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Cardiometabolic factors and breast cancer risk in U.S. black women

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Abstract

Previous studies have suggested that metabolic syndrome may be associated with an increased risk of breast cancer, particularly in postmenopausal women, but U.S. black women have not been assessed. We examined the associations of abdominal obesity, type 2 diabetes, hypertension, and high cholesterol individually and in combination with breast cancer incidence in the Black Women's Health Study. By means of Cox regression models, we estimated incidence rate ratios (IRR) and 95 % confidence intervals (CI) for the associations of baseline and time-dependent values of self-reported abdominal obesity, type 2 diabetes, hypertension, and high cholesterol with breast cancer incidence. During 516,452 person years of follow-up (mean years = 10.5; standard deviation = 2.9) from 1995 to 2007, 1,228 breast cancer cases were identified. After adjustment for age, education, body mass index at age 18, physical activity, and individual cardiometabolic factors, neither individual nor combinations of cardiometabolic factors were associated with breast cancer incidence overall; the multivariable IRR was 1.04 (95 % CI 0.86–1.25) for the combination of 3 factors relative to the absence of all factors, and 1.17 (0.85–1.60) for having all four factors. Among postmenopausal women, however, the comparable IRRs were 1.23 (0.93–1.62) and 1.63 (1.12–2.37), respectively. Our findings provide some support for an association between cardiometabolic factors and breast cancer incidence among postmenopausal U.S. black women.

Keywords

Metabolic syndrome; Obesity; Insulin resistance; Breast cancer

Introduction

Metabolic syndrome, also called insulin resistance syndrome, is defined as the clustering of three or more of the following conditions: abdominal obesity (waist circumference ≥ 88 cm), elevated blood pressure (≥ 130 mmHg systolic over ≥ 85 mmHg diastolic), elevated fasting glucose (≥ 100 mg/dL), hypertriglyceridemia (≥ 150 mg/dL), and low high-density lipoprotein (HDL) cholesterol (<50 mg/dL) [1]. The prevalence of each of the components of metabolic syndrome is greater among black women than among white women [2]. In black women, the prevalence of abdominal obesity, elevated blood pressure, elevated fasting glucose, hypertriglyceridemia, and low HDL cholesterol has been estimated to be 62.1, 43.3, 15.5, 14.4, and 34.0 %, respectively [2]. The overall prevalence of metabolic syndrome is estimated to be approximately 26 % among U.S. black women [3].

Limited epidemiologic evidence suggests that metabolic syndrome may be associated with an increased breast cancer risk, particularly among postmenopausal women [4–10]. Individual cardiometabolic factors, such as abdominal obesity, type 2 diabetes, high blood pressure, and high cholesterol, have been associated with increased risks of breast cancer in some studies [4–6, 11–22], but not in others [5, 7, 23–25]. The majority of studies have been composed predominantly of white women [4–9], and if the existing evidence applies to black women remains unknown.

No previous studies have examined the combined effects of cardiometabolic factors on breast cancer risk in U.S. black women, and information on effects of the individual risk factors is relatively sparse. We examined the association between breast cancer incidence and the following cardiometabolic factors: abdominal obesity, type 2 diabetes, hypertension, and high cholesterol, both individually and in combination, using data from the Black Women's Health Study (BWHS).

Methods

Study population

The BWHS is a prospective cohort study of approximately 59,000 U.S. black women aged 21 through 69 years at entry in 1995 [26]. The baseline questionnaire collected information on demographic and lifestyle factors, reproductive history, anthropometric measurements, medical conditions, and medications [26]. Deaths were identified through the National Death Index, postal service, and friends or relatives. The cohort is followed biennially by mailed questionnaire, and 80 % of the original cohort had been followed through 2007.

Women were excluded from the analysis if they did not complete at least one follow-up questionnaire ($N=53$), had prevalent cancer at baseline ($N=1,414$), did not complete the baseline waist circumference question ($N=7,976$), or had type 1 diabetes ($N=412$).

The Boston University Medical Center Institutional Review Board has approved this study.

Cardiometabolic factors

BWHS participants were asked to measure their waist at their navel in the baseline questionnaire. In a validation study among 115 participants, the Spearman correlation coefficient for waist circumference reported in the baseline questionnaire (1995) with a

clinical measurement taken in 2001 was 0.75 [27]. We defined abdominal obesity as a waist circumference of 88 cm or greater [1].

Participants were asked at baseline and in follow-up questionnaires if a physician had told them that they had any of a list of medical conditions that included diabetes, hypertension, and high cholesterol. They were also asked to report medications used 3 times per week, such as insulin, pills to treat diabetes, diuretics, and blood pressure lowering drugs. Cholesterol-lowering medications were reported in an open-text question in the medications section of the baseline questionnaire and the 1997 follow-up questionnaire. Subsequent questionnaires asked specifically about these medications. We defined type 2 diabetes as self-reported diagnosis of diabetes at age 30 years or older [28]; in a validation study of 115 participants who reported diabetes, the physician had confirmed the diagnosis for 95 % [28]. We defined hypertension as reported high blood pressure plus use of diuretics or hypertensive medication [29]; the positive predictive value for self-reported drug-treated hypertension was 99 % in a sample of 139 women for whom medical record data were obtained [29]. We defined high cholesterol as self-reported high cholesterol; no validation data were available for self-report of physician-diagnosed high cholesterol.

Potential confounding variables

Candidate confounding variables were identified a priori from the existing literature [30–36]. Educational attainment at baseline was used as a surrogate for socioeconomic status. We used self-reported height and weight to calculate body mass index (BMI, weight in kilograms divided by height squared in meters). A woman was considered postmenopausal if she reported natural menopause or bilateral oophorectomy, or if she had hysterectomy with removal of <2 ovaries and was age 57 (90th percentile of age at natural menopause in BWHS) or older. She was considered premenopausal if she reported being premenopausal, or if she had a hysterectomy with removal of <2 ovaries and was less than age 43 (10th percentile of age at natural menopause in BWHS). Menopausal status was considered unknown if the woman had a hysterectomy with removal of <2 ovaries and was 43–56 years of age. Family history of breast cancer in a first degree relative (mother, sister), and age at menarche were reported at baseline. Information on parity, age at first birth, oral contraceptive use, female hormone use (i.e., postmenopausal hormone replacement therapy), alcohol consumption, physical activity, smoking, and mammography receipt was collected at baseline and in each follow-up questionnaire. Vigorous physical activity was defined as participation in activities such as basketball, swimming, running, and aerobics. This measure was validated in a BWHS study in which the participants wore activity monitors during their waking hours for 1 week; reported vigorous activity was significantly associated with counts recorded by the activity monitors [37].

Breast cancer ascertainment

Among the 59,000 women included in the BWHS cohort, a total of 1,429 breast cancer diagnoses were reported on follow-up questionnaires from 1997 through 2007. To date, medical records or cancer registry data have been obtained for 1,151 reported cases, of which 99.4 % cases were confirmed. Disconfirmed cases were excluded, leaving a total of 1,228 cases for analysis after previous exclusions.

Statistical analysis

Women were followed from baseline in 1995 until breast cancer diagnosis, death from any cause, loss to follow-up, or the end of follow-up in 2007, whichever came first. Incidence rate ratios (IRRs) and 95 % confidence intervals (CIs) for the association of individual and combinations of cardiometabolic factors with breast cancer risk were estimated using Cox proportional hazards regression models, with duration of follow-up as the time scale [38].

The Cox proportional regression analyses incorporated the Andersen–Gill data structure to account for the time-dependent nature of the cardiometabolic factors [39]. Departures from the proportional hazards assumption were tested by the likelihood ratio test comparing models with and without age by covariate interaction terms [38]. No violations of this assumption were observed. IRRs and 95 % CIs also were calculated for mutually exclusive individual and combinations of cardiometabolic factors compared with the absence of any factor. We also calculated the effect of individual cardiometabolic factors relative to the absence of that risk factor (i.e., hypertension compared with the absence of hypertension). Models were jointly stratified by age (1-year intervals) and questionnaire cycle, and also adjusted for education (12, 13–15, and 16 years), BMI at age 18 (<20, 20–24, 25–29, and 30 kg/m²), vigorous physical activity (none, <5 h per week, 5 h per week), and each of the other cardiometabolic factors. Vigorous physical activity was treated as a time-dependent variable in the Cox models. Adjustment for reproductive history, female hormone use, and oral contraceptive use did not appreciably change the results, and these variables were not included in the final multivariable models.

We also examined the association between baseline values of cardiometabolic factors and breast cancer risk.

All statistical tests were two-sided and conducted using SAS, version 9.1 (Cary, North Carolina).

Results

The final analytic sample consisted of 49,172 BWHS participants, among whom 1,228 incident cases of breast cancer were reported over 516,452 person-years of followup (mean years = 10.5; standard deviation = 2.9) through 2007. The median age at diagnosis among participants with breast cancer was 50 years. Women excluded because they did not report a waist circumference had a higher BMI and were less physically active at baseline than participants included in the analysis. The proportions of participants who reported cardiometabolic factors were as follows: abdominal obesity, 28 %; type 2 diabetes, 3.9 %; drug-treated hypertension, 15 %; and high cholesterol, 28 % (Table 1). Women with any of the cardiometabolic factors were older, more likely to use female hormones, more obese at baseline and at age 18, less physically active, and had an earlier menarche and fewer years of education than women with no cardiometabolic factors (Table 1).

Results from time-dependent analyses of mutually exclusive individual and combinations of cardiometabolic factors, relative to the absence of all cardiometabolic factors, are presented in Table 2. No individual factor or a combination of factors was significantly associated with an increased risk of breast cancer. The multivariable incidence rate ratio (mIRR) for having three or more cardiometabolic factors was 1.04 (95 % CI 0.86–1.25), and for all four factors, it was 1.17 (95 % CI 0.85–1.60).

Table 3 presents time-dependent analyses for individual and combinations of cardiometabolic factors stratified by menopausal status. Among postmenopausal women, having all four cardiometabolic factors was significantly associated with breast cancer risk (mIRR = 1.63; 95 % CI 1.12–2.37). The mIRR for any 3 cardiometabolic factors was 1.23 (95 % CI 0.93–1.62). No individual or combination of cardiometabolic factors was associated with breast cancer risk among premenopausal women (Table 3). When the analysis was restricted to the subset of 362 postmenopausal cases who never used hormone therapy, mIRRs for all four cardiometabolic factors (mIRR = 1.77; 95 % CI 1.14–2.77) and 3 factors (mIRR = 1.30; 95 % CI 0.92–1.83) did not change appreciably from those for all postmenopausal women.

When we repeated the analyses using baseline values of cardiometabolic factors, no significant associations were observed. The mIRRs were 1.09 (95 % CI 0.70–1.71) for having all four cardiometabolic factors, and 1.04 (95 % CI 0.84–1.29) for 3 cardiometabolic factors. Among post-menopausal women, the IRR for any three or more cardiometabolic factors was 1.37 (0.91–2.01), based on 73 affected cases. Only two cases had all four factors at baseline.

Table 4 presents mIRRs and 95 % CIs for time-dependent analyses in which cardiometabolic factors are each considered separately, not as mutually exclusive variables. MIRR for breast cancer were estimated for the presence of a given factor relative to the absence of that factor. None of the cardiometabolic factors was associated with breast cancer risk overall or by menopausal status; mIRRs ranged from 0.80 to 1.13.

Discussion

In this large prospective study of U.S. black women, we found evidence of an increased risk of breast cancer among postmenopausal women associated with having all four cardiometabolic factors under study, with a possible smaller increase for having at least three factors. No such association was observed among premenopausal women. A significant association was observed when cardiometabolic factors were updated over time, but not when baseline exposure was considered, but numbers of affected women were smaller in the latter analyses.

Several hormonal factors, most of which lead to increased levels of circulating estrogen, have been proposed as the underlying mechanisms for the association of breast cancer with individual components of the metabolic syndrome [11, 14, 16]. After menopause, estradiol is produced primarily in adipose tissue. Thus, heavier women tend to have higher circulating levels of estradiol. High estradiol levels are associated with an increased risk of breast cancer, particularly hormone-receptor positive tumors [40]. High levels of circulating insulin also have been associated with breast cancer risk in some studies [41, 42], but not in others [42, 43]. When insulin levels increase, cell proliferation also increases, while sex-hormone binding globulin (SHBG) levels and cell apoptosis decrease [44]. Insulin reduces the production of SHBG and the combination of low SHBG and high triglycerides increase estradiol levels [45]. Adiponectin, an antiinflammatory protein, also may play an important role in a potential pathway between metabolic syndrome and breast cancer. Levels of adiponectin tend to be lower in individuals with low HDL cholesterol, high triglycerides, abdominal obesity, type 2 diabetes, and hypertension [11]. Low levels of adiponectin have been associated with an increased breast cancer risk among postmenopausal women [46]. Moreover, adiponectin levels are lower among women with breast tumors with aggressive characteristics, such as larger tumor size, higher grade, and estrogen receptor-negative status [11]—common characteristics of breast cancer among African-American women [47].

There is growing epidemiologic evidence indicating that metabolic syndrome increases the risk of breast cancer among postmenopausal women [4–10]. Our findings support findings from the Women's Health Initiative (WHI) study of postmenopausal women, which indicated that time-dependent metabolic syndrome (any combination of 3 components) was positively associated with a 77 % (95 % CI 1.01–3.12) increased rate of breast cancer [5]. Osaki et al. [10] reported that metabolic syndrome increased breast cancer risk in Japanese women 55 years old (89 breast cancer cases), regardless of the definition of metabolic syndrome used. BMI was used as a proxy for abdominal obesity [10]. Rosato et al. [8] combined data from two hospital-based case–control studies of Italian and Swiss women and observed that the presence of 3 components of metabolic syndrome was associated with an 80 % increase in risk of breast cancer among postmeno-pausal women (191 cases),

and over a threefold increase in breast cancer risk among women ≥ 70 years. Preliminary findings from a cross-sectional study (50 cases) [6], an Italian nested case-control study (181 cases) [4], and a Brazilian matched case-control study (81 cases) [9] also suggest that metabolic syndrome is positively associated with breast cancer risk among postmenopausal women. In contrast to these positive associations, the MEtabolic syndrome and CANcer Study (Me-Can) cohort, a study of six cohorts from Austria, Norway, and Sweden, found no association of metabolic syndrome with breast cancer risk among women ≥ 50 years old (IRR = 1.04; 95 % CI 0.97–1.12) [7], and there was an inverse association of metabolic syndrome with breast cancer in women <50 years old (IRR = 0.83; 95 % CI 0.76–0.90), particularly among women with high BMI [7].

Studies that have examined individual cardiometabolic factors or components of metabolic syndrome have suggested that certain factors or components increase the risk of breast cancer, particularly among postmenopausal women [4–6, 11–22]. While the strongest associations have been observed for abdominal obesity [12, 22, 48–54] and type 2 diabetes [8, 13, 55–58], some studies suggest null associations [25, 59–62]. Only a few studies provide evidence for a positive association of breast cancer with either hypertension [17, 18, 63] or high cholesterol [19, 21, 64].

The WHI [5] and the Me-Can [7] studies had clinical measurements of the components of metabolic syndrome, whereas we used self-reported data of waist circumference and history of hypertension, diabetes, and high cholesterol. Misclassification in our study would tend to attenuate associations. A majority of the studies evaluating metabolic syndrome and breast cancer risk [4–9], including the WHI [5] and Me-Can [7] studies, were largely of white women, whereas the BWHS considered U.S. black women only. The number of breast cancer cases in the BWHS ($N = 1,228$) and the Me-Can study ($N = 4,862$) was appreciably larger than that in the WHI ($N = 168$).

With regard to individual components of the metabolic syndrome, a positive association between prevalence of high cholesterol and breast cancer has been reported [6]. Low HDL cholesterol level measured at baseline was not associated with breast cancer in the WHI [5] or in women ≥ 50 years old in the Me-Can study [7], but the Atherosclerosis Risk in Communities (ARIC) cohort [24] and a Norwegian cohort [19] observed that low HDL cholesterol levels were significantly associated with a 30 and 67 % increased risk of breast cancer, respectively. The Me-Can study also reported that low HDL cholesterol was inversely associated with breast cancer in women under 50 years old [7]. A positive association between breast cancer and time-dependent high triglycerides was observed in the WHI [5, 7], but the presence of high triglycerides appeared to decrease breast cancer risk in the Me-Can cohort study [7]. *High cholesterol* reported in the BWHS did not distinguish between high triglycerides, high total cholesterol, and low HDL cholesterol. We did not observe a significant association of self-reported high cholesterol with breast cancer incidence.

The ratio of the waist-to-hip ratio has been the most frequently used measurement to assess body fat distribution with upper body, or “central,” obesity being represented by a high ratio. However, waist circumference is considered a better indicator of the visceral adipose tissue and a better predictor of breast cancer risk [12] than waist-to-hip ratio [65]. Several large prospective studies, including the Nurses’ Health Study [12] and the European Prospective Investigation of Cancer and Nutrition (EPIC) study [50], observed that larger waist circumference was associated with an increased breast cancer risk. Several other studies that assessed metabolic syndrome in relation to breast cancer risk also found an association with central obesity [8–10]. In contrast to those findings, waist circumference of ≥ 88 cm was not associated with breast cancer in our study or in the WHI [5]. No association was observed

between waist circumference and breast cancer in a previous analysis in the BWHS [25]. In studies evaluating the association of waist circumference or high BMI with breast cancer risk, the increased risk of breast cancer in white women was attenuated by use of hormone therapy [22, 66, 67]. However, when we restricted our analysis to the subset of postmenopausal women who never used hormone therapy, the results for the association of all four cardiometabolic factors and 3 factors with breast cancer risk did not change. These findings are consistent with a previous analysis of the BWHS cohort that observed high BMI at age 18 was inversely associated with breast cancer risk among postmenopausal women, and the inverse association persisted among non-users of hormone therapy [25].

The Nurses' Health Study [13], a retrospective cohort study of Canadian administrative health care data [55], and several case-control studies [8, 56–58] have reported that a history of type 2 diabetes was significantly associated with a 10–20 % increased risk of breast cancer, particularly among postmenopausal women. In the Nurses' Health Study, the positive association was based on 6,220 women with a history of type 2 diabetes and 5,189 breast cancer cases among the postmenopausal women [13]. However, other studies did not observe an association between type 2 diabetes and breast cancer risk [59–62, 68]. The ARIC study observed that diabetic glucose levels (≥ 125 mg/dL), compared with normal levels (<100 mg/dL), were associated with a non-significant increase in breast cancer risk (IRR = 1.39; 95 % CI 0.86–2.23) [43]. We did not observe a positive association between type 2 diabetes and breast cancer, and results were similar for women who treated their diabetes with oral medication and those who used insulin. Previous studies have suggested that certain type 2 diabetic medications may be associated with breast cancer risk [20, 69, 70]. For example, metformin—an oral antidiabetic medication—may protect against breast cancer [20, 69, 71], while long-acting insulin, such as glargine, may increase risk of breast cancer [70]. Our study lacked data for evaluating glucose levels, and we were unable to assess specific types of antidiabetic medications.

Limited evidence suggests a weak association between hypertension and breast cancer [5, 9, 17, 18]. Two case-control studies reported an association of hypertension with increased risk of breast cancer among postmenopausal women [17, 18], particularly in women who were overweight or obese [17]. Porto et al. [9], reported that high blood pressure ($\geq 135/85$ mmHg) increased breast cancer risk (odds ratio = 3.64; 95 % CI 1.89–6.98) in a Brazilian case-control study of 81 breast cancer cases and 81 matched controls. In addition, the WHI reported that high diastolic blood pressure (≥ 85 mmHg), compared with low blood pressure (<74 mmHg) increased breast cancer risk (IRR = 1.55; 95 % CI 1.02–2.36) [5]. On the other hand, a few studies have found that antihypertensive medications increase breast cancer risk [17, 72]. We did not observe an association between hypertension and breast cancer. We did not have blood pressure measurements to evaluate systolic and diastolic blood pressure separately [5].

This present study is the first to assess the association between cardiometabolic factors and breast cancer in U.S. black women. The prevalence of the cardiometabolic factors was higher in the BWHS for abdominal obesity, drug-treated hypertension and high cholesterol, but lower for type 2 diabetes, than the components of metabolic syndrome reported in previous studies evaluating metabolic syndrome and breast cancer risk [4–10]. Baseline BMI was also higher among BWHS participants than in previous studies [4–10]. Despite these differences in the distribution of cardiometabolic factors, we observed a positive association between all four factors and 3 factors in relation to breast cancer risk among postmenopausal women. The incidence of breast cancer is higher among black women than white women before the age of 45, and metabolic syndrome is more prevalent in black women at all ages [73], yet we did not observe an association among premenopausal women. However, the number of premenopausal breast cancer cases with three or more

cardiometabolic risk factors was relatively small, thereby making it unlikely that differences in risk would have been detectable, even if the association was present.

Strengths of the present study include high rates of participation over 12 years of follow-up, prospective data collection, detailed information on potential confounders, updated exposure status over time, accurate reporting of breast cancer, and the large number of cases. We used definitions for type 2 diabetes [28] and hypertension [29] that were previously validated for our study population, but these were surrogates for the clinical measurements that make up the definition of metabolic syndrome. The correlation between self-reported baseline waist circumference and clinical measurements was good, even though the self-reported measurements were compared with measurements obtained several years later [29]. Previous analyses based on BWHS data have yielded associations, in the expected direction, for physical activity [74] and BMI [25] with breast cancer risk. Although no validation data are available for high cholesterol, we would expect misclassification to be non-differential, thus biasing our results towards the null. The BWHS population may have differed in some respects from black women in the general population, but we were able to control for various potentially known confounding variables in the analysis. Unmeasured confounding may have influenced our findings, but controlling for important breast cancer risk factors [30] did not substantially alter our results. The use of medical care in the BWHS is high. At baseline, 98 % of participants had had a health care visit in the previous 2 years, and 91 % of women aged 40 and older had a mammogram in the previous 2 years. Obesity has been associated with mammographic screening in some studies, but it was not associated with obesity in the BWHS cohort [75]. Finally, the exclusion of women who did not report their waist circumference at baseline may have biased our results toward the null because these women were more likely to have a high BMI and be less physically active and therefore have a higher risk of breast cancer.

In summary, the present study provides some support for an association between the combination of all four cardiometabolic factors (abdominal obesity, type 2 diabetes, hypertension, and high cholesterol) and breast cancer incidence among postmenopausal U.S. black women. The findings of this study do not support an association between individual cardiometabolic factors and breast cancer in black women.

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Abbreviations

ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
BWHS	Black Women's Health Study
CI	Confidence interval
EPIC	European Prospective Investigation of Cancer and Nutrition
HDL	High-density lipoprotein
IRR	Incidence rate ratio

Me-Can	MEtabolic syndrome and CANcer Study
mIRR	Multivariable incidence rate ratio
SHBG	Sex-hormone binding globulin
WHI	Women's Health Initiative;

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Table 1

Frequencies and age-standardized percentages^a for descriptive demographic, reproductive, and behavioral characteristics across individual cardiometabolic factors at baseline in U.S. black women ($N = 49,172$)

Baseline characteristics ^b	No factors ^c		Abdominal obesity		Type 2 diabetes		Hypertension		High cholesterol	
	N	%	N	%	N	%	N	%	N	%
N = 25,235										
N = 14,002										
N = 1,900										
N = 7,396										
N = 13,783										
Age (years)										
<40	17,295	68.5	6,690	47.8	270	14.2	1,310	17.7	4,564	33.1
40–49	6,046	24.0	4,478	32.0	662	34.8	2,697	36.5	4,749	34.5
50	1,894	7.56	2,834	20.2	968	51.0	3,389	45.9	4,470	32.4
Education (years)										
<12	3,782	16.4	3,305	22.8	606	29.1	2,078	23.9	3,093	19.0
13–15	9,182	35.1	5,224	38.2	634	39.1	2,459	38.0	4,614	35.4
16	12,226	48.3	5,445	38.8	656	31.8	2,848	37.9	6,060	45.5
Age at menarche (years)										
11	6,411	24.9	4,688	34.1	637	38.5	2,228	32.0	4,089	31.6
12–13	13,555	53.5	6,961	49.6	891	36.4	3,713	50.8	6,996	50.7
14	5,172	21.3	2,286	15.8	360	24.6	1,423	16.9	2,629	17.9
Age at first birth (years)										
Nulliparous	10,758	36.6	4,235	33.5	312	23.7	1,412	32.9	3,760	37.6
<20	4,641	20.4	3,575	24.2	624	24.4	2,339	26.2	3,599	21.8
20–29	8,234	35.9	5,263	36.1	848	47.4	3,152	35.6	5,479	34.7
30	1,411	6.2	807	5.4	96	3.8	413	4.4	820	5.1
BMI in 1995 (kg/m ²)										
<25	14,850	56.5	611	4.5	191	8.5	1,314	21.4	3,613	30.5
25–29	7,731	32.3	3,502	24.8	539	24.3	2,406	27.7	4,659	31.1
30	2,467	10.4	9,758	69.9	1,142	66.2	3,589	50.0	5,381	37.7
BMI at age 18 (kg/m ²)										
<20	11,857	48.3	3,427	22.6	625	27.0	2,793	30.9	5,562	36.9
20–24	11,220	43.5	6,251	44.2	796	36.7	3,211	42.0	6,025	44.5
24	1,879	6.9	4,126	31.9	437	34.8	1,256	25.8	1,993	17.4

Baseline characteristics ^b	No factors ^c		Abdominal obesity		Type 2 diabetes		Hypertension		High cholesterol	
	N	%	N	%	N	%	N	%	N	%
	N = 25,235		N = 14,002		N = 1,900		N = 7,396		N = 13,783	
Vigorous physical activity										
None	6,014	26.3	5,878	40.3	974	35.4	3,524	39.8	5,290	32.6
<5	14,025	53.4	6,406	47.4	677	49.2	2,897	46.6	6,505	52.1
5	4,403	16.6	1,165	8.7	122	11.5	564	9.7	1,404	12.0
Oral contraceptive recency										
Nonuse or <1 year	9,701	41.4	6,668	46.3	1,188	41.0	4,163	48.3	6,515	41.1
1–4 years	6,990	26.1	3,584	26.5	354	29.4	1,494	25.1	3,251	26.5
5 years	8,544	26.0	3,750	27.1	358	29.6	1,739	26.7	4,017	32.4
Recency of mammogram at baseline										
Never	13,171	42.7	5,077	42.2	224	38.6	1,045	38.9	3,259	39.6
<1 year ago	5,385	27.5	4,480	28.2	994	29.6	3,742	31.2	5,890	30.8
1 year ago	6,394	28.7	4,268	28.3	641	29.8	2,496	28.5	4,476	28.6
1 alcoholic drink/week	6,386	26.3	3,453	24.5	320	20.0	1,908	25.9	3,455	24.2
Female hormone use	2,280	13.4	2,524	15.8	622	23.0	2,474	19.1	3,706	18.1
Current smoking	3,809	16.3	2,392	16.6	357	16.5	1,437	17.6	2,347	15.8
Positive family history of breast cancer	1,495	6.6	942	6.3	157	5.6	589	5.7	1,048	6.4

^aPercentages were standardized to the 1995 age distribution of the cohort

^bMissing covariate values are not included in the table

^cWomen without abdominal obesity, type 2 diabetes, hypertension, and high cholesterol at baseline

Mutually exclusive individual and combinations of time-dependent cardiometabolic factors in relation to breast cancer risk in U.S. black women

Table 2

Time-dependent mutually exclusive cardiometabolic factors	Cases (N)	Person years (N)	Age adjusted ^a		Multivariable adjusted ^b	
			IRR	95 % CI	IRR	95 % CI
No risk factors	387	222,618	1.00	Reference	1.00	Reference
OBES only	126	65,784	1.00	0.81–1.22	1.05	0.85–1.29
DIAB only	4	2,120	0.61	0.23–1.62	0.61	0.23–1.65
HTN only	36	11,543	0.96	0.68–1.36	0.98	0.69–1.39
CHOL only	161	62,819	1.04	0.86–1.25	1.04	0.86–1.25
OBES and DIAB only	8	2,443	1.13	0.56–2.29	1.22	0.60–2.47
OBES and HTN only	30	7,708	1.25	0.86–1.25	1.33	0.91–1.95
OBES and CHOL only	79	27,933	1.10	0.86–1.81	1.15	0.90–1.48
DIAB and HTN only	3	940	0.82	0.26–2.55	0.86	0.28–2.70
DIAB and CHOL only	9	2,873	0.89	0.46–1.72	0.92	0.47–1.79
HTN and CHOL only	175	48,136	1.05	0.87–1.27	1.07	0.88–1.29
OBES, DIAB, and HTN only	4	1,339	0.80	0.30–2.14	0.89	0.33–2.39
OBES, DIAB, and CHOL only	7	3,642	0.61	0.29–1.28	0.64	0.30–1.37
OBES, HTN, and CHOL only	124	37,581	1.00	0.81–1.23	1.06	0.85–1.32
DIAB, HTN, and CHOL only	26	6,856	0.91	0.61–1.37	0.93	0.62–1.41
OBES, DIAB, HTN, and CHOL	49	12,117	1.08	0.80–1.47	1.17	0.85–1.60
3 cardiometabolic factors	210	61,535	0.98	0.82–1.17	1.04	0.86–1.25

OBES abdominal obesity, DIAB type 2 diabetes, HTN hypertension, CHOL high cholesterol

^a Adjusted for age

^b Adjusted for age, education, BMI at age 18, vigorous activity

Mutually exclusive individual and combinations of time-dependent cardiometabolic factors in relation to breast cancer risk, stratified by menopausal status

Table 3

Time-dependent mutually exclusive cardiometabolic factors	Premenopausal		Postmenopausal			
	Cases (N)	IRR ^a	95 % CI	Cases (N)	IRR ^a	95 % CI
No risk factors	251	1.00	Reference	88	1.00	Reference
OBES only	70	0.94	0.72–1.24	34	1.13	0.76–1.69
DIAB only	3	1.37	0.44–4.28	1	0.31	0.04–2.25
HTN only	8	0.83	0.41–1.69	20	1.03	0.63–1.68
CHOL only	66	0.97	0.74–1.28	76	1.23	0.90–1.67
OBES and DIAB only	5	1.70	0.70–4.16	3	1.00	0.32–3.17
OBES and HTN only	5	0.75	0.31–1.82	16	1.45	0.84–2.48
OBES and CHOL only	34	1.14	0.79–1.65	33	1.18	0.79–1.77
DIAB and HTN only	1	1.75	0.25–12.6	2	0.95	0.23–3.89
DIAB and CHOL only	3	1.34	0.43–4.19	4	0.67	0.25–1.84
HTN and CHOL only	34	0.87	0.60–1.26	119	1.29	0.97–1.71
OBES, DIAB, and HTN only	0	–	–	3	1.15	0.36–3.66
OBES, DIAB, and CHOL only	2	0.63	0.16–2.54	5	0.88	0.36–2.18
OBES, HTN, and CHOL only	27	0.83	0.55–1.26	75	1.19	0.86–1.63
DIAB, HTN, and CHOL only	3	1.02	0.32–3.20	19	0.96	0.58–1.60
OBES, DIAB, HTN, and CHOL	2	0.26	0.06–1.05	44	1.63	1.12–2.37
Any 3 factors	34	0.72	0.49–1.06	146	1.23	0.93–1.62

There were 172 case subjects with unknown menopausal status

OBES abdominal obesity, DIAB type 2 diabetes, HTN hypertension, CHOL high cholesterol

^a Adjusted for age, education, BMI at age 18, vigorous activity

Individual time-dependent cardiometabolic factors in relation to breast cancer risk compared with the absence of that factor, overall and stratified by menopausal status

Table 4

Time-dependent Individual cardiometabolic factors	Overall		Premenopausal		Postmenopausal	
	Cases (N)	IRR ^a	95 % CI	Cases (N)	IRR ^a	95 % CI
OBEs	427	1.08	0.95–1.22	145	0.97	0.78–1.19
No OBEs	801	1.00	Reference	369	1.00	Reference
DIAB	110	0.92	0.75–1.13	19	0.93	0.58–1.49
No DIAB	1,118	1.00	Reference	495	1.00	Reference
HTN	447	1.05	0.92–1.19	80	0.80	0.60–1.05
No HTN	781	1.00	Reference	434	1.00	Reference
CHOL	630	1.03	0.90–1.17	171	1.03	0.84–1.27
No CHOL	598	1.00	Reference	343	1.00	Reference

There were 172 case subjects with unknown menopausal status

OBEs abdominal obesity, DIAB type 2 diabetes, HTN hypertension, CHOL high cholesterol; cardiometabolic factors are updated at each questionnaire cycle

^a Adjusted for age, education, BMI at age 18, vigorous activity, and other individual cardiometabolic factors