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Metabolic syndrome risk components and mortality after triple negative breast cancer diagnosis in postmenopausal women in the Women's Health Initiative (WHI)

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Additional information: A full list of all the investigators who have contributed to Women's Health Initiative science appears at: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.

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Abstract

BACKGROUND: Triple Negative Breast Cancer (TNBC) has high recurrence risk and poor clinical outcomes. Associations between metabolic syndrome (MetS) risk components and mortality in postmenopausal women with TNBC were examined in the Women's Health Initiative (WHI).

METHODS: 544 postmenopausal women were diagnosed with non-metastatic TNBC. Baseline risk components included: high waist circumference (≥88cm), high blood pressure, hypercholesterolemia, and diabetes. Groups were categorized by number of MetS risk components: none, 1–2, and 3–4. Hazard ratios (HR) and 95% confidence intervals (CI) across groups were computed using multivariable adjusted Cox models. Outcomes included breast cancer-specific mortality and breast cancer overall mortality (breast cancer followed by death from any cause). Variables in the multivariable model included age at TNBC diagnosis; race/ethnicity; income; education; clinical/observational trial status; history of oral contraceptive, hormone, and/or statin use; cancer stage; chemotherapy and/or radiation treatment status.

RESULTS: Of 544 participants with TNBC, 29% had no MetS risk components (n=178), 53% had 1–2 components (n=323), and 7% had 3–4 components (n=43). After 8.3 years (median) follow-up from diagnosis, multivariable results showed that women with 3–4 risk components had non-significantly higher risk of breast cancer mortality (HR: 1.94, CI: 0.95–3.97; trend p=0.106) and significantly higher risk of overall mortality (HR: 1.73, CI: 1.03–2.90; trend p=0.027) versus women with 0 components,

CONCLUSION: Postmenopausal women with TNBC and 3–4 MetS risk components have non-significantly higher breast cancer mortality risk and significantly higher overall mortality risk, likely due to negative influences of metabolic risk factors on several causes of death.

Precis:

Postmenopausal women with 3–4 metabolic risk components who were diagnosed with triple negative breast cancer have higher breast cancer-specific and overall mortality rates.

Keywords

Triple negative breast cancer; metabolic syndrome; risk factors; postmenopausal women; Women's Health Initiative

INTRODUCTION

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) amplification. Despite initial high response to chemotherapy, TNBCs are generally more aggressive and are associated with poor prognosis[1]. Common prognostic factors for TNBC include age, tumor size, grade, nodal status, presence of lymphovascular invasion, presence of tumor infiltrating lymphocytes, and response to neoadjuvant therapy. More recently, TNBC molecular heterogeneity and subtyping were shown to be associated with response to neoadjuvant chemotherapy and prognosis[2].

Metabolic syndrome (MetS), defined by the presence of at least 3 of 5 metabolic risk factors (abdominal obesity, high blood pressure, reduced high-density cholesterol [HDL], elevated triglyceride and fasting glucose levels), is associated with an increased risk of cardiovascular disease, diabetes, and other chronic diseases[3]. There is growing evidence that MetS, as well as its individual components such as abdominal obesity, diabetes, and hypertension, were associated with increased incidence of breast cancer[4, 5] and higher breast cancer-specific mortality in some[6–8], but not all studies[9, 10].

Data on the impact of MetS on TNBC incidence and mortality are limited, concerning mainly single components of MetS. A positive association between abdominal obesity and increased incidence of TNBC were seen some studies[11, 12] while the impact of obesity on TNBC-specific mortality remain controversial[13, 14]. We have found limited data associating breast cancer mortality with MetS composite status in postmenopausal women with TNBC. To address this issue, the current study was designed to specifically examine mortality from and after TNBC diagnosis by MetS risk components individually and as composite in postmenopausal women participating in the Women's Health Initiative (WHI).

METHODS

The design of the WHI has been previously described[15]. The WHI included four clinical trials (N=68,132) as well as an observational cohort (N=93,676). Eligible patients were postmenopausal women aged 50–79 years with anticipated three-year survival with additional eligibility requirements for clinical trial participation based on specified safety and adherence criteria. For WHI clinical trial eligibility, a mammogram that was not suspicious for cancer was required, which was followed by serial mammography. Ongoing mammography was not required for observational study participants, but information on mammography frequency was collected. Participants were recruited from 40 US clinical centers between 1993 and 1998. Follow-up after the original protocol end date in 2005 required serial written re-consents (for 2005–2010 and beyond 2010) obtained from 83% and 86% of surviving participants willing to be contacted, respectively.

At study entry, self-administered questionnaires collected information on demographics, medical, reproductive, and family histories as well as information regarding dietary and lifestyle factors including recreational physical activity. Waist circumference, weight, and

height were measured by trained personnel using a standardized approach with body mass index (BMI) computed as weight (kg)/[height (m)]^2.

Information on medical outcomes in the clinical trials was collected at 6-month intervals during the intervention period of the clinical trials with subsequent updates annually. Outcome ascertainment in the observational study occurred annually. Reports of breast cancer were verified initially by medical record and pathology report review by trained physician adjudicators at the local clinical centers. Final adjudication and coding were performed at the WHI Clinical Coordinating Center. Human epidermal growth factor receptor 2 (HER2) and estrogen receptor (ER) and progestin receptor (PR) status were based on local laboratory determinations. Breast cancer therapy was directed by the participants' own physicians. Reports of deaths were verified by medical record or death certificate review and, in some cases, by reports from relatives. Serial National Death Index queries through December, 2018 provided additional survival information including cause of death regardless of re-consent status resulting in survival information which is 98% complete[16]. Treatment information for TNBC was ascertained through the WHI Life and Longevity After Cancer (LILAC) Study[17].

Clinical outcomes include breast cancer-specific mortality (breast cancer followed by death attributed to the breast cancer), and breast cancer overall mortality (breast cancer followed by death from any cause) examined for all TNBCs diagnosed throughout 19.9 median years (interquartile range (IQR): 16.6–21.0) follow-up through September, 2018.

A convenient construct has been developed to assess metabolic risk factors in the WHI[9]. Metabolic risk components (as defined below, available on 152,584 of 161,808 study participants) were determined at study entry and included: 1) high waist circumference, 2) high blood pressure, 3) history of hypercholesterolemia, and 4) history of diabetes. Information on triglyceride levels was not available. Women were classified as having 0, 1–2, or 3–4 MetS risk components, consistent with previously reported methodology[9, 18].

High waist circumference was defined as ≥ 88 cm[19]. High blood pressure (BP) was defined as systolic ≥ 130 mm Hg and/or diastolic ≥ 85 mm Hg, or a normal blood pressure but use of anti-hypertensive medications. Blood pressure was measured using standardized procedures by certified personnel. High cholesterol was defined by positive response to the question "Has a doctor ever told you that you had high cholesterol requiring medication?" or reported use of cholesterol-lowering medication. Diabetes was defined by positive response to the baseline question "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?" or reported use of diabetes-related medication. This definition has been validated and is consistent with medication inventories and fasting glucose measurements[20].

The current study population includes only WHI participants diagnosed with incident TNBC (N=744) while on study. Additional exclusions were women with a history of any cancer (except non-melanoma skin cancer) prior to breast cancer diagnosis as well as women with metastatic TNBC. Participants enrolled on the dietary modification treatment arm were also excluded, resulting in 544 women with localized TNBC for the present analysis (Table S1).

STATISTICAL ANALYSIS

The primary analytic variable was MetS risk component category (0, 1–2, 3–4). The primary endpoints were breast cancer-specific mortality and breast cancer overall mortality. All breast cancer mortality analyses were measured from the date of TNBC diagnosis. Breast cancer overall mortality is a commonly accepted endpoint in adjuvant breast cancer trials[21].

Multivariable adjusted Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to quantify the association between MetS risk component category (0, 1–2, 3–4) and mortality after TNBC. Included in the multivariable model were age at diagnosis, race/ethnicity, income, education, clinical/observational trial status, history of oral contraceptive use, history of hormone use, history of statin use, cancer stage, chemotherapy treatment status, and radiation treatment status. These factors were selected for the multivariable model based on clinical relevance; univariate results can be found in Table S2. The proportional hazards assumption was verified by visual inspection of linear time-varying coefficients. Trend tests were computed by MetS component categories using the likelihood ratio test. Forest plots were used for graphical presentation of HRs and CIs from the multivariable model. Median follow-up from TNBC diagnosis was 8.3 years (IQR: 3.8–13.2).

Cumulative hazard curves were used to depict 5- and 10-year breast cancer specific mortality across groups, with p values based on the Fine and Gray method. [22] Kaplan Meier curves were used to depict 5- and 10-year breast cancer overall mortality, with the log rank test used to determine statistical difference across groups.

Follow-up time for all endpoints was calculated from the date of TNBC diagnosis to the date of last follow-up or death through September 2018, whichever came first. Participants still alive at last contact were censored at their date of last contact. A two-sided p-value<0.05 was considered statistically significant. Analyses were performed in SAS statistical software 9.4.

RESULTS

Of 544 WHI postmenopausal participants diagnosed with non-metastatic TNBC, 33% had no MetS risk factors (n=178), 59% had 1–2 risk factors (n=323), and 8% had 3–4 risk factors (n=43) (Table 1). Women in the highest MetS risk component group were more often African American (28% for 3–4 vs. 4% for none, p<0.001), had incomes <$50,000/year (based on 1995 income, inflation adjusted to 2020 would be $85,500) (79% for 3–4 vs. 44% for none, p<0.001), had lower rates of menopausal hormone therapy use (51% for 3–4 vs. 74% for none, p=0.006), and had higher rates of statin use (40% for 3–4 vs. 0% for none, p<0.001). Women with more MetS risk components had higher BMIs, higher systolic and diastolic blood pressures, larger waist circumference, were more likely to have diagnosed diabetes, and were more likely using cholesterol-lowering medications (all p<0.001). Over half of these postmenopausal women diagnosed with non-metastatic TNBC were never smokers but smoking history did not differ by MetS risk component category.

The cumulative median follow-up time from study entry was 19.9 years (IQR: 16.6–21.0) and the median time after TNBC diagnosis was 8.3 years (IQR: 3.8–13.2). There were no differences in breast cancer histology, stage, or grade across baseline MetS component groups. The use of chemotherapy, radiation therapy, or surgery as initial management also did not differ across baseline MetS groups; however, these data represented only women who participated in the supplemental LILAC study, in this case 68% of study participants (Table 2).

A total of 213 women with early stage TNBC died, with cause of death available in 199 cases (Table 3): 30% of women with 0 MetS risk components, 42% with 1–2 risk components, and 54% with 3–4 risk components died during follow-up. Breast cancer was the most common cause of death, occurring in 49% of women.

Based on the multivariable adjusted analysis, the risk of breast cancer-specific mortality was the highest in women with 3–4 MetS risk components (HR: 2.05, CI: 0.94–4.47; trend p=0.114) compared to those with no MetS risk components, although results were not statistically significant (Figure 1). Risk of breast cancer overall mortality after TNBC was highest in women with 3–4 MetS risk components (HR: 1.73, CI: 2.13–3.71) compared to those no MetS risk components, with significantly higher risk in those with 1–2 MetS components as well (HR: 1.41, CI: 1.01–1.98) (trend p=0.006).

As illustrated in Figure 2, breast cancer mortality was highest in those with the highest number of MetS risk components, with 10-year breast cancer mortality at 16.3%, 20.9%, and 36.9% for those with 0, 1–2, and 3–4 metabolic risk components, respectively (Fine and Gray p=0.12). Overall mortality after TNBC was also highest in those with the highest number of MetS risk components, with 10-year morality rates at 28.7%, 35.1%, and 55.5% for those with 0, 1–2, and 3–4 metabolic risk components, respectively (log rank p=0.008) (Figure 3).

DISCUSSION

For women with TNBC who had 3–4 MetS risk components, 10-year breast cancer overall survival was 27% lower than for women with TNBC with no MetS risk components. These findings are consistent with MetS risk components influencing multiple causes of death in women with TNBC.

The association of MetS and breast cancer mortality can vary based on hormone receptor status, menopausal status, and the number of MetS risk components. MetS individual risk components such as obesity was strongly associated with hormone receptor (HR) positive breast cancer, but not HR negative breast cancer[23]. Maiti and colleagues[24] reported a higher rate of MetS in patients with TNBC (52% vs. 34% in TNBC vs. non-TNBC, p=0.017, N=176). In the National Institute of Health-American Association of Retired Persons (NIH-AARP) cohort study with 5,380 breast cancers, Dibaba and colleagues[25] found that MetS was significantly associated with breast cancer mortality, especially among post-menopausal women in a dose-response manner; with 3-fold higher breast cancer mortality among women with 4 MetS components compared with women with none. These findings are consistent

with two previous studies in the US showing that women with breast cancer with MetS had 26% to 2-fold higher risk of breast cancer mortality[6, 8], and with a European study reporting patients with MetS had 23% higher risk of breast cancer mortality[26].

The mediating factors underlying the association of MetS with adverse breast cancer outcomes are complex, including potential roles for visceral adiposity, hyperinsulinemia, IGF pathway activation, estrogen signaling, and inflammation[27]. Previous studies have linked the presence of MetS to a state of chronic inflammation with increasing tumor-associated biomarkers such as CRP, IL-6, and TNF-α[28]. Adipokines such as adiponectin reduction and high leptin are associated with increased visceral adiposity, breast oncogenesis, and MetS[12, 29]. In addition, insulin resistance and hyperinsulinemia increase the bioavailability of insulin-like growth factor-1 (IGF-1), which affects metabolism, cell differentiation, proliferation, and suppression of apoptosis[30].

Certain findings suggest women with 3 or 4 MetS components may have had their cancer therapy/follow-up compromised. Findings supporting such an explanation include differences in race/ethnicity, income, diabetes, and frequency of nodal examinations. However, there are also factors against such an explanation as being determinate. First is the nature of the study WHI population. For WHI participation, women had to consent for clinical trials with placebo/no therapy randomizations or for an observational study with requirement for regular clinical visits and blood draw with no individual benefit. As a result, a relative healthy population was recruited and 95% of participants <65 years of age had health insurance while 98.2% of older participants had health insurance [31]. Second, three of the four metabolic syndrome components (blood pressure, waist circumference, cholesterol) are risk factors rather than comorbidities likely to limit breast cancer therapy and/or follow-up. Finally, albeit with missing data, there were no significant differences in surgery, chemotherapy, or radiation therapy among metabolic component defined groups. Thus, compromised breast cancer therapy is an unlikely major mediator of the higher mortality seen in women with TNBC who had 3 or 4 MetS components. Regardless of the actual mediating factors, the current findings raise several hypotheses which warrant clinical attention, including correcting metabolic syndrome components and/or attention to adherence to breast cancer therapy regimens.

Several interventions targeting MetS components have been evaluated for influence on breast cancer outcome. In the Women's Health Initiative Dietary Modification trial, 48,835 postmenopausal women with no prior breast cancer were randomized at 40 US clinical centers to a low-fat dietary pattern incorporating increase in fruits, vegetables, and grains or a usual diet comparison group. Previously, this intervention has been shown to significantly reduce MetS components[23]. After 8.5 years of dietary intervention and with19.6 years cumulative follow-up, the dietary intervention significantly reduced deaths from breast cancer (HR: 0.79; 95% CI: 0.64–0.97, p=0.02)[32]. Similarly, long-term statin use (>5 years) was associated with higher disease free and overall survival in women with breast cancer regardless of receptor subtype, even after adjusting for metabolic comorbidities[33].

Integration of the straightforward MetS component assessment in the current study could inform clinical decision-making and identify a population at high risk of mortality requiring

attention to other health risks in addition to the substantial risk associated with a diagnosis of TNBC. A reasonable clinical strategy for women with localized TNBC, albeit one without prospective validation of efficacy, would be to target reversal of individual metabolic risk factors such as blood pressure control and weight loss. Thus, future evaluation of lifestyle interventions to reduce adverse TNBC outcomes could be considered.

Strengths of the current study include the well-characterized original cohort of 161,808 racial/ethnically diverse postmenopausal women in which 544 women were diagnosed with verified incident TNBC. These women had 8.3 years post-TNBC diagnosis follow-up during which 213 died, with cause of death available on all but 14 cases. With respect to MetS component assessment, standardized and defined procedures were employed at all clinical centers for determination of blood pressure and waist circumference measurements; validated questionnaire-based assessment of diabetes was also employed.

Study limitations include associations based on assessment of MetS components at baseline with subsequent breast cancer mortality years later. Study limitations also include indirect measures of cholesterol and diabetes status and use of non-standard criteria for categorizing MetS components. However, our approach identified clear separation of populations with substantially different risk of breast cancer overall mortality and this approach has successfully identified high mortality risk subpopulations in colorectal cancer and in breast cancer[9]. Final limitations were that information on breast cancer therapy was incomplete and only postmenopausal women with TNBC were evaluated in this study. Future studies will be needed to evaluate how current findings apply to younger women with TNBC.

In conclusion, postmenopausal women with 3–4 MetS risk components who are diagnosed with TNBC experience non-significantly higher breast cancer mortality risk and significantly higher breast cancer overall mortality risk, likely due to a negative influence of metabolic risk factors on several causes of death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Women's Health Initiative (WHI) Data Sharing Statement:

- Will individual participant data be available? Deidentified individual participant data is available.
- What data in particular will be shared? All of the deidentified participant data collected during the trial.
- What other documents will be available? Study protocol, study procedures, data collection forms and other documents.
- When will data be available (start and end dates)? Data is available through the WHI online resource, https://www.whi.org/researchers/data/Pages/Home.aspx, while the WHI remains funded and indefinitely through BioLINCC, https://biolincc.nhlbi.nih.gov/studies/whi_ctos/. Eligible researchers may download the data directly at the WHI online resource. Other researchers may download the publicly available data through BioLINCC, in accordance with NHLBI's BioLINCC guidelines.
- For what types of analyses? Eligible researchers with an approved specified purpose. Other researchers in accordance with NHLBI's BioLINCC guidelines.
- By what mechanism will data be made available? Data are available at the aforementioned links. https://www-whi-org.s3.us-west-2.amazonaws.com/wp-content/uploads/WHI-Data-Sharing-Statement.pdf

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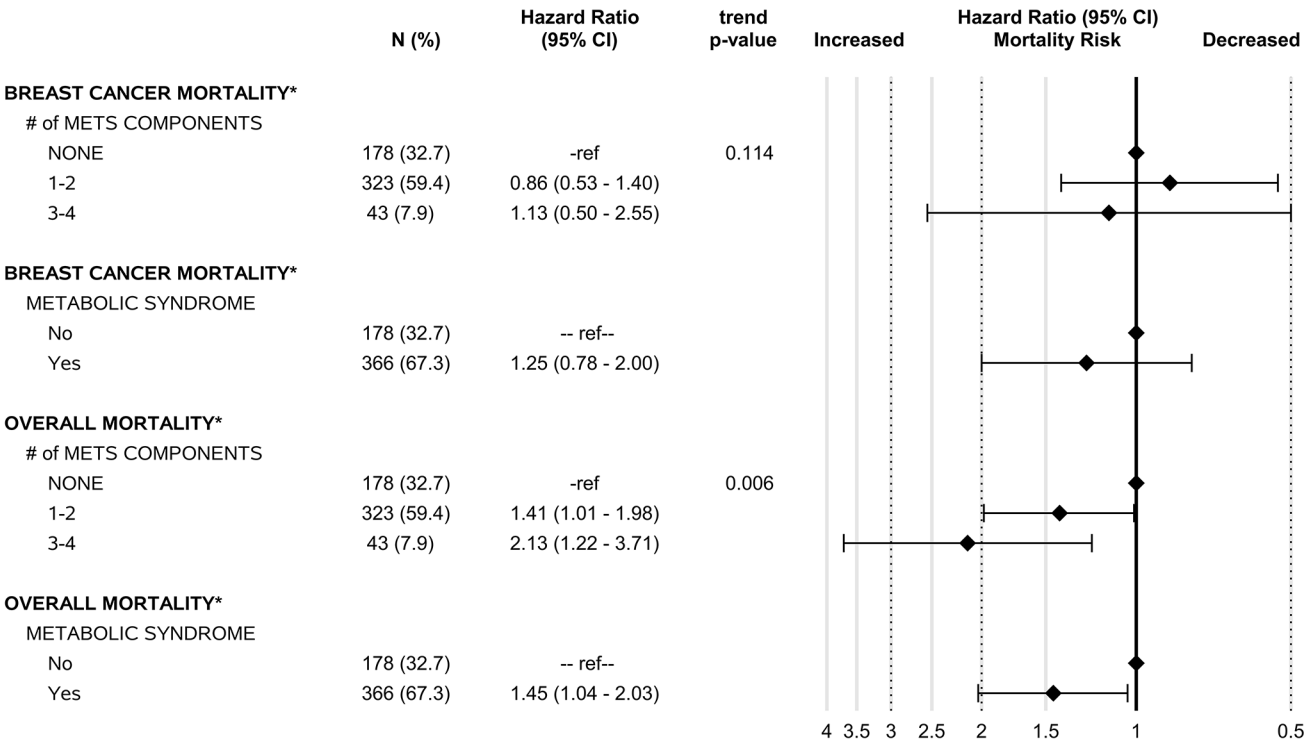
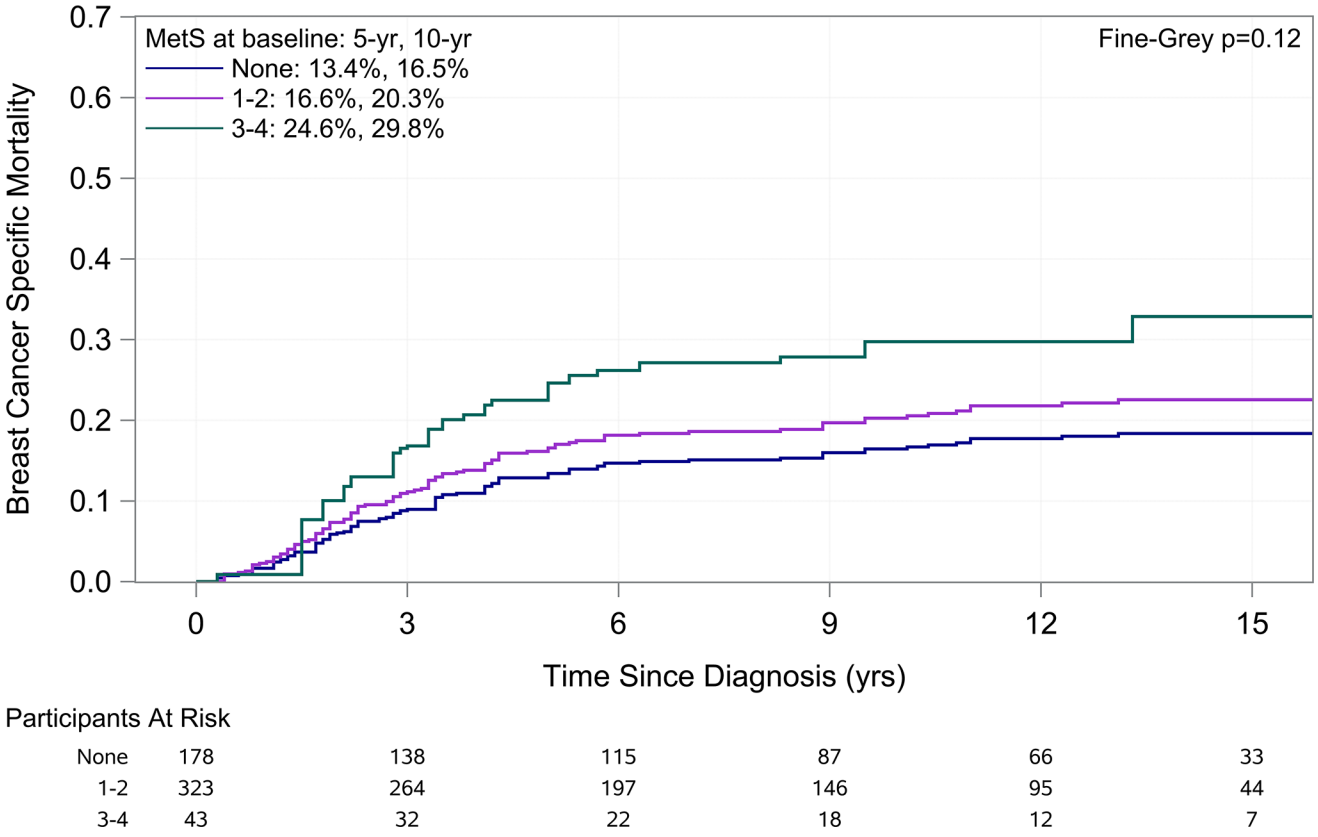


Abbreviations: METS, metabolic syndrome.
*Results were adjusted the following co-variates: age group at diagnosis, race/ethnicity, income, education level, clinical/observational trial status, history of oral contraceptive use, history of hormone therapy use, history of statin use, breast cancer stage, chemotherapy treatment status, and radiation treatment status.

Figure 1.

Counts and multivariable adjusted hazard ratios (HR) with 95% confidence limits (95% CI) for the models examining MetS risk component categories (none, 1–2, 3–4) tertiles and risk of breast cancer specific mortality and breast cancer overall survival (breast cancer followed by death from any cause) measured from cancer diagnosis, in 544 women with early stage, triple negative breast cancer over 19.9 years total median follow-up since study enrollment.

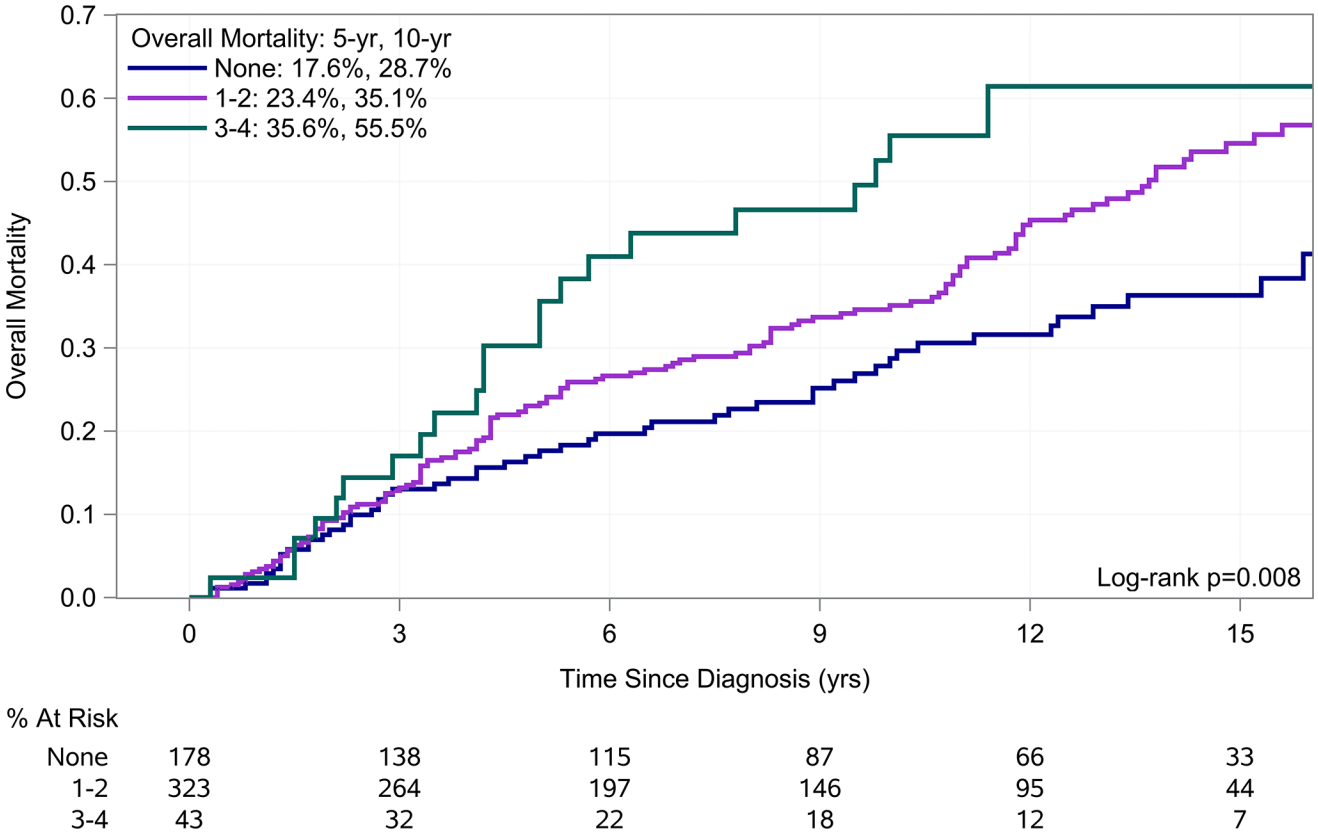


Participants At Risk

None	178	138	115	87	66	33
1-2	323	264	197	146	95	44
3-4	43	32	22	18	12	7

Figure 2.

Cumulative hazard plots and Fine and Gray p-values depicting breast cancer specific mortality by MetS risk component category (none, 1–2, 3–4) tertiles measured from cancer diagnosis, in 544 women with early stage, triple negative breast cancer over 8.3 years total median follow-up since early stage, triple negative breast cancer diagnosis.



% At Risk

None	178	138	115	87	66	33
1-2	323	264	197	146	95	44
3-4	43	32	22	18	12	7

Figure 3.

Kaplan-Meier plots and log-rank p-values depicting overall mortality after breast cancer by MetS risk factor component (none, 1–2, 3–4) tertiles measured from cancer diagnosis, in 544 women with early stage, triple negative breast cancer over 8.3 years total median follow-up since early stage, triple negative breast cancer diagnosis.

Table 1.

Baseline characteristics of women with triple negative breast cancer by baseline MetS component group (N=544).

		None N=178 N (%)	1–2 N=323 N (%)	3–4 N=43 N (%)	p-value*
DEMOGRAPHIC CHARACTERISTICS					
Age at diagnosis	Median (IQR)	71 (64.8–77.2)	72 (66.5–78.1)	74 (69.2–77.6)	0.100
Age Group	Younger Age (<70)	82 (46)	124 (38)	13 (30)	0.092
	Older Age (≥70)	96 (54)	199 (62)	30 (70)	
Race/Ethnicity	White	162 (91)	248 (77)	30 (70)	<.001
	Black	8 (4)	58 (18)	12 (28)	
	Hispanic	3 (2)	6 (2)	1 (2)	
	American Indian	2 (1)	1 (0)	0 (0)	
	Asian/Pacific Islander	3 (2)	8 (2)	0 (0)	
	Unknown	0 (0)	2 (1)	0 (0)	
Education	High school or less	28 (16)	69 (21)	12 (28)	0.147
	>High school/GED	147 (83)	252 (78)	31 (72)	
	Unknown	3 (2)	2 (1)	0 (0)	
Income	<50,000	78 (44)	188 (58)	34 (79)	<.001
	≥50,000	82 (46)	117 (36)	7 (16)	
	Unknown	18 (10)	18 (6)	2 (5)	
EXPOSURE INFORMATION					
WHI status	Observational Arm	126 (71)	199 (62)	25 (58)	0.082
	Clinical Trial Arm	52 (29)	124 (38)	18 (42)	
Oral contraceptive use ever	No	83 (47)	191 (59)	30 (70)	0.004
	Yes	95 (53)	132 (41)	13 (30)	
Female hormones ever	No	42 (24)	107 (33)	20 (47)	
	Yes	132 (74)	209 (65)	22 (51)	0.006
	Unknown	4 (2)	7 (2)	1 (2)	
History of statin use	No	178 (100)	288 (89)	26 (60)	<.001
	Yes	0 (0)	35 (11)	17 (40)	
PHYSICAL/METABOLIC CHARACTERISTICS					
BMI kg/m2	Median (IQR)	24 (22–26.6)	28 (25.2–32.6)	31 (27.8–35.4)	<.001
Body-mass Index (BMI)(kg/m2)	<25	108 (61)	77 (24)	5 (12)	<.001
	25-<30	63 (35)	121 (37)	13 (30)	

		None N=178 N (%)	1–2 N=323 N (%)	3–4 N=43 N (%)	p-value*
	30-<35	4 (2)	70 (22)	14 (33)	
	35+	2 (1)	52 (16)	11 (26)	
	Unknown	1 (1)	3 (1)	0 (0)	
Systolic Blood Pressure	Median (IQR)	114 (107–122)	132 (119–143)	142 (132–151)	<.001
Diastolic BP	Mean (±SD)	70.6 (±7.6)	77.2 (±9.4)	78.1 (±7.3)	<.001
High blood pressure	No	178 (100)	121 (37)	4 (9)	<.001
	Yes	0 (0)	202 (63)	39 (91)	
High waist circumference	No	178 (100)	140 (43)	1 (2)	<.001
	Yes	0 (0)	183 (57)	42 (98)	
Diabetes	No	178 (100)	313 (97)	18 (42)	<.001
	Yes	0 (0)	10 (3)	25 (58)	
High cholesterol	No	170 (96)	252 (78)	13 (30)	<.001
	Yes	0 (0)	56 (17)	29 (67)	
	Unknown	8 (4)	15 (5)	1 (2)	
SMOKING STATUS					
Smoking status	Never smoker	88 (49)	171 (53)	20 (47)	0.881
	Past smoker	75 (42)	128 (40)	20 (47)	
	Current smoker	14 (8)	22 (7)	3 (7)	
	Unknown	1 (1)	2 (1)	0 (0)	
DISEASE HISTORY					
Cardiovascular disease ever	No	144 (81)	251 (78)	32 (74)	0.536
	Yes	26 (15)	56 (17)	9 (21)	
	Unknown	8 (4)	16 (5)	2 (5)	
Cardiac arrest ever	No	31 (17)	65 (20)	9 (21)	0.868
	Yes	1 (1)	2 (1)	0 (0)	
	Unknown	146 (82)	256 (79)	34 (79)	
Congestive heart failure ever	No	25 (14)	52 (16)	8 (19)	0.643
	Yes	1 (1)	4 (1)	0 (0)	
	Unknown	152 (85)	267 (83)	35 (81)	
Atrial fibrillation ever	No	169 (95)	298 (92)	39 (91)	0.392
	Yes	6 (3)	20 (6)	2 (5)	
	Unknown	3 (2)	5 (2)	2 (5)	
Angina ever	No	176 (99)	296 (92)	37 (86)	<.001
	Yes	2 (1)	25 (8)	6 (14)	

		None N=178 N (%)	1–2 N=323 N (%)	3–4 N=43 N (%)	p-value*
	Unknown	0 (0)	2 (1)	0 (0)	
Peripheral arterial disease ever	No	175 (98)	315 (98)	38 (88)	0.384
	Yes	3 (2)	6 (2)	2 (5)	
	Unknown	0 (0)	2 (1)	3 (7)	
Fracture at Age 55+	No	106 (60)	218 (67)	33 (77)	0.888
	Yes	17 (10)	32 (10)	4 (9)	
	Unknown	55 (31)	73 (23)	6 (14)	
FAMILY HISTORY					
Female relative had breast cancer	No	47 (26)	77 (24)	8 (19)	0.317
	Yes	35 (20)	86 (27)	9 (21)	
	Unknown	96 (54)	160 (50)	26 (60)	

Abbreviations: MetS=metabolic syndrome, IQR=Interquartile Range, SD=Standard Deviation, GED=General Education Degree.

*Missing data were excluded from the chi-square analyses.

Median follow-up time since enrollment was 19.9 years.

Median follow-up time since breast cancer diagnosis was 8.3 years.

Table 2.

Breast cancer characteristics and therapy in women diagnosed with triple negative breast cancer by MetS component group (N=544).

		None N=178 N (%)	1–2 N=323 N (%)	3–4 N=43 N (%)	p-value*
CANCER CHARACTERISTICS					
Tumor Size	<1 cm	36 (20)	51 (16)	9 (21)	0.754
	1–<2cm	66 (37)	130 (40)	18 (42)	
	≥2cm	72 (40)	133 (41)	16 (37)	
	Paget or Diffuse	0 (0)	2 (1)	0 (0)	
	Unknown	4 (2)	7 (2)	0 (0)	
# Positive lymph nodes	0	120 (67)	210 (65)	26 (60)	0.062
	1–3	29 (16)	60 (19)	3 (7)	
	≥4	11 (6)	25 (8)	4 (9)	
	+ nodes NOS	2 (1)	4 (1)	0 (0)	
	None examined	16 (9)	24 (7)	10 (23)	
Stage	Localized	128 (72)	231 (72)	33 (77)	0.772
	Regional	50 (28)	92 (28)	10 (23)	
Grade	Well differentiated	13 (7)	13 (4)	1 (2)	0.582
	Moderately differentiated	42 (24)	70 (22)	11 (26)	
	Poorly differentiated	107 (60)	218 (67)	27 (63)	
	Anaplastic	7 (4)	12 (4)	1 (2)	
	Unknown	9 (5)	10 (3)	3 (7)	
Cancer Histology	Ductal	153 (86)	285 (88)	39 (91)	0.412
	Lobular	10 (6)	8 (2)	0 (0)	
	Ductal and lobular	7 (4)	15 (5)	1 (2)	
	Other histology	8 (4)	15 (5)	3 (7)	
CANCER TREATMENT CHARACTERISTICS					
Hormone therapy	No	87 (49)	126 (39)	11 (26)	0.822
	Yes	6 (3)	12 (4)	1 (2)	
	Unknown	85 (48)	185 (57)	31 (72)	
Chemotherapy	No	43 (24)	87 (27)	9 (21)	0.644
	Yes	62 (35)	108 (33)	16 (37)	
	Unknown	73 (41)	128 (40)	18 (42)	
Radiation therapy	No	36 (20)	73 (23)	9 (21)	0.777
	Yes	69 (39)	117 (36)	16 (37)	
	Unknown	73 (41)	133 (41)	18 (42)	

		None N=178 N (%)	1–2 N=323 N (%)	3–4 N=43 N (%)	p-value*
	No	1 (1)	2 (1)	1 (2)	0.433
Surgery	Yes	104 (58)	201 (62)	25 (58)	
	Unknown	73 (41)	120 (37)	17 (40)	

Abbreviations: MetS=metabolic syndrome.

*Missing data were excluded from the chi-square analyses.

Median follow-up time since enrollment was 19.9 years.

Median follow-up time since breast cancer diagnosis was 8.3 years.

Table 3.

Cause of death by MetS component group (N=544).

	MetS Group		
Cause of Death	**None N (%) (N=178)**	**1–2 N (%) (N=323)**	**3–4 N (%) (N=43)**
Breast Cancer	28 (53)	64 (47)	13 (57)
CVD	5 (9)	27 (20)	3 (13)
Other Cancer	3 (6)	17 (12)	3 (13)
Alzheimer's/Dementia	4 (8)	7 (5)	0 (0)
Other	8 (15)	14 (10)	3 (13)
Unknown	5 (9)	8 (6)	1 (4)

Abbreviations: MetS=metabolic syndrome.

Of 544 participants, 213 died during study (None n=53 and 1–2 n=137 and 3–4 n=23); 331 were still alive at last follow-up (none n=125 and 1–2 n=186 and 3–4 n=20).

Median follow-up time since enrollment was 19.9 years.

Median follow-up time since breast cancer diagnosis was 8.3 years.