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Associations of Metabolic syndrome and C-reactive protein with Mortality from total cancer, obesity-linked cancers and Breast Cancer among Women in NHANES III

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Abstract

Although metabolic syndrome (MetS) is a prognostic factor for cancer occurrence, the association of MetS and cancer mortality remains unclear. The purpose of this study was to evaluate whether MetS, components of MetS and C-reactive protein (CRP) are associated with cancer mortality in women.

A total of 400 cancer deaths, with 140 deaths from obesity-linked-cancers (OLCas), [breast (BCa), colorectal, pancreatic and endometrial], linked through the National Death Index, were identified from 10,104 eligible subjects aged ≥18 years. Cox proportional hazards regression was used to estimate multivariable-adjusted hazard ratios (HR) for cancer mortality.

MetS was associated with increased deaths for total-cancer [HR=1.33, 95% confidence interval (CI) 1.04-1.70] and BCa [HR=2.1, 95% CI, 1.09-4.11]. The risk of total-cancer [HR=1.7, 95% CI, 1.12-2.68], OLCas [HR=2.1, 95% CI, 1.00-4.37] and BCa [HR=3.8, 95% CI, 1.34-10.91] mortality was highest for women with all MetS components abnormal, compared to those without MetS. Linear associations of blood-pressure [HR=2.5, 1.02-6.12, Quartile (Q) 4 vs Q1, *p-trend=0.004*] and blood-glucose [HR=2.2, 1.04-4.60, Q4 vs Q1, *p-trend=0.*04] with total-OLCas mortality were observed. A three-fold increased risk of BCa mortality was observed for women with enlarged waist circumference, ≥100.9cm, [HR=3.5, 1.14-10.51, *p-trend=0.008*] and in those with increased blood glucose, ≥101mg/dL, [HR=3.2, 1.11-9.20, *p-trend=0.03*] compared to those in Q1. None of the components of MetS were associated with total-cancer mortality. CRP was not associated with cancer mortality.

In conclusion, MetS is associated with total-cancer and breast-cancer mortality, with waist circumference, blood pressure and blood glucose as independent predictors of OLCas and BCa mortality.

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Keywords

Metabolic syndrome; C - reactive protein; cancer mortality; obesity-linked cancers; breast cancer; women; cohort study; epidemiology

Introduction

In 2017, it is estimated that 852,630 new cases and 282,500 cancer deaths will occur[1] among women in the U.S. Obesity-linked cancers, breast[2, 3], colorectal[4, 5], pancreatic[6, 7] and endometrial[8] cancers, account for 45% of all new cancer cases and 33% of all cancer deaths among women in the United States.[1] In the U.S., more than one third (37%) of adult women are obese and 30% overweight.[9] It is estimated that 50% of women in the U.S will be obese by the year 2020 and 58% by 2030.[10]

Obesity is the major determinant of metabolic syndrome[11, 12] and approximately 25% of the U.S. population has metabolic syndrome.[13, 14] According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), metabolic syndrome (MetS) for women is defined as a cluster of at least three of the following five factors: high-density lipoprotein (HDL) cholesterol (<50 mg/dL), triglycerides (>150 mg/dL), systolic blood pressure (>130 mm Hg), blood glucose (>100 mg/dL) and waist circumference (>88 cm).[12, 15] The prognostic use of MetS has been demonstrated in obesity linked cancers. However, few studies have examined MetS or the components in relation to total cancer, breast[16, 17] and colon[18, 19] cancer mortality in women. Furthermore, MetS has been shown to be highly correlated with CRP [20], which has previously been suggested as a component of the MetS. [21] While the joint effect of MetS and CRP may offer new insights into the link between obesity and cancer, to our knowledge this has not been assessed. The association between MetS, its individual components and CRP with cancer mortality in women remains unclear.

The purpose of this study was to evaluate the possible interrelationships between metabolic syndrome, C-reactive protein and cancer mortality (total, obesity-linked and breast) among women in the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative population. Since CRP has previously been suggested as a component of the MetS,[21] we also explored the joint effect of MetS and CRP on the risk of cancer mortality. Our findings will provide insights to health care providers about the risk for mortality among those diagnosed with MetS and underscore the need for interventions to treat and prevent MetS.

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.[22] In brief, in the NHANES III, subjects were recruited from the civilian, noninstitutionalized U.S. population using a

stratified and multistage probability sampling strategy. Those who had a low income, were older (≥60 years of age), or were members of minority groups (African or Mexican Americans) were oversampled. 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 were de-identified and publicly accessible.

Study population

This study focused on 10,425 women aged 18 years or older who participated in NHANES III and were followed over 17 years. A total of 322 pregnant women were excluded because of increased waist circumference and potential metabolic changes during pregnancy. Given the objective of the present study, participants who died from a cancer diagnosed at baseline (i.e. date of health examination) were excluded from analysis (n=89). These exclusions led to 10,014 participants in the cohort. A total of 400 cases of cancer deaths were documented from, the 10,014 participants during a follow-up of 132,557 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. The anatomic sites of cancer for the 400 cases included total-obesity-linked cancers (n=118): breast (n=55), colorectal (n=33) pancreas (n=18), and endometrial (n=12). Of the 10,014 participants, 7,770 had data on all five components of metabolic syndrome, including 293 total cancer deaths, 83 total-obesity-linked cancer deaths and 41 breast cancer deaths.

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.[22] Obesity-linked cancer mortality included deaths from endometrial, pancreatic, breast and colorectal cancer mortality as defined by the 10thth revision of the International Classification of Diseases.[23]

Standardized household interviews followed by extensive physical and health examinations were conducted at mobile examination centers (MEC). During the home interview, data on demographic, socioeconomic, anthropometric characteristics, medical conditions, and medications used were collected. The NHANES III included components of metabolic syndrome (i.e. 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.[24] 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 were determined using the glucose hexokinase method with Hitachi 737 Analyzer.[24] Waist circumference was determined at the iliac crest after a normal exhalation of breath.[24] High sensitivity CRP concentration was quantified using latex-enhanced nephelometry, and reported in mg/dL to the nearest hundredth (0.01).[24]

Statistical Analysis

Descriptive statistics showing the characteristics of study participants by severity of metabolic syndrome were performed. The Pearson chi-square tests and ANOVA tests were performed to compare the frequencies and distributions of covariates and exposures of interest (components of MetS and C-reactive protein). Cox proportional hazards regression was used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for total cancer mortality and obesity-linked cancers mortality in relation to each of individual MetS components and the composite score. Site-specific associations of MetS, its individual components and breast cancer were also assessed. There were too few colorectal, pancreatic, and endometrial cancer deaths to conduct site-specific analysis. 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 trends across quartiles were performed by including in the models an ordinal variable with the median value of each quartile. A composite score of the 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. Using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) cutoffs, a score of 0 was assigned for waist circumference <88cm, systolic blood pressure <130mg/dL, blood glucose <100 mg/dL, triglycerides <150mg/dL and HDL-cholesterol >50mg/dL.[12, 15] The composite score therefore ranged from 0 to 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 metabolic syndrome, subjects with the composite score of 2 or less were classified as not having this metabolic disorder.

The potential confounders adjusted for in the model were largely based on their relevance to MetS and cancer risk.[14] 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 had a p-value (<0.25) for their regression coefficients.[25] The multivariable models were adjusted for age (years), race (non-Hispanic White, non-Hispanic Black, and other race), education (less than high school, high school, college/graduate education), physical activity (active, not active), cigarette smoking (never, former, and current), alcohol intake (yes, no), and use of insulin (or diabetes), hypertension controlling medication and cholesterol-lowering medications (yes or no for each of the medications).

To assess the joint effect of CRP on the association of MetS and cancer mortality, we defined four risk levels based on the presence or absence of MetS or CRP cutoff levels, the clinical significance level for CRP was defined as ≥1.00 mg/dL.[26-28] The 4 risk levels were: 1) No MetS and CRP<1.00 mg/dL (reference group); 2) No MetS and CRP ≥1.00 mg/dL; 3) MetS and CRP <1.00 mg/dL and 4) MetS and CRP ≥1.00 mg/dL. *P*-values of <0.05 were considered statistically significant and all statistical analyses were conducted using SAS (version 9.3).

Results

A third of all women in this study had MetS, (30.5%, n= 2,369). A summary of the distributions of demographic factors and components of MetS by severity of MetS in the

study population are shown in Table 1. Women with all 5 abnormal components were most likely to be non-Hispanic white and older, with a mean age 65.4 (±13) when compared to those without MetS (mean age 41.7 (±18). Additionally, women with all 5 components had higher smoking rates (22% vs 15%) and lower education levels compared to those without MetS. A third (32.0%) of women with no MetS had a college education or greater compared to 16% of women with most severe MetS (all 5 components of MetS abnormal). As expected, waist circumference, systolic blood pressure, and serum concentrations of triglycerides, glucose and CRP increased but serum concentrations of HDL-cholesterol decreased, with an increasing number of abnormal metabolic syndrome components.

Results for the association of individual components of MetS with cancer mortality in women are presented in Table 2. All components of MetS except triglycerides and HDL-cholesterol were associated with obesity-linked and breast cancer mortality but not with total cancer mortality. Women with waist circumferences greater than 100.9 cm (Quartile 4) had a three-fold increased hazard for breast cancer mortality (HR=3.5; 95% CI, 1.14-10.51, *p-trend=0.008)* when compared to those with less than 79.1cm (Quartile 1). Additionally, having an increased systolic blood pressure (≥136 mg/dL) was associated with greater than two-fold increased hazard for obesity-linked cancers (HR 2.5, *p-trend=0.004*) when compared to those in the lowest quartile. Increase in blood glucose was associated with an increase in risk of obesity-linked cancers (HR 2.2, *p-trend=0.04*) and breast cancer mortality (HR=3.2, *p-trend=0.03*). An elevated CRP (>1.0 mg/dL) was not associated with risk of total cancer mortality, obesity-linked cancers mortality as well as site-specific breast cancer mortality.

Table 3 shows the hazard ratios of cancer mortality in relation to metabolic syndrome and severity of MetS. Adjusting for age, race/ethnicity, education, physical activity, cigarette smoking status, alcohol intake and medications (insulin, hypertension and cholesterol) having MetS was associated with total cancer mortality (HR=1.3; 95% CI 1.04-1.71) and breast cancer mortality (HR=2.1; 95% CI 1.09-4.11) but not with obesity-linked-cancers mortality (HR=1.1; 95% CI 0.70-1.81). However, when hazard of mortality was assessed for each of the 3 high risk levels of MetS, women with 5 abnormal components had increased hazard for total cancer mortality (HR=1.7; 95% CI 1.12-2.68) and borderline significance of obesity-linked cancers mortality (HR=2.1; 95% C.I. 1.00-4.37) as compared to women with no MetS. Of note, women with the most severe MetS had greater than three-fold increased hazard for breast cancer mortality (HR=3.8; 95% CI 1.34-10.91) compared to those without MetS.

The second research question explored the relationship of cancer mortality and the joint effect of MetS and CRP. As shown in Table 4, women with a CRP of ≥1.00 mg/dL and MetS had an increased risk for total cancer mortality (HR=1.8; 95% C.I. 1.18-2.61) and breast cancer mortality (HR=3.5; 95% C.I. 1.42-8.63) when compared to women with no MetS and CRP <1.00 mg/dL. In contrast, the hazard for obesity-linked cancer mortality among women with a CRP of ≥1.00 mg/dL and MetS was not significant. Moreover, a non-significant increased hazard for total and breast cancer mortality was observed for women with a CRP <1.00mg/dL and MetS compared to with no MetS and CRP <1.00 mg/dL.

Discussion

This study examining metabolic syndrome and C-reactive protein (CRP) suggests that the severity of MetS is associated with an increased risk of total cancer mortality, obesity-linked cancers mortality and breast cancer mortality. All individual components of MetS, except triglycerides and HDL-cholesterol, were significantly associated with risk of mortality from obesity-linked cancers and breast cancer. The risk for total cancer mortality and breast cancer mortality increased with an increasing number of abnormal metabolic syndrome components. CRP was not significantly associated with increased risk for total, obesity-linked cancers, or breast cancer mortality. Assessing the joint effect of MetS and CRP on the risk of cancer mortality yielded similar results as those for MetS and cancer mortality.

Few epidemiologic studies have evaluated the influence of MetS and its components on the mortality of total cancer and site-specific cancers in women. In our study, having the MetS was associated with total cancer mortality in women. However, Lee et al., assessed total (all sites) cancer mortality in women and did not find an association with MetS and risk of cancer mortality when compared to women with no MetS.[29] Regarding the individual components, in our study none of the components were associated with total cancer mortality. This is similar to Lee's study which found no association between cancer mortality and any components except for blood pressure (HR=1.70; 95% CI, 1.07-2.69),[29] a result confirmed in another study.[30] The conflicting results may be in part because the cancers summed up may vary across the studies. Therefore, using total cancer mortality as an outcome may attenuate the true relationship of MetS and cancer mortality in part because it includes lung cancer which has not been linked to MetS[31] and because of the differences in risk factors associated with each cancer site. To address this limitation, we assessed the relationship of MetS with mortality from cancers that have strongly been linked to obesity. Although MetS was not associated with total-obesity-linked cancers mortality, those with all 5 components abnormal were at an increased risk of total-obesity-linked cancers mortality compared to those with no MetS. The most important components that elevated risk of total-obesity-linked cancers were blood pressure and blood glucose. This provides useful information that may have been confounded when risk was assessed using total cancer mortality and underscores the need to assess risk for site-specific cancers.

Several studies have shown that obesity is associated with increased risk of breast cancer mortality.[32-35] However, only a few studies have assessed MetS and risk of breast cancer mortality in women.[16, 17] Previous studies have shown that women with MetS had an increased risk of breast cancer compared to those who did not.[16, 36] This is similar to our study where we revealed that in addition to increased risk, breast cancer mortality increased with an increasing number of metabolic syndrome components, suggesting a synergistic effect of these risk factors. Regarding specific components, we found waist circumference and blood glucose to be the only significant predictors of breast cancer mortality. In previous studies, the components of MetS have also been associated with breast cancer mortality, but the results are inconsistent for some components. We found elevated blood glucose increased breast cancer mortality, these results are supported by two other cohort studies[16, 17] but contradicted in another study.[36] This study and others did not show an association of triglycerides and HDL-cholesterol with breast cancer mortality.[16, 17, 36] While

our study used waist circumference as a measure of central obesity other studies used BMI or weight.[16, 17, 36] Regardless of the measure, BMI or waist circumference, the results are consistent that central obesity is associated with increased risk of breast cancer mortality.[16, 17, 36]

Elevated levels of high sensitivity CRP are associated with all the features of the MetS.[20] Regardless of diverse definitions used for the MetS in different studies, there is an emerging consensus that CRP levels are also associated with the presence of MetS itself as an entity.[21] We are not aware of any studies that have looked at the joint effect of CRP and MetS with cancer mortality. In our study, CRP was not associated with risk of total cancer mortality and this finding is similar to that of other studies.[37, 38] Similarly, women with an elevated CRP were not found to have a greater risk of breast cancer death in our study and in other studies as well.[37, 39] The joint effect of CRP and MetS on cancer mortality has not been explored previously. Our results indicate that assessing MetS together with CRP showed a marked difference in risk estimates from using MetS alone. The HR estimates increased when MetS and CRP were jointly assessed for total cancer mortality (HR=1.8 95% CI 1.18-2.61 vs. HR 1.3; 95% CI 1.04-1.71) and breast cancer mortality (HR=3.5 95% CI 1.42-8.63 vs. HR 2.1 95% CI 1.09-4.11) compared to when MetS were assessed alone. Though not significant, the HR for obesity-related cancer mortality increased as well. CRP was correlated with all the components of MetS in our study and elsewhere.[20] The increased HR estimates indicate that it may be important to assess MetS jointly with CRP, since having MetS and an elevated level of CRP (≥1.00mg/dL) was found to be associated with increased risk of cancer mortality higher than the risk of MetS alone. Further studies are needed to confirm these findings.

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.[40, 41] Visceral obesity has been shown to be associated with insulin resistance and elevated insulin-like growth factor 1 (IGF-1).[42, 43] Adipose tissue is an important source of estrogen[44] and estrogen induces proliferation of endometrial and breast (post-menopausal) cancer cells.[45, 46] Considering that insulin, IGF-1, and estrogen have been identified as risk factors for obesity-linked cancers, perhaps it could be that obesity promotes cancer cell proliferation at least in part through obesity-initiated metabolic syndrome. Inflammatory responses are characterized by an increase of cytokines and markers of active inflammation (C-reactive protein and fibrinogen). The acute-phase C-reactive protein (CRP) is an inflammatory cell compound that has been associated with diabetes mellitus.[47] There is growing evidence that CRP is associated with risk of cancer, especially obesity-linked cancers,[48-50] however, it is not known if CRP by itself is a risk factor, or if it is due to the link between CRP and obesity or MetS.

A key strength in our study is that the data were based on a national representative sample of the U.S. population; therefore, the results can be generalized to the US population. This study included a large number of women which allowed the testing and adjusting of 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 total, obesity-linked and breast cancer mortality in our study. Unlike previous studies which have focused on total cancer mortality, we also assessed the relationship of MetS and CRP with cancers that have been linked to obesity as a risk factor. There is strong evidence that breast, colorectal, pancreatic 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-linked cancer mortality could not be evaluated. While the study includes a large number of women overall, the smaller number of deaths from colorectal, pancreatic, and endometrial cancers limited the ability to assess these site-specific relationships of CRP, MetS and its components. As in other observational studies, it is possible that residual confounding due to unmeasured confounders might have somewhat distorted the results obtained. It was not practical to control for all possible risk factors, such as dietary factors and menopausal status. Due to the sample limitations, including all factors into the multivariate model would result in overfitting. Also, although menopausal status is an important factor in breast cancer, [44] a large number of women did not complete this question at baseline and we do not have follow-up data on their menopausal status, and more so due to the small sample for breast cancer mortality n=55 it is not possible to stratify by menopausal status. We also did not have data on the type of breast cancer, pre or post-menopausal, at diagnosis to determine if breast cancer mortality was from pre or post-menopausal breast cancer. In summary, severe metabolic syndrome and the components of MetS, especially waist circumference, blood glucose and blood pressure appear to be associated with mortality of obesity-linked cancers and breast cancer in women. The findings of the present study offer novel evidence for the potential role of MetS, CRP and the joint effect of MetS and CRP in carcinogenesis and mechanisms for the associations between obesity and cancer risk. If the results of this study are confirmed in other studies, especially prospective cohort studies, the importance of maintaining healthy levels of the components of the MetS will be underscored.

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Abbreviations

MetS	Metabolic syndrome
CRP	C reactive protein
OLCas	Obesity linked Cancers
BCa	Breast cancer
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
HDL	High density lipoprotein
NCHS	National Center for Health Statistics
CDC	Centers for Disease Control and Prevention
MEC	Mobile Examination Center
ANOVA	Analysis of Variance
CI	Confidence Interval

Novelty and Impact

Although metabolic syndrome (MetS) incidence has increased over the years, how this disorder influences cancer mortality in women remains unclear. Overall, MetS and especially women with all 5 components abnormal, was associated with increased risk of cancer mortality and breast cancer mortality. Further, the joint effect of MetS and C-reactive protein yielded similar results. Our study is among the first to reveal these associations, offering new insights on obesity related markers and cancer risk.

Table 1

Baseline characteristics of participants stratified by the number of abnormal metabolic syndrome components in the Third National Health and Nutrition Examination Survey

		No. of abnormal metabolic syndrome components			
	0-2 (n=5,401)	**3 (n=1,296)**	**4 (n=759)**	**5 (n=314)**	
	Mean (SD)				pvalue
Follow-up period (months)	170.30 (36.8)	156.65 (46.4)	145.05 (51.9)	137. 04 (50.8)	<.0001
Age (year)	41.68 (18.2)	54.00 (18.0)	61.05 (15.3)	65.35 (12.6)	<.0001
Waist circumference (cm)	85.88 (13.6)	100.52 (12.2)	103.73 (13.1)	105.44 (10.8)	<.0001
Serum triglycerides (mg/dL)	99.68 (54.0)	172.49 (101.8)	221.02 (112.3)	289.78 (152.6)	<.0001
Serum HDL-cholesterol (mg/dL)	58.13 (15.2)	48.71 (13.7)	44.04 (11.6)	39.16 (6.7)	<.0001
Systolic blood pressure (mmHg)	116.74 (17.5)	133.48 (21.7)	140.43 (20.0)	149.39 (15.4)	<.0001
Serum glucose (mg/dL)	89.36 (18.4)	108.68 (46.6)	126.89 (60.0)	159.42 (74.1)	<.0001
C-Reactive Protein (mg/dL)	0.43 (0.72)	0.63 (0.8)	0.78 (1.3)	0.78 (0.9)	<.0001
		N (%)			**X^2 [df], p-value**
Race					
Non-Hispanic White	2213 (40.97)	543 (41.90)	344 (45.32)	168 (53.50)	49.06 [6], <.0001
Non-Hispanic Black	1607 (29.75)	344 (26.54)	166 (21.87)	52 (16.56)	
Other race	1581 (29.27)	409 (31.56)	249 (32.81)	94 (29.94)	
Education					
Less than High school	1734 (39.27)	584 (45.27)	414 (54.69)	176 (56.05)	268.16 [6], <.0001
High school education	1921 (35.75)	439 (34.03)	216 (28.53)	89 (28.34)	
College/Graduate education	1718 (31.97)	267 (20.70)	127 (16.78)	49 (15.61)	
Cigarette Smoking					
Never	3361 (62.23)	767 (59.18)	482 (63.50)	206 (65.61)	57.56 [6], <.0001
Former	1221 (22.61)	275 (21.22)	117 (15.42)	40 (12.74)	
Current	819 (15.16)	254 (19.60)	160 (21.08)	68 (21.66)	
Alcohol Intake					
Yes	2356 (43.44)	373 (28.78)	177 (23.32)	53 (16.88)	243.49 [3], <.0001
No	3055 (56.56)	923 (71.22)	582 (76.68)	261 (83.12)	

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

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Table 2

Hazard Ratios (HR) with 95% Confidence Intervals (CI) for Cancer Mortality according to Quartiles of the Five individual Components of MetS and CRP in the National Health and Nutrition Examination Survey

	Total Cancers Mortality		**Obesity-linked Cancers Mortality**		***b*** **Breast Cancer Mortality**	
	No. of Cases n=400	**HR (95% CI)*a***	**No. of Cases n=118**	**HR (95% CI)*a***	**No. of Cases n=55**	**HR (95% CI)*b***
Waist Circumference (cm)						
Q1 (≤79.1)	46	Reference	16	Reference	4	Reference
Q2 (79.2-89.6)	69	0.88 (0.60-1.28)	21	0.78 (0.40-1.51)	7	1.31 (0.38-4.52)
Q3 (89.7-100.8)	92	0.98 (0.68-1.41)	14	0.40 (0.19-1.83)	12	1.96 (0.61-6.27)
Q4 (≥100.9)	103	1.13 (0.78-1.62)	38	1.00 (0.53-1.89)	22	**3.46 (1.14-10.51)**
p-trend		*0.2545*		*0.7138*		***0.0049***
Systolic Blood Pressure (mmHg)						
Q1 (≤107)	31	Reference	8	Reference	8	
Q2 (108-118)	45	0.88 (0.55-1.40)	11	0.98 (0.39-2.48)	7	0.69 (0.25-1.93)
Q3 (119-135)	86	0.98 (0.63-1.53)	23	1.36 (0.57-3.24)	10	0.69 (0.24-1.97)
Q4 (≥136)	166	1.32 (0.83-2.09)	53	**2. 50 (1.02-6.12)**	21	1.44 (0.50-4.14)
p-trend		***0.0225***		***0.0034***		*0.1768*
Triglycerides (mg/dL)						
Q1 (≤75)	34	Reference	11	Reference	6	Reference
Q2 (76-107)	74	1.48 (0.98-2.23)	24	1.54 (0.74-3.18)	13	1.84 (0.69-4.90)
Q3 (108-159)	112	**1.76 (1.18-2.61)**	27	1.41 (0.68-2.93)	12	1.46 (0.52-4.09)
Q4 (≥160)	106	1.48 (0.98-2.22)	27	1.29 (0.61-2.74)	12	1.56 (0.55-4.42)

	Total Cancers Mortality		Obesity-linked Cancers Mortality		[b] Breast Cancer Mortality	
	No. of Cases n=400	**HR (95% CI)[a]**	**No. of Cases n=118**	**HR (95% CI)[a]**	**No. of Cases n=55**	**HR (95% CI)[b]**
p-trend		*0.3985*		*0.9929*		*0.7424*
HDL-cholesterol (mg/dL)						
Q1 (≤43)	87	1.31 (0.96-1.78)	25	1.15 (0.65-2.04)	13	1.49 (0.64-3.48)
Q2 (44-52)	88	1.30 (0.96-1.77)	17	0.72 (0.39-1.36)	10	1.01 (0.41-2.51)
Q3 (53-62)	69	0.99 (0.72-1.37)	21	0.97 (0.54-1.73)	10	1.14 (0.47-2.76)
Q4 (≥63)	82	Reference	26	Reference	10	Reference
p-trend		***0.0421***		*0.8831*		*0.4206*
Blood Glucose (mg/dL)						
Q1 (≤84)	50	Reference	10	Reference	5	Reference
Q2 (85-90)	52	0.98 (0.66-1.45)	16	1.56 (0.70-3.46)	6	1.37 (0.42-4.52)
Q3 (91-100)	95	1.06 (0.74-1.51)	24	1.47 (0.69-3.14)	14	2.40 (0.84-6.86)
Q4 (≥101)	124	1.39 (0.98-1.98)	38	**2.18 (1.04-4.60)**	17	**3.19 (1.11-9.20)**
p-trend		***0.0163***		***0.0337***		***0.0176***
[*]C-Reactive protein (mg/dL)						
< 1 mg/dL		Reference		Reference		Reference
≥1mg/dL		1.26 (0.94-1.70)		1.27 (0.73-2.19)		1.53 (0.72-3.26)

[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), physical activity (active, not active), 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 colon 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), physical activity (active, not active), and cigarette smoking (current, former, and never).

[*]The median, mode and 25th percentile of CRP were equal at 0.2mg/dL, therefore we resulted to using the clinical significance cutoff points.

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Table 3

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

	Total Cancer Mortality		Obesity-linked Cancers Mortality		Breast Cancer Mortality	
	n (%)	HR (95% CI)[a]	n (%) Cases	HR (95% CI) [a]	n (%) Cases	HR (95% CI) [b]
Presence of Metabolic Syndrome						
No	147 (50.17)	Reference	44 (53.01)	Reference	19 (46.34)	Reference
Yes	146 (49.83)	**1.33 (1.04-1.71)**	39 (46.99)	1.13 (0.70-1.81)	22 (53.66)	**2.11 (1.09-4.11)**
No. of metabolic syndrome components						
0-2	147 (50.17)	Reference	44 (53.01)	Reference	19 (46.34)	Reference
3	68 (23.21)	1.25 (0.93-1.67)	17 (20.48)	1.03 (0.58-1.84)	11 (26.83)	1.96 (0.91-4.24)
4	50 (17.06)	1.33 (0.94-1.86)	11 (13.25)	0.93 (0.46-1.87)	6 (14.63)	1.76 (0.67-4.63)
5	28 (9.56)	**1.73 (1.12-2.68)**	11 (13.25)	2.09 (1.00-4.37)	5 (12.20)	**3.83 (1.34-10.91)**

[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), physical activity (active, not active), 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), physical activity (active, not active), and cigarette smoking (current, former, and never).

Table 4

Hazard Ratios (HR) with 95% Confidence Intervals (CI) for cancer mortality by joint effect of Metabolic Syndrome and CRP

	n (%)	Total Cancer Mortality	n (%)	Obesity-linked cancers mortality	n (%)	[b]Breast Cancer Mortality
No MetS / CRP < 1.00 mg/dL	135	Reference	41	Reference	18	Reference
No MetS / CRP ≥ 1.00 mg/dL	12	0.95 (0.52-1.71)	3	0.77 (0.24-2.49)	1	0.58 (0.08-4.32)
MetS / CRP < 1.00 mg/dL	113	1.23 (0.94-1.61)	27	0.93 (0.55-1.57)	15	1.68 (0.80-3.50)
MetS / CRP ≥ 1.00 mg/dL	33	**1.76 (1.18-2.61)**	12	1.91 (0.97-3.75)	7	**3.50 (1.42-8.63)**

[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), physical activity (active, not active), 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), physical activity (active, not active) and cigarette smoking (current, former, and never).