WEIGHT FLUCTUATION AND CANCER RISK IN POST-MENOPAUSAL WOMEN: THE WOMEN'S HEALTH INITIATIVE

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ABSTRACT

Purpose: To examine the role of weight fluctuation during early to mid- adulthood and associated risk of breast, endometrial, and colorectal cancer in postmenopausal women.

Methods: 88,006 postmenopausal women (baseline age: 63.6±7.4 years) in the Women's Health Initiative Observational Study were categorized by self-reported weight change (weight stable; weight gain; lost weight; weight cycled [1-3, 4-6, 7-10, >10 times]) during early to mid- adulthood. Incident breast, endometrial, and colorectal cancer events were collected annually over 20 years. Overall and site specific associations were investigated using Cox proportional hazard models.

Results. 8,585 (breast=6,450; colorectal=1,471; endometrial=884) incident cancer cases were identified during a mean 12.8 years of follow-up. Compared with weight stability, weight gainers and cyclers presented with an overall increased risk of cancer (HR=1.20 [1.13-1.26] and HR=1.11 [1.05-1.17], respectively). Adjustment for baseline BMI attenuated all associations between weight cycling and cancer risk. Weight cycling "4-6 times" was most consistently associated with cancer risk, showing a 72% increased risk for endometrial cancer (95% CI: 1.38-2.13) compared to weight stable women.

Conclusion. Weight gain and weight cycling were positively associated with risk of postmenopausal breast, endometrial, and colorectal cancer. This association may be mitigated by overall obesity.

INTRODUCTION

Cancer is the second leading cause of death in the United States and most commonly develops in older adults.[1] In postmenopausal women, cancers of the breast, endometrium, and colorectum represent nearly half of all newly diagnosed cancer cases each year.[2] In addition to age, many conventional risk factors also contribute to cancer onset and progression, including obesity. Indeed, one in eight (13%) cases of breast, endometrial, and colorectal cancers are directly attributable to obesity,[3] a problem which is augmented in older women due to the pervasiveness of the condition.[4]

Approximately two-thirds of postmenopausal women report attempting weight loss at any given time.[5] Given the futility of long-term weight loss maintenance,[6] weight fluctuation (or cycling) is a common occurance.[7] Weight cycling has previously been associated with negative changes in body composition[8] and health outcomes,[9,10] and recent research has begun exploring associations between weight cycling and cancer. Currently, eleven observational studies have been conducted with some,[11–18] but not all,[19–21] suggesting a positive association between weight cycling and cancer risk – as much as a three-fold increase for renal cell carcimoma[11,12] and endometrial cancer.[13,16] However, in many cases, modest findings are attenuated after adjustment for current weight/BMI.[15–18] In addition, robust evidence from longitudinal cohort studies is limited and disparate,[11,18,20,22] with only a few studies reporting on breast[18,20,21] and colon/colorectal[18,20] cancer outcomes.

Utilizing data available in the well-characterized Women's Health Initiative Observational Study (WHI OS),[23] we will add to the current body of literature by clarifying

the role of weight fluctuation throughout adulthood on risk of developing three highly prevalent cancers in postmenopausal women. We hypothesize that adult female weight cyclers and weight gainers will be at increased risk of developing breast, endometrial, and/or colorectal cancers, compared to postmenopausal women who were weight stable in early and mid- adulthood. Secondarily, we hypothesize that the frequency of weight cycling in early and middle adulthood will be (a) linearly associated with postmenopausal onset of breast, endometrial and/or colorectal cancers and (b) independent of baseline BMI.

REVIEW OF LITERATURE

Cancer

Public Health Significance of Cancer

It is estimated that there were 14.5 million individuals living with a history of cancer in the United States as of January 1, 2014, and by 2024, the number of people living with cancer is projected to increase to almost 19 million survivors.[24] Development of cancer occurs over time in a series of steps, characterized by the uncontrolled growth and spread of abnormal cells.[25] Cancers have characteristically diverse behavior due to the origin of the abnormal cells, spreading at varied rates.[1] In 2010, Mariotto and colleagues estimated the total cost of cancer in the US amounted to $124 billion, and projected costs to increase by 27% totaling $158 billion by 2020.[26] According to the Agency for Healthcare Research and Quality, it is estimated that half of all direct medical cancer costs (total $75 billion)[27] are from outpatient care at the hospital or visits to the doctor's office, 35% from inpatient hospital stays, and an estimated 11% from prescription drugs.[1,28]

Cancer most commonly develops in older adults, and people 50 years of age or older account for 86% of all cancer diagnoses.[27] Due to continued population growth and longer life expectancy,[29] the number of US incident cancer cases is expected to reach 1,685,210 in 2016,[27] and could reach 2.25 million by 2030.[30] Cancer is the second leading cause of death in the US, accounting for almost 600,000 deaths,[27] behind the leading cause, heart disease and stroke, accounting for approximately 740,000 deaths per year.[31]

The leading incident cancers (excluding all types of skin cancer) in women are those of the breast, lung and bronchus, and colon and rectum.[27,32] In fact, for American women, the lifetime risk of developing any cancer is slightly greater than one in three.[1]

Among American women, 843,820 new cancer cases are expected to be diagnosed, and over a quarter million cancer deaths[2] are estimated to occur in 2016 alone.[27] Because cancer is the leading cause of death among older women (ages 55-84 years)[33] and almost half of all new cancer cases occur in this population, it is essential to understand the impact that specific cancers impose on postmenopausal women.

The most commonly diagnosed cancer among older women is breast cancer, followed by colorectal and endometrial cancer,[1,32,34] amounting to 44% of all new cancer cases and 26% of all cancer deaths in women.[2] Together, these three cancers are among the top six leading causes of cancer death among women and have a combined mean diagnosis at age 63.[2] It is projected that one in five Americans will be aged 65 and older by 2030.[35] As older women make up an increasingly larger proportion of the population,[36] identification and treatment of risk factors for cancer is emerging as a significant public health research priority. Discussion of the epidemiology of breast, endometrial, and colorectal cancers in postmenopausal women will be the focus of the following sections.

Prevalence and Incidence of Breast, Endometrial, and Colorectal Cancers

Over 3 million US women are living with breast cancer as of January 2014.[37] Among American women, it is estimated that roughly a quarter million new cases of breast cancer will be diagnosed this year.[27] Breast cancer is the second leading cause of cancer death among US women (after lung cancer),[32] leading to 40,450 deaths in 2016.[27] Although there has been a decline in breast cancer related mortality over the last few decades, the largest decrease has been shown in younger women.[1]

The second most common cancer among women in the U.S following breast cancer is uterine cancer.[37] In 2014, approximately 624,890 women were living with a diagnosis of

uterine cancer. The most common type of uterine cancer occurs in the endometrium (the lining of the uterus),[38] with 60,050 cases of endometrial cancer estimated to be diagnosed this year.[27]. Incidence rates of endometrial cancer rose by 2.4% per year from 2007 to 2011 up to 7%, and approximately 75% of endometrial cancer cases are found in women ages 55 and older.[1] Despite the large occurrence of cancer onset being in older women, endometrial cancer is the most common gynecologic cancer,[25,38] attributing to more than 10,000 deaths in 2016.[27]

Colorectal cancer ranks as the third most common cancer in the U.S.[32] An estimated 624,340 women are living with a history of colorectal cancer, and 63,670 new cases are estimated to be diagnosed in the U.S. this year.[27] Although colorectal cancer incidence has decreased by 4.3% among adults age 50 and older in recent years,[1] it is the third leading cancer killer in women, accounting for roughly 23,170 deaths annually.[27]

Risk Factors for Breast, Endometrial, and Colorectal Cancers

Given their prevalence, it is of great public health interest to examine what risk factors contribute to the development and onset of breast, endometrial, and colorectal cancers in postmenopausal women. In general, a combination of internal and environmental factors act together, or in sequence, to increase risk for developing these cancers.[1] Common risk factors, by cancer type, are presented below, with some more treatable than others.

Both modifiable and non-modifiable factors contribute to breast cancer risk, and can be monitored throughout early and middle adulthood. Risk factors for breast cancer include experiencing menarche at a younger age and menopause at a later age (i.e. greater exposure to estrogen), family and/or personal history of breast cancer, changes in breast-

cancer related genes, and aging. Other risk factors include never having children or having first birth at an older age, chest radiation treatments, long-term hormone replacement therapy (HRT) use, alcohol use, and being overweight or obese.[39] Several factors listed are non-modifiable; however, it is generally understood that women can decrease their risk for breast cancer by maintaining a healthy weight and regular exercise routine throughout the lifespan, and breastfeeding.[39]

All women are at risk for developing endometrial cancer, however, most of the established risk factors for endometrial cancer influence the balance of the estrogen and progesterone hormones. Risk factors include aging, number of menstrual cycles, infertility, family history of endometrial and/or colorectal cancer, personal history of breast and/or ovarian cancer, and pelvic radiation treatment. Further risk factors include never having children, smoking, HRT use, poor diet and lack of exercise, diabetes, and overweight and obesity.[38,40]

Similar to breast cancer, there are preventative screening measures that can be taken in order to decrease risk of colorectal cancer development. Risk factors include genetics, age, personal or family history of colorectal cancer and/or polyps, and inflammatory bowel diseases. Other more modifiable lifestyle factors include lack of physical activity, poor diet, alcohol and tobacco use, and overweight and obesity. Some researchers believe that diets which have been shown to reduce risk for chronic cardio-metabolic diseases may also contribute to a risk reduction in colorectal cancer.[41]

Because obesity is one of the few known modifiable risk factors associated with breast, endometrial, and colorectal cancer risk, interventions to reduce obesity should, in theory, reduce risk of these cancers in postmenopausal women. The next section discusses

the public health significance of obesity and associations between obesity and cancer risk. We begin, however, with a brief overview of the condition, along with common methodology to quantify it.

Obesity

Obesity can be simply defined as having an excess amount of body fat, yet the consequences of this health condition are quite complex. Obesity occurs over time when an individual consumes more energy than expended. However, the energy balance between calories-in and calories-out varies greatly by individual. Factors that might affect an individual's energy balance include genetic makeup, overeating, eating high-fat highly processed foods, and not being physically active.[42]

Methods of Defining Obesity

There are many methods to estimate and quantify total body fat mass as a means to quantify obesity. These include body mass index (BMI), bioelectrical impedance analysis, multi-site skinfolds measurements, hydro-densitometry, dual-energy x-ray absorptiometry, computed tomography, and magnetic resonance imaging. Of those listed, only computed tomography and magnetic resonance imaging are able to distinguish between subcutaneous and visceral abdominal adipose tissue. However, the majority of these measurement tools are too costly, complex, and time-consuming to be used as an estimate of adiposity in the general population or large-scale longitudinal studies.[42] Therefore, obesity is most commonly defined using BMI, and is calculated by dividing an individual's body weight (in kilograms) by their height (in meters) squared.[43] The National Institutes of Health and World Health Organization classify obesity as having a BMI equal to or greater than 30.0 kg/m^2, overweight as 25.0 to 29.9 kg/m^2, and normal weight as 18.5 to 24.9 kg/m^2. [43,44]

Prevalence of Obesity

Over the last several decades, obesity (BMI $\geq$ 30kg/m^2) has become increasingly prevalent across the globe, with rates more than doubling worldwide since 1980.[43] Currently, more than two in three US adults are classified as overweight and/or obese, with 34.9% adults categorized as obese.[4,45] Obesity rates tend to increase to middle age, then decline in later life, and are slightly higher among adult women (36.4%) than men (33.5%).[4,46,47] Indeed, Ogden and colleagues reported that 38.1% of US women aged 60 years and older in 2012 were classified as obese, compared to only 32.0% of men in the same age group.[4] What's more, the only significant trend reported in this study of obesity prevalence from 2003 to 2012 was found among the women 60 years and older age/gender group (31.5% to 38.1%).[4]

Impact of Obesity on Cancer

According to the World Cancer Research Fund, in economically developed countries, an estimated one-third of cancer cases can be attributed to modifiable risk factors such as overweight or obesity, poor diet, and/or lack of physical activity,[1] with this number varying by specific types of cancer. If current trends continue, obesity is projected to contribute to an additional 500,000 cases of cancer in the US by 2030.[42] What's more, the American Cancer Society reports that as many as one in five cancer-related deaths per year have been attributable to excess body weight.[48] However, Calle and colleagues estimated that by maintaining a normal weight (BMI < 25kg/m^2), 90,000 cancer deaths could be prevented per year.[42]

Approximately 7% of all cancers in women were attributable to obesity in 2007.[3] However, the proportion of breast, endometrial, and colorectal cases attributable to obesity

was slightly higher (13%), with the highest attributable percentage among women diagnosed with endometrial cancer (41%).[3] In other words breast, endometrial, and colorectal cancers account for almost two-thirds of all incident obesity-related cancers.[49]

Indeed, three of four of the most common cancers in aging women (breast, colorectal, and endometrial cancer) are heavily related to obesity status.[44] Numerous epidemiological studies have indicated that obesity is associated with an increased incidence of several cancers and/or cancer mortality.[32,42,50] The following section reviews the current literature on obesity and the associated risk of breast, endometrial, and colorectal cancers.

Effects of Obesity on Breast, Endometrial, and Colorectal Cancer Risk

Breast Cancer

The International Agency for Research on Cancer (IARC) concluded in their 2002 review of physical activity, weight, and cancer incidence that obesity was attributable for 9% of postmenopausal breast cancer cases.[51] Studies show that risk for breast cancer rises during a woman's postmenopausal years, as there has been evidence to suggest that overweight and obesity are negatively associated with breast cancer risk in premenopausal women.[32] According to the 2011 Annual Report to the Nation on Cancer, obese women have a 25% greater risk for developing postmenopausal breast cancer versus normal weight women.[52]

In a 2008 meta-analysis, Renehan and colleagues observed a 12% increased risk for breast cancer in women per 5-unit increase in BMI.[49] Neuhouser and colleagues reported similar findings using the Women's Health Initiative cohort, concluding the risk of breast cancer is 58% greater among postmenopausal women who are class II obese (BMI

≥ 35kg/m^2) compared to normal weight women (BMI < 25kg/m^2).[53] Cheraghi and colleagues conducted a comprehensive meta-analysis to assess both cohort and case-control studies which examined the association between BMI (overweight and obese) and breast cancer according to pre- and post-menopausal status.[54] The results from this review concluded overweight or obese postmenopausal women were at an increased risk for postmenopausal breast cancer; however, when stratified by study quality, the statistical significance disappeared for high quality cohort studies. Overall, it can be said that breast cancer risk in postmenopausal women can be altered by obesity, however, there is much left to be understood about the causal relationship between these variables.

Endometrial Cancer

High BMI and/or excess body fatness has been established as a major modifiable risk factor for endometrial cancer.[50,55] An estimated 40% of endometrial cancer is associated with obesity-related factors.[51,56] The IARC 2002 report[51] and a review on obesity and cancer[57] indicated that obesity increases risk for endometrial cancer by 2 to 5 times when compared to normal weight individuals. When comparing obese with normal weight postmenopausal women, Chang and colleagues[58] found that obese women were over 3 times as likely as normal weight women to develop endometrial cancer. These results are supported in another prospective study, in which overweight/obese (≥ 27.5 kg/m^2) women were 2.63 to 7.72 times as likely as women with a normal BMI (< 22.5 kg/m^2) to develop endometrial cancer.[59] Similar finding were reported in a case-control study.[15]

Han and colleagues tackled the question of whether obesity in early adulthood (age 25) could impact risk of cancer in later adulthood. In at least one study, investigators found

that women who were obese at age 25 were 2.87 times as likely as normal weight women to develop endometrial cancer during postmenopausal years.[60] Similarly, Yang and colleagues observed an increased risk for endometrial cancer in postmenopausal women associated with women who self-described as having a "plumper" body size at age ten.[59] Yet, there was no evidence of excess risk after further adjustments for current BMI and other related reproductive and lifestyle risk factors. Body size and cancer risk remained unassociated when analyzing body size at age 20 as well. Dougan and colleagues reported similar findings,[61] in which results showed positively associated risk ratios until current BMI adjustments removed significance. Overall, current obesity is a known risk factor for endometrial cancer, as demonstrated by a meta-analysis reporting a 60% increase in endometrial cancer per five unit increase in BMI among women.[62]

Colorectal Cancer

A growing body of evidence shows obesity is positively related to colorectal cancer in older adults, but several reviews have shown associations between elevated BMI and colorectal cancer in women to be inconsistent.[51,63–66] Among postmenopausal women in a pooled analysis, relative risk for colorectal cancer was greatest among obese postmenopausal women, in whom the risk was 24% higher compared to those with a BMI less than 23.0 kg/m^2.[67] There was a 12% increase in colon cancer risk among women per 5-unit increase in BMI in a 2008 meta-analysis, but only 8 of 21 individual studies had significant results.

Similar positive findings were found in a review by Schlesinger et al,[68] but when the statistical model controlled for waist circumference, the associated risk was attenuated. Additionally, investigators from the Framingham Heart Study determined that obesity was

not significantly associated with colon cancer among obese women compared to normal weight.[69] What's more, abdominal obesity is related to metabolic factors such as insulin resistance and hyperinsulinemia[70] which contribute to many other nutrition-related risk factors previously mentioned for colorectal cancer,[51] and one meta-analysis found eight studies who reported these factors to be useful in predicting cancer risk in addition to obesity status.[66] Although obesity has been shown to be associated with colorectal cancer in postmenopausal women, further research is needed to determine the biologic link between obesity and colorectal cancer.

Although numerous studies have established obesity (BMI $\geq$ 30kg/m^2) as a modifiable risk factor for cancer, studies should continue to evaluate the attributable risk of obesity in early and mid- adulthood on risk of cancer later in life.[71] It is known that maintaining a healthy weight throughout the lifespan is important for health,[61] and investigators should continue to examine how body fat distribution and weight change behavior may impact cancer risk.[59] Due to the modifiable nature of obesity, it is possible that many incident cancer cases could be prevented by implementing strategies to reduce obesity prevalence in the U.S. and worldwide. Indeed, Wang and colleagues[72] recently projected that roughly 100,000 new cases of cancer may be avoided if every adult were to reduce their BMI by 1% (~1kg weight loss). However, the long term effectiveness of such weight loss strategies is questionable, thus the influence of weight fluctuation on cancer risk should be considered.

Strategies to Reduce Obesity and Their Long-Term Effectiveness

The primary management of obesity involves healthy lifestyle promotion through caloric restriction, increased physical activity, dietary modification, and pharmacotherapy.

Health professionals recommend a modest 5-10% body weight reduction, sufficient enough to positively affect health.[73,74] Yet, the long-term efficacy of current weight loss therapies and interventions are variable. In a meta-analysis of randomized control trials implementing a number of different weight loss strategies, investigators found that only a handful of trials have been able to successfully facilitate weight loss maintenance after initial treatment subsides.[6] This is because it becomes increasingly challenging to continue to follow a weight maintenance program over a prolonged period of time, and eventually individuals regain lost weight. Thus, despite initial success, evidence suggests roughly one third of weight lost is regained within one year of intervention.[6,75] Typically, the trend continues until baseline weight is reached roughly five years after initial weight loss.[75,76] This is problematic, given that the health benefits may only last as long as the weight reduction is sustained,[6] and may disproportionately affect overweight and obese postmenopausal women, as 60%-70% reported currently attempting weight loss.[5]

Intentional weight loss followed by weight regain is known as weight cycling, and is also referred to as yo-yo dieting, weight fluctuation, weight variability, weight instability, and/or episodic variation in weight over time.[9,10,77] Findings from Syngal et al. suggested over one-third of middle-aged women intentionally lost and subsequently regained more than 10 pounds at least one time in their lifetime,[7] and numerous observational studies found between 18-57%[11,18,20,22] of women reported weight cycling, although precise definitions vary across studies, making cross-study comparisons difficult. Additionally, in at least one study, more women than men tend to report weight cycling, as well report a higher frequency of weight cycles.[18] Despite this common weight change

pattern in adult women, little is known about the effect of differing weight fluctuation patterns on cancer risk.

Effects of Weight Fluctuations on Breast, Endometrial, and Colorectal Cancer Risk

Weight Loss and Associated Risk for Cancer

Several studies have suggested intentional weight loss can reduce the risk of cancer, particularly when the weight loss is after menopause.[78–80] Indeed, Wang and colleagues[72] recently projected that roughly 100,000 new cases of cancer may be avoided if every adult were to reduce his or her BMI by 1% (~1kg weight loss). However, intentionality of weight loss has not been well documented, and at least one review implicated that the results of observational studies on weight loss and cancer are less clear.[81] In a review of intentional weight loss and cancer risk, Byers and colleagues concluded that both biomarkers for cancer and cancer incidence decrease following both dietary intervention and bariatric surgery weight loss strategies.[82]

A 2012 systematic review examining the association of weight loss and cancer incidence identified a clear association between intentional weight loss and reduction in cancer incidence among women.[81] What's more, this association was particularly evident among obesity-related cancers in overweight and/or obese populations. However, only 16 of 34 studies reviewed found statistically significant results. Similarly, overweight or obese women in the Women's Health Initiative who lost weight did not significantly lower their risk of breast cancer.[53] It is important to note that these risk reductions for cancer are only apparent provided the weight loss is maintained.

Weight Gain and Associated Risk for Cancer

The association between adult weight gain and postmenopausal cancer risk suggests an increased risk,[11,58,83–95] but is not consistent across studies.[96–102] Results from a recent meta-analysis demonstrated that women who gained weight throughout early and middle adulthood had increased risk for certain cancers.[65] This dose-response meta-analysis reviewed the association between adult weight gain and risk of ten adiposity-related cancers (colorectal, prostate, breast, endometrial, kidney, pancreatic, gallbladder, ovarian, and thyroid), and found sufficient evidence of a dose-response relationship in six of the ten cancer sites (breast, colon, endometrium, prostate, ovary, and pancreas). A 5 kg increase in adult weight gain lead to an 11% increased risk for developing these cancers.[65]

The HUNT study, a Norwegian cohort of almost 30,000 women age 55 years and older (postmenopausal) with anthropometric data over a span of 30 years, found that weight gain in adulthood was associated with increased breast cancer risk. Weight gain before (<45 years) and around (between 45 and < 55 years) menopausal age was linearly associated with increased breast cancer risk by 38% and 69%, respectively, compared to stable weight individuals. Postmenopausal women (> 55 years) who gained weight had no such associated risk.[84]

In the U.S., almost 100,000 women were followed prospectively[83] to examine weight change during specific intervals of adulthood (age 18, 35, 50, current). Weight gain during each time period from early reproductive years to peri- and post-menopausal years were associated with increased breast cancer risk in menopausal HRT nonusers compared with stable weight during those periods, but no association was observed in current menopausal HRT users.

In a recent meta-analysis, Schlesinger et al.[68] found that high body weight gain (mean gain 15.2 kg) increased colon cancer risk by 22% compared to remaining weight stable. However, when analyzed by sex, men were at a slightly greater risk (36%) than women (9%).[68] In recent dose-response analyses and reviews, similar sex-specific results were observed.[65,68,103] The Schlesinger review additionally observed that an associated increased risk persisted even after adjusting for body weight at younger age. In other words, despite the individual's BMI in early adulthood, weight gain during early and middle adulthood further elicited a significant increased risk for colon cancer.

Similar findings suggest a woman's risk for endometrial cancer is increased by 49 to 83%, per 5 kg/m^2 increment in BMI.[32,50,55,59,60] It may be speculated that progressive adult weight gain may contribute to the development and onset of cancer,[104] and suggests that avoiding weight gain may be important for maintaining a lower risk for cancer.[68]

Weight Cycling and Associated Risk for Cancer

Because of the known futility of weight loss maintenance practices, evaluating whether weight cycling is associated with cancer risk has significant public health implications. A greater emphasis should be given to encouraging weight loss maintenance or to avoiding weight gain throughout adulthood if weight cycling is associated with risk of cancer. To review the epidemiologic literature on the association of weight cycling and cancer risk, we conducted a search of PubMed for all publications through 2015. Key terms were used to search based on the exposure ('weight cycling', 'weight variability', 'weight changes', 'weight history', 'weight change patterns', 'body weight changes') and the outcome ('cancer', 'neoplasms', 'cancer incidence prevalence', 'postmenopause'). The language was limited to English and no other restrictions were imposed. Abstracts and

unpublished results were not included. The reference lists of all relevant articles were also reviewed for additional studies.

Given the lack of data outlining the effects that weight cycling throughout adulthood could pose on cancer risk in postmenopausal women, eleven out of twelve relevant articles were considered for further review, which included men and all types of cancer. Specifically, eight studies suggested an association between weight cycling and cancer risk,[11–16,18,22] and three studies did not.[19–21] It is important to note that half of all studies with positive findings were attenuated to non-significance after adjustment for baseline BMI or body weight.[15,16,18,22] Major study characteristics and associations are summarized in **Table I (Appendix A)**.

The earliest study discovered to examine multiple weight change patterns over adulthood and cancer incidence in postmenopausal women found varied results.[14] Women aged 55-69 years retrospectively self-reported weight at age 18, 30 and 50 years. They were then classified as "weight loss regainers," or weight cyclers, if they reported losing at least 10% of their body weight from age 18 to 30 years, and regained 10% or more of their weight from age 30 to age 50 years. Among women who were normal weight at age 18, those who weight cycled had 55% increased odds for cancer compared to stable weight women (OR=1.55 [1.18-2.03]). Yet, among weight cyclers who were overweight at age 18, there was no associated risk between weight cycling and cancer incidence in postmenopausal women.[14]

Three studies have examined weight cycling and associated risk of renal cell cancer.[11,12,19] Lindblad and colleagues investigated the association between the frequency women who "gained or lost" at least five kilograms of body weight during adulthood and

odds of renal cell cancer. Subjects with renal cell cancer were at a 2.31 greater odds of having weight cycled compared to women without cancer, but found no association for men.[12] The authors noted that weight cycling may likely be a confounder of the association between obesity and risk of cancer in women, suggesting that weight cycling was an independent risk factor for renal cell cancer in women. In a case-control study of women aged 20-79, weight cycling was discussed as likely a greater risk factor for renal cell cancer in women versus men, but found no significant associated risk.[19] Additionally, a more recent prospective study using the Women's Health Initiative[11] showed that women who reported weight cycling at least 10 times were 2.6 times more likely than weight stable women to develop renal cell carcinoma.

Three studies have investigated the association between weight cycling and breast cancer risk in postmenopausal women.[18,20,21] In a case-control study which included over 5,000 cases of women aged 50-79 years old, women with breast cancer did not have an increased odds of previous weight cycling, regardless of the magnitude, recency, or frequency of weight cycles, compared to women without breast cancer.[21] In two prospective cohort studies,[18,20] weight cycling was not associated with breast cancer in postmenopausal women. Similarly, there is a paucity of data examining weight cycling and colorectal cancer risk. In the two studies which investigated this relationship,[18,20] weight cycling was not suggestive of increased risk of colon cancer.

Endometrial cancer was the most investigated cancer outcome among weight cycling studies, with some,[13,15,16,18,22] but not all,[18,20] showing a positive association. Three case-control studies found that women with endometrial cancer had a 2-[15] to 3-fold[13,16] increased odds of weight cycling compared to women without cancer. Of the three

prospective cohort studies,[18,20,22] women who reported weight cycling showed no associated risk,[20] one found a 6% increased risk,[18] and the other showed risk increase by 45-113% as frequency of cycling increased.[22] However, most positive findings were rendered non-significant after adjustment for BMI at baseline[15,18,22] or for current weight.[16] These sparse and conflicting results could be due to differences in study design and population, and definition of weight cycling.

Conclusion

Overall, more prospective longitudinal studies on lifetime weight change patterns are needed in order to better evaluate the relationship between obesity, weight fluctuation and breast, endometrial, and colorectal cancer risk in postmenopausal women. Women are becoming more obese and it is common for women to gain weight with age. It has been established that obesity is a modifiable risk factor for common cancers in aging women. Indeed, this age group of women is disproportionately obese with approximately two-thirds of these women report trying to lose weight at any given time.[5] However, weight regain commonly occurs after an initial weight loss which may have metabolic and hormonal effects on women, especially after menopause. Given the discordant findings from previous observational cohorts as to the association between weight cycling and cancer risk, as well as a clear dearth of data assessing weight-sensitive cancers in postmenopausal women, the purpose of the present study is to examine the role of weight fluctuation, and in particular weight cycling, during early and mid- adulthood and associated risk of breast, endometrial, and colorectal cancer in postmenopausal women.

Utilizing data from the well characterized Women's Health Initiative Observational Study, we hypothesize that adult weight gainers and cyclers have an increased risk of

developing breast, endometrial, and/or colorectal cancers, compared to postmenopausal women who were weight stable in early and mid-adulthood. What's more, we hypothesize that the frequency of weight cycling in early and mid-adulthood is linearly associated with postmenopausal onset of breast, endometrial and/or colorectal cancers. Lastly we hypothesize weight cycling, independent of obesity (BMI $\geq$ 30kg/m^2), is a risk factor for breast, endometrial, and/or colorectal cancers in postmenopausal women.

METHODS

Women's Health Initiative

The Women's Health Initiative (WHI) is a large, multicenter clinical trial (CT) and observational study (OS) examining the leading causes of morbidity and mortality in postmenopausal women (aged 50 to 79 years old). 161,808 women were recruited from 40 US clinic centers from 1993 to 1998. Of those, 93,676 women joined the OS, and are being followed through 2020.[23] Study protocols and procedures were approved by the institutional review boards at all 40 clinical centers, and are overseen by the coordinating center as well as a study-wide data and safety monitoring board.[105] All participants signed informed consent forms. Women were excluded if they had medical conditions with a predicted survival of less than three years, if they had adherence or retention issues, or if they were currently involved in another clinical trial. A general breakdown of the study flow, design, and reasons for exclusion in the WHI cohort are illustrated in **Table II** and **Figures 1** and **2 (Appendices B-D).** Full details can be found in the published recruitment and methods[106] and design papers.[23]

Current Study Sample

The current study sample includes only women from the WHI OS who completed relevant interviews, self-administered questionnaires (personal habits and food frequency), and physical measurements at baseline. Baseline demographics of all OS participants are listed in **Table III (Appendix E)**, and full baseline characteristics are listed in detail elsewhere.[23,106,107] **Figure 3** shows the study flow of how we obtained our final sample for analysis. Briefly, we excluded 5,670 women - 818 for missing weight-change pattern

category and 4,852 missing pertinent baseline covariates of interest (listed below) - leaving a final analysis sample of 88,006 women.

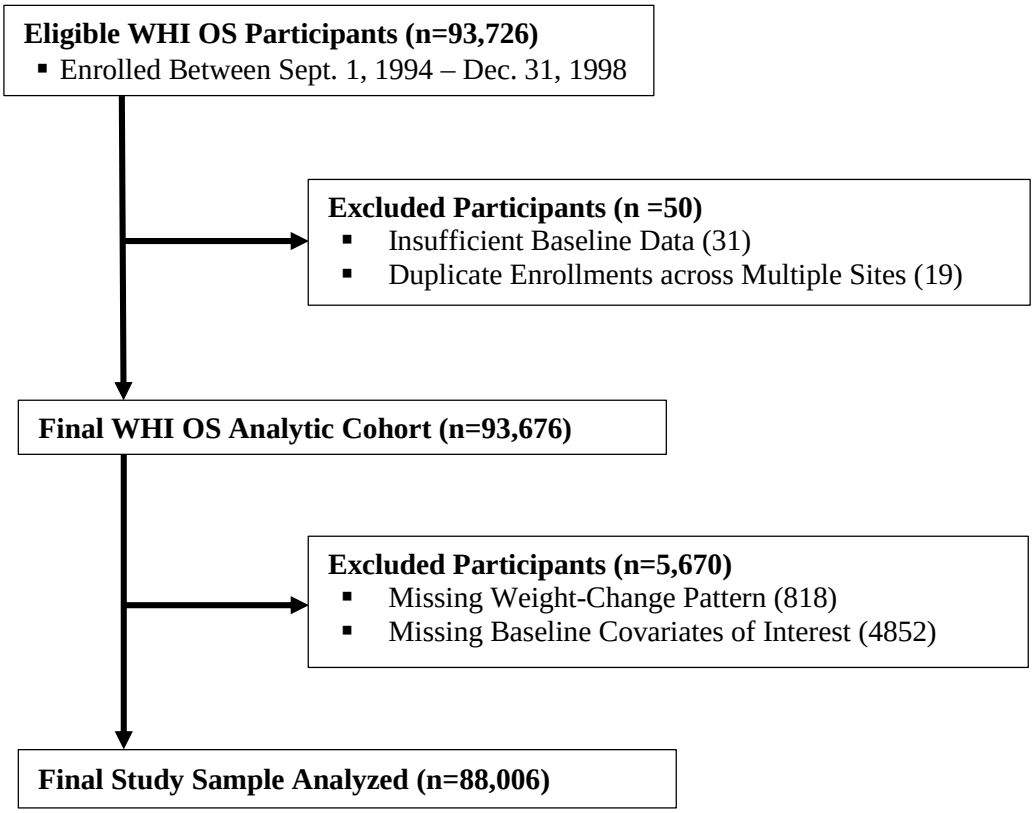

Figure 3. Study sample flow diagram.

Weight-Change Pattern Classifications

Weight changes were obtained through participants' responses to two questions on the self-reported baseline personal habits questionnaire. The first question asked women to mark the one answer that best described their weight changes during their adult life, excluding times when pregnant or sick. Possible responses were as follows: (1) weight has stayed about the same (within 10 pounds), (2) steady gain in weight, (3) lost weight as an adult and kept it off, or (4) weight has gone up and down again by more than 10 pounds.

If (4) was marked, an additional sub-question asked about how many times weight went up and down again by more than 10 pounds (1 to 3 times, 4 to 6 times, 7 to 10 times, 11 to 15 times, or more than 15 times). A weight cycle for the purposes of this evaluation was defined by a participant marking response (4), targeting intentional weight loss and subsequent regain, and further classification by the number of weight cycles reported, using definitions previously employed in the Women's Health Initiative.[11]

Ascertainment of Cancer Cases

Women were queried annually about new cancer diagnoses on annual mailed questionnaires during follow-up.[23] The question asked on the medical history update questionnaire was as follows: "has a doctor told you for the first time that you have a new cancer, malignant growth or tumor?" If the participant marked "yes" to this question, a sub-question was asked to determine the type of cancer or malignancy. All cancer cases were verified by medical record review and pathology reports by physician adjudicators at the clinical centers using standardized criteria in accordance with the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) coding guidelines. Information was obtained on outcomes and cause of death in participants who were lost to follow-up and/or known to be dead by routinely searching the National Death Index. Our analyses focused on identifying mutually exclusive categories of incident breast, endometrial, and colorectal cancers, as well as a composite of all three cancers.

Baseline Covariates of Interest

The following variables, collected at baseline, represent potential confounders between exposure and outcome, and are included in our subsequent statistical modeling. All demographic, personal and family medical history, personal habits and risk exposure

data were captured by self-administered questionnaire and interview at baseline. Following a standardized written protocol, certified and trained staff additionally measured height and weight and waist/hip circumference during the baseline clinic visit.[23]

The confounders included in multivariable analyses include: age at enrollment; ethnicity (Caucasian, African American, Hispanic/Latina); family income (less than $50,000/year, $50,000/year or more); education (less than a college degree, college degree or more); smoking status (never, former, current); alcohol intake (<1 drink/week, ≥1 drink/week); physical activity (metabolic equivalent tasks [MET]-hour/week;[108] hormone therapy use (never, ever); Healthy Eating Index (HEI-2005 Score, 0-100);[109] and body mass index (BMI, kg/m^2) at baseline.

Statistical Analysis

Baseline data were summarized using descriptive statistics, and equivalence of means and proportions across weight change patterns were compared using ANOVA and Pearson Chi-Square tests, respectively. Hazard ratios (HR) and 95% confidence intervals (CI) from Cox proportional models[110] were used to estimate the association between weight change patterns and incident breast, endometrial, colorectal cancer, and all cancers combined. Each cancer outcome was modeled separately for cancer-types (breast, endometrial, colorectal cancers) and a composite of all 3 cancer outcomes defined as incidence of any of the three. The relationship between cancer risk and weight-change pattern was adjusted for age, race, education, income, smoking status, alcohol intake, hormone therapy use, physical activity level, healthy eating index score, and baseline BMI, as specified above. *P*-values for trend were estimated by modeling number of weight cycle events as an ordinal predictor. Person-years of follow-up were calculated as the time

elapsed from the completion of the baseline questionnaire to the cancer event or to last follow-up contact. Unadjusted survival distribution across weight-change pattern categories were presented as Kaplan-Meier curves.[111] All statistical analyses were conducted by using SAS v9.4 (SAS Institute, Cary, NC) assuming a Type I error rate of 0.05 with no adjustment for multiplicity of comparisons.

RESULTS

Study Sample Characteristics

Average age of the study sample (n = 88,006) was 63.6 ± 7.4 years with a mean BMI of 27.3 ± 5.9 kg/m^2. Nearly half of all women reported obtaining college education or higher (42%), and over one-third had an annual family income of at least $50,000 (39%). Compared to women in the WHI OS excluded from the present analysis (n=5,670), women in our analyses were significantly younger and less physically active, and were more likely to be white (83 vs 79%). Additionally, our sample of women was more likely to report past and current smoking habits, higher alcohol intakes, and hormone therapy use (60 vs 55%) (all $p<0.05$).

At the baseline examination, 37% of women described themselves as adult weight cyclers, 32% as maintaining a stable weight, 28% as steadily gaining weight, and 3% as losing weight and keeping it off. Among weight cyclers, 43% reported weight cycling 1 to 3 times, and the prevalence of weight cycling declined as frequency increased (4-6 times, 32%; 7-10 times, 14%; more than 10 times, 11%). Characteristics of women at baseline, overall and by weight-change pattern, are shown in **Table IV.** Hormone therapy use was the only baseline covariate of interest that was not significantly different across weight-change pattern groups (59.7%).

Table IV. Baseline characteristics of the study sample, overall and by type of life-time weight change pattern.

Baseline Characteristic	**Overall N=88,006**	**Stable Weight N=27,693**	**Stable Gain N=25,014**	**Lost Weight N=2,526**	**Weight Cycle N=32,773**
Age (years)	63.6 ± 7.4	64.7 ± 7.4	62.9 ± 7.2	65.1 ± 7.6	62.9 ± 7.3
Ethnicity (%)					
Caucasian	83.8	82.8	85.1	83.0	83.6
African American	8.0	7.3	7.1	5.3	9.5
Hispanic/Latina	3.7	3.7	3.4	5.5	3.8
Education, college or more (%)	42.2	43.0	43.7	46.2	40.0
Income, $50,000/year or more (%)	39.3	39.8	41.1	38.3	37.5
BMI (kg/m^2)	27.3 ± 5.9	23.8 ± 4.1	29.1 ± 5.5	23.0 ± 4.0	29.2 ± 6.0
Hormone Therapy Use, ever (%)	59.7	59.8	59.8	55.5	59.9
Alcohol intake, $\geq$ 1 drink/week (%)	38.3	42.6	39.2	39.9	33.8
Smoking Status (%)					
Past Smoker	42.9	37.6	44.3	37.3	46.7
Current Smoker	6.3	7.0	5.2	8.3	6.5
Physical Activity Level (MET-h/week)	13.7 ± 14.3	15.7 ± 15.3	11.6 ± 12.5	16.9 ± 16.1	13.3 ± 14.3
Health Eating Index (HEI-2005 Score)	69.2 ± 10.5	70.0 ± 10.4	68.2 ± 10.6	71.2 ± 10.3	69.2 ± 10.6

Abbreviations: BMI, body mass index; MET, metabolic equivalents.

When comparing baseline demographic characteristics across weight-change pattern categories, in comparison to women in both the lost weight and weight stable groups, women who gained and cycled weight were younger with higher BMI at baseline, and were more likely to be past smokers and have lower physical activity levels. Weight cyclers were more likely to be African American than women who lost weight (9.5% vs 5.3%), and less likely to report consuming alcohol (34%) versus all other weight-change groups. Weight gainers were more likely to be white (85%), but least likely to be current smokers compared to all other weight-change pattern groups (all $p<0.01$). In addition, women in the lost weight group were least likely to report hormone therapy use (55.5%), but most likely to be current smokers, and reported the highest levels of physical activity across all groups (16.9±16.1 MET-h/week).

With an average of 12.8 years of follow-up, a total of 8,585 incident cases of cancer (breast cancer, n=6,450, 75.1%; endometrial cancer, n=884, 10.3%; colorectal cancer, n=1,472, 17.1%) were identified among women who met study criteria. These women had a similar average BMI compared to the total study sample (27.5±5.8 kg/m^2). Women who reported colorectal cancer were slightly older, more likely to be African American and current smokers, but less likely to report hormone therapy use (51%) and had lower alcohol intake compared to women with either breast or endometrial cancers (data not shown).

Weight-Change Patterns and Incident Cancer

Figure 4 presents risk of overall cancer incidence by weight-change pattern category. These curves are unadjusted survival distribution plots over the twenty year follow-up period. Women who lost weight showed a lower incidence rate than women who were weight stable. Weight gainers were most likely to report a cancer diagnosis and weight cyclers followed a similar pattern throughout the follow-up period, showing higher incidence rates compared to stable weight women.

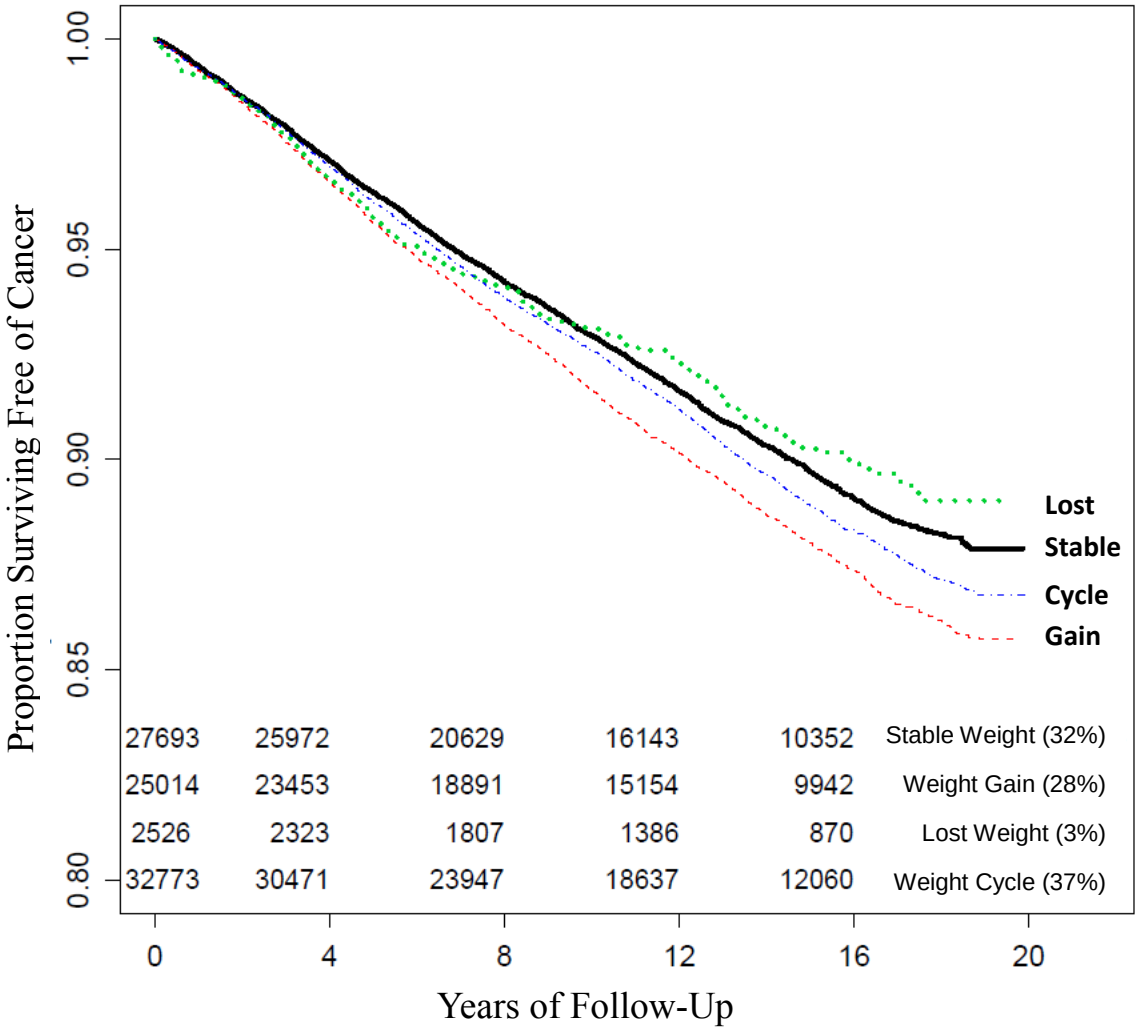

Figure 4. Kaplan-Meier curves for risk of incident breast, endometrial and/or colorectal cancer among postmenopausal women who gained, lost, or cycled weight, compared with stable weight women during 20 years of follow-up.

In minimally adjusted models (age, race, education, income), self-reported weight cycling and gain were significantly associated with an increased risk of cancer overall (12% and 21%), and by site (8-44% and 19-38%) (**Table V**), respectively. The one exception lies between weight cycling and colorectal cancer (HR, 1.13 [0.99-1.28]). After multivariate adjustment of common risk factors (smoking, alcohol, hormone therapy, physical activity, and healthy eating index score), weight gainers had a slight attenuation of risk, however there were no changes among weight cyclers. Further adjustment for baseline BMI rendered all previously significant associations between weight cycling and cancer risk non-significant. However, weight gain remained significantly associated with risk of cancer overall and breast cancer. Weight loss and risk of cancer overall was not affected after Model 2 adjustment, and was not associated with cancer risk in any of the models.

In analyses examining the association between frequency of weight cycling (defined as the number of times weight cycled 10 pounds or more) and cancer incidence, weight cycling 4 to 6 times was most consistently associated with increased risk of any cancer type, increasing endometrial cancer risk by 72 percent (95% CI: 1.38 – 2.13) when compared to weight stability (**Table VI**). Cycling frequency was not significantly associated with risk of colorectal cancer with the exception for women who reported cycling 4 to 6 times, in minimally adjusted models. All associations were non-significant when a frequency of at least 7 times was reported. Indeed, after further adjustment for BMI at baseline, only weight cycling 4 to 6 times persisted in significantly increasing risk for endometrial cancer alone (HR: 1.36, CI: 1.08-1.71). Interestingly, *P* for trend indicated a negative dose-response relationship in the BMI-adjusted model for weight cycling frequency and risk of overall cancer and breast cancer alone (all $p<0.01$).

Table V. Risk of incident cancer, overall and by type, by life-time weight-change pattern.

	Model 1 (95% CI)	**Model 2 (95% CI)**	**Model 3 (95% CI)**
Stable Weight	1.0	1.0	1.0
All Cancer (N=8585)			
Weight Gain	1.21 (1.15,1.28)	1.20 (1.13,1.26)	1.12 (1.05,1.18)
Lost Weight	0.93 (0.80,1.07)	0.93 (0.81,1.08)	0.93 (0.80,1.08)
Weight Cycle	1.12 (1.06,1.18)	1.11 (1.05,1.17)	1.03 (0.97,1.09)
Breast Cancer (N=6450)			
Weight Gain	1.19 (1.11,1.26)	1.17 (1.10,1.25)	1.12 (1.05,1.20)
Lost Weight	0.88 (0.74,1.04)	0.89 (0.75,1.05)	0.87 (0.73,1.04)
Weight Cycle	1.08 (1.02,1.15)	1.08 (1.02,1.15)	1.03 (0.96,1.10)
Endometrial Cancer (N=884)			
Weight Gain	1.38 (1.16,1.65)	1.35 (1.13,1.62)	1.06 (0.87,1.29)
Lost Weight	0.96 (0.60,1.53)	0.97 (0.61,1.55)	0.98 (0.60,1.61)
Weight Cycle	1.44 (1.22,1.71)	1.45 (1.22,1.72)	1.10 (0.91,1.33)
Colorectal Cancer (N=1472)			
Weight Gain	1.24 (1.09,1.42)	1.20 (1.05,1.37)	1.11 (0.96,1.28)
Lost Weight	1.09 (0.80,1.50)	1.07 (0.78,1.47)	1.10 (0.80,1.52)
Weight Cycle	1.13 (0.99,1.28)	1.09 (0.96,1.24)	1.01 (0.88,1.16)

Model 1: Age, race, education, income.
Model 2: Model 1 + smoking status, alcohol intake, physical activity, hormone therapy use, health eating index.
Model 3: Model 2 + BMI at baseline.

Table VI. Risk of incident cancer, overall and by type, by weight cycling frequency.

	Model 1 (95% CI)	Model 2 (95% CI)	Model 3 (95% CI)
Stable Weight	1.0	1.0	1.0
All Cancer			
1 – 3 times	1.12 (1.05,1.19)	1.12 (1.05,1.20)	1.07 (1.00,1.14)
4 – 6 times	1.16 (1.08,1.24)	1.15 (1.07,1.24)	1.05 (0.97,1.14)
7 – 10 times	1.06 (0.96,1.18)	1.06 (0.95,1.17)	0.94 (0.84,1.05)
> 10 times	1.04 (0.93,1.18)	1.02 (0.90,1.16)	0.89 (0.78,1.01)
P for trend	0.24	0.12	< 0.01
Breast Cancer			
1 – 3 times	1.11 (1.03,1.20)	1.11 (1.03,1.20)	1.08 (0.99,1.16)
4 – 6 times	1.10 (1.01,1.20)	1.11 (1.02,1.21)	1.03 (0.94,1.13)
7 – 10 times	1.04 (0.92,1.17)	1.04 (0.92,1.18)	0.96 (0.84,1.09)
> 10 times	0.95 (0.82,1.10)	0.94 (0.81,1.09)	0.85 (0.73,0.99)
P for trend	0.03	0.02	< 0.01
Endometrial Cancer			
1 – 3 times	1.24 (1.01,1.53)	1.28 (1.04,1.59)	1.13 (0.91,1.41)
4 – 6 times	1.68 (1.36,2.08)	1.72 (1.38,2.13)	1.36 (1.08,1.71)
7 – 10 times	1.29 (0.93,1.78)	1.31 (0.95,1.83)	0.93 (0.65,1.31)
> 10 times	1.62 (1.16,2.28)	1.65 (1.17,2.32)	1.11 (0.77,1.60)
P for trend	0.12	0.21	0.41
Colorectal Cancer			
1 – 3 times	1.09 (0.93,1.28)	1.07 (0.91,1.25)	1.02 (0.86,1.20)
4 – 6 times	1.20 (1.01,1.43)	1.15 (0.96,1.37)	1.05 (0.87,1.26)
7 – 10 times	1.11 (0.86,1.43)	1.03 (0.80,1.34)	0.92 (0.70,1.21)
> 10 times	1.13 (0.84,1.50)	1.03 (0.77,1.39)	0.88 (0.64,1.20)
P for trend	0.79	0.83	0.47

Model 1: Age, race, education, income.
Model 2: Model 1 + smoking status, alcohol intake, physical activity, hormone therapy use, healthy eating index score.
Model 3: Model 2 + BMI at baseline.

DISCUSSION

Main Findings

The purpose of our study was to evaluate the role of weight fluctuation during adulthood and risk of breast, endometrial, and colorectal cancers in the well-characterized cohort of postmenopausal women in the WHI OS. In this large prospective study, with an average 12.8 years of follow-up, we observed that weight cycling, particularly a prior frequency of 4-6 times, was associated with increased risk of overall cancer, and breast and endometrial cancers in postmenopausal women. Similarly, weight gain was associated with all cancers. However, all associations were attenuated to non-significance after adjustment for BMI, suggesting that baseline weight may be a more important predictor of cancer risk than prior weight fluctuation. Weight cyclers may have a higher risk of cancer because they tend to have a higher BMI, thus underscoring the important health implications of maintaining a healthy body weight during adulthood.

Results showing a positive association between weight gain and cancer incidence are in general agreement with a large body of data linking obesity to increased cancer risk.[50,65] Similarly, weight cycling findings align with some,[13,15,16,18,22] but not all[18,20,21] prior studies suggesting a positive association between weight cycling and cancer incidence. For instance, three case control studies show a 2[15] to 3[13,16] -fold increase in the odds of weight cycling in women who developed endometrial cancer, compared to those who were cancer free. Likewise, two[18,22] (of three[20]) prospective cohort studies suggest a positive association between weight cycling and endometrial cancer risk, with hazard ratios ranging from 1.06[18] to 2.13,[22] compared to non-cyclers. All prior studies assessing the

association between weight cycling and breast cancer risk in postmenopausal women present null findings.[18,20,21] However, one[18] of two[20] studies suggest a positive association between weight cycling and colorectal cancer, suggesting that weight cycling 1 to 4 times as an adult increased risk of colorectal cancer by 12% versus prior non-cyclers.[112] However, in most studies, positive results were attenuated to non-significance after adjustment for baseline BMI or body weight.[15,16,18,22] Results from the present analysis confirm prior work suggesting that the positive association found between past weight cycling and cancer risk may be superseded by current body weight, further contributing to the current debate of weight cycling and cancer risk in postmenopausal women. In contrast, our study shows that prior weight cycling and weight gain behavior may have a similar impact on breast and endometrial cancer risk, thereby extending prior work to suggest that weight cycling as an adult may contribute to cancer risk through mechanisms similarly indicated among weight gainers and/or obese persons.

Biologic Plausibility

Many plausible hypotheses exist connecting weight regain and cycling to cancer via biologic mechanisms similar to those for obesity, including metabolic[57] and endocrine[42] pathways, as well as enhanced inflammatory responses[113–115] and immune changes.[116–118] This makes sense biologically, as prior observational studies demonstrate fat mass is preferentially regained after a weight loss episode,[8,119–123] suggesting that both weight cycling and weight regain negatively impact body composition and are associated with increased adiposity. One possibility for how weight cycling may be metabolically linked to cancer may be via elevated insulin,[118] suggested by observations of weight cycling associated with redistribution of body fat to the upper body.[120,124] Hyperinsulinemia

increases insulin-like growth factor-1 (IGF-1)[125,126] and decreases IGF binding protein (IGFBP) production,[127] leading to greater cell proliferation and survival.[57,128,129] At least one study suggested women with endometrial cancer had higher levels of circulating IGF-1 and reduced IGFBP compared to a control group.[130] Despite this, a meta-analysis showed little association between IGF-1 and IGFBP levels and risk of colorectal and breast cancers.[131]

Obesity is also associated with increased estrogen levels,[57] another risk factor for women-specific cancers of the breast and endometrium. Higher amounts of bioavailable estrogens[57,132] likely contribute to a greater risk of breast and endometrial cancers,[40,128,133] and one study found breast cancer risk was lowered by 65% when aromatase, an enzyme converting androgens to estrogens, was inhibited.[134] Additionally, higher levels of circulating estrogen leads to more interactions with IGF, further contributing to cell division and the inhibition of apoptosis.[132,135] Other hormones secreted by adipose tissue include leptin and adiponection, and obesity alters these hormones to signal a cascade of physiological processes which inhibit apoptosis and promote cell growth and proliferation.[90,136] At least one study suggests weight cycling alters leptin hormones in the same pattern as obesity,[137] and higher leptin levels have been reported to be associated with colon cancer.[138] Adiponectin, inversely correlated with obesity, has been reported to also be inversely associated with breast,[139] endometrial,[140] and colon cancer.[141]

Another hypothesis involves obesity's role in chronic low-grade inflammation and may contribute to tumor-promoting mechanisms.[113] A recent study examined the role of obesity, inflammation and tumor growth in the liver,[142] with results supporting a positive obesity-inflammation-carcinogenesis relationship. C-reactive protein, a known marker of

inflammation, was studied and shown to be associated with previous weight variability in men.[115] However, a recent review concluded that there is not yet enough evidence to support this relationship,[143] citing only one study which found an association between C-reactive protein and colorectal cancer in women.[144] Little research has been conducted on weight cycling and immune function, however, one study suggested that frequent weight loss and regains may impact immune function via changes in natural killer cells.[116,117] Yet, at present, the data are too limited to provide evidence suggesting immune function changes relate to cancer risk.

Strengths and Limitations

This is the first study to comprehensively assess the role of various weight-change patterns and risk of breast, endometrial and colorectal cancers in postmenopausal women, independent of BMI, while also analyzing dose-response information on frequency of weight cycling across all cancers. The most important strength of this study is its large study population and the prospective nature of the WHI OS providing assurances as to proper temporal sequence between exposure and outcome variables. Other strengths include a large number of weight cyclers, intentionality of weight loss, and number of weight cycles, which permitted a dose-response analysis for weight cycling frequency. Lastly, reported cancers were adjudicated locally and centrally for accuracy and only independent, first-time cancer diagnoses were assessed to ensure that previous cancer diagnoses did not impact future cancer outcomes.

However, there are some limitations to this study to consider. Weight-change data was self-reported and recalled. Correlations between recalled weight and objectively measured weight gradually decrease over time,[145] and may be underestimated more so

among women[146] and heavier individuals.[147] Despite this, studies[11–16,18,20–22] have used self-reported recall data to report weight cycling exposure. Additionally, the data on specific magnitude and rate of weight loss and regain, and timing of weight cycles throughout adulthood, is not available. Although we attempt to put our findings in context of the larger body of literature, a single, uniform definition of weight cycling does not exist, and differed significantly across studies – from 5% and 10%,[20] to ten pound[11,12,18,22] (in the present study), and 20 pound,[13,15,16,21] making cross-study comparisons difficult. Although we attempt to present dose-response information, these comparisons are limited by small sample sizes, particularly among high weight cycling frequency categories. Whether BMI is a result of, or contributes to, weight cycling behavior throughout adulthood remains elusive, and residual confounding should be considered after adjusting for BMI at baseline due to the statistical limitations of controlling for current body weight in an analysis of weight trajectory. Finally, results for our all cancer outcome are heavily influenced by the large number of breast cancer cases reported (75% of total). Future studies should incorporate objective measures of weight over the course of adulthood and gather information on magnitude, duration, and timing of weight cycles to better characterize weight changes and risk of future health outcomes.

Conclusion

In summary, the results of our study suggest that weight gain and weight cycling throughout adulthood contributes to modest increases in risk of breast, endometrial, and colorectal cancer in postmenopausal women. Although these associations are attenuated after adjustment for baseline BMI, collectively, these data emphasize the importance of adopting effective ideal body weight maintenance practices during adulthood to prevent

future cancer risk. Further research is needed to clarify the mechanisms relating weight cycling to cancer incidence.

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APPENDIX

Appendix A: Table I. Published studies investigating the association between weight cycling and risk of cancer.

Author, year	Study Design	Study Purpose	Study Population	Exposure	Findings*
French et al,[14] 1996	Cross-Sectional Survey	To describe the prevalence of weight loss maintenance and other weight change patterns in early adulthood and associated disease prevalence in older age	17,233 postmenopausal women (aged 55-69) from Iowa Women's Health Study in 1986.	Self-report WC category: 10% WL between age 18-30 & 10% regain from age 30-50 Ref: Weight stable (<5%) between age 18-30 and 30-50.	**Cancer** *Not overweight @ age 18:* OR **1.55**; 95% CI, 1.18 – 2.03 *Overweight @ age 18:* OR 0.58 (0.33 – 1.02)
Lindblad et al,[12] 1994	Case-Control	To simultaneously analyze the independent effects of a high BMI at different ages, weight cycling, physical exercise, and pharmacological treatment of obesity on renal cell cancer.	Cases: 379 individuals residing in Sweden (aged 20-79) from an international population-based study base from 1989-91. Controls: 353 individuals randomly selected from study base (frequency matched based on expected sex and age distribution)	Self-report & Recall WC category: Intentional weight change (gain or loss) > 5kgs after age 20 in women Number of cycles: 1, 2, ≥ 3x Ref: No weight changes	***BMI adjustment:*** **Renal Cell Cancer** *2 changes:* OR 1.31 0.68 – 2.52) *≥ 3 changes:* OR **2.31** (1.04 – 5.12)
Swanson et al,[16] 1995	Case-Control	To explore the relation between body size and risk of endometrial cancer.	Cases: 434 women (aged 20-79) from multicenter US case-control study between 1987-90. Controls: 313 age, race, location matched using RDD and HCFA techniques	Self-report WC category: WL + WR 20lbs at least 5x Ref: Non-cycler	**Endometrial Cancer** RR **2.9** (1.7 – 5.0) ***Body Weight Adjustment:*** RR 1.6 (0.8 – 2.9) ***Stratified by weight:*** *<78kg at baseline:* RR **3.4** (1.3 – 8.9) *78+kg at baseline:* RR 1.4 (0.5 – 3.6)

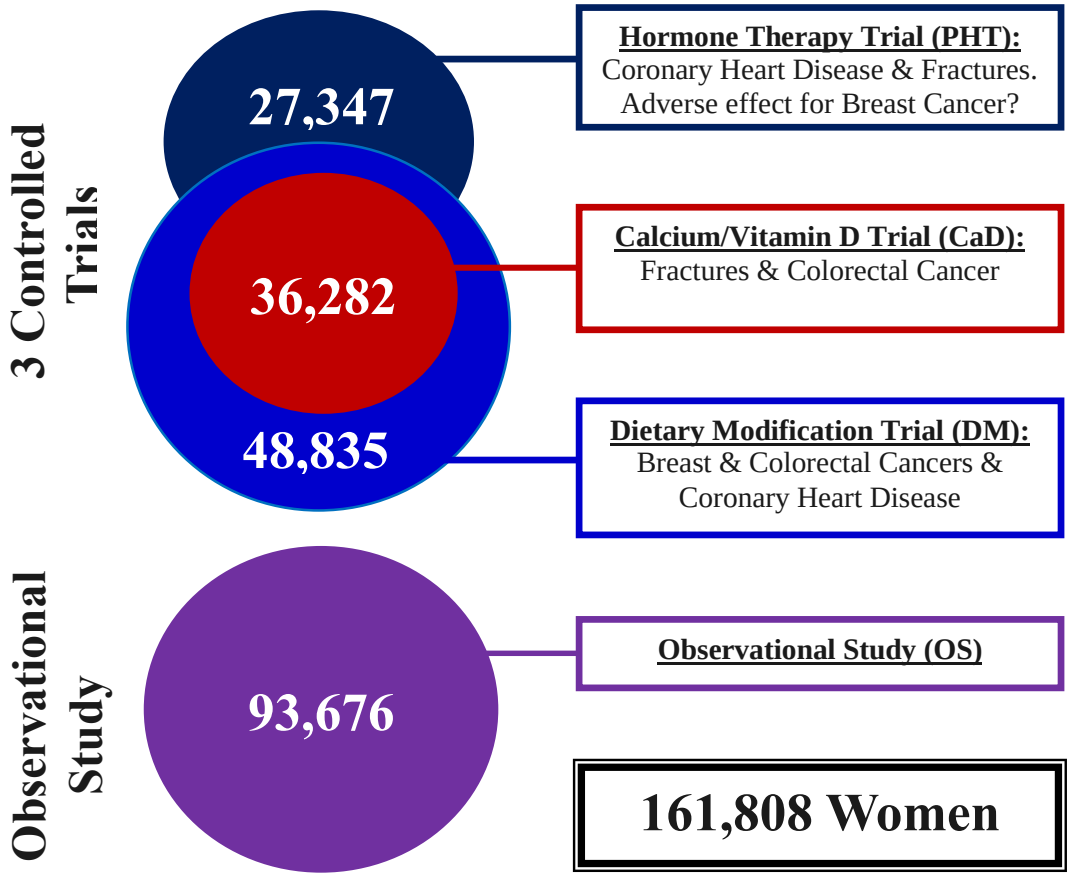
Author, year	Study Design	Study Purpose	Study Population	Exposure	Findings*
Trentham-Dietz et al,[21] 2000	Case-Control	To examine the risk of postmenopausal breast cancer associated with different patterns of weight change.	Cases: 5,031 women (aged 50-79) from Wisconsin, Massachusetts and New Hampshire, with new diagnosis of invasive breast cancer between 1992-94 Controls: 5,255 randomly selected (drivers license and Medicare)	Self-report and recall WC category: ≥ 20 lbs WL + WR ≥ half back within 1 year Ref: Non-cycler	**Breast Cancer** OR 1.0 (0.9 – 1.1)
Trentham-Dietz et al,[15] 2006	Case-Control	To explore the associations between weight change since 20 years and endometrial cancer risk.	Cases: 740 women (aged 40-79) of Wisconsin and New Hampshire with new diagnosis of invasive endometrial cancer between 1991-94. Controls: 2,342 randomly selected (drivers license and Medicare)	Self-report WC category: ≥ 20 lbs WL + WR ≥ half back within 1 year Ref: Non-cycler	**Endometrial Cancer** OR **1.72** (1.37 – 2.15) ***BMI adjustment:*** OR 1.27 (1.00 – 1.61) *1 cycle:* OR 1.20 (0.84 – 1.71) *2-4 cycles:* OR 1.36 (0.98 – 1.88) *≥ 4 cycles:* OR 1.26 (0.80 – 1.97)
Nagle et al,[13] 2013	Case-Control	To determine whether there is an association between different adult weight trajectories, weight cycling and risk of endometrial cancer.	Cases: 1398 women (aged 18-79) from the Australian National Endometrial Cancer study Controls: 1538 women randomly selected from the Australian electoral role to match residence and age	Self-report WC category: Intentional WL & WR >9kg at least one time *Obese= at age 20, max, or recent Ref: Non-cycler	**Endometrial Cancer** ***BMI adjustment:*** OR **2.30** (1.55 – 3.43) *Never Obese:* OR 1.18 (0.56 – 2.51) *Ever Obese:* OR **2.92** (1.78 – 4.79)

Author, year	Study Design	Study Purpose	Study Population	Exposure	Findings*
French et al,[20] 1997	Prospective Cohort	To evaluate the association between weight variability and disease incidence in women.	33,834 women (aged 55-69) selected from Iowa Women's Health Study. Weight ascertained at intervals: 18, 30, 40, 50 years of age. Follow-up: Maximum 5 years	Self-report WC category: Large cycle – at least one ≥10% gain & at least one ≥10% WL within at least one age interval Ref: No weight change + small gain (<5%)	***BMI adjustment:*** **Breast Cancer** RR 0.83 (0.60 – 1.14) **Endometrial Cancer** RR 0.95 (0.52 – 1.75) **Colon Cancer** RR 1.13 (0.71 – 1.81)
Luo et al,[11] 2007	Prospective Cohort	To understand the role of body size, body fat distribution, and weight cycling in relation to renal cell cancer risk in postmenopausal women.	140,057 postmenopausal women (aged 50-79) from Women's Health Initiative Follow-up: 7.7 years	Self-report WC category: Weight had gone up & down again by more than 10lbs Number of cycles: 1-3, 4-6, 7-10, 11-15, >15x Ref: Weight stable (within 10lbs)	**Renal Cell Cancer** RR **1.5** (1.1 – 2.0) *> 10 cycles:* RR **2.8** (1.7 – 4.5) ***WHR adjustment:*** RR 1.4 (1.0 – 1.9) *> 10 cycles:* RR **2.6** (1.6 – 4.2)
Stevens et al,[22] 2012	Prospective Cohort	To investigate the association of 3 levels of weight cycling with the risk of endometrial cancer in postmenopausal women, independent of BMI.	38,148 women (aged 50-74) from the Cancer Prevention Study II Nutrition Cohort, 1992. Follow-up: Until cancer diagnosis, death, last returned survey, or 2007.	Self-report WC category: Purposeful WL ≥ 10lbs + WR as much as 10lbs that had been previously lost Number of cycles: 1-4, 5-9, ≥ 10x Ref: Non-cycler	**Endometrial Cancer** *1-4 cycles:* RR **1.45** (1.19 – 1.77) *5-9 cycles:* RR **1.95** (1.48 – 2.58) *10+ cycles:* RR **2.13** (1.63 – 2.78) ***BMI adjustment:*** Non-significant ***Stratified by BMI:*** Non-significant

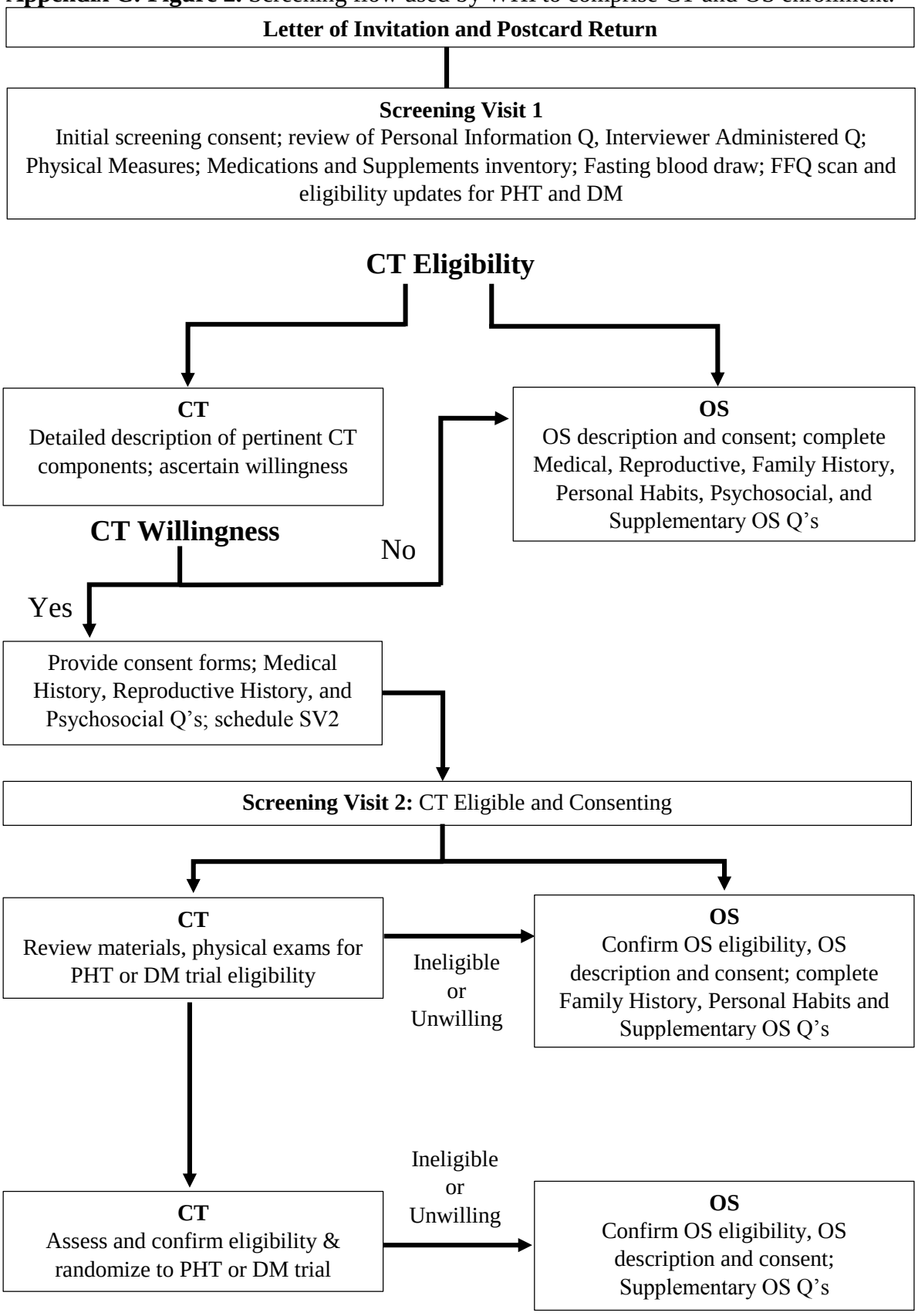
Author, year	Study Design	Study Purpose	Study Population	Exposure	Findings*
Stevens et al,[18] 2015	Prospective Cohort	To examine the association between weight cycling and overall cancer incidence (15 specific cancers) in aging men and women.	69,520 postmenopausal women, 62,792 men (aged 50-74) from Cancer Prevention Study II, Nutrition Cohort, 1992 Follow-up: Until cancer diagnosis, death, last returned survey, or 2009.	Self-report WC category: Purposeful WL ≥ 10lbs + WR as much as 10lbs that had been previously lost Number of cycles: 1-4, 5-9, ≥ 10x Ref: Non-cycler	**All Cancer** RR 1.02 (1.00 – 1.03) **Breast Cancer** RR 1.02 (1.00 – 1.04) **Endometrial Cancer** RR **1.06** (1.01 – 1.10) **Colon Cancer** RR 1.02 (0.97 – 1.07) ***BMI adjustment:*** Non-significant for any cancer ***Stratified by Obesity:*** Non-significant for any cancer

Abbreviations: BMI, body mass index; BW, body weight; WL, weight loss; WR, weight regain, WC, weight cycle.
***Risk Ratios:** RR, relative risk; OR, odds ratio; HR, hazard ratio and (95% confidence interval)
Statistically significant risk ratios are indicated in bold type

Appendix B: Figure 1. Total enrollment of the Women's Health Initiative**.**



Appendix C: Figure 2. Screening flow used by WHI to comprise CT and OS enrollment.



Appendix D: Table II. Major reasons for exclusion from WHI study components.[a]

Component	Criterion for exclusion	Total ineligible[b] (%)
PHT	No consent/not interested	81.2
	Clinic impression of ineligibility	4.8
	Stratum full or closed	4.6
	History of breast cancer	4.5
DM	No consent/not interested	50.3
	FFQ percent calories from fat/energy intakes	41.9
	Stratum full or closed	11.0
	10+ meals away from home/week	5.3
	History of breast cancer	4.8
CaD	Not willing to limit use of vitamin D	73.0
	No consent/not interested	44.3
	History of kidney stones	13.1
	Clinic impression of ineligibility	5.8
OS	No consent/not interested	76.6
	Stratum full or closed	9.9

PHT, postmenopausal hormone therapy; DM, dietary modification; CaD, calcium and vitamin D; OS, observational study; FFQ, food frequency questionnaire.

[a]Only includes reasons with >4% of total ineligible.

[b]A participant may be ineligible for more than one reason.

Appendix E: Table III. Baseline demographic characteristics of WHI OS participants.

	Observational Study N = 93,676	
	N	*%*
Age (years)		
50-59	29,705	31.7
60-69	41,397	44.5
70-79	22,774	24.3
Race/ethnicity		
White	78,013	83.3
African American	7,639	8.2
Hispanic	3,623	3.9
Education		
College degree or higher	39,002	42.0
Income		
≥ $50,000/year	35,094	40.5
BMI (kg/m^2)		
Underweight (< 18.5)	1,107	1.2
Normal Weight (18.5-24.9)	36,687	39.6
Overweight (25.0-29.9)	31,463	34.0
Obese (≥ 30.0)	23,311	25.3

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2. Bruce Crawford Morrison Rummel Scholarship, JMU Kinesiology, 2013

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BIBLIOGRAPHY:

Abstracts/Scientific exhibits/Presentations at national meetings

1. **Welti LM**, Beavers DP, Sangi-Haghpeykar H, Vitolins MZ, Beavers KM. Weight fluctuation and cancer risk in post-menopausal women: the women's health initiative. Presented at the SEACSM 44th Annual Meeting. Greenville, SC. February 2016.

2. **Welti LM**, Beavers DP, Sangi-Haghpeykar H, Vitolins MZ, Beavers KM. Weight fluctuation and cancer risk in post-menopausal women: the women's health initiative. Presented at Aging: Re-Imagined Symposium, Winston-Salem, NC. March 2016.

3. **Welti LM**, Beavers DP, Sangi-Haghpeykar H, Vitolins MZ, Beavers KM. Weight fluctuation and cancer risk in post-menopausal women: the women's health initiative. Presented at Wake Forest University's Graduate Research Day, Winston-Salem, NC. March 2016.

PRESENTATIONS: (Listed in chronologic order)

1. Aging and Exercise: How Much Exercise is Enough? Wake Forest Baptist Health, Translational Science Institute Speakers Bureau. Winston-Salem, NC. 9/15/2015.

2. Aging and Exercise: How Much Exercise is Enough? Wake Forest Baptist Health, Translational Science Institute Speakers Bureau. Greensboro, NC. 9/9/2015.

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4. Implantation Devices: Modifications to Exercise Testing and Prescription. Wake Forest University, Graded Exercise Testing and Prescription. Winston-Salem, NC. 4/23/2015.

5. Social Support Interventions. Wake Forest University, Health Psychology. Winston-Salem, NC. 3/19/2015.

6. Aging and Exercise: How Much Exercise is Enough? Wake Forest Baptist Health, Translational Science Institute Speakers Bureau. Asheboro, NC. 3/18/2015.

7. Muscle, Aging, and Bone Health. James Madison University, Morrison Bruce Center – Alumnae Health and Fitness Program. Harrisonburg, VA. 4/5/2014.