OBESITY AND OBESITY-RELATED MARKERS ASSOCIATED WITH BREAST AND COLORECTAL CANCER OCCURRENCE AND MORTALITY

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For Wangechi, Wangari and Murage
“we all have our forte, follow your forte persistently with the eyes of your heart”

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It remains true then and now that ‘it takes a village to raise a child’. I am forever indebted to many that invested their time and money to make me a great researcher. Dr Victoria Champion my teacher and mentor believed in me, guided me and was committed to seeing me grow as a researcher. Dr Yiqing Song and Dr Patrick Monahan for the many hours spent working with me on all my manuscripts. Dr Terrell Zollinger who encouraged me to put in my application and his steadfast leadership in my doctoral committee. Dr Tom Imperiale, for allowing me access to his data and for indepth review of my work. Dr Jianjun Zhang who together we published my first peer reviewed paper. To the National Cancer Institute who designed the program to fund ‘minority’ researchers, you made my PhD degree possible.

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“The village has raised a scientist”

Wambui Grace Gathirua-Mwangi

Obesity and Obesity-Related Markers Associated with Breast and Colorectal Cancer Occurrence and Mortality

Purpose: Obesity is a growing public health problem and the second most preventable cause of death in the US. Obesity has been linked as a risk factor for several cancers. However, there are limited studies that have examined the roles of metabolic syndrome (MetS) and C-reactive protein (CRP), as well as change in body composition from early adulthood to late adulthood on the risk of cancer. The overall objective of this dissertation was to determine the association of obesity and obesity-related markers with breast and colorectal cancer occurrence and mortality.

Methods: Three datasets were used. The first study used 4,500 asymptomatic adults who were surveyed during a colorectal cancer screening study. The second study was based on the National Health and Nutrition Examination Survey (NHANES) 2005-2010. The dataset had 172 breast cancer survivors and 2,000 women without breast cancer. The last manuscript resulted from the NHANES follow-up study (NHANES III). A total of 120 cancer deaths from breast and colorectal deaths were identified from 10,103 women aged 18 years or older.

Results: Overall, obesity and obesity related markers were associated with breast and colorectal cancer occurrence and mortality. BMI change and WC change were positively associated with increased risk of advanced colorectal neoplasia (AN). WC measures (both static and dynamic) were generally a better predictor of AN compared to BMI. In the second study involving breast cancer

survivors, neither MetS nor CRP were associated with having a breast cancer diagnosis. Also, none of the individual components of MetS (WC, Triglycerides, HDL, fasting blood glucose and blood pressure) were associated with a breast cancer diagnosis. In the last study, MetS was associated with increased risk of mortality from obesity-related cancers. In addition, all components of MetS, except dyslipidemia, were associated with increased risk of mortality for the obesity-related cancers.

Conclusion: Obesity expressed in terms of BMI and WC, or their change, MetS and CRP are important factors in regard to the occurrence, survivorship and mortality of breast and colorectal cancer. The results of this research underscore the importance of maintaining a healthy weight.

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LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
AN	Advanced Colorectal Neoplasia
BMI	Body Mass Index
CI	Confidence Interval
CRC	Colorectal Cancer
CRP	C-reactive Protein
HDL	High Density Lipoprotein
HR	Hazard Ratio
MetS	Metabolic Syndrome
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratios
WC	Waist Circumference

INTRODUCTION

Obesity is a growing public health problem and the second most preventable cause of death in the US (1). Obesity occurs when there is chronic energy imbalance, that is, when energy consumption regularly exceeds energy needs over a long period of time. According to the World Health Organization, in 2014 more than 1.9 billion adults, 18 years and older, were overweight; of these over 600 million were obese (2, 3). Developed countries were found to have the highest obesity prevalence; more than one third of adults in the US were estimated to be obese in 2012 (2, 4). Moreover, it was estimated that at the end of 2015, 41% of adults in the US were obese (5).

There is growing evidence that obesity is a risk factor for many cancers (6). Epidemiological evidence indicates that obesity is associated with increased risk of the following cancers: endometrial, esophageal adenocarcinoma, colorectal and postmenopausal breast cancer (6). To understand the link between obesity and cancer, several aspects of obesity and how it links with cancer continue to be explored. Weight gain earlier in life, from age 18-50, appears to confer a greater risk of chronic diseases, such as cancer, than later life weight gain (7, 8). Also, those who are obese have been shown to have insulin resistance and chronic inflammation (9, 10); two of the five components of MetS.

This research focused on obesity, MetS and inflammatory markers and their association with risk and mortality of breast and colorectal cancer. These

three inter-related studies as shown in the conceptual framework (fig. 1) were designed to meet the three publishable papers requirement.

SIGNIFICANCE

Obesity is a growing global problem and accounts for 20% of cancer cases and deaths in the United States (11, 12). In the US, 41% of the adult population is estimated to be obese (4, 13). The prevalence of obesity differs across demographic characteristics. When compared to men (33%), women (36%) are more likely to be obese (4, 13). According to the Center for Disease Control and prevention (CDC), non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%) when compared to non-Hispanic whites (32.6%) (4, 14). Obesity rates also differ by age, middle aged (40-59) persons have a higher prevalence of obesity (39.5%) compared to young adults aged age 20-39 (30.3%) (4, 14).

Obesity is associated with the incidence and mortality of both colorectal cancer and post-menopausal breast cancer (6). Colorectal cancer (CRC) is the third most common cancer and the second most frequent cause of cancer-related death among men and women in Western countries (15, 16). Breast cancer is the most common cancer and the second leading cause of cancer mortality among women in the developed world (15, 16). Both breast and colorectal cancer can be prevented through maintaining a healthy weight (15, 16).

Excessive weight can be measured in the form of a person's Body Mass Index (BMI: kg/m^2) value, which is a common and universal anthropometric measure used to define obesity (17). Other anthropometric measures are those associated with visceral adiposity such as waist circumference and the waist-to-

hip ratio (17). In understanding risk associated with unhealthy BMI, several aspects of excessive weight should be explored. Longitudinal change in adiposity, cross-sectional measures of BMI and WC, MetS and CRP may add insights into the biological relationship of obesity with both breast and colorectal cancer.

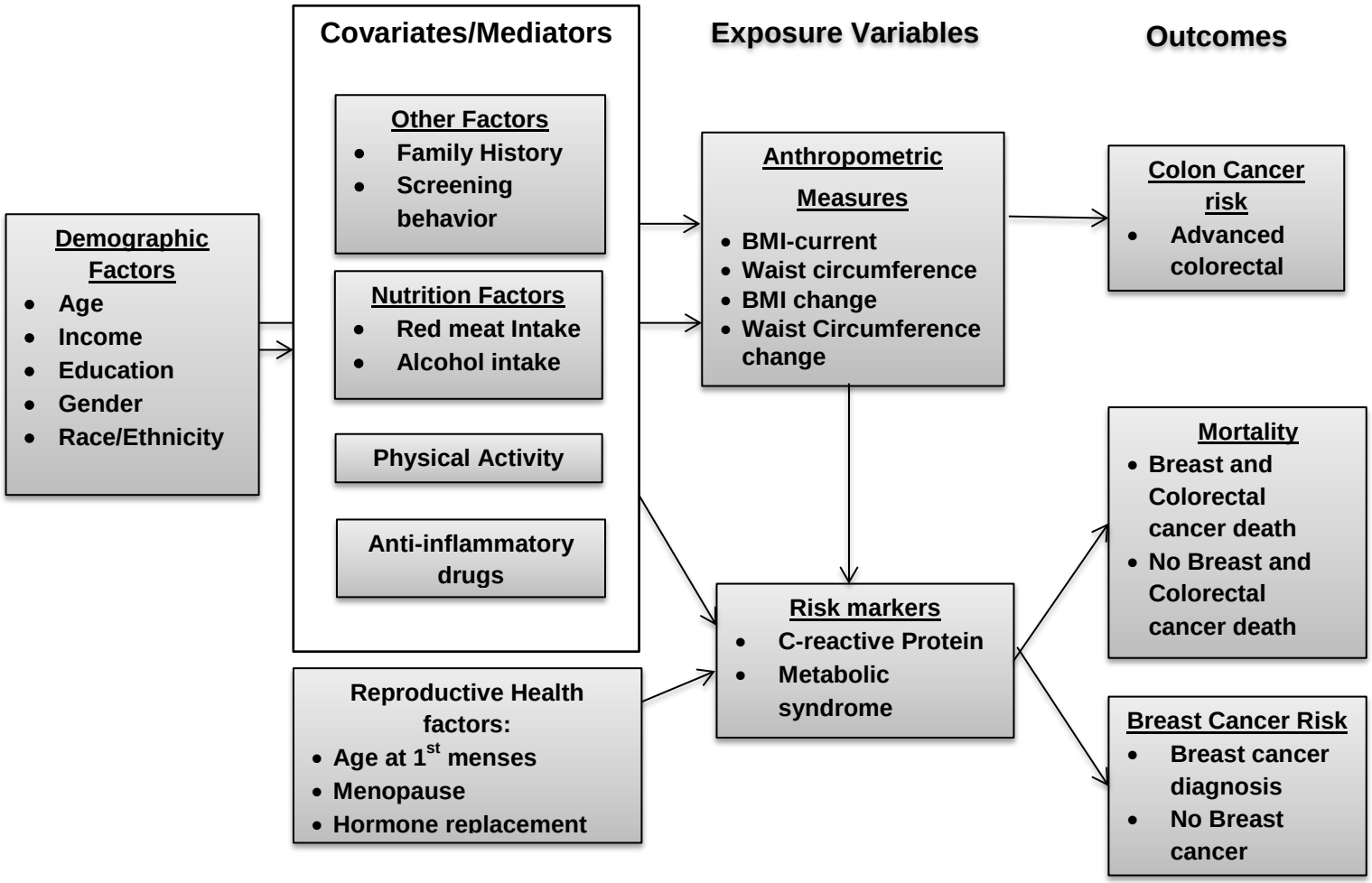
Several studies have assessed the association of weight gain and the risk of colorectal cancer (18-21). However, there are limited studies that have assessed the association of weight gain and risk of colon polyps (22, 23). Weight gain in earlier adult life from age 18-50, because it results in visceral fat accumulation (24), appears to confer a greater risk of chronic diseases than later life weight gain (7, 8, 25). In addition, waist circumference (WC), as a reliable surrogate of visceral adiposity, is suggested to be a better predictor of colorectal cancer, because it is more closely related to obesity-associated cardio metabolic disorders (25). Unlike most other cancers, removal of the adenoma, which is the precursor lesion for colorectal cancer, renders an opportunity for prevention of cancers at that site (26). Therefore, understanding if BMI or WC changes are associated with an increased risk of advanced colorectal neoplasia (AN) may provide an opportunity to underscore the need to maintain a healthy weight to prevent development of advanced colorectal neoplasia and ultimately colorectal cancer.

There is growing evidence on the impact of obesity biological markers, specifically MetS and CRP on the risk of cancer. It is estimated that 1 in 4 adults in the US have MetS (27, 28). MetS is a clustering of three or more of the

following: large waist circumference; elevated triglycerides, blood pressure, and fasting blood glucose; and low HDL cholesterol (29-31). These components have been shown to increase the risk of several cancers (32, 33), including breast cancer (1, 31, 34-37). The link between obesity and breast cancer is believed to be related to chronic inflammation (9, 10) while insulin resistance is the best established pathway linking obesity and colorectal cancer (38). Inflammatory responses are characterized by the increase of cytokines and markers of active inflammation (such as CRP and fibrinogen) (9, 10). High-sensitivity CRP has been investigated extensively as a robust marker of systemic inflammation for predicting the risk of cardiovascular disease (CVD) and diabetes (39, 40), but not in cancer. These three chronic diseases have obesity as a common risk factor. Obesity rates remain high among breast cancer survivors putting them at risk of recurrence of cancer and mortality (41, 42).

It is under these premises, change in BMI and WC and obesity markers as risk factors to specific cancers, that this research was built. The first manuscript assessed change in adiposity measures (BMI and waist circumference) and their associated risk for advanced colorectal neoplasia. The second manuscript assessed obesity markers (MetS and CRP) among breast cancer survivors and compared them to healthy women. The last manuscript assessed the association of obesity markers with risk of breast and colorectal cancer mortality. The three studies are inter-related as shown in the following conceptual framework (fig. 1).

FIGURE 1. OVERALL DISSERTATION CONCEPTUAL FRAMEWORK



CHAPTER 1: BMI CHANGE AND RISK OF ADVANCED COLORECTAL NEOPLASIA

Abstract

Objective: There is strong evidence that obesity is associated with risk for colorectal cancer (CRC); however, little is known about how change in body mass index (BMI) and waist circumference (WC) measures from early adult life (age 21) influence the risk of advanced colorectal neoplasia (AN). The study objectives were to examine the association between BMI change and WC change and risk of AN, as well as to determine whether changes in BMI and WC better predict risk of AN when compared to static measures.

Methods: A cross-sectional study of 4500 adults aged 50-80 years was conducted among participants undergoing first-time screening colonoscopies. Participants were excluded if they had previous CRC or adenomatous polyps, inflammatory bowel disease, or polyposis syndrome. Participants reported current weight, height and waist circumference and their historical measures at age 21. Models adjusted for known risk factors for colorectal neoplasia.

Results: Participants who were obese in early adulthood and remained obese later in life, had an increased risk of AN (OR=1.87; 95% CI: 1.08-3.23) compared to those who maintained a normal BMI. Those with a stable high-risk WC (females ≥35 inches and males ≥40 inches) at age 21 and time of screening had increased risk of AN (OR=2.15; 95% CI: 1.35-3.45) compared to those with a

stable-low risk WC. For static measures, obesity at age 21 but not obesity at time of screening increased the risk of AN (OR=1.91, 95% CI: 1.22-3.00). Having a high-risk WC at age 21 and at screening compared to those with a low-risk WC was associated with increased risk of AN. Both static and dynamic measures have similar model statistics and were significantly associated with risk of AN. WC measures (static and dynamic) were generally better predictors of AN than BMI. The omnibus BMI variable at age 21, and the stable-obese indicator variable for BMI change, were significantly associated with AN when BMI was entered alone. However, when both BMI and WC were entered together in the models, only WC (not BMI) was significantly associated with AN (for both the "current" model and the "change" model) indicating that WC provided unique prediction of AN separate from the characteristics that WC and BMI share in common.

Conclusions: Adiposity in early adulthood and maintaining an unhealthy BMI and WC from early adult life may increase an individual's risk for advanced neoplasia. WC provided unique prediction of AN.

Impact: These findings support growing evidence that early adult life adiposity and change in adiposity increases the risk of advanced colorectal neoplasia.

Introduction

Colorectal cancer is a global public health problem (16), the third most common cancer and the third leading cause of cancer death in both men and women in the U.S. (43, 44). The American Cancer Society estimated 136,830 new cases would be diagnosed and 50,310 colorectal cancer (CRC) deaths would occur in 2014 (44). In addition to regular screening to remove polyps, several preventable lifestyle factors, such as weight management, healthy diet and exercise, have been linked to reduced risk of colorectal cancer. Obesity is one of the established risk factors for CRC in both men and women (12, 45, 46), with a stronger link reported in men (41, 47, 48). Epidemiological data suggests that 30% to 70% increased risk of CRC can be attributed to obesity (49).

Several studies have assessed the association of weight gain and the risk of CRC (18-21). However, only a few studies have assessed the association of weight gain and risk of precancerous colorectal polyps (22, 23). Although weight gain in adulthood results in visceral fat accumulation (7, 8, 24), which has been linked to risk of colorectal cancer and other chronic diseases (25), increase in weight over time may be a better indicator of risk for advanced colorectal neoplasia (the composite of colorectal cancer and advanced precancerous polyps) as compared to cross-sectional (static) waist circumference and body mass index (BMI) values (50) at specific points in time. There are even fewer studies assessing the impact of change in waist circumference on risk for advanced neoplasia (51). It is unclear whether the timing of weight gain or the

duration of being overweight or obese are relevant determinants of risk for advanced neoplasia (AN).

We hypothesized that an increase in BMI and waist circumference from early (age 21) to later adulthood (time of screening) may be associated with an increased risk for advanced colorectal neoplasia. To test this hypothesis, we analyzed data from a cross-sectional study of participants aged 50-80 year who were having their first screening colonoscopy. The primary aim of the analysis was to determine the association of changes in BMI and waist circumference and the risk of having advanced colorectal neoplasia. Additionally, we sought to determine if changes in BMI or WC better predicted risk of advanced colorectal neoplasia compared to static measures.

Methods

This study was conducted at Indiana University Medical Center in Indianapolis and was approved by the institutional review boards at Indiana University and the Richard L. Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana.

Study population.

The study methods have been discussed in detail elsewhere (52). The study was initiated in December 2004 to assess the factors associated with the risk for advanced colorectal neoplasia (AN). Study participants were eligible for the study if they were aged 50 to 80 years and were undergoing first-time colonoscopy screening. Participants were initially recruited from two large corporations that provided screening colonoscopy for their employees, retirees, and their dependents. Due to slow uptake of screening colonoscopy through these company-based programs, additional recruitment was required from Indianapolis Gastroenterology and Hepatology, a large single-specialty practice in Indianapolis as well as from several of the affiliate hospitals of Indiana University Medical Center, including, Wishard Memorial Hospital, Roudebush Veterans Affairs Medical Center, and from Margaret Mary Community Hospital in Batesville, IN, which is an outreach site. Participants were excluded if they had previous colorectal cancer or adenomatous polyps, inflammatory bowel disease, or familial or non-familial polyposis syndrome.

Eligible subjects who were already scheduled for screening colonoscopy received a letter of introduction describing the study along with a 12-page, 50-

item self-administered questionnaire and a 72-inch tape measure. Participants received a follow-up call to clarify eligibility and answer questions about the study. The study questionnaire gathered data on a variety of factors: demographic variables, family history of colorectal cancer, personal medical history (including previous lower endoscopic procedure findings and non-endoscopic screening test results), lifestyle habits (diet, exercise, cigarette smoking, alcohol use), medication use (particularly aspirin, non-steroidal anti-inflammatory drugs, and post-menopausal hormone replacement therapy), and anthropometric measures.

Weight and weight history

Participants were asked about their weight, height, and waist circumference history. The weight history question was 1) “When you were age 21, what was your approximate weight and approximate waist circumference?” The participants were also asked to estimate their current weight (without shoes) and their waist size. In addition, a tape measure and instructions were provided in the package for the participants to accurately record their waist circumference by measuring the smallest part, above the navel, body naturally erect, and abdomen neither drawn in nor protruded. On the day of the colonoscopy, nursing personnel at each site recorded physical measures (height, weight, waist and hip circumference).

BMI was calculated as a ratio of weight and height (kg/m^2) and grouped into three categories: normal (<25.00), overweight (≥ 25.00 to 29.99), and obese (≥ 30.00) using the World Health Organization’s criteria (53). In calculating BMI

change comparisons were made to assess changes in obesity over time: BMI at age 21 was the baseline BMI and was compared with that at Time 2 (current-time of screening). BMI changes were defined in 9 specific categories within three broad areas (54): **A. Maintained BMI:** 1) *Stable-Normal:* those whose BMI remained normal at both time points; 2) *Stable-Overweight:* those whose BMI was overweight at both time points; and 3) *Stable-Obese:* those whose BMI was obese at both time points. **B. Increased BMI:** 4) *Normal to Overweight:* those whose BMI increased from normal to overweight, 5) *Normal to Obese:* those whose BMI increased from normal to obese; and 6) *Overweight to Obese:* those whose BMI increased from overweight to obese. **C. Reduced BMI** from 7) *Overweight to Normal*; 8) *Obese to Overweight* and 9) *Obese to Normal.*

Self-reported waist circumference (WC) at age 21 and reported current WC were categorized into two risk groups using recommended international gender specific cutoffs: low risk (females <35 inches and males <40 inches) and high risk (≥35 inches for females and ≥40 inches for males) (29). WC change was categorized as follows: 1) *Stable low-risk*: those who had a low risk WC at both time points; 2) *High-low risk*: those who had a high risk WC at age 21 but reduced to a low risk; 3) *Low-high risk*: those who had a low risk WC at age 21 and increased to high risk and 4) *Stable-high risk*: those who had a high risk WC at both time points.

Outcome Ascertainment

Colonoscopy and pathology reports were reviewed and coded by trained personnel who were blinded to survey information. Results of the colonoscopies

were coded based on the most advanced histological findings. Advanced precancerous polyps were defined as an adenoma ≥1 cm or one with villous histology or high-grade dysplasia.

Statistical Analysis

Descriptive statistics comparing the characteristics of those with and without advanced colorectal neoplasia (advanced neoplasia) were performed. Pearson chi-square tests and two-sided t-tests were performed to compare the distributions and means of covariates and exposures of interest (BMI and waist circumference) by advanced neoplasia status. Multiple logistic regression analysis was used to estimate the risk of advanced neoplasia based on changes in BMI and changes in waist circumference. Three separate models were assessed: 1) BMI change alone as the risk factor; 2) waist circumference change alone as the risk factor; and 3) both change in BMI and change in waist circumference as the risk factors. Very few participants reduced their BMI (n=11) or reduced their WC-high-low risk WC (n=26), therefore, these individual cases were excluded from the analytical dataset. The statistical power has a reduced chance of detecting a true effect. These exclusions led to reduced BMI change and WC change categories. Two broad BMI change categories and 6 specific categories were used in the models with maintenance of normal weight as the reference category. For WC change three categories were used with maintenance of a low-risk WC as the reference category. Several known risk factors for CRC were controlled in the logistic model: age, race, gender, education, smoking, NSAID use, physical activity, alcohol intake, family history,

red meat intake, vegetable intake, and estrogen use in women (55). These factors were assessed as confounding variables by comparing the crude and adjusted odds ratios (OR) of the BMI/waist circumference risk factors in the presence of potential confounders.

To assess whether the dynamic measures (change from age 21 to time of screening) of BMI and waist circumference were better at predicting risk of advanced neoplasia, compared to the static measures, we focused on the model statistics when the individual variables were included in the analyses together with the confounding factors. The variables of interest (static BMI, static WC, dynamic BMI, and dynamic WC) were entered into separate models. In addition, static BMI and WC variables were entered together, and both BMI change and WC change were simultaneously considered, to determine whether BMI or WC could add significant unique association with AN after adjusting for each other. Both dynamic and static measures of BMI and WC were correlated. The Spearman correlations for BMI and WC were: at age 21 rho=0.31, *p*-value <.0001, at time of screening rho=0.56, *p*-value <.0001 and WC change and BMI change rho=0.39, p-value <.0001. Since the variables were correlated, we assessed collinearity diagnostics. Other than a minor collinearity involving the intercept, the collinearity diagnostics did not indicate that the correlations of the two measures at the different time points were affecting the conclusions drawn from the analysis. Static and dynamic measures were not entered in the model together because they were highly correlated and collinearity problems were observed. The static and dynamic BMI variables were not entered together in the

same model, nor were the static and dynamic WCs variables, because this would have resulted in statistical redundancy. The dynamic variables are created from the static measures and therefore, share a lot of the variation in predicting AN.

The model statistics of interest were Akaike Information Criterion (AIC), c-statistic, the Type 3 (i.e., adjusted for other variables in the model) omnibus likelihood ratio test for the variable of interest, and the Hosmer and Lemeshow goodness-of-fit test. Models with lower AIC, higher c-statistic, and lower p-value were considered better models statistically. All statistical analyses were performed using SAS for WINDOWS software, version 9.4. *P*-values less than .05 were considered statistically significant.

Results

The mean age of the participants was 57.3 (± 6.8) years; 52% were women. Most of the study participants were non-Hispanic whites and had lower levels of education. Descriptive characteristics of the participants are summarized in Table 1.1. Those with advanced neoplasia were more likely to be men, and to have higher rates of CRC in their families, cigarette smoking, alcohol use, Aspirin/NSAID intake and red meat intake, and lower rates of vegetable intake and reported physical activity. Women with AN reported high rates of estrogen use.

Association of Static BMI and Waist Circumference and AN Risk

Table 1.2 shows regression results comparing static measures of BMI and waist circumference at different time points on the risk of AN. At age 21, being obese and having a high risk WC was significantly associated with increased risk of AN. At the time of screening colonoscopy, WC but not BMI was associated with increased risk of AN. More importantly, only WC at the time of screening remained significant when both BMI and WC were in the model. Neither WC nor BMI at age 21 were significant when both were in the model.

Association of BMI Change and Waist Circumference Change and Risk of AN

Table 1.3 shows the results of multiple logistic regressions analyses assessing the relationship between change in BMI and change in WC on the risk of AN. Maintaining obesity status between age 21 and current age (stable-obese compared to stable-normal) was positively associated with AN (OR=1.87). Increasing BMI was associated with numerically increased but statistically non-

significant risk of AN. Stable-high risk WC was associated with increased risk of AN, irrespective of whether changes in WC and BMI were modeled separately or together. Increase in WC (low-high risk) was associated with numerically increased but statistically non-significant risk of AN. When both WC change and BMI change were adjusted for each other, none of the BMI change categories were significant. However, those with a stable-high risk WC (OR=2.49) and those who increased their WC from low-high risk (OR=1.43), from age 21 to time of screening, had increased risk for AN, irrespective of whether BMI change was considered (Table 1.3).

To assess whether the dynamic measures (BMI change and WC change) were better at discriminating between participants with versus without AN, compared to the static measures (current and age 21) of BMI and waist circumference, we focused on the model fit statistics as shown in Table 1.4. Overall, the models, including covariates, were comparable in terms of predictive power and goodness-of-fit. As indicated by the c-statistic, all models had a high (76%) and comparable predictive power to discriminate those with AN from those without. Furthermore, as shown by the Hosmer and Lemeshow goodness of fit, the data fit well in all the models. For all models, the likelihood ratio test of the significance of the overall model had chi-square values that were significant. As expected, the base model (with covariates only) had the largest AIC indicating that the model was improved when adding either BMI or WC. Therefore, we focused on the omnibus test for the variable of interest.

Overall, models with dynamic measures and those with static measures did not differ substantially in discriminating those with versus those without AN. However, WC was generally a better predictor of AN than BMI when comparing models with either change or static measures at age 21 and at the time of screening. Even when BMI and WC were assessed in the model together, WC remained significant in predicting risk of AN, except at age 21. It was noted that results from this study was that in general, models with BMI and WC measured at age 21 had better model statistics compared to models with BMI and WC measured at the time of screening.

Discussion

In this study, we observed a positive association of waist circumference and BMI in early adult life (age 21) but only waist circumference at the time of screening, with risk of advanced colorectal neoplasia. To our knowledge, this is one of the few studies to examine the association of both BMI and waist circumference change with the risk of advanced colorectal neoplasia. Maintaining an obese status or a high risk waist circumference over time was associated with increased risk of AN. The data fit well in models with both static and dynamic measures, with no substantial differences in overall model statistics (such as AIC and c-statistic) when dynamic or static measures of BMI and WC were used to predict risk of AN. However, WC was generally a better predictor of AN when compared to models with BMI.

There are limited studies conducted on the association between advanced neoplasia and weight change. A large case control study by Bird et al, showed that large weight increases during adulthood were associated with adenomatous polyps (22). That study assessed weight change as the difference between current weight, weight gained 10 years before sigmoidoscopy and weight at age 18. Compared to those who reported a weight loss, those with net weight gains of 1.5-4.5kg had increased odds of adenoma (OR=2.5; 95% CI: 1.2-5.6) (22). In another study, weight gain over the past 10 years prior to screening was significantly associated with increased risk of colon adenomas (OR=2.2; 95% CI: 1.0-4.8), ≥ 6kg vs -2 kg (23). We conducted a sensitivity analysis using similar methods and actual weight difference, but did not find any significant weight

groups (OR= 1.0; 95% CI: 0.70-1.36 Quartile 4 vs Quartile 1) associated with risk for AN. The association of weight change and risk of colorectal cancer has been studied but the results are conflicting. In some studies, weight increase has been associated with increased risk for colorectal cancer (18, 34, 56) while others did not find a significant relationship (19).

Waist circumference is considered a reliable surrogate of visceral obesity because it is more closely related to obesity-associated cardio metabolic disorders (25, 57). To our knowledge, this may be the first study to examine the association of waist circumference change and risk of AN. The findings of our study indicate that participants who at age 21 and at screening had waist circumference equal to or larger than the recommended maximum value (women 35 inches and men 40 inches) had increased risk of advanced neoplasia and the risk was higher when BMI change was adjusted in the analyses. Also those who increased their WC from age 21 to time of screening had an increased risk of AN, but only when their change in BMI was adjusted in the model. The highest risk for AN was observed in the WC change measure compared to the static measures. When both BMI change and WC change were in the model together, WC change remained significant; this conveys that WC change provides a significant association with AN after removing or adjusting for the effects of BMI change. These results indicate that WC provided unique prediction of AN separate from the characteristics that WC and BMI share in common.

The findings of this study that WC and BMI at age 21 are associated with risk of AN are unique and of potential public health importance. These results

add to new evidence that early adult life body adiposity may affect the risk of colorectal cancer many decades later (58, 59). Having a large WC at age 21 was associated with an increased risk of AN (OR=1.9); this may be the first study to show this association. Our findings indicate that being obese (BMI ≥30) at age 21, but not at screening was associated with increased risk of AN. Our findings differ from those in a study by Bird et al., which sought to examine the association between colorectal adenomas with BMI over time. Bird et al., reported that BMI at exam (OR=1.4; 95% CI: 1.0-2.0, Quartile 2 vs Quartile 1) was associated with increased risk for adenomas (22), but found no association between BMI at age 18 and risk for adenomas (22). To define early adult life we used age 21 while Bird et al. used age 18. It is possible that this 3 year age difference accounts for the discrepant findings, although the age difference is small. Perhaps the time between ages 18 and 21 may be important as it is related to the difference between early and late full adult development. Another reason for the discrepant findings may be in how BMI was categorized. We categorized BMI using WHO criteria but Bird and others have used continuous BMI categorized in quartiles. Therefore, while current measures of WC and BMI are important, we may consider an individual's measures at early adult life to better predict risk, which further underscores the importance of weight management early in life to prevent AN.

Another novel aspect of this study was that we examined whether changes in BMI and WC better predict risk of AN when compared to static measures. The findings of our study indicate that dynamic measures of BMI and

WC were not substantially different in predicting risk of AN compared to the static measures. However, the WC measures overall were better at predicting risk of AN compared to the BMI measures. This may be supported by the fact that waist circumference is strongly related to visceral obesity than BMI. One remarkable finding was that BMI and WC measured at age 21 were better at predicting AN compared to static measures at screening. There is growing evidence that early adult life obesity measures are associated with future risk of some cancers (58, 59) making the results of our study important for managing population health. Knowledge of the potential of future risk in early adult life underscores the need to maintain healthy behaviors early in life. Additionally, dynamic measures may be useful in identifying and stratifying those who are most at risk for AN.

The results of the current study support the link between obesity and increased risk of colorectal cancer (38, 46, 60). The findings of the current study are strengthened by the concurrent assessment of both waist circumference and BMI in relation to risk of advanced colorectal neoplasia. In adulthood, waist circumference has been shown to be a better predictor of obesity-related health risk than BMI (61). Indeed a combination of both BMI and waist circumference has been shown to better estimate the health risk than either factor alone (62). This is because health risk increases from the normal weight through obese BMI categories, but within each BMI category, those with higher waist circumference values have a greater health risk than those with normal waist circumference values (63). Although we did not create a single variable that combined both waist circumference and BMI, we adjusted for the effect of the other in the

regression models. Additional strengths of the study include the large sample size and weight history assessment. The findings of this study may be generalizable to the non-Hispanic white population who were a majority in the study. Although, most of the participants were non-Hispanic white, the obesity rates in our study are comparable to the national age-adjusted obesity rates (35.9% vs 34.9%) (64).

Study limitations are those inherent in an observational study. There was the possibility of intentional and unintentional errors in self-reported height and weight which were used to calculate BMI. However, self-reported and measured weights have previously been reported to be highly correlated (65, 66). The associations were modeled based on self-reported historical weight and height, which may lead to a recall misclassification of waist circumference and BMI. However, it is likely that the same amount of misclassification (non-differential) occurred in those with and without AN, so the misclassification error may not have affected the study findings. In this study we could not assess the impact of BMI decrease on risk of advanced neoplasia because so few subjects reduced their weight. Nonetheless, we adjusted several of the known colorectal cancer risk factors in an attempt to isolate the specific impact of adiposity measures on advanced colorectal neoplasia. Finally, our assessment was based on neoplasia diagnosis rather than occurrence of AN, which may have developed a considerable amount of time before the diagnosis, and this lag time may have led to errors in estimating the period at risk. Due to these limitations, causal relationships should not be drawn from this study.

In conclusion, our results support previous findings that early adulthood BMI and maintaining an unhealthy BMI and waist circumference are independent risk factors for AN. Both static and dynamic measures have similar overall model statistics, and both were significant predictors of the risk of AN. The results emphasize the importance of maintaining a healthy BMI throughout adult life for preventing AN. Weight gain expressed in terms of movement between BMI categories may be more practical and useful in clinical practice than current measures alone but this remains to be determined from future studies. Health care providers may use the findings as a prevention strategy for colorectal cancer when counseling patients, in line with the American Society of Clinical Oncology's prioritization of educating providers and patients on the role of energy balance as a strategy to reduce the impact of obesity on cancer (67). Prospective studies should be conducted to validate our findings and to explore the associations of reducing, increasing and maintaining BMI (as well as changes in waist circumference) and risk of advanced colorectal neoplasia.

Table 1.1 Characteristics of Study Subjects by Advanced Neoplasia Status				
	Advanced Neoplasia (n=410)	No-Advanced Neoplasia (n=4,090)		
	Mean (SD)		**t value**	*p value*
Age (year)	61.4 (9.0)	56.9 (6.3)	568.7	<.0001
Pack years	20.8 (26.1)	8.7 (16.6)	36.5	<.0001
Vegetable intake-wkl	15.1 (8.2)	15.9 (7.5)	140.0	0.05
Red meat intake-wkly	5.1 (3.0)	4.1 (2.5)	111.3	<.0001
	n (%)		**X^2 [DF]**	
Gender				
Male	250 (61.0)	1,928 (47.1)	28.6 [1]	<.0001
Female	160 (39.0)	2,162 (52.9)		
Education				
High School	152 (37.1)	1060 (26.0)	47.8 [3]	<.0001
Trade/Vocational	62 (15.1)	401 (9.8)		
College Educatio	141 (34.4)	1682 (41.2)		
Postgraduate	55 (13.4)	940 (23.0)		
Race				
Non-Hispanic White	358 (87.3)	3884 (95.0)	76.8 [2]	<.0001
Non-Hispanic Black	44 (10.7)	106 (2.6)		
Other	8 (1.9)	100 (2.4)		
Alcohol Use				
No problem drinking	357 (87.07)	3704 (90.67)	5.54 [1]	0.02
Problem drinking	53 (12.93)	381 (9.33)		
Aspirin-NSAID intake				
Low	258 (62.9)	2649 (64.8)	6.6 [2]	0.04
Medium	46 (11.2)	581 (14.2)		
High	106 (25.9)	860 (21.0)		
Estrogen (Females)				
No	37 (23.1)	918 (42.3)	23.3 [1]	<.0001
Yes	123 (76.9)	1238 (57.4)		
Exercise				
0-<2 hrs./week	239 (58.3)	1743 (42.6)	38.7 [2]	<.0001
2 to <4hrs./week	153 (37.3)	2054 (50.2)		
>4 hrs./week	9 (2.2)	102 (2.5)		
Family History of Colorectal Cancer				
Yes	55 (13.4)	372 (9.1)	8.1 [1]	0.004
No	355 (86.6)	3718 (90.0)		

Table 1.2 Association of BMI and Waist Circumference at different Time points and risk of Advanced Neoplasia				
	Measures at Age 21		**Measures at Time of Screening**	
	Models a WC and BMI in separate models	**Model b** WC and BMI in model together	**Models a** WC and BMI in separate models	**Model b** WC and BMI in model together
BMI Categories				
Underweight/Normal (<25 Kg/m²)	Reference	Reference	Reference	Reference
Overweight (25-29.99 Kg/m²)	1.27 (0.96-1.67)	1.22 (0.92-1.62)	1.02 (0.76-1.37)	0.92 (0.68-1.26)
Obese (≥30 Kg.m²)	**1.91 (1.22-3.00)**	1.62 (0.97-2.69)	1.07 (0.79-1.45)	0.81 (0.56-1.19)
Waist Circumference Categories				
Low Risk	Reference	Reference	Reference	Reference
High Risk	**1.85 (1.19-2.86)**	1.45 (0.88-2.39)	**1.29 (1.02-1.63)**	**1.43 (1.06-1.93)**

The table shows results of analyses conducted for each time point to assess the association of individual anthropometric measurements (where applicable, both waist circumference and BMI are in the model) and risk of advanced colorectal neoplasia. All models were adjusted for age (continuous), race (non-Hispanic white, non-Hispanic black, Other), gender (male vs female), and education (high school, trade/vocational, college education and postgraduate), family history of colorectal cancer (yes/no), smoking (pack years), exercise, alcohol use (yes/no), red meat intake (daily), vegetable intake (daily), use of aspirin /other NSAIDs and estrogen use (yes/no).

Table 1.3 Association of BMI Change, Waist Circumference Change and risk of Advanced Neoplasia

		Change from Age 21 to Current	
	Distribution of those with AN n (%)	**Models a** WC change and BMI change in separate models	**Model b** WC change and BMI change in model together
Waist Circumference change			
Stable-Low risk	199 (49.63)	Reference	Reference
Low-High risk	175 (43.64)	1.23 (0.97-1.57)	**1.43 (1.05-1.96)**
Stable-High risk	27 (6.73)	**2.15 (1.35-3.45)**	**2.49 (1.38-4.51)**
BMI Change			
Maintained BMI			
Stable-Normal BMI	81 (20.98)	Reference	Reference
Stable-Overweight	37 (9.59)	1.54 (0.97-2.45)	1.37 (0.86-2.20)
Stable-Obese	23 (5.96)	**1.87 (1.08-3.23)**	1.01 (0.52-1.99)
Increased BMI			
Normal to Obese	80 (20.73)	1.14 (0.80-1.62)	0.87 (0.57-1.33)
Normal to Overweight	113 (29.27)	1.00 (0.72-1.38)	0.90 (0.64-1.26)
Overweight to Obese	52 (13.47)	1.04 (0.69-1.57)	0.74 (0.46-1.19)

The table shows results of several analyses conducted to assess the association of individual and combined measurements and risk of advanced colorectal neoplasia. All models were adjusted for age (continuous), race (non-Hispanic white, non-Hispanic black, Other), gender (male vs female), and education (high school, trade/vocational, college education and postgraduate), family history of colorectal cancer (yes/no), smoking (pack years), exercise, alcohol use (yes/no), red meat intake (daily), vegetable intake (daily), use of aspirin /other NSAIDs and estrogen use (yes/no).

Table 1.4 Statics to compare models with Static and dynamic measures of Body Mass Index (BMI) and Waist circumference

		AIC	c-stat	Likelihood Ratio Test for overall model			Type 3 Omnibus Likelihood Ratio Test of Variable of Interest			Hosmer and Lemeshow Goodness-of-Fit Test		
				χ^2	DF	p-value	χ^2	DF	p-value	χ^2	DF	p-value
M0:	Base model-covariates only	2306	0.754	370.78	21	<.0001				1.9806	8	0.98
	Static Measures											
M1:	M0 + BMI Current	2289	0.758	362.57	23	<.0001	0.23	2	0.89	1.81	8	0.90
M2:	M0 + BMI at age 21	2274	0.759	371.70	23	<.0001	8.93	2	**0.012**	8.05	8	0.43
M3:	M0 + Waist Current	2281	0.760	367.66	22	<.0001	4.59	1	**0.03**	4.00	8	0.86
M4:	M0+ Waist at age 21	2279	0.759	370.78	22	<.0001	6.81	1	**0.009**	10.41	8	0.24
M5:	M0 + BMI Current + WC Current	2279	0.759	363.09	24	<.0001	BMI: 1.20 WC: 5.56	2 1	0.55 **0.02**	3.53	8	0.90
M6:	M0 + BMI age 21 + Waist age 21	2269	0.760	369.36	24	<.0001	BMI: 4.24 WC: 2.04	2 1	0.12 0.15	6.58	8	0.58
	Dynamic Measures											
M7:	M0 + BMI Change	2215	0.757	344.63	26	<.0001	8.49	5	0.13	8.02	8	0.43
M8:	M0 + Waist Change	2259	0.762	368.53	23	<.0001	10.18	2	**0.006**	3.07	8	0.92
M9:	M0 + BMI Change + WC Change	2189	0.761	346.98	28	<.0001	BMI: 5.49 WC: 9.87	5 2	0.36 **0.007**	6.29	8	0.62

M0 = age (years), gender, race (non-Hispanic white, non-Hispanic black, Mexican American, and other race), education (no education, less than high school, high school, college education, and graduate education), family history of colorectal cancer, smoking (pack years), exercise (low, moderate, high), alcohol use (yes or no), red meat intake, vegetable intake, use of aspirin /other NSAIDs and estrogen use (yes/no).

CHAPTER 2: METABOLIC SYNDROME AMONG BREAST CANCER SURVIVORS

Abstract

Purpose: Several studies suggest that breast cancer risk is associated with metabolic syndrome (MetS) and C-reactive protein (CRP), but no nationally representative study has investigated CRP and MetS among breast cancer survivors. This study investigated the distributions and proportions of CRP, MetS, and its components (high fasting glucose and triglycerides, low HDL-cholesterol, high blood pressure, and abdominal obesity) among breast cancer survivors and their associations with breast cancer risk in a large nationally representative sample of US adults.

Methods: Women aged 50 and above enrolled in the National Health and Nutrition Examination Survey 2005-2010-NHANES were included in the study. Pregnant women, those with other cancer diagnosis, as well as those with diabetes and cardiovascular diseases were excluded, resulting in a sample 2,172, of which 172 were breast cancer survivors. MetS was defined as the presence of three or more MetS components. Models were adjusted for known risk factors for breast cancer.

Results: The prevalence of MetS among breast cancer survivors was 42.6% and this prevalence did not differ significantly from the 44.2% prevalence among women without breast cancer. Neither MetS (OR=0.92, 95% CI: 0.53-1.60, MetS diagnosis vs. no MetS diagnosis) nor elevated CRP (OR=1.04, 95% CI: 0.45-

2.42, CRP ≥1.0mg/dl vs <1.0mg/dl) were associated with increased risk of breast cancer. However, those with 3 abnormal MetS components had a non-significant association with breast cancer. The individual MetS components measured did not show a significant association with breast cancer. Only waist circumference (OR=1.29, 95% CI: 0.82-2.04) and HDL (OR=1.19, 95% CI: 0.74-1.91) had increased but non-significant association with breast cancer. Also, there was no joint association of MetS and CRP with risk of breast cancer.

Conclusion: These null findings challenge the assumption that MetS and CRP which are directly linked to obesity are prevalent and associated with breast cancer risk. This supports the need to assess differences by survival years in a larger prospective study.

Introduction

Breast cancer is the second most prevalent cancer among women in developed countries (16, 68). In the US it is estimated that 1 in 8 women will be diagnosed with breast cancer in their lifetime (68). The 5-year survival rate for localized breast cancer is 99% (69). However, breast cancer recurrence remains a major concern among survivors. Obesity has been repeatedly shown to increase the risk for breast cancer recurrence and mortality (42, 70-72).

Obesity is a growing public health problem and the second most preventable cause of death (1). In the US one in three (37%) women is obese (2). Obesity is the major determinant of MetS, which has been linked an increased risk of breast cancer (36). MetS is defined as a cluster of at least three of the following five factors: high-density lipoprotein (HDL) cholesterol (<50 mg/dl for women), triglycerides (≥150 mg/dl), systolic blood pressure (≥130 mm Hg), fasting blood glucose (≥100 mg/d) and waist circumference (≥88 cm for women) (29-31). It is estimated that 33% adult women in the US have MetS (27, 28). The link between obesity and breast cancer is believed to be related to chronic inflammation which induces aromatase expression and estrogen synthesis (9, 10). Inflammatory responses are characterized by the increase of cytokines and markers of active inflammation (such as CRP and fibrinogen) (9, 10). High-sensitivity CRP has been investigated extensively as a robust marker of systemic inflammation for predicting the risk of cardiovascular disease (CVD) and diabetes (39, 40). Elevated CRP has been previously proposed as a component of the MetS (73). A few studies have examined the relationship of MetS and CRP with

breast cancer risk, recurrence, and survival but the results have been inconsistent (74-76).

A number of studies have examined the relationship between obesity and breast cancer; however, few nationally representative population studies have examined the relationship between MetS and CRP in breast cancer cases as compared to cancer-free women (75, 77, 78). Furthermore, there is limited research on the joint association of CRP and MetS on the risk of breast cancer (77). Therefore, we first sought to examine the distribution and prevalence of obesity markers (CRP and MetS) among breast cancer survivors compared to those free of breast cancer from the NHANES data. Second, we examined whether CRP and MetS (and its individual components) were associated with breast cancer diagnosis. Lastly, we further explored if CRP and the MetS jointly modified risk of breast cancer. A better understanding of the presence of MetS and CRP among breast cancer survivors will help support the management of comorbid metabolic disorders.

Materials and Methods

Study Design and Study population

To answer the research questions, data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES). The design, questionnaires, and examination methodology of NHANES are described in detail at the Center for Disease Control and Prevention (CDC) website (79). The data used in this study were from the 2005/06, 2007/08 and 2009/10 surveys (n=2,172 who had CRP or MetS components measured). In these three surveys, low-income individuals, individuals 60 years of age and older, African Americans and Mexican Americans were oversampled; therefore, sampling weights were added to allow the estimates to be generalizable to the US population. The NCHS Institutional Review Board approved the survey protocols, and informed consent was obtained from all subjects. The present study was not reviewed by the Institutional Review Board of Indiana University as the data analyzed are de-identified and publicly accessible.

Women who participated in the NHANES study were eligible if they were 50 years or older to limit the study to post-menopausal breast cancers. Women were excluded if they were pregnant and had been diagnosed with cancers other than breast cancer. Breast cancer survivors were compared with women without breast cancer diagnosis. The controls who had been diagnosed with diabetes or cardiovascular diseases were excluded because these two diseases were strongly linked to MetS. A total of 2,172 women met the study inclusion and exclusion criteria, of these 172 women were breast cancer survivors.

Variables

The outcome variable of interest was having or not having a breast cancer diagnosis. Participants who reported being diagnosed with breast cancer were defined as the 'cases' while those without a diagnosis of cancer were defined as 'controls.' The exposure variables were MetS and CRP. The components of MetS (waist circumference, triglycerides, HDL-cholesterol, blood pressure and blood glucose) were measured during the physical examination. Waist circumference was determined at the iliac crest after a normal exhalation of breath. Serum concentrations of HDL-cholesterol and triglycerides were measured enzymatically with Hitachi 704 Analyzer. Fasting blood samples were drawn by a trained phlebotomist to assess blood glucose levels. Serum fasting glucose levels were determined using the glucose hexokinase method with Hitachi 737 Analyzer. Systolic blood pressure (mmHg) was measured using a mercury sphygmomanometer while subjects were in a seated position. Three measurements were taken and then averaged for each subject to minimize measurement error (80). High sensitivity CRP concentration was quantified using latex-enhanced nephelometry, and reported in mg/dl to the nearest hundredth (0.01) (80).

Statistical Analysis

Chi square and t-tests were performed to compare the crude distributions and means of exposure variables and covariates by breast cancer status. Multiple logistic regression analysis was used to measure the association

between obesity makers (MetS and CRP) and the prevalence of breast cancer while controlling for the covariates: age, race/ethnicity, education, marital status, age at menarche, age at menopause, smoking, hormone replacement and alcohol intake. A weight statement and variable were included in the Proc SurveyLogistic SAS analysis model. Two models of each variable of interest were conducted with different covariates: Model 1 was adjusted for age and race and Model 2 was controlled for all the listed covariates.

To assess the joint effects of CRP and MetS on breast cancer risk we defined four categories using both CRP and MetS variable. The categories were: 1) *Low-risk* defined as no MetS diagnosis and low CRP levels; 2) *High risk I* defined as participants with no MetS diagnosis but with an elevated CRP; 3) *High risk II* defined as participants with a MetS diagnosis but with low CRP level; 4) *High Risk III* defined as participants with a MetS diagnosis and with elevated CRP. This composite variable and the covariates were entered as an independent variables in a multiple logistic regression analysis. For all analyses SAS version 9.4 was used and *P*-values less than .05 were considered statistically significant.

The NHANES database included measures of all components of MetS and CRP available for analysis. However, the CRP values were missing twenty percent of the participants, which was one of the exposure variables of interest. Those with missing CRP were assessed but no apparent pattern demographic or clinical patterns were identified. Therefore, CRP was imputed using multiple imputations (81, 82). Multiple imputations allow all participants to be included in

the analysis and therefore, preventing biased estimates of the association between MetS and CRP with the breast cancer diagnosis outcome. SAS software was used to generate imputed data. First, using PROC MI, 30 imputation files were created. Multiple logistic regressions were then conducted by imputation files using the procedure PROC MI analyze. All covariates stated above were included in the PROC MI analyses.

Results

Of the 2,172 eligible women who met the inclusion criteria, 172 were breast cancer survivors. The demographic and clinical characteristics of the study population are presented in Table 2.1. The majority of women enrolled were non-Hispanic white, married, non-smoking and with a college education. The prevalence of MetS among breast cancer survivors (42.6%) was not significantly different from that of the control group (44.2%). Although non-significant, breast cancer survivors overall had better measures of the components of MetS compared to women without breast cancer. The survivors had enlarged WC, but lower fasting blood glucose, triglycerides and HDL levels, though the means did not significantly differ from the means in the controls. The breast cancer survivors had a significant and slightly higher mean CRP level compared to the controls.

Table 2.2 shows the association of components of MetS and CRP among breast cancer survivors compared to the control. After adjustment for all covariates, WC was not significantly associated with (OR=1.29, 95% CI 0.82-2.04) breast cancer survivors compared to women with no breast cancer. Neither was HDL (<50mg/dl vs. ≥50mg/dl) associated with breast cancer diagnosis. All the other components-triglycerides, blood pressure and blood glucose-when comparing those with high risk and low risk were also found not to be associated with risk of having a breast cancer diagnosis.

Table 2.3 shows the association of MetS as a composite variable with breast cancer risk. In the adjusted multiple logistic regression model, breast

cancer risk was not associated with MetS when those with MetS were compared to those without MetS (OR=0.92, 95% CI: 0.53-1.60). The severity of MetS defined as having 3, 4 or 5 abnormal components was also not associated with a breast cancer diagnosis. CRP was not associated with breast cancer survivorship when women with CRP ≥ 1.0mg/dl were compared to those with CRP <1.0mg/dl (OR=1.04, 95% CI: 0.45-2.42). In a joint association model of CRP and MetS (Table 2.4) on breast cancer risk, no association was found for those with both elevated CRP and MetS with risk for breast cancer.

Discussion

Findings from this study indicate that the prevalence of MetS and CRP values among breast cancer survivors do not differ significantly from the prevalence among healthy women based on a nationally representative sample in the US. Hence the presence of MetS diagnosis and elevated CRP were not associated with breast cancer risk. Furthermore, of the individual components of the MetS, none showed a significant association with breast cancer.

The prevalence of MetS among breast cancer survivors in this study was high, but did not differ significantly from the prevalence in the healthy control group. Other studies have reported similarly high prevalence of MetS among breast cancer survivors (74-76). Our primary question was to assess the association of MetS with breast cancer risk. Although the prevalence of MetS has been shown to be high among breast cancer survivors, very few studies have compared survivors with healthy controls. The results of this study did not show a significant difference in MetS and its components, among breast cancer survivors compared to women without a diagnosis of breast cancer. However, other studies compared breast cancer survivors with a control group and found that MetS was higher in the breast cancer group (75, 83). Results of studies examining the association of MetS with incident and overall breast cancer risk have been inconsistent (84-88) .

Waist circumference was associated with risk of breast cancer in some studies (83). However, consistent with our results, other studies have not found waist circumference to be associated with a diagnosis of breast cancer (83, 86,

87). While waist circumference is a reliable surrogate of visceral obesity because it is more closely related to obesity-associated cardio metabolic disorders (25, 57), BMI is a more widely used obesity measure. Some studies used BMI in place of waist circumference when defining MetS and found increased BMI to be associated with risk of breast cancer (84). We conducted sensitivity analysis using participant's current BMI but the association of being obese (BMI≥ 30) and breast cancer was not significant in the current study (OR=0.98, 95% CI: 0.63-1.53).

High fasting blood glucose levels have been associated with breast cancer risk in some studies (83, 86). However, other studies (84, 87, 89) did not find a significant association, as was the case in this current study. As an alternative to fasting blood sugar, one study used diabetes diagnosis as one of the components of the MetS and found a significant association (85). Blood pressure either reported as actual values or defined as having a hypertension diagnosis has been used as one of the components of MetS. Similar to both waist circumference and blood glucose levels the results of studies examining the relationship between high blood pressure with breast cancer have been inconsistent. High blood pressure was found to increase risk of breast cancer in some studies (83, 85, 89) and, like our current study, other studies did not find a significant association (84, 86, 87).

Our study assessed separately the associations of high triglycerides levels and low HDL cholesterol levels with breast cancer risk. Wang et al. and Rosato et al. assessed the association of dyslipidemia (proxy of triglycerides and HDL

cholesterol) with breast cancer risk (84, 85). In the study by Wang et al., dyslipidemia was associated with 3.2 higher odds of postmenopausal breast cancer (84). However, hyperlipidemia was not associated with an increased risk of breast cancer (OR=1.08; 95% CI: 0.95-1.22) (85). Although our study and other studies (86, 89) did not find an association of triglycerides and HDL-cholesterol with breast cancer risk, other studies reported significant associations (83, 87).

Studies evaluating the association between CRP, a marker of systemic inflammation, and breast cancer risk are limited and the results were inconsistent. In our study of 172 breast cancer survivors, the presence of elevated CRP was not associated with breast cancer diagnosis, which was in agreement with the findings of some studies (90, 91). However, other studies have reported a significant association between CRP and breast cancer risk (92, 93).

The biological mechanisms linking obesity and breast cancer is believed to be related to insulin resistance and inflammation, which induce aromatase expression and estrogen synthesis (9, 10). Adipose tissue is a major source of estrogenic hormones and both aromatase expression and estrogen synthesis are linked to increased risk of breast cancer (94). Insulin has a gonadotrophic effect and upregulates aromatase activities (95). Additionally, the inflammation pathway originates in tissues involved in metabolism: adipose tissue, liver and muscle tissues (96). These tissues in response to metabolic stimuli trigger the

inflammatory response (93, 96). Inflammatory responses are characterized by an increase of cytokines and markers of active inflammation (CRP and fibrinogen).

While a biological mechanism linking obesity to breast cancer has been proposed (9, 10), the non-significant results of this study do not support they hypothesis. However, we noted that breast cancer survivors had significantly lower measures of blood glucose, blood pressure and triglycerides when compared to women without breast cancer. Visceral adiposity is central to the definition of MetS because it contributes to hypertension, high serum cholesterol, low HDL-cholesterol, and hyperglycemia (97). However, the mean waist circumference of women who had a breast cancer diagnosis did not differ significantly from that of women without breast cancer. These findings suggest that breast cancer survivors, have similar metabolic characteristics to the general population. The prevalence of obesity in this study and as reported elsewhere (98) did not differ between women with breast cancer and women without breast cancer. Even in another nationally representative sample, no differences were shown between survivors (58%) and those without cancer (55%) in overweight and obesity status (99) prevalence. However, in sensitivity and a subset analysis of obese women in our study, MetS was associated with breast cancer diagnosis for women (n=31) who had 10 or more years of survival (OR=5.0, 95% CI: 1.27-19.33). This perhaps implies that the impact of MetS varies by obesity status and the number of survival years. It is important that to note while studies have assessed the prevalence of MetS in breast cancer survivors, very few studies

included a control group with whom to compare the measures of MetS and CRP with.

Although not significantly different, women who had a breast cancer diagnosis had a higher education level compared to those without a cancer diagnosis. Higher educational levels have previously been correlated with healthier lifestyle factors; lower smoking rates, higher fruit and vegetable intake, alcohol consumption and increased physical activity (100). All these factors may have a role in reducing the risk from the components of MetS and CRP which are highly correlated with BMI. In a case control study, short term breast cancer survivors followed multiple behavioral recommendations when they were compared to controls; however, long term survivors were less likely to follow the recommendations (101). This study supports the results of our sensitivity analysis that the association of MetS may in part vary by short and long term survival years. Perhaps the experience of cancer diagnosis encouraged cancer survivors to modify their lifestyle choices, in addition to constant recommendations and close monitoring by their physicians. However, older and less educated survivors may be less likely to discuss with their physician health promotion interventions (102).

The study limitations are those inherent in observational studies. A limitation of this study design is potential uncontrolled confounding differences between those with breast cancer diagnosis and those without breast cancer that were not included in the analyses. This study involved women who survived breast cancer and therefore, a survival bias may exist. Another limitation is the

inability to determine temporal sequence between the risk factors and the outcome due to the cross-sectional study design; reverse causation may exist since the obesity markers were measured after cancer diagnosis. Although the components of MetS and CRP were measured by trained professionals, they are based on a single assessment. This study included a modest sample size of women with breast cancer, the number was too small to generate an adequate distribution in the categories of MetS and CRP.

Despite these limitations, the results are robust given that we controlled for several potential confounders, beyond the demographic factors, that may influence the association between MetS, CRP and breast cancer risk. In addition, this study included data from a large survey (NHANES) with a nationally representative sample. The study also included a modest sized sample of women with breast cancer and a large control group. Lastly, the exposure variables, components of MetS, including waist circumference, triglycerides, HDL-cholesterol, blood glucose and blood pressure were objectively measured, therefore removing recall bias.

The findings of this nationally representative sample suggest that MetS and high levels of CRP are prevalent among breast cancer survivors but no association was established with being a cancer survivor compared to women with no breast cancer diagnosis. Longitudinal studies should be conducted to assess the association of Mets and CRP among both early stage and late stage breast cancer survivors. It is possible that the association of Mets and CRP with breast cancer may vary by the years of survival.

Table 2.1 Weighted Demographic and Health Related Characteristics of Breast Cancer Survivors and those without Breast cancer			
	Breast Cancer Survivors N=172	**No Breast Cancer** N=2000	
	Mean (SD)	**Mean (SD)**	**p-value**
Age	66.0 (8.3)	61.2 (8.6)	**<.0001**
Age at menarche	12.7 (1.7)	12.8 (1.7)	0.24
Age at last menstrual period	46.9 (7.5)	46.4 (7.6)	0.39
Blood pressure	128.6 (19.6)	131.3 (21.3)	0.74
Fasting blood glucose	106.4 (28.6)	110.3 (40.4)	0.09
HDL-Cholesterol	59.8 (17.5)	61.1 (16.9)	0.38
Triglycerides	117.7 (77.3)	131.3 (90.4)	0.06
Waist Circumference	98.0 (15.1)	95.9 (14.3)	0.13
C-reactive protein	0.51 (1.8)	0.47 (0.8)	0.004
Body Mass Index (BMI)	29.2 (7.4)	28.5 (6.5)	0.28
	n (%)	**n (%)**	X^2 [DF] *p*-value
Education			
Less than high school	44 (17.7)	516 (15.3)	3.40 [2] 0.18
High school graduate	37 (17.2)	550 (30.1)	
College education	91 (65.1)	934 (54.6)	
Race			
Non-Hispanic White	91 (88.8)	1064 (79.0)	11.95 [2] 0.001
Non-Hispanic Black	22 (6.6)	403 (9.6)	
Others	18 (4.6)	533 (11.4)	
Marital Status			
Married/Have partner	100 (65.8)	1094 (62.7)	0.76 [1] 0.38
Not married	72 (34.2)	906 (37.3)	
Smoked at least 100 cigarettes in life			
Never	96 (58.6)	1171 (57.0)	11.95 [2] 0.003
Past Smoker	57 (29.7)	509 (27.2)	
Current Smoker	19 (11.8)	319 (15.8)	
Had at least 12 drinks/year			
Yes	101 (66.1)	1065 (64.1)	1.61 [1] 0.21
No	59 (33.9)	772 (35.9)	
Use of Hormones			
Yes	64 (42.4)	756 (45.0)	0.08 [1] 0.78
No	95 (57.6)	1071 (55.0)	
Metabolic Syndrome			
Yes	52 (42.6)	690 (44.2)	0.11 [1] 0.74
No	70 (57.4)	871 (55.8)	

Table 2.2 Odds Ratios (OR) with 95% Confidence Intervals (CI) for Breast Cancer according to Components of Metabolic Syndrome in the National Health and Nutrition Examination Survey, 1988-2006

	No. of Cases n=172	OR (95% CI)[a]	OR (95% CI)[b]
Waist Circumference			
Low risk (<88 cm)	41	Reference	Reference
High risk (≥88 cm)	121	1.01 (0.64-1.61)	1.29 (0.82-2.04)
Systolic Blood Pressure			
Low risk (<130 mm Hg)	80	Reference	Reference
High risk (≥130 mm Hg)	77	0.62 (0.42-0.91)	0.65 (0.43-1.01)
Triglycerides			
Low risk (<200 mg/dl)	124	Reference	Reference
High risk (≥ 200 mg/dl)	28	0.61 (0.37-1.02)	0.72 (0.37-1.46)
HDL-cholesterol			
Low risk (≥50 mg/dl)	103	Reference	Reference
High risk (<50 mg/dl)	50	1.01 (0.65-1.57)	1.19 (0.74-1.91)
Blood Glucose			
Low risk (<100 mg/dl)	75	Reference	Reference
High risk (≥100 mg/dl)	78	1.03 (0.69-1.55)	0.89 (0.58-1.36)

[a]Adjusted for age (continuous) and race/ethnicity. [b] Adjusted for age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, and Others), education (less than high school education, high school graduate and college education), marital status (married or living with partner Yes/No), age at menarche (continuous), age at menopause (continuous), smoking (never, current and past), alcohol intake (number of drinks/year) and hormone use (Yes/No).

Table 2.3 Odds Ratios (OR) with 95% Confidence Intervals (CI) for Breast Cancer according to Metabolic Syndrome and C-Reactive Protein in the National Health and Nutrition Examination Survey

	No. of Cases n=172	OR (95% CI)[a]	OR (95% CI)[b]
C-Reactive protein			
Low risk (<1.0 mg/dl)	143	Reference	Reference
High risk (≥ 1.0 mg/dl)	29	1.01 (0.46-2.21)	1.04 (0.45-2.42)
Presence of metabolic syndrome			
No	100	Reference	Reference
Yes	72	0.79 (0.47-1.33)	0.92 (0.53-1.60)
No. of abnormal metabolic syndrome components			
0-2	100	Reference	Reference
3	52	1.03 (0.62-1.72)	1.09 (0.65-1.84)
4 and 5	20	0.59 (0.26-0.98)	0.57 (0.29-1.12)

[a]Adjusted for age (continuous) and race/ethnicity. [b] Adjusted for age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, and Others), education (less than high school education, high school graduate and college education), marital status (married or living with partner Yes/No), age at menarche (continuous), age at menopause (continuous), smoking (never, current and past), alcohol intake (number of drinks/year) and hormone use (Yes/No).

Table 2.4 Odds Ratios (OR) with 95% Confidence Intervals (CI) of Joint association for Metabolic Syndrome and C-Reactive Protein in relation to Breast Cancer status

	No. of Cases n=172	OR (95% CI)[a]	OR (95% CI)[b]
Mets and CRP risk			
No Mets + No elevated CRP	60	Reference	Reference
No Mets + elevated CRP	10	0.69 (0.26-1.84)	0.69 (0.24-2.02)
Mets + No elevated CRP	45	0.77 (0.47-1.27)	0.85 (0.51-1.42)
Mets + Elevated CRP	7	0.89 (0.28-2.83)	0.92 (0.29-2.96)

[a]Adjusted for age (continuous) and race/ethnicity. [b] Adjusted for age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, and Others), education (less than high school education, high school graduate and college education), marital status (married or living with partner Yes/No), age at menarche (continuous), age at menopause (continuous), smoking (never, current and past), alcohol intake (number of drinks/year) and hormone use (Yes/No).

CHAPTER 3: METABOLIC SYNDROME AND CANCER MORTALITY IN WOMEN

Abstract

Objective: Metabolic syndrome (MetS) is an important prognostic factor for the occurrence of cancer. However, little is known about the association of MetS and cancer mortality in women. The purpose of this study was to evaluate whether MetS and its components are associated with risk of obesity-related cancer mortality. We also sought to evaluate if the association of MetS and cancer mortality differed by levels of C-reactive protein (CRP).

Methods: A total of 140 deaths from obesity-related cancers (breast, colorectal and endometrial) linked through the National Death Index, were identified from 10,103 eligible subjects aged ≥18 years. The exposure variables were MetS and CRP. Cox proportional hazards regression, adjusted for confounders, was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for cancer mortality in relation to MetS, the components of MetS, and CRP.

Results: Overall, MetS was associated with increased risk of mortality from obesity-related cancers. The mortality HR from obesity-related cancer was 2.33 (95% CI: 1.02-5.33) for women with the most severe MetS (all 5 components abnormal) compared to those without MetS. MetS was not associated with site-specific (breast and colorectal) cancer mortality. All components of MetS, except dyslipidemia, were associated with increased risk of mortality for obesity-related cancers and breast cancer. There was a greater than two-fold increased risk for mortality from obesity-related cancers for women with enlarged waist

circumference [HR=2.23, 1.10-4.42, quartile (Q) 4 vs. Q1,], and high systolic blood pressure [HR=2.69, 1.08-6.71, Q4 vs. Q1, *p*-trend=0.0085] and blood glucose [HR=2.5, 1.20-5.32, Q2 vs. Q1]. Women with CRP ≥ 1.0 mg/dl compared to those with CRP <1.0 mg/dl had an increased risk of mortality from obesity-related cancers [HR=2.64, 1.53-4.66] as well as breast and colorectal cancer mortality. When joint MetS and CRP association was assessed, women with low CRP (<1.0mg/dl) levels and with 5 abnormal components of MetS had a significantly higher risk of mortality from obesity related cancers compared to those without MetS (HR=3.47; 95% CI: 1.34-8.98).

Conclusion: C-reactive protein and metabolic syndrome are associated with obesity-related cancer mortality in women.

Key words: Obesity, Metabolic syndrome, C - reactive protein, cancer mortality, breast cancer, colorectal cancer, cohort study, and epidemiology

Introduction

Breast, colorectal and endometrial cancers are three of the 5 most common cancers among women in the US ranking first, third and fourth respectively (103). In 2015 it was estimated that among women, these would account for 810,170 new cancer cases and 277,280 cancer deaths (103). These three cancers account for 44% of all new cancer cases and 28% of all cancer deaths among women in the U.S. (103). One factor shown to be related to the development of breast (104-106), colorectal (49, 107) and endometrial (108) cancers is obesity.

Obesity has reached epidemic proportions in the developed countries (16, 109). In the U.S., more than one third (37%) of adult women are obese and 30% overweight (110). It is estimated that if the current trends continue 50% of women in the US will be obese by the year 2020 and 58% by 2030 (111). Obesity is the major determinant of MetS (1, 31) which is a growing problem in Western populations, with a prevalence of approximately 25% in the U.S.(27, 28). According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), MetS for women is defined as a cluster of at least three or more of the following five factors: high-density lipoprotein (HDL) cholesterol (<50 mg/dl), triglycerides (≥ 50 mg/dl), systolic blood pressure (≥ 130 mm Hg), blood glucose (≥100 mg/d) and waist circumference (≥ 88 cm) (29, 31). MetS and CRP have been shown to be related (112) and CRP has previously been suggested as a component of the MetS (73).

The prognostic use of Mets (36, 113, 114) and CRP (115) has been demonstrated in breast, colorectal and endometrial cancer. However, no studies to our knowledge have assessed both MetS and CRP levels and their association with risk of cancer mortality. We therefore sought to evaluate the possible interrelationships between MetS, CRP and obesity-related cancer mortality (breast, colorectal and endometrial) among participants in the Third National Health and Nutrition Examination Survey (NHANES III). Additionally, we sought to find out if CRP modified the association of the MetS with obesity-related cancer mortality.

Materials and Methods

Sample Design

This study is based on data collected from the NHANES III (1988-1994). NHANES III was conducted by the U.S. National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The survey design and methodology of the NHANES III have previously been described in detail elsewhere (77). In brief, NHANES III uses a stratified, multistage probability design. Low income individuals, older persons, African Americans and Mexican Americans were oversampled to provide adequate numbers of these groups in the study. This increases the reliability and precision of estimates for these population subgroups. Using sampling and weighting, the NHANES estimates are considered generalizable to the US population. The NCHS Institutional Review Board approved the survey protocols and informed consent was obtained from all subjects. Since this study involved secondary data analysis of publicly available data and the data were de-identified, this study was determined by the Indiana University IRB as exempt from review.

Study population

This study focused on 10,103 women aged 18 years or older who participated in NHANES III and were followed up. A total of 322 pregnant women were excluded because of increased waist circumference and potential metabolic changes during pregnancy. Of the 9,781 remaining subjects, 140 deaths from obesity-related cancers (including 80 breast, 46 colorectal and 14 endometrial)

were identified during the follow-up period of 133,032 person-years. The follow-up period for each of the subjects was calculated as the time from the date of health examination to the occurrence of cancer death or the censor date (December 31, 2006), whichever occurred first.

Data Collection

Mortality data for each of the participants was ascertained by probabilistic match between NHANES III database and the death certificate records of the U.S. National Death Index (77). Obesity-related cancer mortality included deaths from endometrial, breast and colorectal cancer mortality as defined by the 9th revision of the International Classification of Diseases (ICD). Endometrial cancer mortality refers to cancers coded as mortality occurring from malignant neoplasms of corpus uteri and uterus (ICD-9-CM Diagnosis Code 180). The ICD codes for breast and colorectal cancer were ICD-9-CM 174 and ICD-9-CM 153 respectively.

The NHANES III database included the results of standardized household interviews followed by an extensive physical and health examinations were conducted at a mobile examination center. During the home interview, demographic, socioeconomic, and anthropometric characteristics, medical conditions, and medications used were collected. The NHANES III included components of MetS: blood pressure, blood glucose, waist circumference, triglycerides, and HDL-cholesterol, which were measured during the physical examination. Systolic blood pressure (mmHg) was measured using a mercury sphygmomanometer while subjects were in a seated position. Three

measurements were taken and then averaged for each subject to minimize measurement error (78). Fasting blood samples were drawn by a trained phlebotomist. Serum concentrations of HDL-cholesterol and triglycerides were measured enzymatically with Hitachi 704 Analyzer, while serum levels of glucose was determined using the glucose hexokinase method with Hitachi 737 Analyzer (78). Waist circumference was determined at the iliac crest after a normal exhalation of breath (78). High sensitivity CRP concentration was quantified using latex-enhanced nephelometry, and reported in mg/dl to the nearest hundredth (0.01) (78).

Statistical Analysis

Descriptive statistics were calculated to show the characteristics of study participants by severity of MetS. Pearson chi-square tests and analysis of variance were performed to compare the distributions of covariates and exposures of interest (components of MetS and CRP). Cox proportional hazards regression was used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for obesity-related cancer mortality in relation to each of individual MetS components and the composite score. Site-specific (breast and colorectal) HR were also assessed; there were too few endometrial cancer deaths to perform a specific analysis for that site. For the individual components of MetS, the HRs and 95% CIs were calculated with subjects in the lowest quartile used as the reference group. Tests for linear trend across quartiles were performed by including ordinal variables in the models using the median value of each quartile. A composite score of MetS was created; for each individual component, a score

of 0 was assigned if the level of each component was within normal range and a score of 1 was assigned if the component was abnormal. A score of 0 was assigned for waist circumference <88 cm, systolic blood pressure <130 mg/dl, blood glucose <100 mg/dl, triglycerides <150mg/dl and HDL-cholesterol >50mg/dl. The composite score ranged 0-5, with 0 indicating no abnormal MetS components and 1 to 5 representing the presence of 1 to 5 abnormal components, respectively. Based on the diagnostic criteria of MetS, subjects with a composite score of 3 or more were classified as having metabolic disorder.

The potential confounders were largely based on their relevance to MetS and cancer risk (28). The variables were adjusted as confounders in the regression models if they altered parameter estimates for the primary exposure variables of interest by 10% or more or had a *p*-value (<0.25) for their regression coefficients (116). The multivariable models were adjusted for age (years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), education (less than high school, high school, college and graduate education), cigarette smoking (never, former, and current), alcohol intake (yes/no), and use of insulin (or diabetes), hypertension, and cholesterol-lowering medications (yes or no for each of the medications).

To assess the effect of CRP on the association of MetS and obesity-related cancers mortality, CRP, MetS and the interaction term were included in the multivariable Cox proportional hazard regression model. The effect of CRP on the association of MetS and specific colorectal cancer mortality was not tested because of the small number of colorectal cancer deaths and the multiple levels

of severity of the MetS. A weight variable was included in all analytical procedures to account for complex survey design, survey non-response, and post-stratification (117). *P*-values of <0.05 were considered statistically significant and all statistical analyses were conducted using SAS (version 9.3).

Results

A total of 2,447 (31.3%) women respondents met the NCEP criteria for MetS. The distributions of demographic factors and values for the components MetS of those with and those without the syndrome in the study population are shown in Table 3.1. Women with all 5 abnormal components were more often non-Hispanic white and were older, with a mean age 65.5 (±12). Additionally, women with all 5 components had lower education levels and higher smoking rates compared to those without MetS. More of the women without MetS had a college education or greater compared to women with all 5 components of MetS (43% vs. 22%).

Results for the association of individual components of MetS with risk of obesity-related cancer mortality in women and sub-site cancers are presented in Table 3.2. All components of MetS except triglycerides and HDL-cholesterol were associated with total and breast cancer mortality. Women with waist circumferences greater than 102.2 cm (Quartile 4) had increased hazard for obesity-related cancers mortality and breast cancer mortality which had a significant p-trend (*p*-trend=0.009) when compared to those with less than 82 cm (Quartile 1). Additionally, having an increased systolic blood pressure (≥137 mg/dl) or a blood glucose of 86 to 92 mg/dl was associated with greater than two-fold increased hazard for both total and breast cancer mortality when compared to those in the lowest quartile. An elevated CRP (>1.0 mg/dl) was associated with increased risk of obesity-related cancers mortality as well as site-specific breast and colorectal cancer mortality.

Table 3.3 shows the hazard ratios of obesity-related cancer mortality in relation to MetS and severity of MetS. In adjusted models MetS was not associated with obesity-related cancer, breast or colorectal cancer mortality. However, when mortality was assessed for each of the 3 high risk levels (having 3, 4 or 5 components), women with all 5 abnormal components had increased hazard for obesity-related cancer mortality (HR=2.33; 95% CI: 1.02-5.33) when compared to women with no MetS. Of note, the risk of breast cancer mortality increased with an increasing number of abnormal MetS components, although this trend was not statistically significant. Women with the most severe MetS (all 5 components abnormal) had a non-significant three fold and two fold increased hazard for breast and colorectal cancer mortality respectively compared to women with no MetS.

The second research question explored the relationship of MetS and cancer mortality by CRP levels. The *a priori* specified interaction of MetS and CRP was significant (*p*-value=0.02) and the results indicate that the association of MetS and obesity-related cancers was restricted to women with a CRP of <1.00 mg/dl. As shown in Table 3.4, women with a CRP of <1.00 mg/dl and with 5 abnormal components had a three-fold increased hazard for obesity-related cancer mortality (HR=3.47; 95% CI: 1.34-8.98) when compared to women with no MetS. In contrast, the hazard for obesity-related cancer mortality among women with a CRP of ≥1.00 mg/dl and with 5 abnormal components was clearly non-significant with a 95% CI that markedly spanned both sides of the null value of 1.0 (0.13-2.95). The MetS and CRP interaction with breast cancer mortality

was not significant (*p*-value=0.0533); women with a CRP <1.00 mg/dl and 3 or 5 abnormal components had a non-significant increased hazard for breast cancer mortality.

Discussion

This study examining MetS and CRP suggests that the severity of MetS is associated with an increased risk of obesity-related cancer mortality. This association was stronger among women with low levels of CRP. All individual components of MetS, except triglycerides and HDL-cholesterol, were significantly associated with risk of mortality from obesity-related cancer and breast cancer. Though not significant, the risk for breast cancer mortality increased with an increasing number of abnormal MetS components. Having a high CRP level was significantly associated with increased risk for obesity-related cancers, breast and colorectal cancer mortality.

Few studies have examined MetS or the individual components in relation to breast (118, 119) and colorectal (120, 121) cancer mortality. Lee et.al assessed total (all sites) cancer mortality in women and similar to our study they did not find an association with MetS and risk of cancer mortality when compared to women without MetS (122). However, while our study found significant associations with individual components of Mets (waist circumference, blood pressure, and blood glucose) and risk of obesity-related cancer mortality, Lee et al. only found blood pressure to be significantly associated with total cancer mortality. Additionally, elevated blood pressure in women has been associated with total cancer mortality in a previous study (123). While the two studies assessed total cancer mortality in women, our study focused on only mortality from cancers that have strongly been linked to obesity; thus, this in addition to our sample size, may contribute to the conflicting results.

In our study, CRP was associated with increased risk of obesity-related cancer mortality, breast cancer and colorectal cancer mortality in women. To our knowledge, very few studies have examined the association of CRP and obesity related cancer mortality. In one study, total cancer mortality in women was not associated with CRP [HR=1.24; 95% CI: 0.75-2.06] (124). However, site-specific assessments have shown that women with an elevated CRP were found to have a greater risk of colorectal cancer death when compared to those with lower levels (125, 126).

The effect of CRP on the association of MetS and cancer mortality has not been explored previously. In our study, CRP is correlated with all the components of the metabolic syndrome (data not shown) and the strongest correlation observed with CRP and waist circumference (r=0.25, p <.0001). In a population based study, positive correlations were reported for all components of the MetS, except with HDL-cholesterol which showed an inverse correlation (112). Our study showed that the association of MetS and obesity-related cancer mortality was stronger for women with a low-CRP level. However, no clear explanation exists on this effect, other than CRP has been shown to be an independent prognostic marker for other chronic diseases (73). CRP levels have also been previously associated with cancer risk (127). Perhaps the synergistic effect seen in our study indicates that CRP may be an important prognostic factor for obesity-related cancers, in addition to the MetS.

Breast Cancer Mortality. Several studies have shown that obesity is associated with increased risk of breast cancer mortality (128-131). However, to

our knowledge there are limited studies that have assessed MetS and risk of breast cancer mortality (118, 119). Previous studies have demonstrated that women with MetS had an increased risk of breast cancer mortality compared to those who did not (118, 132). Our study found an increased but not significant association of MetS with risk of breast cancer mortality. This non-significant association may be attributed to the small number of cases of breast cancer mortality in our study.

The components of MetS have also been associated with breast cancer mortality but the results are inconsistent. Our findings that elevated blood pressure and blood glucose levels increase breast cancer mortality are supported by two other cohort studies (118, 119) but another study found no association (132). This study and others (118, 119, 132) did not show an association of triglycerides and HDL-cholesterol with breast cancer mortality. There are different criteria for characterizing MetS, while our study used waist circumference as a measure of central obesity other studies used BMI or weight as a measure of central obesity (118, 119, 132). Regardless of the measure, BMI or waist circumference, the results are consistent that central obesity is associated with increased risk of breast cancer mortality.

Colorectal Cancer Mortality. Several studies have assessed obesity and colorectal cancer mortality (133, 134). To the best of our knowledge no studies have assessed MetS and colorectal cancer mortality. Although we conducted data analysis on the association of MetS with colorectal cancer mortality in women, these results should be interpreted with caution since only a small

number (n=46) of colorectal deaths were recorded. However, even with a small sample, women with elevated blood pressures had a non-significant but increased cancer mortality compared to those with lower blood pressure values.

Endometrial Cancer Mortality. We did not conduct site-specific hazard statistics for endometrial cancer because of the small number of deaths. However, it is important to note that obesity is one of the strongest risk factors for endometrial cancer (135). Furthermore, the components of the MetS have independently been associated with risk for endometrial cancer (114, 136). In a SEER–Medicare linked case control study, the risk estimates were: overweight/obesity, fasting glucose, high blood pressure, and high triglycerides (136). However, low HDL-cholesterol has not been associated with risk of endometrial cancer (114, 136).

There are some potential biological mechanisms by which MetS modulates cancer risk. The link between obesity and cancer is believed to be related to endogenous estrogen, insulin resistance and inflammation (9, 10, 38). Visceral obesity has been shown to be associated with insulin resistance and elevated insulin-like growth factor 1 (IGF-1) (32, 137). Insulin resistance, a component of the MetS, is the best established pathway linking obesity and colorectal cancer (38). Adipose tissue is an important source of estrogen (94) and estrogen induces proliferation of endometrial and breast (post-menopausal) cancer cells (138, 139). Considering that insulin, IGF-1, and estrogen have been identified as risk factors for obesity-related cancers (breast, colorectal and endometrial), perhaps it is plausible that obesity promotes cancer cell

proliferation at least in part through obesity-initiated MetS. Inflammatory responses are characterized by an increase of cytokines and markers of active inflammation (CRP and fibrinogen). The acute-phase CRP is an inflammatory cell compound that has been associated with diabetes mellitus (140). There is growing evidence that CRP is associated with risk of cancer, especially obesity-related cancers (141-143).

A key strength in our study is that the data were based on a national representative sample of the U.S. population. The study included a large number of women therefore allowing us to test and adjust for potential confounders appropriately for the associations of interest. Recall bias was minimized in the study; all five anthropometric, physiological, and biochemical components of MetS were objectively measured with validated assessment tools or experimental methods. More importantly, MetS as a whole, its individual components, and their combinations were evaluated in relation to the risk of obesity-related and breast cancer mortality in our study. Unlike previous studies, our study focused primarily on cancers that have been associated with obesity. There is strong evidence that breast, colorectal and endometrial cancers are associated with obesity.

Some limitations exist in the present study. The components of MetS were measured only once, and therefore the effect of changes in these risk factors over time on obesity-related cancer mortality could not be evaluated. While the study has a large number of women overall, the smaller number of deaths from colorectal and endometrial cancers limits the ability to compare severity levels of

MetS with confidence. CRP, MetS and its components in relation to endometrial cancer were not examined due to small sample size and low statistical power. However, we had 96% and 91% statistical power to assess the association of Mets with obesity-related cancers and breast cancer mortality, respectively. As in other observational studies, it is possible that residual confounding due to unmeasured confounders might have somewhat distorted the results obtained from the present study.

In summary, severe MetS, the components of MetS and CRP appear to be associated with mortality of obesity-related cancers in women. The findings of the present study offer novel evidence for the potential role of MetS, CRP and their interaction in carcinogenesis and mechanistic data for the associations between obesity and cancer risk. If the results of this study are confirmed in other observational studies, especially prospective cohort studies, the importance of maintaining healthy levels of the components of the MetS and CRP would be accentuated. This would perhaps result in a reduction in cancer mortality in women.

Table 3.1 Baseline characteristics of participants by the number of abnormal metabolic syndrome components in the Third National Health and Nutrition Examination Survey, 1988-1994

		No. of abnormal metabolic syndrome components			
	0-2 (n=5,367)	3 (n=1,308)	4 (n=803)	5 (n=336)	
	Mean (SD)				F value, p-value
Age (year)	41.68 (18.3)	53.62 (18.1)	61.06 (15.3)	65.47 (12.4)	511.0, <.0001
Waist circumference (cm)	85.79 (13.5)	100.16 (12.1)	103.76 (13.3)	105.21 (10.9)	870.2, <.0001
Serum triglycerides (mg/dl)	98.90 (51.7)	171.13 (102.7)	220.00 (112.7)	285.99 (149.4)	1254.4, <.0001
HDL-cholesterol (mg/dl)	58.22 (15.2)	48.82 (13.8)	44.36 (11.5)	39.67 (6.9)	440.7, <.0001
Systolic blood pressure (mmHg)	116.67 (17.4)	132.93 (21.6)	140.43 (20.0)	149.22 (15.3)	806.0, <.0001
Serum glucose (mg/dl)	89.19 (17.9)	108.22 (46.2)	126.17 (59.5)	157.33 (73.0)	673.8, <.0001
C-Reactive Protein (mg/DL)	0.43 (0.72)	0.63 (0.8)	0.77 (1.3)	0.76 (0.9)	61.1, <.0001
		N (%)			**X^2 [DF], p-value**
Race					
Non-Hispanic White	2200 (75.55)	544 (75.00)	368 (75.16)	180 (83.31)	17.66 [9], 0.07
Non-Hispanic Black	1601 (11.57)	347 (12.04)	178 (11.04)	53 (7.86)	
Hispanic	1318 (4.52)	362 (6.08)	226 (5.71)	95 (4.52)	
Other race	248 (8.36)	55 (6.89)	31 (8.09)	8 (4.31)	
Education					
Less than High school	893 (8.14)	351 (16.39)	275 (18.23)	127 (17.42)	262.96 [9], <.0001
High school education	2736 (48.47)	675 (54.78)	392 (60.17)	157 (60.29)	
College education	1423 (35.20)	229 (23.70)	113 (19.37)	43 (18.28)	
Graduate education	287 (8.19)	48 (5.13)	20 (2.23)	9 (4.00)	
Cigarette Smoking					
Never	3340 (55.64)	765 (49.29)	509 (56.69)	220 (59.20)	92.85 [6], <.0001
Former	1215 (26.36)	283 (27.86)	124 (16.20)	41 (11.61)	
Current	812 (18.00)	260 (22.85)	170 (27.10)	75 (29.19)	
Alcohol Intake					
Yes	2329 (52.62)	388 (37.71)	187 (27.03)	56 (21.64)	269.56 [3], <.0001
No	3038 (47.38)	920 (62.29)	616 (72.97)	280 (78.36)	

Percentages were calculated using sample weights to report estimates that would be representative of the U.S. population.

Table 3.2 Hazard Ratios (HR) with 95% Confidence Intervals (CI) for Cancer Mortality according to Quartiles of Components of Metabolic Syndrome and C-Reactive Protein in the National Health and Nutrition Examination Survey, 1988-2006

	Obesity-Related Cancers Mortality		[b] Breast Cancer Mortality		[b] Colorectal Cancer Mortality	
	No. of Cases n=140	HR (95% CI)[a]	No. of Cases n=80	HR (95% CI)[a]	No. of Cases n=46	HR (95% CI)[b]
Waist Circumference (cm)						
Q1 (<82)	18	Reference	6	Reference	9	Reference
Q2 (82-92.1)	25	1.29 (0.62-2.67)	12	1.28 (0.62-2.66)	11	0.46 (0.17-1.27)
Q3 (92.2-102.1)	19	0.91 (0.40-2.10)	16	0.91 (0.39-2.09)	2	0.15 (0.03-0.70)
Q4 (≥102.2)	41	**2.23 (1.10-4.52)**	25	**2.24 (1.11-4.55)**	11	0.79 (0.30-2.11)
p-trend		*0.20*		***.001***		*0.12*
Systolic Blood Pressure						
Q1 (<111)	18	Reference	14	Reference		
Q2 (112-121)	10	0.83 (0.31-2.22)	8	0.83 (0.31-2.22)	13	Reference (<137 mmHg)
Q3 (122-136)	25	2.03 (0.88-4.72)	14	2.03 (0.87-4.71)		
Q4 (≥137)	56	**2.69 (1.08-6.71)**	25	**2.69 (1.08-6.72)**	24	2.08 (0.87-4.97)
p-trend		***0.009***		*0.41*		*0.007*
Triglycerides (mg/dl)						
Q1 (<78)	18	Reference	10	Reference	6	Reference
Q2 (79-102)	27	1.74 (0.81-3.75)	17	1.74 (0.48-1.97)	7	2.53 (0.58-10.95)
Q3 (113-169)	32	1.45 (0.66-3.18)	18	1.44 (0.66-3.17)	10	1.94 (0.45-8.31)
Q4 (≥170)	26	1.21 (0.52-2.83)	14	1.20 (0.51-2.81)	11	1.73 (0.38-7.86)
p-trend		*0.27*		*.37*		*0.93*

	Obesity-Related Cancers Mortality		[b] Breast Cancer Mortality		[b] Colorectal Cancer Mortality	
HDL-cholesterol (mg/dl)						
Q1 (<40)	19	Reference	12	Reference	6	Reference
Q2 (41-48)	21	0.90 (0.43-1.88)	15	0.89 (0.35-2.26)	6	1.08 (0.30-3.97)
Q3 (49-59)	23	0.49 (0.22-1.08)	14	0.39 (0.14-1.13)	5	0.39 (0.08-1.81)
Q4 (≥60)	40	1.00 (0.51-1.97)	18	0.73 (0.30-1.81)	17	1.42 (0.45-4.47)
p-trend		*0.67*		*0.82*		*0.34*
Blood Glucose (mg/dl)						
Q1 (<85)	14	Reference	8	Reference	6	Reference
Q2 (86-92)	24	**2.53 (1.20-5.32)**	15	**2.53 (1.20-5.32)**	6	2.31 (0.65-8.21)
Q3 (93-101)	24	1.04 (0.43-2.52)	13	1.04 (0.43-2.52)	8	0.94 (0.22-3.93)
Q4 (≥102)	37	1.83 (0.80-4.19)	20	1.83 (0.80-4.21)	13	1.46 (0.38-5.66)
p-trend		*0.12*		*0.14*		*0.96*
*C-Reactive protein (mg/dl)						
< 1 mg/dl	81	Reference	47	Reference	26	Reference
≥ 1mg/dl	20	**2.64 (1.53-4.66)**	11	**2.53 (1.15-5.58)**	7	**2.93 (1.28-6.71)**

[a] Adjusted for age (years), race (non-Hispanic white, non-Hispanic black, Mexican American, and other race), education (no education, less than high school, high school, college and graduate education), cigarette smoking (current, former, and never), alcohol intake (yes or no), and use of insulin or diabetes, hypertension, and cholesterol-lowering medications (yes or no for each of the medications). Because of the number of breast and colorectal cancer deaths, the number of variables in the model was reduced: [b] Models adjusted for age (years), race (non-Hispanic white, non-Hispanic black, Mexican American, and other race) and cigarette smoking (current, former, and never). *The median and 25 percentile for CRP were equal at 0.2 therefore we used the clinical significance cutoff points.

Table 3.3 Hazard Ratios (HR) with 95% Confidence Intervals (CI) for Cancer Mortality by the Components of Metabolic Syndrome

	Obesity-Related Cancers Mortality		Breast Cancer Mortality		Colorectal Cancer Mortality	
	n (%)	HR (95% CI)[a]	n (%) Cases	HR (95% CI)[a]	n (%) Cases	HR (95% CI)[b]
Presence of Metabolic Syndrome						
No	49 (53.26)	Reference	27 (51.92)	Reference	16 (53.33)	Reference
Yes	43 (46.64)	1.19 (0.72-1.98)	25 (48.08)	1.77 (0.87-3.60)	14 (46.67)	0.77 (0.35-1.71)
No. of metabolic syndrome components						
0-2	49 (53.26)	Reference	27 (51.92)	Reference	16 (53.33)	Reference
3	19 (20.65)	1.17 (0.87-3.60)	12 (23.08)	1.68 (0.75-3.77)	5 (16.67)	0.73 (0.26-2.03)
4	12 (13.04)	0.83 (0.36-1.91)	8 (15.36)	1.66 (0.57-4.83)	3 (10.00)	0.23 (0.03-1.55)
5	12 (13.04)	**2.33 (1.02-5.33)**	5 (9.62)	2.85 (0.76-10.67)	6 (20.00)	2.06 (0.72-5.86)

[a] Adjusted for age (years), race (non-Hispanic white, non-Hispanic black, Mexican American, and other race), education (no education, less than high school, high school, college and graduate education), cigarette smoking (current, former, and never), alcohol intake (yes or no), and use of insulin or diabetes, hypertension, and cholesterol-lowering medications (yes or no for each of the medications). [b] Models were adjusted for age (years), race (non-Hispanic white, non-Hispanic black, Mexican American, and other race) and cigarette smoking (current, former, and never).

Table 3.4 Hazard Ratios (HR) with 95% Confidence Intervals (CI) for Cancer Mortality by the Components of Metabolic Syndrome Stratified by C-Reactive Protein

	Obesity-related Cancers Mortality		Breast Cancer Mortality	
	C-Reactive protein <1.00mg/dl	C-Reactive protein ≥1.00mg/dl	C-Reactive protein <1.00mg/dl	C-Reactive protein ≥1.00mg/dl
No. of metabolic syndrome components				
0-2	Reference	Reference	Reference	Reference
3	1.51 (0.78-2.91)	0.30 (0.06-1.37)	2.02 (0.87-4.71)	0.07 (0.00-15.32)
4	0.35 (0.08-.58)	0.98 (0.34-2.83)	0.56 (0.08-3.92)	2.53 (0.56-11.52)
5	**3.47 (1.34-8.98)**	0.62 (0.13-2.95)	2.24 (0.38-13.14)	2.13 (0.29-15.73)

[a] Adjusted for age (years), race (non-Hispanic white, non-Hispanic black, Mexican American, and other race), education (no education, less than high school, high school, college and graduate education), cigarette smoking (current, former, and never), alcohol intake (yes or no), and use of insulin or diabetes, hypertension, and cholesterol-lowering medications (yes or no for each of the medications). [b]Models were adjusted for age (years), race (non-Hispanic white, non-Hispanic black, Mexican American, and other race) and cigarette smoking (current, former, and never). The *p*-values for the interactions were: Obesity-related cancers mortality- MetS*C-Reactive protein, *p*-value=0.0244 and Breast cancer mortality-MetS*C-Reactive protein, *p*-value=0.0533

CONCLUSION

Findings from the three studies provide important insights into the role of obesity, obesity markers on breast and colorectal cancer occurrence and mortality. A positive association of waist circumference and BMI in early adult life (age 21), with risk of advanced colorectal neoplasia was observed. In addition, we also observed that the association of both BMI and waist circumference change increased the risk of AN. Metabolic syndrome (MetS) and C-reactive protein (CRP) are a growing public health problem because they are directly linked to obesity, which is a known risk factor for several chronic diseases including some types of cancer. Findings from this study indicated that the prevalence of MetS among women with breast cancer does not differ significantly from the prevalence among healthy women based on a nationally representative sample in the US. However, MetS and CRP were associated with increased risk of obesity-related cancer mortality among women. This association was stronger among women with low levels (<1 mg/dl) of CRP. All individual components of MetS, except triglycerides and HDL-cholesterol, were significantly associated with risk of mortality from obesity-related cancer and breast cancer.

The findings of this dissertation research are novel because there are limited studies that have examined these associations. BMI change has been explored in relation to colorectal cancer but not in relation to AN, the combination of colorectal cancer (CRC) and advanced precancerous polyps. There are very limited studies that have assessed WC change with any chronic diseases let alone cancer, yet, WC has been shown to be a better measure of visceral

adiposity. Studies focusing on MetS and CRP in relation to cancer remain scarce. The few studies that have examined MetS and CRP with colorectal and cancer have focused on risk prior to diagnosis of the cancers. This dissertation examined MetS and CRP among breast cancer survivors who may be at risk of recurrence as a result of obesity and obesity related markers. Overall, there are very few studies which have examined MetS and CRP in relation to breast and colorectal mortality.

The results of this dissertation research support the link between obesity and increased risk of post-menopausal breast and colorectal cancer (144). Hyperinsulinemia is one of the strongest established biochemical link between obesity and colorectal cancer (38). The link between obesity and breast cancer is believed to be related to endogenous estrogen, insulin resistance and inflammation (9, 10). Adipose tissue is a major source of estrogenic hormones and both aromatase expression and estrogen synthesis are linked to increased risk of breast cancer (94). The inflammation pathway originates in tissues involved in metabolism: adipose tissue, liver and muscle tissues (96). The tissue in response to the stimulus triggers the inflammatory response (93, 96). Inflammatory responses are characterized by an increase of cytokines and markers of active inflammation (CRP and fibrinogen). Persons who are overweight and obese experience low grade chronic inflammation and (96) have increased blood insulin levels (145) .

In conclusion, our results confirm previous findings that early adulthood BMI, waist circumference and their change overtime are independently

associated with increased risk for advanced colorectal neoplasia. MetS and elevated CRP are prevalent among breast cancer survivors and has been associated with increased risk of breast and colorectal cancer mortality. The results highlight the importance of maintaining a healthy BMI throughout adult life for preventing advanced neoplasia as well as both colorectal and breast cancer mortality. Health care providers may use the findings as a prevention strategy for breast and colorectal cancer when counseling their patients, in line with the American Society of Clinical Oncology's prioritization of educating providers and patients on the role of energy balance as a strategy to reduce the impact of obesity on cancer (67).

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145. Powell DR, Suwanichkul A, Cubbage ML, et al. Insulin inhibits transcription of the human gene for insulin-like growth factor-binding protein-1. *The Journal of biological chemistry* 1991;266(28):18868-76.

CURRICULUM VITAE

Wambui Grace Gathirua-Mwangi

EDUCATION

1995-1999 B.Sc., Environmental Health
Moi University, Eldoret, Kenya
Research Project: *An Assessment of Knowledge, Attitude and Practice on Malaria prevention and control among Mothers with children under 5 in Langas, Eldoret, Kenya*

2003-2005 MPH., Behavioral Health Science
Indiana University, IUPUI
Thesis: *"The influence of Gender, Race, Physical Activity and Socioeconomic status on Body Mass Index among US adults"*

2011-2016 Ph.D, Epidemiology and minor in Behavioral Oncology
Indiana University, IUPUI
Dissertation: *Obesity and Obesity-related Markers associated with Breast and Colon Cancer occurrence and Mortality*

PROFESSIONAL APPOINTMENTS

2011- 2016 Research Associate Instructor, Indiana University School of Nursing.

2011- 2016 Associate Instructor/Teaching Assistant, Department of Epidemiology, Fairbanks School of Public Health

2006- 2008 Research Grant Coordinator, Indiana University. Nutrition intervention research grant ($750, 000), Global Livestock collaborative Research Support Program, GLCRSP.

2005 Program Evaluator, Indiana Minority Health Coalition

2004 Research Assistant, Bowen Research Center, IUPUI

2004 Program Coordinator, Adolescent Substance Abuse Prevention Program (ASAP), IUPUI

2003-2005 Data Specialist, Division of Biostatistics, School of Medicine, IUPUI

2002-2003 Consultant, CARITAS International, Training grassroot women

2001-2002	Program Manager, National Health Research and Development Center, NHRDC
2000	Consultant, Wayne State University, “Cultural Lactation Practices and Breast Cancer Risk markers among native African and urban American women”
1999	Consultant, Ministry of Health, Kenya. Malaria needs assessment

PROFESSIONAL ORGANIZATIONS

2012-Present	Delta Omega, Public Health
2014-Present	Member, Society of Epidemiologic Research

HONORS AND AWARDS

2013-2016	R25-Minority Supplement, National Cancer Institute, NIH Continuing Umbrella of Research Experiences (CURE)- PI. Victoria L. Champion, R25 CA117865-07S1
2014-2016	K05 Mentee, National Cancer Institute, K05CA175048.
2013	Mary Margaret Walther Program for Cancer Care Research
2005	Service Learning Scholarship
2004	Adolescent Substance Abuse Prevention Scholarship
2003-2004	International Fellow, American Association of University Women (AAUW)

PEER-REVIEWED PUBLICATIONS

1. **Gathirua-Mwangi**, W. G, Monahan P., Stump T., Rawl S., Skinner, C. S., and Champion V. (2015). Mammography Adherence in African American Women: Results of a randomized controlled trial. *Annals of Behavioral Medicine*. (In press) doi: 10.1007/s12160-015-9733-0
2. **Gathirua-Mwangi**, W.G, Zollinger T.W., Murage M.J., Pradhan K and Champion V.L. (2015). Adult BMI change and Risk of Breast Cancer: NHANES 2005-2010. *Breast Cancer, 22 (6),* 648-656 doi: 10.1007/s12282-015-0638-3
3. Pradhan, K., Mund, J., Case, J., Gupta, S., Liu, Z ., **Gathirua-Mwangi,** W.G., . . Champion, V. L. (2015). Differences in Circulating Endothelial Progenitor Cells among Childhood Cancer Survivors Treated with and without Radiation. *Journal of Hematology & Thrombosis*, 1(1), 4.
4. Champion, V.L., Rawl, S.M., Bourff, S.A., …, **Gathirua-Mwangi.,** W.G., Skinnger, C.S (2014). Randomized Trial of DVD, Telephone, and Usual Care for Increasing Mammography Adherence. *J Health Psychol.* doi: 10.1177/1359105314542817

5. **Gathirua-Mwangi., W.G** and Zhang, J. (2014). Dietary Factors and Risk for Advanced Prostate Cancer. *Eur J Cancer Prev, 23(2), 96-109.* doi: 10.1097/CEJ.0b013e3283647394

Submitted

1. **Gathirua-Mwangi WG,** Monahan P., Murage M and Zhang J. Metabolic Syndrome and Total Cancer Mortality in the Third National Health and Nutrition Examination Survey (Submitted to Cancer Causes and Control)

In preparation

1. **Gathirua-Mwangi** WG, Monahan P, Song Y, Zollinger TW, Champion V and Imperiale T. Adult BMI change, Waist Circumference change and Risk of Advanced Colorectal Neoplasia **(Dissertation paper 1)**
2. **Gathirua-Mwangi et.al**, Song Y, Monahan P, Champion V and Zollinger TW**.** Metabolic Syndrome and C-reactive Protein in Breast Cancer Survivors and Women without Breast Cancer **(Dissertation paper 2)**
3. **Gathirua-Mwangi** WG, Monahan P, Song Y, Champion V and Zollinger TW. Creactive Protein, Metabolic Syndrome and Cancer Mortality in Women: Third National Health and Nutrition Examination Survey (NHANES III) **(Dissertation paper 3)**
4. **Gathirua-Mwangi** WG, Cohee A, Monahan P, and Champion V. Factors driving the effectiveness of a Mammography Adherence Intervention.

PRESENTATIONS

1. **Gathirua-Mwangi**, W. G, Monahan P., Stump T., Rawl S., Skinner, C. S., and Champion V. Increasing Mammography adherence in African-American Women. ***American Society of Preventive Oncology***, Columbus, OH*, March, 2016*. **[Poster]**
2. **Gathirua-Mwangi**, W. G, Terrell W. Zollinger, Mwangi J. Murage, Kamnesh Pradhan and Victoria L. Champion. Adult BMI change and Risk of Breast Cancer: NHANES 2005-2010. Annual meeting for ***Society of Epidemiologic Research***, June 2015 **[Poster]**
3. **Gathirua-Mwangi**, W. G, Monahan P., Stump T., Rawl S., Skinner, C. S., and Champion V. Mammography Adherence in African American Women: Results of a randomized controlled trial. ***Indiana University Simon Cancer Center Cancer Research Day***, Indianapolis, IN*, May, 2015*. **[Poster]**
4. **Gathirua-Mwangi**, W. G, Terrell W. Zollinger, Mwangi J. Murage, Kamnesh Pradhan and Victoria L. Champion. Adult BMI change and Risk of Breast Cancer: NHANES 2005-2010. . ***Indiana University Simon Cancer Center Cancer Research Day***, Indianapolis, IN*, May, 2015*. **[Poster]**

5. Gathirua-Mwangi, WG.**,** Monahan, P., Murage, J and **Zhang, J.** The metabolic syndrome and total cancer mortality. Annual meeting of the ***American Association for Cancer Research*** in San Diego, CA, **April, 2014 [Poster]**
6. **Gathirua-Mwangi, WG,** Monahan, P., Murage, J and Zhang, J. Components of metabolic syndrome and total cancer mortality. ***Indiana University Simon Cancer Center Cancer Research Day,*** Indianapolis, IN, 5/29/2014. Awarded **First place**, Population Science and Epidemiology section (Graduate student) **[Poster]**
8. **Gathirua-Mwangi, WG** and Zhang, J. Dietary factors and Risk of prostate: ***American College of Epidemiology***, September, 2014 **[Poster]**
9. Gathirua-Mwangi, WG**, Joan Henkle**, Folake Odelowo, Jennifer Taylor and Tiffany Robinson. Creating a Health Promotion and Health Prevention Environment in a Faith-Based Food Pantry. ***APHA 134th Annual meeting***, Nov 2006, Boston. **[Round Table]**
10. **Gathirua-Mwangi, WG.,** Murage, JM., and Kinyua, RW. Overcoming barriers to HIV/AIDS Stigma and Discrimination among Women in Kenya: ***APHA 133rd Annual meeting***, Dec. 2005, Philadelphia **[Podium]**

TEACHING ASSISTANT/LECTURE

Term	***Course #***	***Course Title***
FA 2015	E629	Introduction to Genetic Epidemiology [Online Class] Lectured: • Cancer Genetics
SU 2012	P300	This Stress is Killing Me: Stress and Its Effects on You
SP 2012	A316	Environmental Health Science Lectured: • Pestborne Diseases and Public Health • Population Dynamics, Impact and Control
FA 2011	P551	Biostatistics
FA 2011	A316	Environmental Health Science • Pestborne Diseases and Public Health • Population Dynamics, Impact and Control

PROFESSIONAL SERVICE

Ad hoc Reviewer of Manuscripts:

2014-Present *Review Medicine, Nursing Research, Journal of Behavioral Medicine*