

TRIAL OF BEHAVIORAL WEIGHT LOSS AND METFORMIN TREATMENT TO
LOWER INSULIN GROWTH FACTOR IN CANCER SURVIVORS

Protocol

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1. INTRODUCTION

The ability to diagnose and treat cancer at early stages has led to an increased number of cancer survivors, and this has prompted the study of behavioral and pharmacologic interventions for improving survival and quality of life in cancer survivors.

Insulin-like growth factor-1 (IGF-1) is a central biomarker of interest for the study of interventions in survivors of solid tumors, and is associated with increased risk of several common cancers including breast, colorectal, prostate, and lung.¹ Some studies suggest higher IGF-1 levels are associated with higher mortality in patients with cancer,² and it has been hypothesized that reducing IGF-1 might prevent cancer in persons without cancer (primary prevention) and cancer recurrence among cancer survivors (secondary prevention).

IGF-1 is a mitogen that promotes cell-cycle progression and cellular transformation by rapid cell turnover. Over 80% of IGF-1 circulating in blood is bound to the insulin-like binding protein (IGFBP)-3. Two putative strategies that might lower IGF-1 include pharmacologic (e.g., metformin) and non-pharmacologic (e.g., weight loss) approaches. Metformin and weight loss are particularly appealing interventions, given their beneficial effects in treating other conditions, their widespread use, and their well-documented safety profiles.

Metformin is associated with decreased risk of several types of cancer in patients with diabetes³⁻⁵. There are multiple mechanisms by which metformin might inhibit cancer development and growth. In addition to its effects on glucose lowering and insulin sensitivity,⁶ preliminary evidence suggests that metformin may decrease circulating levels of IGF-I and other growth factors.

While the relationship of IGF-1 with adiposity is inconsistent,⁷⁻⁹ there is a positive association between IGFBP-3 (reflective of bound IGF-1) and BMI, indicating lower biologically active IGF1 levels among obese women.¹⁰ Also, lifestyle changes including weight loss and other healthy behaviors have also been shown to improve insulin sensitivity

In this context, we propose a randomized, 3-arm trial to compare the effects of self-directed weight loss, coach-directed weight loss, and metformin treatment on IGF-1 and the IGF-1 to IGFBP3 ratio. This trial will enroll ~120 cancer survivors (~50% female, ~50% African American) who will be randomized to one of 3 arms:

A. Self-Directed Weight Loss

B. Coach-Directed Behavioral Weight loss

C. Metformin Treatment

The duration of intervention and follow-up will be 12 months. The primary outcomes will be changes in IGF-1 and the IGF-1:IGFBP-3 ratio at 6 months. Primary outcome assessment will occur at 6 months to maximize data collection at the time of the most anticipated weight loss and to minimize a decrease in sample size due to censoring from recurrent cancer. However, data from 12 months will also be reported.

2. SPECIFIC AIMS

Primary Aims

- 1) Test the hypothesis that participants in the coach-directed behavioral weight loss arm will experience greater decreases in IGF-1 and IGF-1:IGFBP3 than those in the self-directed weight loss arm at 6 months.
- 2) Test the hypothesis that participants in the metformin arm will experience greater decreases in IGF-1 and IGF-1:IGFBP3 than those in the self-directed weight loss arm at 6 months.

Secondary Aims

- 3) Test the hypothesis that participants in the metformin arm will experience greater decreases in IGF-1 and IGF-1:IGFBP3 than those in the coach-directed behavioral weight loss arm at 6 months.
- 4) Determine the effects of coach-directed behavioral weight loss and metformin separately on IGF-1 and IGF-1:IGFBP3 at 12 months (Aims 1 – 3 at 12 months)
- 5) Determine the effects of coach-directed behavioral weight loss and metformin separately on the following outcomes at 6 and 12 months:
 - Weight, Body Mass Index
 - EuroQol
 - Dietary intake and physical activity
 - Glucose, insulin, hemoglobin A1c
 - IL-6, IL-8, CRP
 - Side effects questionnaire
- 6) Conduct exploratory analyses (Aims 1 – 5 above) in key, pre-specified subgroups, defined by sex, race, type of cancer, and baseline levels of IGF-I and the IGF-1: IGFBP-3 ratio.

- 7) Explore the association of physical activity levels with IGF-1 and the IGF-1: IGFBP-3 ratio.
- 8) Collect and store specimens of blood and stool for other assays. Candidate assays include leptin, adiponectin, VEGF, HGF, and EGF, SLC22A1, SLC22A2, and SLC47A1 gene variants and 16S bacterial whole genome sequencing (stool).

3. BACKGROUND AND RATIONALE

3.1 Epidemiology of Overweight/Obesity among Cancer Survivors

Obesity is a prevalent and modifiable factor that negatively affects the risk of cancer, and survival from solid tumor cancers.¹¹⁻¹⁴ In the United States, rates of overweight and obesity as measured by Body Mass Index (BMI) have been steadily increasing since the 1960s.¹⁵ In 2011-2012, 68.5% of US adults were obese or overweight (BMI ≥ 25 kg/m²).¹¹ In Maryland, the prevalence of obesity is 27.1%,¹⁶ in Baltimore city, 33.8 % of adults were found to be obese in the 2010 Baltimore City Community Health Survey.¹⁷ Due to the high prevalence of overweight and obesity in the general population, as well as the association between obesity and incidence of many common cancers,¹³ it is likely that obesity and overweight are common among cancer survivors.

There are an estimated 14.5 million cancer survivors living in the United States in 2014,¹⁸ and this number is expected to increase due to improvements in treatment and early detection as well as the aging of the general population.¹⁹ Among male cancer survivors in the US, the most common forms of cancer are prostate (43%), colon & rectum (9%), and melanoma (8%); for female cancer survivors, breast (41%), uterine corpus (8%) and colon & rectum (8%) cancers are most common.¹⁸ In the 2009 Behavioral Risk Factor Surveillance System (BRFSS) study sample, 27.5% of cancer survivors were obese (with significant variation by state), and 31.5 % of cancer survivors had not completed any leisure-time physical activity in the last 30 days.¹⁹

3.2 Evidence of Association between Overweight/Obesity and Cancer

Incidence: In 2007, The International Agency for Research on Cancer (*IARC*) published a comprehensive review of the association between obesity and cancer. This report concluded that there is “convincing” evidence that greater body fatness, most commonly measured by BMI, is a cause of cancers of the esophagus, pancreas, colon and rectum, breast (postmenopause), endometrium, and kidney; and is likely a cause of cancer of the gallbladder.¹² Additionally, the available evidence is “suggestive” of an association of body fatness with liver cancer.¹² Lung cancer is an exception to the general pattern of increased risk of cancer with increasing BMI. *IARC* concludes that despite epidemiological evidence that high BMI is protective of lung cancer, associations are likely due to residual confounding from cigarette smoking or reverse causation stemming from weight loss among those with

undiagnosed lung cancer.¹² A recent study of electronic medical records from the United Kingdom followed over 5 million individuals to evaluate the relationship between average effects of a 5 kg/m² increase in BMI on cancer risk. An elevated risk of incident cancer was found for cancers of the esophagus, colon, rectum, liver, gallbladder, pancreas, postmenopausal breast, cervix, uterus, ovaries, kidney, brain, thyroid, and leukemia.¹³

Survival: In one prospective study of nearly 900,000 men and women in the Cancer Prevention Study II cohort, the risk of death from any cancer was significantly higher among men and women in the highest BMI categories (calculated from self-reported height and weight at study enrollment), compared to normal weight men and women.²⁰ BMI was significantly associated with increased risk of death from cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney among men and women. Additionally, among men, greater BMI was associated with death due to stomach and prostate cancer; for women, death from breast, uterine, cervical, and ovarian cancer.²⁰ A pooled analysis from a recent review of 82 studies of breast cancer and survival related to body mass index found that BMI in the obese and overweight range prior to diagnosis of breast cancer was significantly associated with an increased risk of both all-cause mortality and breast cancer mortality, compared to normal weight women.²¹ Additionally, higher BMI measured within a year after diagnosis and one year or later after diagnosis was still associated with all-cause and breast cancer specific mortality.²¹ In a retrospective cohort study of 4376 Swedish men with prostate cancer, obese men had a 47% (HR 1.47, 95% CI 1.03-2.10) higher risk of mortality from any cause compared to men of normal weight, but no significant association was found between BMI and prostate specific mortality or prostate cancer progression.¹⁴ However, men who gained more than 5% of their bodyweight after diagnosis had a significantly increased risk of prostate-specific cancer risk.¹⁴

Recurrence: Among participants in the Nurse's Healthy Study with a diagnosis of breast cancer, BMI prior to diagnosis was positively correlated with recurrence, among never-smokers and post-menopausal women.²² Obesity is also associated with increased risk of prostate cancer recurrence,²³⁻²⁴. Obesity both five years before surgery and 1 year after surgery was associated with an increased risk of recurrence, compared to those of normal weight, in a prospective study of 1337 men who had received a prostatectomy from the same surgeon.²⁴ Thus, it is likely that obesity confers increased risk of cancer recurrence for several types of cancer, and that decreasing rates of obesity might decrease the rates of cancer recurrence in cancer survivors.

3.3 Weight Gain and Weight Loss in Cancer

Weight gain after diagnosis of breast cancer has been well documented. According to a review of studies evaluating weight gain after breast cancer diagnosis, between 50-96% of women diagnosed with early stage breast cancer were found to have gained weight after diagnosis.²⁵ Results from the same review suggest that weight gain is associated with the type of treatment, with women receiving chemotherapy more likely to gain weight than those receiving

surgery and/or radiation.²⁵ Data from the WHEL study demonstrated that only 10% of women returned to their pre-diagnosis weight after six years of follow-up.²⁶ Among survivors of prostate cancer, patterns of weight gain and weight loss are less clear. In a study of Swedish men diagnosed with localized prostate cancer, 14.8% reported a weight gain of more than 5% after diagnosis, but 8.9% experienced a loss of more than 5%, among those still alive after a median of four years after diagnosis.¹⁴ Joshi et al found similar results in a retrospective cohort study of men who had received a prostatectomy: 13.9% of men gained more than 2.2kg and 12.7% of men lost more than 2.2kg between 5 years prior to the surgery and one year after.²⁴

The weight gain that accompanies cancer diagnosis and treatment has been linked to increased recurrence of cancer. Of the 50 studies reviewed by Vance et al, ten evaluated the effect of weight gain after survival on recurrence of cancer.²⁵ Six of these studies found no relationship between weight gain after diagnosis and recurrence of breast cancer, but four of the studies found that weight gain was associated with increased recurrence, including a subsample of the Nurses' Health Study.²⁵ In the study by Joshi et al. mentioned above, the risk of recurrence was twice as high for men who gained more than 2.2kg compared to men for whom weight remained stable.²⁴ Bonn and colleagues also found an almost two-fold increase in the prostate-cancer specific mortality among men who gained more than 5% of their weight at diagnosis, compared to men with stable weight.¹⁴

3.4 Insulin-Like Growth Factor and Adiposity

Insulin-like growth factor I (IGF-1) is a mediator of growth hormone (GH) and is important for cell development and replication. When IGF-1 binds to the insulin-like growth factor I receptor (IGF-1R), pathways for the expression of genes related to cell growth, replication, and apoptosis are activated.²⁷ IGF binding proteins, including the most common, IGFBP-3, regulate IGF by increasing the half-life of IGFs and controlling their ability to bind to receptors.²⁷ IGFBP-3 may also stimulate apoptosis and block cell proliferation through mechanisms independent of IGFs.¹

Several recent observational, cross-sectional studies suggest that IGF-1 has a U-shaped relationship with BMI, with a peak in IGF-1 occurring around a BMI of 25 and then falling at higher BMI levels.²⁸⁻³¹ Another observational study using a racially diverse NHANES sample found that BMI was inversely associated with IGF-1 levels for all sex and race/ethnicity subgroups.³² In obese people, average total IGF-1 is often much lower than total IGF-1 among normal weight people, while free IGF-1 increases as BMI increases.³³

The relationship between weight loss and IGF-1 is unclear. In a small study, 71 obese women were randomized to receive restricted calorie diets or restricted calorie diets plus the weight loss drug Orlistat. Women in the Orlistat group lost more weight and had larger increases in IGF-1 after six months. However, it is unclear if the changes in IGF-1 are a function of the increased weight loss or Orlistat.³⁴ An earlier study of 20 women did not find any change in IGF-I related to weight loss after eight weeks of a low-calorie, low-carbohydrate diet.³⁵ In a recent clinical trial evaluating the effects of diet and exercise interventions on 68 postpartum

women who were overweight or obese prior to pregnancy, neither the diet nor the exercise intervention were associated with significant changes to IGF-I levels, despite weight loss in both intervention groups at both 12 weeks and 1 year.³⁶

A cross-sectional analyses among 700 breast cancer patients indicated higher physical activity levels were associated with lower IGF-I and IGF-3 levels.³⁷ Clinical trials have also demonstrated that exercise programs among breast cancer patients result in lower IGF levels.^{38,39} It was suggested that the strongest association among physical activity and IGF levels among breast cancer patients was associated with higher BMI, lower baseline physical activity levels and the absence of tamoxifen therapy.³⁸ However many of the extant trials have focused on exercise programs that were independent of weight loss efforts. It is not clear if aerobic exercise recommendations associated with a weight loss also result in decreases of IGF levels. Moreover the association among physical activity and IGF appears strongest among breast cancer survivors. No association was found between physical activity and IGF among prostate cancer survivors in three different trials.³⁸

There is some evidence that the type of diet can influence IGF-1 levels. A high-protein diet has been shown to increase IGF-1 among men with prostate cancer,⁴⁰ men with type II diabetes,⁴¹ and among middle-aged non-obese persons.⁴² Reduction in calories, however, has not been noted to lead to decreased IGF-1 levels,^{35,42,43} except when weight loss was substantial.³⁴

Among healthy adults, IGF-1 measurements have been shown to be stable over time.⁴⁴⁻⁴⁷ For example, In a study of over 800 older adults, a correlation of $r=0.94$ was found for IGF-1 levels measured by Immunoradiometric assay 8-54 days apart.⁴⁴ In a study of 1000 Brazilian adults 21-70, IGF-1 levels measured 12 weeks apart had a correlation of $r=0.91$, and the variation between the two measurements was 20% or less in 99% of people.⁴⁷ Regardless of body mass index, IGF-1 and IGFBP-3 were stable throughout a 24-hour observation period in both normal weight and overweight and obese participants.⁴⁸ IGF-1 has also been demonstrated to be stable in cancer patients, both throughout the day⁴⁹ and across several months.⁵⁰⁻⁵²

3.5 Insulin-like Growth Factor and Cancer Incidence and Recurrence

High levels of circulating IGF-1 have been implicated in the development of cancer.²⁷ High levels of circulating IGF-1 are associated with an increased risk of some common cancers, such as prostate, premenopausal breast, and colorectal; while high levels of circulating IGFBP-3, the main binding protein of IGF-1, is associated with a decreased risk of these cancers.¹ In vitro studies provide evidence that IGF-IR is over expressed on some types of cancer cells and that IGF-IR enhances cell replication and decreases apoptosis.⁵³ In animal models with decreased IGF-1 production, decreased tumorigenesis was seen, while mouse models with high IGF-1 had increased occurrence of cancer.⁵³

In epidemiological studies, there is also evidence that higher levels of IGF-1 are associated with cancer risk. Using data from The European Prospective Investigation into Cancer and

Nutrition (EPIC) study, a prospective study of more than 500,000 Europeans, researchers have found that higher level of IGF-1 increased incidence of prostate cancer⁵⁴, estrogen receptor positive breast cancer,⁵⁵ and thyroid cancer.⁵⁶ High levels of circulating IGF-1 have also been implicated in increased risk of colon and lung cancer.²⁷ Pathways of Metformin on Cancer potentially works on different pathways,⁵⁷ it may augments the effect if various chemotherapy, decreases level of oxidation, decrease production of reactive oxygen species, it may promote weight loss, and most importantly it may decrease the level of insulin-like growth factor 1.

3.6 Metformin and Cancer Risk

Metformin, an oral biguanide antihyperglycemic agent, is the drug most often prescribed to treat type 2 diabetes. The American Diabetes Association Clinical Practice Recommendations 2014 recommend metformin as the first line therapy for type 2 diabetes.⁵⁸ Metformin lowers glucose by inhibiting glucose production in the liver by activating the AMP-activated protein kinase pathway, through a liver kinase BI (LKB1) dependent pathway.^{57,59} Metformin also improves sensitivity to insulin and slows absorption of glucose by the gastrointestinal tract, which lowers glucose levels in the blood.⁵⁷ Several large retrospective studies suggest that individuals with diabetes maintained on metformin vs. other types of diabetic drugs have a lower incidence of several types of cancer, including hepatocellular, pancreatic, and colon cancers³ The mechanism by which metformin might decrease cancer incidence is unknown, and does not appear to be due to glycemic control alone.⁶⁰ Other possible mechanisms include metformin-associated reductions in weight, IGF-1, and other growth factors.

3.7 Metformin and Weight Loss

In addition to its direct impact on glucose homeostasis, metformin use is associated with minimal but sustained weight loss in patients with and without diabetes. In a meta-analysis including >5,000 patients with diabetes, metformin decreased weight by 2.6 and 2.7 kg compared to sulfonylureas and thiazolidinediones, respectively.⁶¹ In the Diabetes Prevention Program trial, participants randomized to the lifestyle intervention group lost more weight than those in the metformin or placebo groups, although those in the metformin group did experience weight loss.⁶² Mean weight loss was 0.1, 2.6, and 5.6 kg in the placebo, metformin, and weight loss groups, respectively.⁶² These results continued during 7-8 years of follow-up on the open label extension study, with the metformin group having reduced body weight compared to the placebo group.⁶³ Several small trials of metformin in patients with other conditions (polycystic ovarian syndrome,⁶⁴ and antipsychotic-related weight gain⁶⁵) have demonstrated similar effects of metformin on weight reduction.

3.8 Metformin and Insulin-like Growth Factor

As noted above, metformin has its primary action on glucose homeostasis through LKB1dependent activation of AMPK.⁶⁶ Outside of effects on glucose levels, activation of AMPK has generally catabolic and anti-synthetic effects, including inhibition of fatty acid and protein synthesis; in the setting of tumorigenesis, which is dependent on unregulated cell growth, AMPK activation would be expected to be inhibitory.⁶⁷ AMPK activation may also more directly inhibit the cell cycle.⁶⁷

Consistent with the anti-synthetic effects of metformin as an AMPK activator, metformin appears to lower IGF-1 in preclinical and human studies. Studies of cancer cell lines and mouse models suggest that metformin may decrease levels of IGF-1.⁵⁷ It also lowers levels of insulin, which is known to promote the growth of cancer.⁵⁷ Using human pancreatic cancer cell lines, Karnevi et al demonstrated in pancreatic cancer cells that treatment with metformin decreased cell proliferation and plasma IGF-1, through an activation of the AMP-activated protein kinase AMPKThr172 and blocking the IGF-1 receptor activation and insulin receptor signal (IRS-1).⁶⁸

In humans, metformin treatment has reduced IGF-1 levels in trials in patients with diabetes,⁶⁹ in a small study (n=40) of patients with endometrial cancer after four weeks of treatment;⁵ in women with polycystic ovary syndrome;⁷⁰ and in healthy men (n=15).⁷¹

Taken together, several preclinical studies and small, short-term human studies suggest that metformin lowers IGF-1 levels, but additional evidence in clinical trials, especially with cancer survivors, is necessary to confirm these results.

3.9 Current Public Health Recommendation

The *International Agency for Research on Cancer* recommends, when possible and when not recommended otherwise by a medical professional, that cancer survivors also follow the recommendations for the general population for maintaining a healthy weight, diet, and physical activity.¹² This includes maintaining a stable body weight in the normal range and avoiding weight gain and increases in waist circumference.¹² The dietary recommendations of IARC include limiting intake of energy-dense foods, sugar sweetened beverages, starchy foods, red meat, alcoholic beverages, salt, and processed grains; and eating the recommended five servings of fruits and vegetables each day. IARC also recommends a minimum of 30 minutes of physical activity each day, with a goal of 60 minutes of moderate or 30 minutes of vigorous physical activity per day.¹² Recommendations for cancer survivors published by the American Cancer Society,⁷² the American Institute for Cancer Research,⁷³ and the Centers for Disease Control and Prevention⁷⁴ echo IARC's recommendations.

3.10 Practicality of Intentional Weight Loss among Cancer Survivors

A recent review of ten small randomized controlled trials of weight loss intervention among breast cancer survivors concluded that “there is a small but growing body of evidence to suggest that weight loss is feasible and safe in women following treatment for breast cancer.”⁷⁵ Of the ten RCTs included in the review, only three included information about adverse events, and none reported a serious adverse event.⁷⁵ A recent study aimed at increasing physical activity among 86 young adult cancer survivors used a social media-based intervention.

Participants in the intervention group reported that they enjoyed participating in the study and that they would recommend the intervention to other cancer survivors. Weight loss was seen in the intervention group, although this was not a primary outcome of the trial, and no adverse events were reported.⁷⁶ A larger study of older adult colorectal, prostate, and breast cancer survivors spanning two years found that the study group made changes in diet and physical activity, and also lowered BMI from an average of 29.1 at baseline to 28.3 at the 2 year followup ($p < .001$). Of the events reported during the course of the study, six were found to be attributable to the intervention, and only one was serious (hospitalization for dehydration).⁷⁷ These studies support the IARC and ACS recommendations that cancer survivors maintain a healthy body weight, through weight loss if necessary.¹²

3.11 Rationale for a Randomized Clinical Trial of Weight Loss and Metformin on IGF among Cancer Survivors

As treatment and early detection of cancer continues to improve, the US will be faced with a growing population of cancer survivors. Many of these cancer survivors will be overweight or obese, and maintaining a healthy weight is an important element of healthy survival.¹² The time after cancer diagnosis represents a potentially important time for intervention in the overall health of survivors.

Every year, more than 24,000 people living in Maryland are diagnosed with cancer:⁷⁸ prostate, female breast, lung, and colon & rectum are most common types in both Maryland and the US as a whole.⁷⁹ Cancer is the second leading cause of death in the state of Maryland.⁷⁸ The Maryland Comprehensive Cancer Control Plan estimates that the annual cost of cancer in the state of Maryland is \$3.9 billion, including \$1.5 billion in direct medical costs.⁷⁸

As we mentioned previously, High levels of circulating IGF-1 have been implicated in the development of cancer. High levels of circulating IGF-1 are associated with an increased risk of some common cancers. Prostate, female breast, lung, and colon & rectum cancer have all been associated with higher levels of IGF-1.¹ Other studies have suggested that higher levels of IGF-1 are also associated with increased risk of mortality among cancer patients.² It

has been hypothesized that reducing IGF-1 might prevent cancer in persons without cancer (primary prevention) and cancer recurrences among cancer survivors (secondary prevention).

Metformin is a low-cost therapy with few major side effects.⁵⁷ Among patients with diabetes, it has been observed that metformin decreases the incidence of certain cancers, and animal and cell line studies suggest that metformin may lower IGF-1 levels.^{3-5,57} Promising results from in vitro, human, and epidemiological studies suggest that metformin may inhibit cancer development and progression through IGF-related pathways among non-diabetic patients as well. The weight loss program has been shown effective among the general population, is easily scalable and is expected to have very few negative side effects.

A wealth of evidence depicts the relation between IGF-1 and cancer. However, there is a paucity of data on the impact of weight loss or metformin on IGF-1, especially clinical trials among cancer survivors. A randomized trial in cancer survivors to test the effects of weight loss or metformin on IGF-1 level will help clarify the relationship between these variables, and could identify new methods to decrease risk of cancer recurrence amongst cancer survivors.

4. OVERVIEW OF TRIAL DESIGN

This is a prospective, single-center randomized trial with three arms, and an allocation ratio of 1:1:1. The study design is an efficacy study to evaluate the effect of metformin and coachdirected behavioral weight loss versus self-directed weight loss on IGF-1 and IGF-1 to THE IGFBP-III ratio blood levels after 6 and 12 months of intervention. The coach-directed Behavioral Weight Loss arm is a web-based remote delivery and communication system that promotes healthy behavioral changes. The Metformin arm is a pharmaceutical intervention of oral metformin. This is a secondary prevention study for men and women who have survived solid malignant tumors.

5. STUDY POPULATION

Participants are cancer survivors – persons who self-report a malignant solid tumor diagnosis and have completed curative intent treatment and have no ongoing or planned active treatment (surgery, radiation therapy or chemotherapy (other than chemoprophylaxis)). We aim to recruit

~120 participants, ~40 participants in each of the three arms. Eligibility will be determined by a series of web, phone, and in-person contacts.

5.1 Inclusion Criteria

- Women and men ages 18 or older
- Have been previously diagnosed with a malignant solid tumor, completed their required surgical, and/or chemotherapy and/or radiation curative intent therapy at least three months prior to enrollment, and have an anticipated treatment-free life span of 12 months or longer. Chemoprophylaxis with tamoxifen or aromatase inhibitors for breast cancer in women and anti- LHRH therapy for prostate cancer in men will be permitted.
- Have a BMI of 25 kg/m² or greater and weight <=400 lbs.
- Willingness to accept randomization to each of the three arms
- Willingness to change diet, physical activity, and weight
- Regular access to computer with a reliable Internet connection
- Ability to send and receive emails
- Ability to complete online forms
- Access to phone
- Willingness to provide written informed consent

5.2 Exclusion Criteria

- Women who are breastfeeding, pregnant, or planning pregnancy within the next year
- Medication-treated diabetes
- Non-fasting blood glucose ≥ 200 mg/dL, or HbA1C $\geq 7\%$
- Current or prior regular use of metformin within the past 3 months
- Uncontrolled concurrent medical condition likely to limit compliance with the study interventions
- Received any chemotherapy (unless anti-hormonal therapy) and/or radiation three months or less prior to the proposed intervention date
- Have a prior history of lactic acidosis by self-report
- Prior or planned bariatric surgery
- Have significant renal disease or dysfunction defined as eGFR<45
- Have significant hepatic dysfunction (AST/ALT ≥ 2 x ULN or reported liver disease)
- Self-reported average consumption of > 14 alcoholic drink per week
- Currently enrolled or planned to enroll in weight loss program
- Hemoglobin <9 g/dl
- Platelet count <100
- WBC <2.5
- Plans to relocate from the area within one years
- Use of prescription weight loss medication(s) (e.g., lorcaserin, topiramate/phentermine, phentermine, liraglutide, and bupropion/naltrexone), including off label use of drugs for

weight loss or over-the-counter weight loss medications such as Orlistat within the past 6 months.

Study clinicians will meet regularly to review the eligibility of screenees.

5.3 Inclusion of Minorities

Men and women of all races and ethnic groups are eligible to participate in this trial. We aim to enroll ~50% women, ~50% African Americans.

6. RECRUITMENT

This trial will recruit cancer survivors who are overweight or obese and who reside in the Baltimore Metro area. Trial investigators recognize the challenges of recruiting participants. Accordingly, they will simultaneously implement several recruitment strategies and will also develop backup plans should initial recruitment efforts fail to yield the required number of participants. Targeted mailings to cancer survivors is likely to be the most efficient and effective approach to enrolling participants. Accordingly, the primary recruitment strategies will include targeted mailings of invitational materials (invitational letter and/or brochure) to lists of persons who are cancer survivors. Such lists are publicly available from commercial vendors. Specifically, this study is using the Mt Royal Printing Company. The investigative team will not receive names or addresses of the people who are on the vendor's mailing lists. Secondary strategies will include a) placement of brochures in physician offices in Hopkins-affiliated clinics and distribution of flyers in various community settings (e.g. health fairs), b) direct referral from study physicians, c) word-of-mouth, and d) advertisement in local newspapers. Enrollment of participants will take place at the ProHealth clinic in Woodlawn (West Baltimore), where data collection visits will take place.

A public website (spirittrial.org), managed by the study team, will be listed on recruitment materials. The home page displays brief information about the study and provides a way for interested persons to submit their contact information, which would be stored on the Qualtrics server, which is approved by the ICTR for the secure storage of PHI. We also provide general information about SPIRIT. Text for these sections is primarily pulled from IRB-approved materials. We also list contact information for ProHealth in case people would prefer to contact the study staff directly rather than leave their own contact information.

In addition, we will conduct online advertising with paid banner ads on websites (Google, Facebook, and possible other sites) that direct individuals to the SPIRIT website's landing page (spirittrial.org).

Interested individuals will be asked to contact us by phone or email. After the individual provides verbal consent, a pre-screen telephone interview will occur over the phone. Those who remain interested and eligible will be invited to attend a screening visit at the ProHealth

research clinic. During the in-person screening visit, written informed consent will be obtained, along with other baseline measurements.

Recruitment will be conducted by the study coordinator and ProHealth staff. All recruitment material and potential participants' data will be protected in an encrypted study computer with password protection. Hard copies will be locked in a secure cabinets and rooms. Locally, we will retain the identifiers of those persons who provide written informed consent, as well as those who agree to be contacted for future studies. The identifiers of other participants will be destroyed.

7. RANDOMIZATION AND ASSIGNMENT

Participants will be randomized to one for the three following arms:

- Self-Directed weight loss
- Coach-Directed Behavioral weight
- Metformin treatment

Randomization will be stratified by race and BMI. To prevent prediction of randomization, we will generate the randomization schedule in variable blocks sizes. A biostatistician will generate the allocation sequence. Randomization will take place after the study coordinator confirms that all screening activities have occurred, individual meets all eligibility criteria, and all baseline data have been collected. Individuals who do not meet eligibility or who lack proper documentation of eligibility or key data elements will not be randomized. An unmasked study coordinator or staff member who is not involved in follow-up data collection will carry out assignment allocation.

8. INTERVENTIONS

8.1 Self-Directed Weight Loss

Participants in this arm will continue to receive care from their primary care provider and/or oncologist. Participants in this arm will receive an informational visit with a staff member immediately following the randomization process. At this visit the participant will also receive the National Institutes of Health booklets, *Aim for a Healthy Weight* and *What I need to know about Physical Activity and Diabetes*. They will also receive a link to the Centers for Disease Control and Prevention website *Healthy Weight*.

8.2 Coach-Directed Behavioral Weight Loss

The Remote Lifestyle Coaching intervention is based on the Call Center Directed intervention from the POWER Hopkins Trial.^{80,81} The Lifestyle Coaching intervention has a social cognitive theoretical framework that draws upon the strengths of various approaches including Bandura’s Social Cognitive Theory.^{82,83} The behavioral approaches include teaching participants strategies to increase their self-efficacy, develop social support, and enhance motivation. Both self-efficacy and social support are key components in social cognitive theory and have been identified as important determinants of behavior change.^{84,85} Specific strategies that will be encouraged among the participants will include self-monitoring, goal setting, problem solving.

The coach-directed behavioral weight loss arm is based on the POWER-Remote arm of the POWER Trial, which provided behavioral-based telephonic coaching with web-based support to promote healthy lifestyle and weight loss in overweight and obese adults. We will partner with Healthways, a disease management company, to implement the Coach-Directed Behavioral Weight loss intervention. Johns Hopkins Medicine has an ongoing collaboration with Healthways, the Innergy program, to translate POWER intervention to employees at Hopkins and Healthways. The proposed study will be built on this existing relationship and the intervention will be customized to the cancer survivor population.

Methodology

The goal of this intervention is to achieve at least 5% weight loss in the first six months of the intervention and maintain these improvements through month twelve by meeting dietary and exercise goals shown in Table 1. Participants will receive coaching by a Hopkins coach and have access to a study website for self-monitoring and learning modules. Coaching sessions will be weekly for the first three months and monthly for months 4 through 12. There is a reengagement process includes both automated emails and coach follow-up. The website sends series of automated email reminders to login if there has been no login in the last 7 days. There is a personal coach follow up of emails and calls if the automated email did not prompt a login after 14 days. There is provision of up to two supplemental coaching calls per any sixmonth period to assist individuals with challenging or difficult personal situations. In addition to coaching, the trial will provide bathroom scales to the participants. The scale will be used to track and record weight changes. The study website/phone app calculates calories for all foods and beverages tracked. Participants who do not have access to a phone will be provided with a prepaid cellphone with enough minutes to cover the intervention requirements.

Calls may be recorded for quality control purposes. Audio records will be stored in HIPPA compliant Johns Hopkins cloud based server. Audio records will be destroyed after study completion. .

Table 1. Weight Goals and Behavioral Recommendations

Weight Loss Goal	
Month Six	Minimum 5% weight loss, individually tailored

Month 12	Maintain or exceed 5% weight loss, individually tailored
Behavioral Recommendations	
Total Caloric Intake	Achieved weight loss < 5% 1200 kcal/d if ≤ 170 lb 1500 kcal/d if > 170 lb and < 220 lb 1800 kcal/d if > 200 lb and < 270 lb
	Achieved weight loss ≥ 5% Women: 1500 – 1800 kcal/d Men: 1800-2200 Kcal/d
Diet	DASH dietary pattern: 7-12 servings of fruits/vegetables 2-3 servings of low fat dairy Low sodium ≤ 25% of calories from fat
Exercise	Build to ≥ 180 minutes/week of moderate intensity physical activity in bouts ≥ 10 minutes in length
Self-Monitoring Recommendations: Achieved Weight Loss < 5%	
Weight	Weekly
Dietary Intake	Daily
Exercise	Daily
Login Study Website	At least weekly, preferably daily or daily use of study app
Self-Monitoring Recommendations: Achieved Weight Loss ≥ 5%	
Weight	Daily
Dietary Intake	Daily
Exercise	Daily
Login Study Website	At least weekly, preferably daily or daily use of study app

Table 2. Contact Schedule

Coaching Calls	
Months 1-3	Weekly Calls
Months 4-12	Monthly Calls
Re-engagement	
Automated email reminders	Reminders if no login in the last 7, 11 and 30 days
Coach reminders	Follow-up emails and calls if no login after 14 days
Supplemental Calls	

Coaching Calls	Tailored, no more than 2 per six month period
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Phases and Self-Monitoring

Self-monitoring recommendations have subtle yet important differences depending on the focus of the participant on weight loss or weight loss maintenance.

Weight Loss Focus: The following recommendations are for participants who have not yet achieved 5% weight loss or are working toward a goal of more than 5% weight loss:

- Track dietary intake (all food and beverages) and exercise daily on either the study website or using the related app.
- A self-reported weight should be entered at least weekly on the study website.

Weight Maintenance Focus: The following recommendations are for participants who have achieved at least 5% weight loss and are focused on weight loss maintenance:

- Track dietary intake (all food and beverages) and exercise daily on either the study website or using the related app.
- A self-reported weight should be entered daily on the study website.

Adherence

Adherence will be assessed by completion of coaching sessions and online self-monitoring.

Health Care Provider Engagement

Participants in this arm will continue to receive care from their primary care provider and/or oncologist. The participant will update their physician and care providers on their progress in the lifestyle intervention by printing a summary form from the intervention website to bring to a regular physician visit. These summary forms are designed to provide an overview of progress on both lifestyle change and self-reported weight. Based on selfreport from the website, they illustrate weight loss trends, tracking and participation over time and may facilitate conversations about weight change during the course of a standard physician visit.

Website Operation and Support

We will collaborate with Healthways, a disease management company, who maintained the website in the original POWER trial and will do so in the current trial. Johns Hopkins Medicine has an ongoing collaboration with Healthways. Together, Healthways and Hopkins investigators and staff from the POWER trial developed Innergy, a commercial version of the POWER Remote intervention. The trial will use the Innergy website, adapted for used in this trial by including materials relevant to cancer survivors.

8.3 Metformin Pharmacologic Intervention

Participants in this arm will continue to receive care from their primary care provider and/or oncologist and/or other providers. Participants in this arm will receive medication-related education and counseling from a study staff member immediately following randomization. Participants will receive metformin, an oral medication for type 2 diabetes. It primarily reduces hepatic production of glucose without increasing insulin secretion. Metformin is not currently approved for use as a cancer prevention medication. This study is designed to investigate its efficacy in reducing Insulin-like Growth Factor 1(IGF-1) and IGFBP-III, which in turn may reduce cancer cell growth among cancer survivors. This study is not intended to study the treatment of cancer or prevention of cancer recurrence with metformin. An application for an IND waiver has been submitted, and approved by FDA. FDA granted the approval to use this product for an indication that is not FDA-approved.

Participants randomized to the metformin intervention will receive metformin up to 2,000 mg per day.⁸⁶ Dosing can be flexible, two or three times per day with meals as tolerated for 12 months. See Section 5.2 for exclusion criteria.

Metformin is primarily excreted by the kidney, and the risk of adverse events, although low, increases in patient with impaired renal function. Because aging is associated with reduced renal function, the FDA recommends “treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced “. Because we will measure kidney function and estimate GFR, we will be excluded based on renal function rather than age.⁸⁶ In this fashion, we will increase the opportunity for older individuals to participate in this trial.

Dosing

Oral titration of metformin in an open-label fashion will occur as follows:

- 1) 500 mg by mouth once daily with breakfast for 7 days or longer if needed for tolerance;
- 2) If tolerated, increase metformin to 500mg by mouth twice daily with breakfast and dinner for 7 days or longer if needed for tolerance;
- 3) If tolerated, increase metformin to 1000 mg by mouth in the morning and 1000 mg in the evening for 7 days or longer if needed for tolerance;

Dose modifications: The major limiting side effect for metformin is gastrointestinal discomfort. We do not anticipate other side effects or toxicity. Therefore, determination of tolerance will be based on GI symptoms. We will titrate the dose of metformin to the highest tolerated daily dose possible (based on GI side effects) up to 2,000 mg per day.

Restarting and titration will be based on standard protocols and FDA guidelines in addition to clinical judgment, side effects, and the amount of time off metformin.

Participants who are deemed to have an allergic reaction to metformin will not be continued on metformin. Metformin will be stopped in participants in whom other side effects/toxicities are limiting or unsafe, and restarting of metformin will be based on clinical judgment after discussion with participant, the study’s clinical review committee, and the Data Safety and Monitoring Board if needed.

Planned Stopping and Restarting

Rules for stopping and restarting metformin for medical reasons are as follows:

A- Hospitalization

In case of hospitalization, a participant will discontinue metformin. A plan to restart will be considered after a careful assessment of the cause of hospitalization (including conditions which increase risk of lactic acidosis) and review of eligibility criteria specific to safety of metformin (e.g. eGFR and hemoglobin). Participants in the metformin arm will be provided with card and a letter indicating the potential risk for lactic acidosis associated with certain medical conditions and procedures.

B- Radiological procedures with iodinated contrast media

Participants using metformin who undergo a radiological procedure that involves iodinated contrast material may develop renal insufficiency and resulting lactic acidosis. Any participant planning undergo such a procedure will be advised to stop metformin 24 hours prior to the procedure and for 48 hours after the contrast administration. At least Forty-eight hours after contrast administration, eGFR should be checked. If the eGFR is >45 and stable compared to the baseline eGFR, a study clinician can approve restarting metformin. Participants in the metformin arm will be provided with a card and a letter indicating the potential risk for lactic acidosis associated with certain medical conditions and procedures..

C- Surgical Procedures

Major surgical procedures under general anesthesia carry a risk of metabolic acidosis. Participants in the metformin arm will stop metformin 24 hours prior to procedure involving general anesthesia. In conjunction with the clinicians providing peri-operative care, a decision to restart metformin can be approved by a study clinician after a review of metformin-specific eligibility criteria related to safety (e.g. eGFR and hemoglobin). Participants in the metformin arm will be provided with a card and a letter indicating the potential risk for lactic acidosis associated with certain medical conditions and procedures.

D- Hypoxia and Hypoperfusion

Participants who develop acute myocardial infection or congestive heart failure are at risk of lactic acidosis because of hypoperfusion and/or hypoxia associated with these conditions. Participants in the metformin arm who experience these conditions will be instructed to stop metformin immediately. In conjunction with the clinicians providing care for these conditions, a decision to restart metformin can be approved by a study clinician after a review of metformin-specific eligibility criteria related to safety (e.g. eGFR and hemoglobin). Participants in the metformin arm will be provided with a card and a letter indicating the potential risk for lactic acidosis associated with certain medical conditions and procedures.

E- Pregnancy and breastfeeding

Women who are pregnant or who plan to become pregnant and women who are breastfeeding or plan to breastfeed will be excluded from this study. Premenopausal women will be educated regarding the risk of pregnancy while taking metformin and will be instructed to use a reliable form of birth control while taking metformin. Women who become pregnant during the study will be instructed to stop metformin immediately. Premenopausal women will be asked to stop metformin and contact the study if they believe they may be pregnant or if their menses become irregular. A pregnancy test may be ordered.

Adherence

Assessing participants' adherence to metformin and identifying non-adherent participants will help optimize adherence to the prescribed medicine. Participants in the metformin arm will receive one-on-one education with study staff at baseline and educational materials covering common side effects, administration of metformin, and contact information of study staff and physician. In addition to scheduled face-to-face data collection visits, follow-up phone calls at 2 week and 1 month will be conducted by trained study staff on a one-to-one basis to ensure adherence and address questions. The following are methods to assess adherence among metformin arm participants:

- Pill count by visual inspection during visits when participants bring their containers for refill. In the absence of pill containers, participants will be interviewed about their pill compliance.
- Follow-up phone calls at 2nd week and 1 month. Participants will be instructed to contact study staff if they experience any side effects, especially gastrointestinal symptoms such as nausea and diarrhea.

9. VISITS AND FOLLOW-UP Approach to Data Collection and Visits

Study investigators and staff recognize the need to accommodate participant needs and accordingly will be flexible in implementing the expected data collection procedures. For example, some participants may need to split visits (e.g. having 2 baseline visits), while others might prefer to bundle data collection into fewer visits (e.g. bundling screening and baseline visits). Our general approach will be to accommodate such requests, as long as we collect the required data.

Pre-Screening Call

Recruitment materials will direct interested individuals to contact the study by e-mail, postcard, or the telephone contact information provided in the mailed recruitment materials. A pre-screening phone call will then occur. During the phone call, study staff will provide information about the trial, obtain verbal informed consent, and collect data on eligibility.

Screening Visit 1

Those who remain interested and potentially eligible will be asked to attend the first screening visit in the clinic center in person and meet with study staff. Trained study staff will obtain the following measures:

- Weight & height
- Blood pressure
- non-fasting labs
- Questionnaires (See Table 3)

All potential participants will demonstrate the ability to send and receive emails, ability to complete online forms, and sufficient phone minutes for coaching calls during this visit.

Screening Visit 2

Participants, who remain eligible after the screening visit 1, will be asked to attend the second screening visit after at least 9 hours of fasting. The following activities and measurements will take place:

- Orient the participant about each intervention arm, expectations and related details. -
Weight
- Blood pressure
- Fasting labs
- HbA1c
- Current medication
- Questionnaires (See Table 3)

Randomization Visit

During this visit, study staff will reconfirm the eligibility. Weight and blood pressure will be measured. Each participant will be re-oriented to each intervention arm. Each participant will be randomized and assigned to one of the three interventions arm: self-directed weight loss, coach-directed behavioral weight loss or metformin.

Follow-Up Visits

There are three types of follow-up based on the contact mode: in-person, telephone and website.

In-person follow-up visits will take place at ProHealth at 3-month, 6-month, and 12-month intervals. Participants will be asked to attend those visits after having fasted for at least 9 hours. The following will take place during these visits:

- Weight
- Blood pressure
- Fasting labs and HbA1c
- Patient reported outcomes (EuroQol;)
- Current medication

- Fat screener, fruit screener, physical activities, general symptoms form
- Pill counts for adherence, challenges and enabling factors for adherence
- Any adverse events
- Any other issues raised by the participant that can be addressed within the scope of the study

Additional telephone contacts, for the metformin arm, will take place at the following times after baseline visit: every 2 weeks for the first month and otherwise as needed throughout the intervention period. During these calls, the study staff will ask about adherence and side effects using a standardized study questionnaire.

Throughout the study, email and web contacts will take place to remind participants in the coach-directed behavioral weight loss arm to enter their self-monitoring data, and to followup on adherence and check for adverse events. In-person visits will take place on the 3rd, 6th and the twelfth month for the same reasons.

10. DATA COLLECTION AND OUTCOME MEASURES

All measurements and sample collection will be conducted by trained, certified staff. Any measure-specific devices, instruments, and equipment will be calibrated and standardized. All lab measures will be analyzed in the same labs, and all patient-reported outcomes will be captured by standardized forms. Eligibility, baseline, and follow-up data will be collected by phone, over the web, and at in-person visits. To the extent possible, questionnaire data will be collected through website (for the coach-directed arm) or telephone, rather than on-site. Inperson data collection visits will be conducted mainly at ProHealth, with satellite sites at SKCCC and Johns Hopkins Bayview if needed. Below are the primary and secondary measures that will take place at specific contact points across all arms.

Data Collection Schedule

Table 3: Data Collection Schedule, All Participants

	Prescreen	Screening	Randomization	3 months	6 months	12 months
Data collection						
Eligibility/Interest	X	X				
Informed consent	X	X				
Weight		X		X	X	X
Height		X				
Blood pressure		X	X	X	X	X
IGF-1/IGFBP-III		X	X	X [§]	X [§]	X [§]
Metabolic Panel labs		X		X	X	X

CBC		X				X
HbA1c [§]			X		X	X
CRP. IL-6, IL-8			X		X	X
Stored specimens [†]			X		X	X
Stool Sample			X		X	X
Randomization			X			
Questionnaires						
Demographics		X				
Diet/physical activity		X		X	X	X
Eurol-Qol		X		X	X	X
Medical history		X				
Medications		X	X	X	X	X
Interim events			X	X	X	X

§ Processed as a batch from frozen specimens. † Stored.

Primary Outcome Measure

Insulin-like Growth Factor I (IGF-1): At each in-person visit, participants will be asked to have fasted for at least 9 hours. Phlebotomy, processing, and storage will be done by trained staff members and according to a standardized protocol. Frozen samples will be transported to the University of Maryland School of Medicine Pathology Laboratory where assays for IGF-1 will be conducted using the IMMULITE 2000 Assays.

Insulin-like Growth Factor Binding Protein III (IGFBP-III): At each in-person visit, participants will be asked to have fasted for at least 9 hours. Phlebotomy, processing, and storage will be done by trained staff members and according to a standardized protocol. Frozen samples will be transported to the University of Maryland School of Medicine Pathology Laboratory where assays for IGFBP-III will be conducted using immunoassays

Secondary Outcome Measures

Height: This is a onetime measure during the first in-person visit. Participants will stand straight without shoes, and a standard calibrated wall mounted stadiometer will be used. Precision of height is up to 0.1 of a centimeter.

Weight: At each in-person visit, staff blinded to randomized assignments will measure weight while the participant is shoeless and in light clothing. A calibrated, standardized electronic weight-measuring scale will be used. Measurements are in pounds and later converted to kg for analysis. Weight will be measured twice; if the difference between the two measures is more than 0.1 kg, then another measure will be taken.

Body Mass Index: BMI will be calculated as (weight in kg/height² in meters)

Other Outcome Measures

Lipids: Total cholesterol, triglycerides, and HDL will be measured from overnight fasting plasma. LDL will be calculated by the Friedewald equation.

Glucose and Insulin: Fasting glucose and insulin will be measured after overnight fasting from plasma.

HbA1c: HbA1c measures will be measured from whole blood.

Demographics and Medical History: A self-reported assessment of basic patient characteristics will be collected which will include age, gender, race/ethnicity tobacco use, , health insurance status, , income, employment, education level, post-menopausal status and current health status and co-morbid conditions (e.g., diabetes and hypertension). Additional details on solid tumor malignancy will also be obtained, including organ of origin, date of diagnosis, stage of disease at diagnosis, treatments received, and date of completion of treatment(s).

Diet and Physical Activity: Diet will be assessed with standardized questionnaires. Physical activity will be assessed by both a standardized questionnaire and an accelerometer.

- Fruit & Vegetable Screener is a brief self-report measure of daily fruit and vegetable intake, portion size, frequency and type.
- Block Fat Screener is a brief self-report assessment of percent energy intake from fat; this measure comes from the National Cancer Institute's Risk Factor Monitoring and Methods staff.
- Physical Activity will be measured using the Godin Physical Activity Measure. It will be used to estimate levels of moderate and vigorous physical activity from the previous week.
- 87,88.87 91,92

Quality of Life: The EuroQol measure is drawn from the EQ-5D measure and has 6 questions. The EQ-5D descriptive system consists of five dimensions: 1) mobility; 2) selfcare; 3) usual activities; 4) pain/discomfort; 5) anxiety/depression.

Current Medications: Current medication use will be assessed by self-report of medication names, dosages, routes of intake and frequency.

Serious Adverse Events will be measured using the Serious Adverse Event Form (SAEForm). This form measures the event, characteristics, onset, and severity.

IL-6, IL-8 , both will be measured using commercial sandwich-based enzyme linked immunosorbent assays (ELISAs).

hs-CRP will be analyzed by quantitative immunoturbidimetry.

Stored Specimens

Serum and plasma samples of all our participants will be stored at -80°C for future investigation of other studies. In addition, fecal samples will be collected at baseline visit, and 6th month. Samples will be transported on dry ice to N2 Vapor Freezers or Mechanical Ultra Low Freezers (-80°C) in the Tissue Bank of the Hopkins Conte Digestive Diseases Basic and Translational Research Core Center for long-term storage and analysis at a later time.

Future measures: the following are future measures that are not supported by this trial:

- leptin, adiponectin, VEGF, HGF, and EGF; SLC22A1, SLC22A2, and SLC47A1 gene variants; and 16S bacterial whole genome sequencing of gut microbiome.

11. MASKING OF DATA COLLECTION

Upon confirmation of eligibility and baseline data collection, 120 participants will be randomized in a 1:1:1 ratio to one of the three intervention arms. Randomization will be stratified by race and baseline BMI. Password-protected randomization software will ensure authorized access to the group assignment, which is restricted to designated study personnel only during the execution of the trial. The randomization scheme will be generated by the biostatistician. Intervention assignment is not blinded to the trial participants, nor the intervention staff. However, study staff involved in follow-up data collection will be masked to the randomization assignments. Moreover, the primary outcomes will be measured by labs; and staff in the lab will be blinded to the randomization assignment.

12. DISCONTINUATION OF SUBJECTS

Reasons for discontinuation and withdrawal will be documented in participant's medical record. All study interventions expected to last for 12 months, unless the participant fulfills one or more of the following conditions:

- Diagnosis of new or recurrent illness that may require the participant to stop the intervention, based on the judgment of the principal investigator.
- Diagnoses of recurrent cancer that may require a change in therapy plan, which may prevent the participant from continuing the study's specific intervention.
- Pregnancy
- Patient request to discontinue due to inability to take or tolerate metformin

Reimbursement

Participants enrolled and randomized in the intervention study arms will receive \$50-150 compensation in check for every follow-up visit for a possible total of \$300. Participants who need transportation, cost may be compensated.

13. ADVERSE EVENT

13.1 General

National Cancer Institute/Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be the guideline for this study in describing, grading, and reporting of adverse events. Adverse events believed to be related to weight loss or metformin will be reported. Adverse event information will be collected during each in-person visit from screening phase onward. Only adverse events possibly, probably or definitely related to study interventions will be tabulated and reported according to NIH guideline (insert reference). All serious adverse events, regardless of relation to study interventions must be reported to the principle investigator. All adverse and serious adverse events will be reported to the local institutional review board. Any modification to consent and/or study protocol, resulting from an adverse event, will be provided to IRB with the report of the adverse event.

Definitions

- Adverse event (AE): Any undesirable sign, symptom, or medical condition occurring after starting therapy, even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia), or abnormal results of a procedure (e.g., laboratory findings, biopsies).

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment and are believed to be related to the weight loss or metformin intervention.

- Serious adverse event or reaction: Any untoward medical occurrence secondary to therapy that: results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability, or is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The definition of a serious adverse event (experience) also includes an *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

A hospitalization planned before the start of the study agent(s) and/or for a preexisting condition that has not worsened does not constitute a serious adverse event (e.g., elective hospitalization for breast reconstruction). A hospitalization for a social reason in the absence of an adverse event also does not meet the criteria for a serious adverse event.

- Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational intervention provided in the Investigator's

Brochure, package insert, or safety reports. Any adverse event that is not included in the informed consent is considered “unexpected”.

- Expected (known) adverse event: An adverse event, which has been reported in the Investigator’s Brochure. An adverse event is considered “expected”, only if it is included in the informed consent document as a risk.

Relationship

An investigator will assess the relationship between adverse events to study intervention as follows:

- Definitely: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, for which no alternative cause is present.
- Probably: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, but for which a potential alternative cause may be present.
- Possibly: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, but a potential alternative cause does not exist.
- Unlikely: An adverse event which does not have a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, does not reappear or worsen after re-administration of the investigational drug/agent (if applicable), and for which there is evidence that it is related to a cause other than the investigational drug/agent.
- Unrelated: An adverse event, for which there is evidence that it is definitely related to a cause other than the investigational drug/agent. In general, there is no timely relationship to the administration of the investigational drug/agent, or if there is a timely relationship, the event does not follow a known pattern of response, and there is an alternative cause.

13.2 Potential Risk from Intervention

Side effects associated with weight loss, such as anxiety, may occur. Unlike with our intended lifestyle weight loss target (5% weight loss from baseline), a major weight loss may be associated with side effects including dehydration, electrolyte imbalance, malnutrition, nausea, tachycardia and headaches. Side effects from metformin include nausea, diarrhea, abdominal bloating, metallic taste, anorexia, or flatulence, vitamin B12 deficiency, and rarely, lactic acidosis. When blood samples are collected from participants, blood draw procedures may produce risk.

The followings are potential risk associated with the followings:

Potential risks associated with **Coach-Directed Behavioral Weight Loss** intervention and respective measures to minimize risk:

A- Nutrient Intake

Inadequate nutrition or excessive, rapid weight loss can result from calorie restriction. To minimize these risks, participants are encouraged to maintain adequate calorie level and eat a variety of foods from all food groups. Participants will be advised about serious health risks associated with sustained caloric restriction. Intervention can be suspended, and participant will be referred to the PCP if nutritional deficiency is suspected and participant is unresponsive to advice from study staff.

B- Hypoglycemia

Low blood glucose level can result from severe caloric restriction and exercise. To minimize this risk, participants will be educated about the signs and symptoms of low blood sugar, when to contact their PCP, and adequate calorie levels and the food groups to consume while under the lifestyle intervention. The study team will engage the PCP in this intervention arm.

C- Symptomatic Hypotension

For those who use anti-hypertensive medication, lifestyle medication interventions have the potential to increase the risk of hypotension. Participants are educated about symptoms of hypotension and urged to contact their PCP if they have symptoms suggestive of hypotension. Overall blood pressure management will be under the PCP responsibility.

D- Cardiovascular Events

All participants with cardiovascular disease (CVD) require approval from their PCP prior to enrolling. PCPs are provided with information about safety guidelines for physical activity for people with CVD. In addition, participants are educated about CVD symptoms and urged to contact 911 in case of emergency or their PCP if they have a change in their CVD symptoms. In case a participant develop any CVD event, the intervention will be suspended until a decision to restart is authorized by the participant's PCP and the study principle investigator. Overall CVD management remains under the control of the participants PCP.

Potential risks associated with **Metformin** interventions and measures to minimize potential risks.

A- Gastrointestinal symptoms

B- Nausea, diarrhea, abdominal bloating, metallic taste, anorexia, and flatulence are associated with metformin use. If a participant develops mild symptoms that can be tolerated, then metformin will continue. If symptoms are difficult to tolerate, metformin will be stopped temporarily to establish association with the symptoms. Weekly or lessfrequent titration to maximum tolerated dose will be used to minimize

gastrointestinal symptoms. Restarting and continuation of metformin will be based on clinical judgment regarding severity of symptoms and tolerance of symptoms by participant.

C- Lactic Acidosis

Metformin is rarely associated with lactic acidosis (approximately 0.03 cases/1000 patient-years; no cases reported in 20,000 patient-years of exposure to metformin in clinical trials).⁸⁶ If a participant is hospitalized and develops metabolic acidosis, metformin will be stopped. Clinical judgment will guide the decision to restart metformin after resolution of acidosis based on understanding of the etiology of the cause of the acidosis. D- Anemia Vitamin B12 blood levels decrease to sub-normal levels without any clinical manifestations in approximately 7% of patients treated with metformin in clinical trials;⁸⁶ this is very rarely associated with anemia. However in long term high dose use, there may be a slightly lower hemoglobin level.⁶³ If anemia or vitamin deficiency is suspected, study physician will order vitamin B12 test.

E- Hypersensitivity to metformin

Participants who develop an allergic reaction or hypersensitivity to metformin will discontinue metformin.

F- Other adverse events

Interim events will be ascertained every three months, and serious adverse events will be reported per institutional review board and FDA regulations.

Safety Monitoring and Measures to Reduce Potential Drug-Related Side Effects

Standard laboratory studies will be done for each participant in the metformin arm. eGFR and complete blood count will be measured for eligibility. A complete blood count, and basic metabolic panel (including eGFR) will be measured at 12 months.

The most common side effects, reported by 28% of persons taking metformin, are gastrointestinal symptoms, among which nausea, diarrhea, abdominal bloating, metallic taste, anorexia, or flatulence are included.⁶³ These side effects are usually transient and resolve spontaneously or can be controlled by graduate dosing. Rarely, metformin can cause lactic acidosis among persons with renal or hepatic insufficiency, especially during episodes of hypoxia or circulatory failure. In addition, about 6-9% persons on metformin develop reduced vitamin B12 levels.⁸⁶

Potential risks associated with **blood** draw procedure and measures to minimize potential risks

A- Blood draw may produce discomfort, pain, bruises, and rarely, infection, syncope, or bleeding. Out trained staff will follow standard phlebotomy protocol for infection prevention and control, safety equipment and best practices.

13.3 Alert Levels

Laboratory studies and physical measurements will be obtained. For laboratory studies, we will use the alert values of the laboratory that performs the assays. For example, if the laboratory reports an alert level, study staff will be notified, and a clinician (either study nurse or physician) will contact the participant. Study physicians will also review and sign/initial each laboratory report, which we will then provide participants. ProHealth, a major clinical research unit for cardiovascular disease prevention studies, also has well established procedures and thresholds for other measurements such as blood pressure. If a participant's blood pressure is elevated, study staff will advise the participant to see their personal provider, using wellaccepted BP thresholds.

14. DATA AND SAFETY MONITORING

14.1 Data Management System

All information will be collected through the study website or using case-report forms. All studyrelated data will be reviewed for accuracy by the Project Manager or Database Manager. A periodic review will be done by the data analysis team.

14.2 Meetings

Regular meetings between the co-investigators and the study team will take place; additional meetings will be called as needed. Periodic meetings between the principal investigator, study coordinator, biostatistician, and data manager will take place to discuss study, progress, protocol adherence and objectives.

14.3 DATA Safety Monitoring Board

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (12/6/2012). The Clinical Research Office will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee. The PI is responsible for internally monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study

15. STUDY ADMINISTRATION Trial Organization

This is a single center randomized clinical trial. The Steering Committee (SC) will act as the regulatory, policy, and decision-making body for the study. The SC will have complete oversight over study implementation, provide scientific decisions and advice, monitor protocol adherence, and provide overall management. For the initial part of the trial, the following subcommittees will work with the SC:

- Administrative Sub-Committee: in charge of protocol approval, update, and administrative matters.
- Recruitment Sub-Committee: in charge of developing recruitment strategies and monitoring recruitment progress.

- Metformin Sub-Committee: concerned with the scientific details and implementation of metformin intervention arm
- Coach-Directed Behavioral Weight Loss Sub-committee: concerned with the scientific details and implementation of life style modification arm.
- Data Management and Analysis Sub-committee: concerned with randomization, data management, data quality control, report(s) to DSMB, and statistical analysis.
- Clinician Review Committee: in charge of reviewing eligibility, adverse events, and safety.

Ethics and Good Clinical Practice

This study must and will be implemented according to protocol and Good Clinical Practice as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

Funding Mechanism and Sponsors

This study is supported by the State of Maryland Cigarette Restitution Fund. The Johns Hopkins Kimmel Cancer Center is providing additional support.

16. SAMPLE SIZE

The trial has sufficient resources to enroll ~120 participants, who will be randomly allocated in equal proportions to each of 3 arms:

- Group A: Self-directed weight loss arm.
- Group B: Coach-Directed Behavioral weight loss intervention arm.
- Group C: Pharmacological intervention using metformin.

The primary contrasts are (C vs. A) and (B vs. A). The (C vs. B) contrast is secondary and is not considered in computing power.

The required sample size for the study was powered for testing 2 primary contrasts of change in IGF-1 over time in (1) lifestyle (arm B) vs. self-directed comparison (arm A), and (2) metformin (arm C) vs. self-directed comparison (arm A), each with 80% power and a 2-sided z test with alpha of 0.025. Assuming common SD at baseline and 6-month visit of 60 ng/ml,⁵¹ and a correlation of 0.90 between IGF-1 measures at baseline and 6-month⁴⁷, a total sample of 120 individuals (i.e. N=40 per arm) will allow the detection of a difference of 17.4 ng/ml (~10% reduction) or greater in change of IGF-1 over time between an active intervention arm and the control arm. With 20% random attrition, this trial will still be able to detect a difference

of 19.4 ng/ml or greater in change of IGF-1 over time between an active intervention arm and the control arm.

With the same sample size, the minimal detectable between arm difference in change of IGF1:IGFBP3 ratio over time were evaluated in a similar fashion for (1) arm B vs. A, and (2) arm C vs. A, each with 80% power and a 2-sided alpha of 0.025. Assuming common SD at baseline and 6-month visit of 11 using data available from the POWER trial,⁸¹ and a correlation of 0.80 between IGF-1:IGFBP3 ratio at baseline and 6-month⁴⁷, a total sample of 120 individuals (i.e. N=40 per arm) will allow the detection of a difference of 5.01 (~15% reduction) or greater in the change of IGF-1:IGFBP3 ratio over time between an active intervention arm and the control arm. With 20% random attrition, this trial will still be able to detect a difference of 5.67 or greater in change of IGF-1:IGFBP3 ratio over time between an active intervention arm and the control arm. We will explore the difference in outcome changes over time between arm B and C but this trial is not powered for this test, as the difference between these 2 arms may be small.

17. DATA ANALYSIS & STATISTICAL CONSIDERATION

17.1 Analysis Overview

This is a single center, randomized clinical trial, designed to test the effect of Behavioral Weight Loss and metformin versus self-directed weight loss on blood levels of Insulin-like Growth Factor 1 (IGF1) and IGF1 to Insulin-like Growth Factor Binding Protein III (IGFBP-III) ratio over 12 months among men and women who survived malignant solid tumor after completing all local therapy and/or adjuvant chemotherapy. Participants will be randomized at a 1:1:1 ratio to self-directed weight loss (Group A), Coach-Directed Behavioral Weight Loss (Group B), or metformin pharmaceutical intervention (Group C). Randomization will be stratified by race and BMI, and we are aiming to recruit ~50% African American in this trial. 120 individuals will be enrolled, with 40 participants in each arm.

The distribution of baseline characteristics of the participants by intervention arms will be described using mean and standard deviation for the continuous variables, and % frequency for the categorical variables. The primary analyses will follow the intention-to-treat principles, and be carried out using likelihood based mixed effects linear regression modeling. Evaluation of potential impacts due to missing data, should it occur, on intervention effect estimates will be anchored on analyses assuming missing at random, and supplemented by sensitivity analyses under plausible informative missing scenarios using multiple imputation approach. Potential impacts of treatment adherence on estimates of intervention effects will be explored by on treatment analyses paying special attention to adjusting for characteristics associated with treatment adherence. These analyses will be carried out using the propensity score approaches.

17.2 General Statistical Approach

The primary endpoint of this trial is the 6-month change in level of IGF-1 and IGF1 to IGFBP-III ratio among the Coach-Directed Behavioral Weight Loss arm versus self-direct arm (B vs. A), and metformin arm compared to self-direct arm (C vs. A). Intervention effects will be analyzed using intent-to-treat. Each active intervention arm will be compared with the control arm using

likelihood based mixed effects linear regression models utilizing data from all 3 time points, i.e. baseline, 6, and 12 months, simultaneously, as following.

The primary analysis model: The mean model for the mixed effects regression will be structured to include 2 binary intervention arm indicators (for Group B and C), 3 binary followup time indicators (for 3-, 6- and 12-month follow-up), and the cross-product interaction terms between the group and time indicators (6 interaction terms), and the covariance model will employ a 4x4 unstructured covariance matrix to allow different outcome variances and account for the intra-individual outcome correlations over time. Race and baseline BMI levels, the variables used for stratifying the randomization, will be included in the mean model. Other variables found not to be balanced between the trial arms will also be included as necessary. Outcomes may be transformed as needed to satisfy the distributional assumptions for the likelihood approach.

The primary testing contrasts of this trial will be the 2 aforementioned pairwise comparisons at 6 months, which will be evaluated through the regression coefficients of the Group B by 6month interaction term (B vs. A), and Group C by 6-month interaction term (C vs. A), respectively. The secondary testing contrasts include B vs. C of change in outcomes at 6month, and the 3 pairwise group comparisons of outcome changes at 12 months, which will be evaluated using the same model through the corresponding group by time interaction terms.

For outcomes such as IGF-1, IGF-1:IGFBP3 ratio, weight, BMI, and measures assessed through the metabolic panel labs, where data will be available at 3-month, these information will be utilized through the primary model to enhance model estimation, especially in the event of missing data encountered at 6- and/or 12-month, events though the effect size of the intervention at 3-month is not part of the primary or secondary goals. For outcomes such as EQ-5D, questionnaire outcomes on dietary intake and physical activity, HbA1c, IL-6, IL-8, and CRP, where data will not be available at the 3-month visit, the analysis models will not include any independent variables terms related to that visit.

We will also conduct subgroup analyses to explore for potential differential intervention effects across these pre-specified subgroups. Statistical significance of these subgroup analyses will be evaluated though incorporating appropriate subgroup by intervention by visit interaction terms. To explore the association of physical activity levels with the outcomes of IGF-1 or the IGF-1: IGFBP-3 ratio, time dependent physical activity measures will be further included to augment the primary analysis model to explore for the degree of attenuation of intervention effect by physical activities. Similar analyses could be done for body weight and BMI.

We will also explore for possible treatment effect modification by baseline BMI level to better understand the potential heterogeneity of treatment effects to inform future trials and studies. This will be carried out by including the 3-way interaction terms (Group indicator by Time indicator by BMI) in the primary analysis model. We will also estimate total intervention costs for future trials in a large population.

Missing and incomplete data

Prevention is far superior to a statistical cure, and every effort will be made to collect outcome data on all randomized participants. For example, we will collect outcomes on individuals who have stopped participating in the trial intervention. Due to the high longitudinal correlation, missed “interior” visits won’t decrease information very much for a linear trend. However, they are needed to assess departures from a linear trend.

As detailed in Little and Rubin 2002 and discussed by Mealli , the underlying missing data process determines the biasing effects of missing data and structures valid analytic strategies.^{93,94} If data are missing completely at random (MCAR), then there is no induced bias and a complete case analysis, while inefficient, is valid. If the probability of a potential observation being missing depends on what has been observed, but not on what hasn’t been observed, i.e., data is missing at random (MAR), then estimates based on an appropriate analytic model (on both the mean and error structure) for the observed data will not be biased. Use of a valid statistical model for the observed data would allow the missing data process to be ignored. In this situation either multiple imputation (MI) or development of a valid statistical model for the observed data (appropriate mean structure and correlation structure) will allow valid statistical inferences on the intervention effects. To use all participants when comparing treatments on the (12 month - baseline) outcome changes between groups, we will take advantage of the statistical association between outcomes at baseline, 6 and 12 months, and build a longitudinal model and then use one of these essentially equivalent approaches

In the third type of missing data process the probability of being missing depends on what would have been observed (e.g., the IGF-1 that would have been measured). In this case, neither MI nor developing a model for the observed data will completely eliminate bias. One can never empirically rule out this situation, but comprehensive statistical modeling coupled with sensitivity analysis can assess the stability of findings. We will anchor our sensitivity analyses under the assumption of MAR, and derive a valid model for the observed data under MAR, then alter the mean structure of the model under plausible non-MAR scenarios, and estimate intervention effects through MI approach to examine the robustness of the finding under MAR assumption.

On-treatment Analyses

Primary analyses will be performed on an intention-to-treat basis. However, interpretation of the trial outcomes is complicated because of drop-out from the intervention group and drop-in from the control group. Particularly common are early drop-outs, i.e. individuals randomized to intervention who attend only a few intervention sessions, sometimes none. Such persons are included in ITT analyses. In this setting, we will compute “on treatment” comparisons and variations on this approach that adjust such an analysis for differential correlates of adherence in the treatment groups.

Care is needed in answering such questions, and Bellamy et al. and Mealli et al. provide a useful framework for such analyses.^{94,95} For a basic case, we consider how to handle participants who complete at most 2 intervention “courses”. They will be included in the primary, as randomized, intent to treat analysis. A secondary question is, “how do the

treatment groups compare for those who adhered to treatment?” A straightforward comparison of treatments based only on “compliers” is attractive, but is biased if the compliers differ among the treatment groups. A valid comparison depends on adjusting for these differences, being careful not to adjust away the treatment effect. Propensity score approaches using information available at randomization and up through the first “course” could adjust for this imbalance. More sophisticated approaches using time-varying propensities allow accommodating more complicated patterns of non-adherence.

18. STUDY TIMETABLE

Table 5: Study Time Line

	2014		2015				2016				2017			
Quarter	q3	q4	q1	q2	q3	q4	q1	q2	q3	q4	q1	q2	Q3	Q4
Refine protocol	■	■												
Staff Training		■	■	■										
Pilot and finalize forms	■	■	■	■										
Database Development	■	■	■	■										
Modify intervention platform	■	■	■	■										
Recruitment					■	■	■	■	■	■				
Intervention *					■	■	■	■	■	■	■	■	■	■
Follow-up**					■	■	■	■	■	■	■	■	■	■
Adverse event monitor					■	■	■	■	■	■				
Analysis											■	■	■	■
Paper writing											■	■	■	■

19. HUMAN SUBJECTS Description of Consent Process

Each potential participant will meet with a staff member during in-person visits including the screening visit and randomization visit. Before randomization, a staff member will go through the consent form. The consent form is a printed form created using simple language and approved by the IRB. The staff member will start by explaining the nature and purpose of the trial, the interventions, study length, any potential risks and benefits, and the expectations for participants and study administrators. In addition, participants will be informed that participation is voluntary and that they can withdraw at any point, and that their refusal to participate will have no effect on their current or future treatment with the care provider. Each potential participant will be given time to read the consent form, and if he/she decides to join the study, he/she will sign and date the form. A copy of the signed, dated consent form will be given to the participant.

In accordance with the Health Insurance Portability and Accountability Act (HIPAA), the written informed consent document will include a subject authorization to release medical information to the project sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the project, including subjects' medical history.

Confidentiality

All participants' data will be protected. Hard copies will be locked in a secured cabinet or locked room, and digital copies will be protected in encrypted secure hard drive. Any communication and data transfer will be done using a de-identified data set with a study ID number. Data transfer agreement will be prepared if needed.

20. BIBLIOGRAPHY

1. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *The Lancet*. 2004;363(9418):1346-1353.
2. Duggan C, Wang CY, Neuhaus ML, et al. Associations of insulin-like growth factor and insulin-like growth factor binding protein-3 with mortality in women with breast cancer. *International journal of cancer. Journal international du cancer*. Mar 1 2013;132(5):1191-1200.
3. Decensi A, Puntoni M, Goodwin P, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer prevention research*. Nov 2010;3(11):1451-1461.
4. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes care*. Sep 2009;32(9):1620-1625.
5. Mitsuhashi A, Kiyokawa T, Sato Y, Shozu M. Effects of metformin on endometrial cancer cell growth in vivo: A preoperative prospective trial. *Cancer*. Jun 10 2014.
6. Gallagher EJ, LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. *Annals of the New York Academy of Sciences*. Dec 2011;1243:54-68.
7. Lukanova A, Soderberg S, Stattin P, et al. Nonlinear relationship of insulin-like growth factor (IGF)-I and IGF-I/IGF-binding protein-3 ratio with indices of adiposity and plasma insulin concentrations (Sweden). *Cancer causes & control : CCC*. Aug 2002;13(6):509-516.
8. Schoen RE SJ, Weissfeld JL, Thaete FL, Evans RW, Rosen CJ, Kuller LH. Lack of association between adipose tissue distribution and IGF-1 and IGFBP-3 in men and women. . *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2002;11(6):581-586.
9. Allen NE, Appleby PN, Kaaks R, Rinaldi S, Davey GK, Key TJ. Lifestyle determinants of serum insulin-like growth-factor-I (IGF-I), C-peptide and hormone binding protein levels in British women. *Cancer causes & control : CCC*. Feb 2003;14(1):65-74.
10. Holmes MD, Pollak MN, Hankinson SE. Lifestyle correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. Sep 2002;11(9):862-867.
11. Ogden CL, Carroll MD, Flegal KM. Prevalence of obesity in the United States. *JAMA : the journal of the American Medical Association*. Jul 2014;312(2):189-190.

12. World Cancer Research Fund / American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR;2007.
13. Bhaskaran K, Douglas I, Forbes H, Dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet*. Aug 13 2014.
14. Bonn SE, Wiklund F, Sjolander A, et al. Body mass index and weight change in men with prostate cancer: progression and mortality. *Cancer causes & control : CCC*. Aug 2014;25(8):933-943.
15. Ogden CL, Carroll MD. Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1960–1962 Through 2007–2008. *NCHS Health E-Stats*. 2010.
16. Centers for Disease Control and Prevention DoN, Physical Activity and Obesity, National Center for Chronic Disease Prevention and Health Promotion,. *Maryland State Nutrition, Physical Activity, and Obesity Profile*. 2012.
17. Baltimore City Health Department OoEaP. *Baltimore City Community Health Survey: Summary Results Report*. Baltimore City Health Department, Office of Epidemiology and Planning;2010.
18. American Cancer Society. *Cancer Treatment and Survivorship Facts & Figures 2014-2015*. Atlanta: American Cancer Society;2014.
19. Centers for Disease Control and Prevention. Surveillance of Demographic Characteristics and Health Behaviors Among Adult Cancer Survivors — Behavioral Risk Factor Surveillance System, United States, 2009. *MMWR*. 2012;61(1):1-23.
20. Calle E, Rodriguez C, Walker-Thurmond K, Thun M. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003 Apr 24 2003;348(17):1625-1638.
21. Chan DS, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancersystematic literature review and meta-analysis of 82 follow-up studies. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. Apr 27 2014.
22. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 1 2005;23(7):1370-1378.
23. Laiyemo AO, Doubeni C, Badurdeen DS, et al. Obesity, weight change, and risk of adenoma recurrence: a prospective trial. *Endoscopy*. Sep 2012;44(9):813-818.
24. Joshi CE, Mondul AM, Menke A, et al. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. *Cancer prevention research*. Apr 2011;4(4):544-551.
25. Vance V, Mourtzakis M, McCargar L, Hanning R. Weight gain in breast cancer survivors: prevalence, pattern and health consequences. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. Apr 2011;12(4):282-294.
26. Saquib N, Flatt SW, Natarajan L, et al. Weight gain and recovery of pre-cancer weight after breast cancer treatments: evidence from the women's healthy eating and living (WHEL) study. *Breast cancer research and treatment*. Oct 2007;105(2):177-186.
27. LeRoith D, Roberts CT. The insulin-like growth factor system and cancer. *Cancer Letters*. 2003;195(2):127-137.
28. Friedrich N, Jorgensen T, Juul A, et al. Insulin-like growth factor I and anthropometric parameters in a Danish population. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association*. Mar 2012;120(3):171-174.

29. Rowlands MA, Holly JM, Gunnell D, et al. The relation between adiposity throughout the life course and variation in IGFs and IGFbps: evidence from the ProtecT (Prostate testing for cancer and Treatment) study. *Cancer causes & control : CCC*. Nov 2010;21(11):1829-1842.
30. Fowke JH, Matthews CE, Yu H, et al. Racial differences in the association between body mass index and serum IGF1, IGF2, and IGFBP3. *Endocrine-related cancer*. Mar 2010;17(1):51-60.
31. Brick DJ, Gerweck AV, Meenaghan E, et al. Determinants of IGF1 and GH across the weight spectrum: from anorexia nervosa to obesity. *European journal of endocrinology / European Federation of Endocrine Societies*. Aug 2010;163(2):185-191.
32. Faupel-Badger JM, Berrigan D, Ballard-Barbash R, Potischman N. Anthropometric correlates of insulin-like growth factor 1 (IGF-1) and IGF binding protein-3 (IGFBP-3) levels by race/ethnicity and gender. *Annals of epidemiology*. Dec 2009;19(12):841-849.
33. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. *Trends in endocrinology and metabolism: TEM*. Oct 2006;17(8):328-336.
34. Bougoulia M, Triantos A, Koliakos G. Effect of weight loss with or without orlistat treatment on adipocytokines, inflammation, and oxidative markers in obese women. *Hormones*. Oct-Dec 2006;5(4):259-269.
35. Meckling KA, Gauthier M, Grubb R, Sanford J. Effects of a hypocaloric, low-carbohydrate diet on weight loss, blood lipids, blood pressure, glucose tolerance, and body composition in freeliving overweight women. *Canadian journal of physiology and pharmacology*. Nov 2002;80(11):1095-1105.
36. Brekke HK, Bertz F, Rasmussen KM, Bosaeus I, Ellegard L, Winkvist A. Diet and exercise interventions among overweight and obese lactating women: randomized trial of effects on cardiovascular risk factors. *PloS one*. 2014;9(2):e88250.
37. Irwin ML, McTiernan A, Bernstein L, et al. Relationship of obesity and physical activity with C-peptide, leptin, and insulin-like growth factors in breast cancer survivors. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. Dec 2005;14(12):2881-2888.
38. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *Journal of the National Cancer Institute*. Jun 6 2012;104(11):815-840.
39. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *Bmj*. 2012;344:e70.
40. Dewell A, Weidner G, Sumner MD, et al. Relationship of dietary protein and soy isoflavones to serum IGF-1 and IGF binding proteins in the Prostate Cancer Lifestyle Trial. *Nutrition and cancer*. 2007;58(1):35-42.
41. Gannon MC, Nuttall FQ. Effect of a high-protein diet on ghrelin, growth hormone, and insulinlike growth factor-I and binding proteins 1 and 3 in subjects with type 2 diabetes mellitus. *Metabolism: clinical and experimental*. Sep 2011;60(9):1300-1311.
42. Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. *Aging cell*. Oct 2008;7(5):681-687.
43. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *International journal of obesity*. May 2011;35(5):714-727.
44. Goodman-Gruen D, Barrett-Connor E. Epidemiology of insulin-like growth factor-I in elderly men and women. The Rancho Bernardo Study. *American journal of epidemiology*. Jun 1 1997;145(11):970-976.

45. Milani D, Carmichael JD, Welkowitz J, et al. Variability and reliability of single serum IGF-I measurements: impact on determining predictability of risk ratios in disease development. *The Journal of clinical endocrinology and metabolism*. May 2004;89(5):2271-2274.
46. Chia VM, Newcomb PA, White E, Zheng Y, Potter JD, Lampe JW. Reproducibility of serum leptin, insulin-like growth factor-I, and insulin-like growth factor-binding protein-3 measurements. *Hormone research*. 2008;69(5):295-300.
47. Rosario PW. Normal values of serum IGF-1 in adults: results from a Brazilian population. *Arquivos brasileiros de endocrinologia e metabologia*. 2010;54(5):477-481.
48. Birketvedt GS, Geliebter A, Kristiansen I, Fjergenschau Y, Goll R, Florholmen JR. Diurnal secretion of ghrelin, growth hormone, insulin binding proteins, and prolactin in normal weight and overweight subjects with and without the night eating syndrome. *Appetite*. Dec 2012;59(3):688-692.
49. Haus E, Dumitriu L, Nicolau GY, Bologa S, Sackett-Lundeen L. Circadian rhythms of basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), insulin-like growth factor-1 (IGF1), insulin-like growth factor binding protein-3 (IGFBP-3), cortisol, and melatonin in women with breast cancer. *Chronobiology international*. Jul 2001;18(4):709-727.
50. Lonning PE, Hall K, Aakvaag A, Lien EA. Influence of tamoxifen on plasma levels of insulin-like growth factor I and insulin-like growth factor binding protein I in breast cancer patients. *Cancer research*. Sep 1 1992;52(17):4719-4723.
51. Schernhammer ES, Giobbie-Hurder A, Gantman K, et al. A randomized controlled trial of oral melatonin supplementation and breast cancer biomarkers. *Cancer causes & control : CCC*. Apr 2012;23(4):609-616.
52. Friedlander TW, Weinberg VK, Small EJ, et al. Effect of the somatostatin analog octreotide acetate on circulating insulin-like growth factor-1 and related peptides in patients with nonmetastatic castration-resistant prostate cancer: results of a phase II study. *Urologic oncology*. Jul-Aug 2012;30(4):408-414.
53. Yakar S, Leroith D, Brodt P. The role of the growth hormone/insulin-like growth factor axis in tumor growth and progression: Lessons from animal models. *Cytokine & growth factor reviews*. Aug-Oct 2005;16(4-5):407-420.
54. Price AJ, Allen NE, Appleby PN, et al. Insulin-like growth factor-I concentration and risk of prostate cancer: results from the European Prospective Investigation into Cancer and Nutrition. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. Sep 2012;21(9):1531-1541.
55. Kaaks R, Johnson T, Tikk K, et al. Insulin-like growth factor I and risk of breast cancer by age and hormone receptor status-A prospective study within the EPIC cohort. *International journal of cancer. Journal international du cancer*. Jun 1 2014;134(11):2683-2690.
56. Schmidt JA, Allen NE, Almquist M, et al. Insulin-like growth factor-I and risk of differentiated thyroid carcinoma in the European prospective investigation into cancer and nutrition. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. Jun 2014;23(6):976-985.
57. Rizos CV, Elisaf MS. Metformin and cancer. *European journal of pharmacology*. Apr 5 2013;705(1-3):96-108.
58. Executive summary: standards of medical care in diabetes--2014. *Diabetes care*. Jan 2014;37 Suppl 1:S5-13.
59. Quinn BJ, Kitagawa H, Memmott RM, Gills JJ, Dennis PA. Repositioning metformin for cancer prevention and treatment. *Trends in endocrinology and metabolism: TEM*. Sep 2013;24(9):469-480.

60. Kalender A, Selvaraj A, Kim SY, et al. Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner. *Cell metabolism*. May 5 2010;11(5):390-401.
61. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Annals of internal medicine*. May 3 2011;154(9):602-613.
62. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England journal of medicine*. Feb 7 2002;346(6):393-403.
63. Diabetes Prevention Program Research G. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes care*. Apr 2012;35(4):731-737.
64. Seifarth C, Schehler B, Schneider HJ. Effectiveness of metformin on weight loss in non-diabetic individuals with obesity. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association*. Jan 2013;121(1):27-31.
65. Bjorkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. *Journal of psychopharmacology*. Mar 2011;25(3):299-305.
66. Shaw RJ, Lamia KA, Vasquez D, et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science*. Dec 9 2005;310(5754):1642-1646.
67. Hardie DG, Ross FA, Hawley SA. AMP-activated protein kinase: a target for drugs both ancient and modern. *Chemistry & biology*. Oct 26 2012;19(10):1222-1236.
68. Karnevi E, Said K, Andersson R, Rosendahl AH. Metformin-mediated growth inhibition involves suppression of the IGF-I receptor signalling pathway in human pancreatic cancer cells. *BMC cancer*. 2013;13:235.
69. DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. *The Journal of clinical endocrinology and metabolism*. Dec 1991;73(6):1294-1301.
70. Berker B, Emral R, Demirel C, Corapcioglu D, Unlu C, Kose K. Increased insulin-like growth factor-I levels in women with polycystic ovary syndrome, and beneficial effects of metformin therapy. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology*. Sep 2004;19(3):125-133.
71. Fruehwald-Schultes B, Oltmanns KM, Toschek B, et al. Short-term treatment with metformin decreases serum leptin concentration without affecting body weight and body fat content in normal-weight healthy men. *Metabolism: clinical and experimental*. Apr 2002;51(4):531-536.
72. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA: a cancer journal for clinicians*. Jul-Aug 2012;62(4):243-274.
73. AICR'S Guidelines For Cancer Survivors. 2012; <http://www.aicr.org/patientssurvivors/aicrsguidelines-for-cancer.html>. Accessed 07/15/2014, 2014.
74. Basic Information About Cancer Survivorship. http://www.cdc.gov/cancer/survivorship/basic_info/index.htm. Accessed 7/15/2014, 2014.
75. Reeves MM, Terranova CO, Eakin EG, Demark-Wahnefried W. Weight loss intervention trials in women with breast cancer: a systematic review. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. May 29 2014.
76. Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. *Journal of cancer survivorship : research and practice*. Sep 2013;7(3):355-368.

77. Demark-Wahnefried W, Morey MC, Sloane R, et al. Reach out to enhance wellness homebased 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 : official journal of the American Society of Clinical Oncology*. Jul 1 2012;30(19):2354-2361.
78. Hygiene MDoHaM. *Maryland Comprehensive Cancer Control Plan*.
79. Group. USCSW. United States Cancer Statistics: 1999–2010 Incidence and Mortality Webbased Report. . 2013; www.cdc.gov/uscs. Accessed 8/23/2014, 2014.
80. Jerome GJ, Yeh HC, Dalcin A, et al. Treatment of Obesity in Primary Care Practice: The Practice Based Opportunities for Weight Reduction (POWER) Trial at Johns Hopkins. . *Obesity and Weight Management*. 2009;5(5):216-221.
81. Appel LJ, Clark JM, Yeh HC, et al. Comparative effectiveness of weight-loss interventions in clinical practice. *N Engl J Med*. Nov 24 2011;365(21):1959-1968.
82. Bandura. A. Reflections on self-efficacy. . *Advances in Behavior Research Therapy*. 1978;1:237-269.
83. Bandura A. *Self-efficacy: The exercise of control*. New York: W. H. Freeman and Company; 1997.
84. Miller WR RS. *Motivational interviewing: Preparing people to change addictive behavior*. First Edition ed. ed. New York: Guilford Press; 1997.
85. Services USDoHaH. Healthy People 2020. . <http://healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=33>. Accessed August 5, 2014, 2014.
86. Bristol-Myers Squibb Company. GLUCOPHAGE® (metformin hydrochloride tablets) and GLUCOPHAGE® XR (metformin hydrochloride extended-release tablets).
87. Smith WA, Nolan VG, Robison LL, Hudson MM, Ness KK. Physical activity among cancer survivors and those with no history of cancer- a report from the National Health and Nutrition Examination Survey 2003-2006. *American journal of translational research*. Aug 15 2011;3(4):342-350.
88. Dallal CM, Brinton LA, Matthews CE, et al. Accelerometer-based measures of active and sedentary behavior in relation to breast cancer risk. *Breast cancer research and treatment*. Aug 2012;134(3):1279-1290.
89. Jerome GJ, McAuley E. Enrollment and participation in a pilot walking programme: the role of self-efficacy. *Journal of health psychology*. Feb 2013;18(2):236-244.
90. Young DR, Jerome GJ, Chen C, Laferriere D, Vollmer WM. Patterns of physical activity among overweight and obese adults. *Preventing chronic disease*. Jul 2009;6(3):A90.
91. Chen C, Jerome GJ, Laferriere D, Young DR, Vollmer WM. Procedures used to standardize data collected by RT3 triaxial accelerometers in a large-scale weight-loss trial. *Journal of physical activity & health*. May 2009;6(3):354-359.
92. Jerome GJ, Young DR, Laferriere D, Chen C, Vollmer WM. Reliability of RT3 accelerometers among overweight and obese adults. *Medicine and science in sports and exercise*. Jan 2009;41(1):110-114.
93. Little R, Rubin D. *Statistical Analysis with Missing Data*. Chichester, NY: John Wiley & Sons; 2002.
94. Mealli F, Imbens GW, Ferro S, Biggeri A. Analyzing a randomized trial on breast selfexamination with noncompliance and missing outcomes. *Biostatistics*. Apr 2004;5(2):207222.
95. Bellamy SL, Lin JY, Ten Have TR. An introduction to causal modeling in clinical trials. *Clinical trials*. 2007;4(1):58-73.

