Pakiz 2011 (64)	HWM (68)	33-71 y <14 y after diagnosis Ob/ov	RCT Individualized lifestyle advice: ↓ dietary calories + ↑ PA= Weight losing (↓ 500 -1000 kcal/d)	↑ 1.9 h/week	4 mo. (follow-up 12 mo) (16/3%)	– 5.5 kg body weight – 2.0 kg/m^2 BMI – 4.6 cm WC	Improvement TNF-α and IL-6

Author Year (Ref.)	Study	Subject characteristics	Study Design Intervention target dietary intake	Achieved dietary intake Int. *minus* Co.	Duration (drop-out Int./Co.)	Impact on adiposity Int. *minus* Co.	Clinical Outcome
Christy 2011 (112)	FRESH START (543)	22-85 y BCa, Pca	Multicenter RCT Individualized lifestyle advice for 10 mo: ↑ Fruit &Veg. servings to ≥5/d ↓ Fat to <30%En (baseline 38 %) ↑ PA by 150 min/wk	+ 2.6 diet quality score + 0.3 Fruit & Veg/d – 1.5%En fat	2 y (10%)	– 0.3 kg/m^2 BMI	Feasible and sustainable improvement in dietary quality
Demark 2012 (113)	RENEW (641)	65-87 y ≥ 5 y after diagnosis BCa, PCa or CRC Ob/ov ; sedentary	Randomized cross-over Immediate *or* Delayed intervention: Tailored lifestyle advice to ↑ PA and ↑ diet quality	+ 5.2 diet quality score + 1 Fruit & Veg/d – 1%En fat + 45.8 min PA/week	1-2 y (13/24% at ½ y)	– 1.46 kg body weight – 0.56 kg/m^2 BMI	Sustainable long-term lifestyle improvement in older cancer survivors
Rock 2013 (90)	ENERGY (693)	≥ 21y ≤ 5 y after diagnosis Ob/ov	RCT Lifestyle advice ↓ dietary calories + ↑ PA = Weight losing (↓ 500 -1000 kcal/d)	Ongoing trial (start 2010-2012)	4y	Weight will be followed-up every 6 mo.	Feasibility of sustainable 7% weight loss Impact on quality of life, co-morbidities Vanguard for fully powered future trial investigating disease- and BCa recurrence-free survival Disease-free interval BCa recurrence
Goodwin (91)	LISA (2150 to be enrolled)	Letrozole adjuvant therapy Postmenopausal Ob/ov	RCT Tailored lifestyle advice to ↑ PA and ↑ diet quality= Weight losing (↓ 10% body weight=↓ 500 -1000 kcal/d) ↓ Fat to 20%En ↑ PA to 150-200min/wk	Ongoing trial	8y (end in 2018)	Weight will be followed-up at 6,12,24,36, 48 and 60 mo.	Disease-free survival Overall survival Quality of life Co-morbidities

Author Year (Ref.)	Study	Subject characteristics	Study Design Intervention target dietary intake	Achieved dietary intake Int. *minus* Co.	Duration (drop-out Int./Co.)	Impact on adiposity Int. *minus* Co.	Clinical Outcome
Rack (92)	SUCCESS C (3642)	Anthracyclin-free chemotherapy Her2/neu negative BMI 24-40 kg/m2	German Multicenter Randomized Phase III, 2x2 design (type chemo; lifestyle) Tailored lifestyle advice Weight losing in 6 mo= ↓ 500 - 1000 kcal/d) (↓ 10% body weight if BMI>30) (↓ 5% body weight if BMI 24-29.9) Weight maintenance for 2 yrs ↓ Fat to 20-25%En ↑ Fruit &Veg, wholegrain ↑ PA to 150-200min/wk	ongoing (start 2009)	2y	Follow-up every 6 or 12 mo	Disease-free survival Predictive role of obesity-related biomarkers (insulin, adipokines)

WINS Women's Intervention Nutrition Study; WHEL Women' s Healthy Eating and Living study; RENEW Reach Out to Enhance Wellness; HWM Healthy Weight Management study; ENERGY Exercise and Nutrition to Enhance Recovery and Good Health; LISA Lifestyle Intervention Trial in Adjuvant Treatment of early Breast Cancer; DPP Diabetes Prevention Program; DASH Dietary Approaches to Stop Hypertension; SUCCESS C ; RCT Randomized controlled trial; HR Hazard ratio for intervention vs control (95% confidence intervals); ER estrogen receptor status; Int./Co. Intervention group/Control group; Ob/ov/nl : obese (BMI ≥30 kg/m^2), overweight (BMI 25 or 26-29.9 kg/m^2), normal weight (BMI < 25 or 26 kg/m^2); HRT hormone replacement therapy; ns p-value > 0.10); Int. *minus* Co. difference between the change since baseline in the intervention group and the change since baseline in control group; relapse is defined as a BCa recurrence at any site; disease-free refers to absence of any cancer; PA physical activity; postmenopausal includes perimenopausal; WC waist circumference.

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Reference List

(1) 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.

(2) Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083-96.

(3) Parr CL, Batty GD, Lam TH, Barzi F, Fang X, Ho SC, et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. The Lancet Oncology. 2010 Aug;11(8):741-52.

(4) Center for Disease Control and Prevention. Basic Information about Cancer Survivorship. Accessed 2012 November 12 [Internet]. Available from: http://www.cdc.gov/cancer/survivorship/basic_info/index.htm.

(5) National Cancer Survivorship Initiative. Vision Document. Accessed 2012 November 12 [Internet]. Available from: http://www.ncsi.org.uk/wp-content/uploads/NCSI-Vision-Document.pdf.

(6) Guh D, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis A. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health. 2009;9(1):88.

(7) 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.

(8) Parekh N, Chandran U, Bandera EV. Obesity in Cancer Survival. Annual Review of Nutrition. 2012 Jul 18;32(1):311-42.

(9) 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.

(10) 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.

(11) Sinicrope FA, Dannenberg AJ. Obesity and Breast Cancer Prognosis: Weight of the Evidence. Journal of Clinical Oncology. 2011 Jan 1;29(1):4-7.

(12) 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.

(13) Kumar NB, Cantor A, Allen K, Cox CE. Android obesity at diagnosis and breast carcinoma survival: Evaluation of the effects of anthropometric variables at diagnosis, including body composition and body fat distribution and weight gain during life span,and survival from breast carcinoma. Cancer. 2000 Jun 15;88(12):2751-7.

(14) 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.

(15) 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.

(16)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.

(17) 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.

(18) 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.

(19) 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.

(20) 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.

(21) 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.

(22) 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.

(23) 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.

(24) 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.

(25) 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 Control. 2008 Dec;19(10):1319-28.

(26) World Cancer Research Fund. Continuous Update Project. Breast Cancer. Accessed 2012 October 8 [Internet]. Available from: http://www.dietandcancerreport.org/cup/current_progress/breast_cancer.php.

(27) Kawai M, Minami Y, Nishino Y, Fukamachi K, Ohuchi N, Kakugawa Y. Body mass index and survival after breast cancer diagnosis in Japanese women. BMC Cancer. 2012;12:149.

(28) 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.

(29) 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.

(30) 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.

(31) 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.

(32) 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.

(33) Pfeiler G, K+Ânigsberg R, Fesl C, Mlineritsch B, Stoeger H, Singer CF, et al. Impact of Body Mass Index on the Efficacy of Endocrine Therapy in Premenopausal Patients With Breast Cancer: An Analysis of the Prospective ABCSG-12 Trial. Journal of Clinical Oncology. 2011 Jul 1;29(19):2653-9.

(34) 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.

(35) 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.

(36) American Cancer Society. Breast Cancer Facts & Figures 2011-2012. Accessed 2012 October 8 [Internet]. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/docume....

(37) 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.

(38) American Cancer Society. Cancer Facts & Figures 2012. Accessed 2012 October 8 [Internet]. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/docume....

(39) National Cancer Institute. Office for Cancer Survivorship. Prevalence. Accessed 2012 November 23 [Internet]. Available from: http://cancercontrol.cancer.gov/ocs/prevalence/prevalence.html#allsites.

(40) American Cancer Society. Cancer Treatment and Survivorship 2012-2013. Accessed 2012 November 23 [Internet]. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/docume....

(41) International Agency for Research on Cancer. GLOBOCAN 2008. Accessed 2012 November 23 [Internet]. Available from: http://globocan.iarc.fr/.

(42) Wayne SJ, Lopez ST, Butler LM, Baumgartner KB, Baumgartner RN, Ballard-Barbash R. Changes in dietary intake after diagnosis of breast cancer. Journal of the American Dietetic Association. 2004 Oct;104(10):1561-8.

(43) 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.

(44) Patterson RE, Rock CL, Kerr J, Natarajan L, Marshall SJ, Pakiz B, et al. Metabolism and breast cancer risk: frontiers in research and practice. Journal of the Academy of Nutrition and Dietetics. 2013 Feb;113(2):288-96.

(45) Stebbing J, Sharma A, North B, Athersuch TJ, Zebrowski A, Pchejetski D, et al. A metabolic phenotyping approach to understanding relationships between metabolic syndrome and breast tumour responses to chemotherapy. Annals of Oncology. 2012 Apr 1;23(4):860-6.

(46) 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.

(47) 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.

(48) 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.

(49) Morris PG, Hudis CA, Giri D, Morrow M, Falcone DJ, Zhou XK, et al. Inflammation and Increased Aromatase Expression Occur in the Breast Tissue of Obese Women with Breast Cancer. Cancer Prevention Research. 2011 Jul 1;4(7):1021-9.

(50) Hausman GJ, Richardson RL. Adipose tissue angiogenesis. Journal of Animal Science. 2004 Mar 1;82(3):925-34.

(51) 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.

(52) Litton JK, Gonzalez-Angulo AM, Warneke CL, Buzdar AU, Kau SW, Bondy M, et al. Relationship Between Obesity and Pathologic Response to Neoadjuvant Chemotherapy Among Women With Operable Breast Cancer. Journal of Clinical Oncology. 2008 Sep 1;26(25):4072-7.

(53) 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.

(54) 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.

(55) 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 of the United States of America. 2008 Jun 17;105(24):8215-20.

(56) 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.

(57) Lee C, Raffaghello L, Longo VD. Starvation, detoxification, and multidrug resistance in cancer therapy. Drug Resistance Updates. 2012 Feb;15(1-2):114-22.

(58) Lee C, Safdie FM, Raffaghello L, Wei M, Madia F, Parrella E, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. Cancer Research. 2010 Feb 15;70(4):1564-72.

(59) Norrelund H. The metabolic role of growth hormone in humans with particular reference to fasting. Growth Hormone & IGF Research. 2005 Apr;15(2):95-122.

(60) Cantó C, Auwerx J. PGC-1[alpha], SIRT1 and AMPK, an energy sensing network that controls energy expenditure. Current Opinion in Lipidology. 2009;20(2).

(61) 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.

(62) Jen KL, Djuric Z, DiLaura NM, Buison 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.

(63) Wayne SJ, Neuhouser ML, Ulrich CM, Koprowski C, Baumgartner KB, Baumgartner RN, et al. Dietary fiber is associated with serum sex hormones and insulin-related peptides in postmenopausal breast cancer survivors. Breast Cancer Research and Treatment. 2008 Nov;112(1):149-58.

(64) 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. (64) Davies AA, Davey Smith G, Harbord R, Bekkering GE, Sterne JAC, Beynon R, et al.

(65) Nutritional Interventions and Outcome in Patients With Cancer or Preinvasive Lesions: Systematic Review. Journal of the National Cancer Institute. 2006 Jul 19;98(14):961-73.

(66) Davies NJ, Batehup L, Thomas R. The role of diet and physical activity in breast, colorectal, and prostate cancer survivorship: a review of the literature. British Journal of Cancer. 2011 Nov 8;105(S1):S52-S73.

(67) Robien K, Demark-Wahnefried W, Rock CL. Evidence-Based Nutrition Guidelines for Cancer Survivors: Current Guidelines, Knowledge Gaps, and Future Research Directions. Journal of the American Dietetic Association. 2011 Mar 1; 111[3]: 368-375.

(68) Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. A Cancer Journal for Clinicians. 2012 Jul;62(4):242-74.

(69) Patterson RE, Cadmus LA, Emond JA, Pierce JP. Physical activity, diet, adiposity and female breast cancer prognosis: A review of the epidemiologic literature. Maturitas. 2010 May;66(1):5-15.

(70) Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, et al. Fasting and cancer treatment in humans: A case series report. Aging. 2009 Dec;1(12):988-1007.

(71) 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.

(72) 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.

(73) 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.

(74) 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.

(75) 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.

(76) 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.

(77) 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.

(78) Thomson CA, Rock CL, Thompson PA, Caan BJ, Cussler E, Flatt SW, et al. Vegetable intake is associated with reduced breast cancer recurrence in tamoxifen users: a secondary analysis from the Women's Healthy Eating and Living Study. Breast Cancer Research and Treatment. 2011 Jan;125(2):519-27.

(79) 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.

(80) Belle FnN, 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.

(81) 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 Control. 2011 Apr;22(4):589-98.

(82) 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.

(83) Demark-Wahnefried W, Campbell KL, Hayes SC. Weight management and its role in breast cancer rehabilitation. Cancer. 2012;118(S8):2277-87.

(84) 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.

(85) 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.

(86) Solti M, Webb T. Nutrition and exercise in cancer survivors. Community Oncology. 2012 Aug;9(8):266-8.

(87) National Institute of Health. Clinical Trials registered on "Short term fasting" and "Chemotherapy" or "Cancer". Acessed 30-11-2012. Available from: http://www.clinicaltrials.gov/ct2/results?term=%22short-term+fasting%22+...

(88) Dowling RJ, Niraula S, Stambolic V, Goodwin PJ. Metformin in cancer: translational challenges. Journal of Molecular Endocrinology. 2012 Jun;48(3):R31-R43.

(89) National Institute of Health. Clinical Trials registered on "breast cancer" and "weight". Accessed 2012 November 21 [Internet]. Available from: http://www.clinicaltrials.gov/ct2/results/refine?term=%22breast+cancer+s....

(90) Rock CL, Byers TE, Colditz GA, Demark-Wahnefried W, Ganz PA, Wolin KY, et al. Reducing breast cancer recurrence with weight loss, a vanguard trial: the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) Trial. Contemporary Clinical Trials. 2013 Mar;34(2):282-95.

(91) Clinical Trials NIH. Lifestyle Intervention Study in Adjuvant treatment of early breast cancer LISA. Accessed 2012 November 30 [Internet]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00463489?term=%22breast+cancer....

(92) Rack B, Andergassen U, Neugebauer J, Salmen J, Hepp P, Sommer H, et al. The German SUCCESS C Study – The First European Lifestyle Study on Breast Cancer. Breast Care. 2010;5(6):395-400.

(93) Ballard-Barbash R, Hunsberger S, Alciati MH, Blair SN, Goodwin PJ, McTiernan A, et al. Physical activity, weight control, and breast cancer risk and survival: clinical trial rationale and design considerations. Journal of the National Cancer Institute. 2009 May 6;101(9):630-43.

(94) 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.

(95) 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.

(96) World Cancer Research Fund. Continuous Update Project. Colorectal Cancer. Accessed 2012 April 16 [Internet]. Available from: http://www.dietandcancerreport.org/cancer_resource_center/downloads/cu/C….

(97) 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.

(98) 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.

(99) 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.

(100) 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.

(101) Aronson WJ, Barnard RJ, Freedland SJ, Henning S, Elashoff D, Jardack PM, et al. Growth Inhibitory Effect of Low Fat Diet on Prostate Cancer Cells: Results of a Prospective, Randomized Dietary Intervention Trial in Men With Prostate Cancer. The Journal of Urology 2010 183[1], 345-350.

(102) Aronson WJ, Kobayashi N, Barnard RJ, Henning S, Huang M, Jardack PM, et al. Phase II Prospective Randomized Trial of a Low-Fat Diet with Fish Oil Supplementation in Men Undergoing Radical Prostatectomy. Cancer Prevention Research. 2011 Dec 1;4(12):2062-71.

(103) 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.

(104) Ornish D, Weidner G, Fair Wr, Marlin R, Pettengill 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.

(105) 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.

(106) Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut. 2013 Jun 1;62(6):933-47.

(107) 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.

(108) 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.

(109) Scott E, Daley AJ, Doll H, Woodroofe N, Coleman RE, Mutrie N, et al. Effects of an exercise and hypocaloric healthy eating program on biomarkers associated with long-term prognosis after early-stage breast cancer: a randomized controlled trial. Cancer Causes & Control. 2013;24(1):181-91.

(110) Villarini A, Pasanisi P, Raimondi M, Gargano G, Bruno E, Morelli D, et al. Preventing weight gain during adjuvant chemotherapy for breast cancer: a dietary intervention study. Breast Cancer Research and Treatment. 2012;135(2):581-9.

(111) Campbell KL, Foster-Schubert KE, Alfano CM, Wang CC, Wang CY, Duggan CR, et al. Reduced-Calorie Dietary Weight Loss, Exercise, and Sex Hormones in Postmenopausal Women: Randomized Controlled Trial. Journal of Clinical Oncology. 2012 Jul 1;30(19):2314-26.

(112) Christy SM, Mosher CE, Sloane R, Snyder DC, Lobach DF, Demark-Wahnefried W. Long-term dietary outcomes of the FRESH START intervention for breast and prostate cancer survivors. Journal of the American Dietetic Association. 2011 Dec;111(12):1844-51.

(113) Demark-Wahnefried W, Morey MC, Sloane R, Snyder DC, Miller PE, Hartman TJ, et al. Reach Out to Enhance Wellness Home-Based Diet-Exercise Intervention Promotes Reproducible and Sustainable Long-Term Improvements in Health Behaviors, Body Weight, and Physical Functioning in Older, Overweight/Obese Cancer Survivors. Journal of Clinical Oncology. 2012 Jul 1;30(19):2354-61.