

ARTICLE



Epidemiology

Associations between obesity, metabolic health, and the risk of breast cancer in East Asian women

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BACKGROUND: This study examined the associations between metabolic syndrome (MetS), obesity, their combination as a metabolic obesity phenotype, and the risk of breast cancer in East Asian postmenopausal women.

METHODS: A total of 3,095,336 postmenopausal cancer-free women aged 40–79 years who underwent the National Health Insurance Service health examination between 2009 and 2010 were included. The incidence of invasive breast cancer was followed up until 2018. The presence of obesity (body mass index [BMI] ≥ 25 kg/m²), MetS, and each component of MetS was investigated.

RESULTS: Obesity and MetS were associated with breast cancer risk, but when the effects of obesity and MetS were mutually adjusted, the associations were attenuated, especially for MetS. Only elevated fasting blood glucose levels and waist circumference increased the risk of breast cancer after adjusting for BMI. Compared to metabolically healthy normal-weight women, metabolically unhealthy normal-weight women, metabolically healthy obese, and metabolically unhealthy obese women had an increased risk of breast cancer.

CONCLUSIONS: Obesity and MetS were independently associated with an increased risk of breast cancer in postmenopausal women, despite the relationship between MetS and breast cancer appearing to result from a partial association with BMI. Postmenopausal women should be encouraged to control their weight and metabolic health.

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BACKGROUND

Obesity, a major public health problem worldwide, is a major risk factor for chronic diseases, including cardiovascular disease (CVD) and certain types of cancer. Epidemiological studies have suggested that obesity increases the risk of breast cancer in postmenopausal women, but it has an inverse association in premenopausal women [1, 2]. However, recent studies have indicated a heterogeneous association in Asian women, such as an increased risk of premenopausal breast cancer in women with high adiposity [3–5], suggesting a complex relationship between obesity and breast cancer risk [3, 6]. Similar to obesity in general, metabolic syndrome (MetS) is associated with an increased risk of breast cancer in postmenopausal women, but not in premenopausal women [7, 8]. Obesity and MetS are caused by common mechanisms, such as insulin resistance, inflammatory response, sex hormone metabolism, and energy metabolism [9, 10]. Hence, obesity and MetS may have comparable associations with cancer risk.

Despite the close relationship between MetS and obesity, some individuals with obesity have no other features or components of MetS and are considered to have a metabolically healthy obese (MHO) status. Despite the higher risk of MetS in individuals with MHO status [11, 12], studies have suggested that these individuals are at a lower risk of CVD and mortality than

those of metabolically unhealthy obese individuals because of favourable insulin sensitivity, adipose tissue function, and adipokine function [13, 14]. A previous study has shown that normal-weight individuals with impaired metabolic characteristics (metabolically unhealthy normal weight [MUNW]) have an increased risk of CVD and CVD mortality [14]. However, few studies have investigated whether MHO status increases the risk of cancer or cancer mortality. A recent study by the UK Biobank found an increased risk of 5 of 22 site-specific cancers in MHO individuals [15]. Previous studies have shown that obesity increases the risk of breast cancer in postmenopausal women, irrespective of their metabolic health [15–17]. However, an increased risk of breast cancer has been observed in postmenopausal women with MUNW in a few studies [17]. Most of these studies evaluating the associations between MetS, obesity, and the risk of breast cancer were conducted in Western countries, and limited information is available regarding these associations in Asian women.

The incidence of breast cancer has been increasing, and the MHO status is more common in East Asian postmenopausal women [11]. In addition, different associations between obesity and breast cancer risk according to ethnicity need to be considered [3–5]. Thus, in the present study, we investigated the potential associations between MetS, obesity, and their

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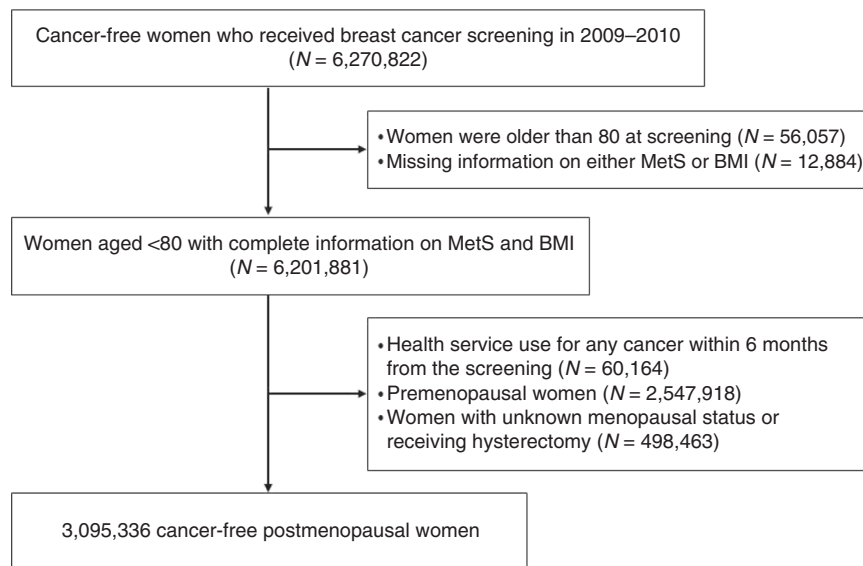


Fig. 1 Flow chart of the selection of study participants.

combination as a metabolic obesity phenotype in terms of metabolically healthy normal weight (MHNW), MUNW, MHO, and metabolically unhealthy obesity (MUO), and the risk of breast cancer in East Asian postmenopausal women using data from a nationwide representative cohort.

METHODS

Study population

The National Health Insurance Service (NHIS) is a single mandatory healthcare insurance system covering the entire population of South Korea. The NHIS provides biennial health examinations and screening for breast cancer in women aged ≥ 40 years. The NHIS health examination includes a self-reported questionnaire about lifestyle factors, family history of chronic diseases and cancer, reproductive factors, anthropometric measurements, and laboratory measurements. Before the health examination, consent for the transfer of results to the national health screening database was obtained from each participant. The rate of participation in the NHIS health examination was approximately 43% in 2002, which increased to 75% in 2017. The details of the NHIS database have been described elsewhere [18]. After review and approval of the study proposal by the National Health Insurance Sharing Service, the NHIS database was made available for research. The Institutional Review Board (IRB) of Hanyang University College of Medicine approved the study protocol (IRB no. HYI-18-175-1), and we obtained national health screening data from the NHIS based on IRB approval.

In this study, women who underwent national breast cancer screening and health examinations between 2009 and 2010 were initially considered because of the biennial cycle of health examinations. Of the 6,270,822 cancer-free women initially considered, those aged >80 years ($N = 56,057$), those with missing information on either MetS or body mass index (BMI) ($N = 12,884$), and those who had availed healthcare services for any type of cancer or catastrophic illness before or within 6 months from the date of health examination ($N = 60,164$) were excluded. In addition, premenopausal women ($N = 2,547,918$), those who reported an unknown menopausal status, or those who had undergone hysterectomy ($N = 498,463$) were excluded. Thus, 3,095,336 postmenopausal women were included in the study (Fig. 1).

Definition of baseline MetS and obesity

The presence or absence of MetS was evaluated according to the results of laboratory investigations. The modified National Cholesterol Rationale Education Program Adult Treatment Program III (NECP-ATP III) defines MetS as the presence of ≥ 3 of the following components: (1) waist circumference (WC) ≥ 80 cm; (2) elevated fasting blood glucose (FBG) levels, defined as fasting plasma glucose levels ≥ 100 mg/dL; (3) triglyceride (TG) levels ≥ 150 mg/dL; (4) high-density lipoprotein cholesterol (HDL) levels

<50 mg/dL for women; and (5) elevated blood pressure (BP) (systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg) [19]. The absence of MetS was defined as the presence of <3 of the above five components. BMI was calculated using anthropometric measurements; obesity was defined as a BMI ≥ 25.0 kg/m² and normal weight was defined as a BMI < 25.0 kg/m² according to the BMI criteria for Asians [20]. Based on the presence of MetS, presence of each component of MetS, and obesity status, participants were classified as having an MHNW (BMI < 25.0 kg/m² and no MetS), MUNW (BMI < 25.0 kg/m² and presence of MetS), MHO (BMI ≥ 25.0 kg/m² and no MetS), or MUO (BMI ≥ 25.0 kg/m² and presence of MetS) status. In addition, for the combined associations between each component of MetS and obesity, MHNW, MUNW, MHO, and MUO were defined according to the presence of each component of MetS (no or yes) and BMI status (BMI < 25.0 kg/m² or BMI ≥ 25.0 kg/m²).

Follow-up and identification of breast cancer incidence

The development of invasive breast cancer among participants was identified using the linkage between the National Health Screening Database and the NHIS healthcare utilisation database until December 31, 2018. The incidence of cancer was defined according to a combination of the International Classification of Disease, 10th version, codes for malignant neoplasms of the breast (C50), and catastrophic illness codes for cancer in the NHIS healthcare utilisation database. The catastrophic illness code is related to the reduced coinsurance rate (from 20% to 5%) for patients with diseases that have a great financial burden in South Korea; thus, it requires relevant clinical information. Hence, the estimation of cancer incidence based on the NHIS database is considered to be reliable [21]. Participants were considered to be censored if they had not developed cancer, had died from any cause, or developed cancer other than breast cancer until December 31, 2018. If a participant had more than two types of cancer, the first cancer was considered. The period from the date of the health examination between 2009 and 2010 until December 31, 2018, date of death, or date of first record of cancer, whichever occurred first, was considered the follow-up period.

Covariates assessment

The adjusted variables in the analysis were age, reproductive factors, lifestyle factors, and family history of any cancer in their first-degree relatives. Age was estimated using the birth year and year of the health examination and treated as a continuous variable. Reproductive factors included age at menarche (<15 , 15–16, or ≥ 17 years), age at menopause (<45 , 45–52, or ≥ 53 years), hormone replacement therapy use after menopause (never used, <5 years, or ≥ 5 years), delivery (nullipara, 1 child, or ≥ 2 children), duration of breastfeeding (none, <1 year, or ≥ 1 year), and oral contraceptive use (ever or never used). Lifestyle factors included drinking frequency per week during the last 1 year (zero, 1 day/week, or ≥ 2 days/week), smoking (never or ever), vigorous physical activity per

week (never, 1–2 days/week, or ≥ 3 days/week), moderate physical activity per week (never, 1–2 days/week, or ≥ 3 days/week), and walking for more than 30 min per week (never, 1–2 days/week, or ≥ 3 days/week). Data on reproductive factors, lifestyle factors, and family history of cancer were collected using a self-reported questionnaire.

Statistical analysis

The basic characteristics of the study participants are presented as numbers and percentages for categorical variables and as mean and standard deviation for continuous variables across the combination of MetS and obesity. The associations between obesity, MetS, number of components of MetS, each component of MetS, and the risk of breast cancer were estimated using a Cox proportional hazards regression model. All analyses were adjusted for age, age at menarche, age at menopause, hormone replacement therapy use after menopause, delivery, duration of breastfeeding, oral contraceptive use, family history of any cancer, drinking frequency per week during the last 1 year, smoking, and physical activity including vigorous physical activity, moderate physical activity, and walking per week. The proportional hazard assumption was tested using Kaplan–Meier curves, and the survival distribution function showed parallel lines. To independently identify the associations between MetS and the risk of breast cancer and between obesity and the risk of breast cancer, we mutually adjusted for each of them. To estimate the risk of breast cancer according to obesity and MetS simultaneously, the hazard ratios (HRs) and 95% confidence intervals (CIs) of the MUNW, MHO, and MUO groups with MHNW as a reference group were calculated. The analysis of the simultaneous associations between each component of MetS and obesity, the HRs of only obese women (MHO), women with each component (MUNW), and women with both obesity and each component (MUO) were analysed using women without each component of MetS and obesity as a reference group (MUNW). The association between the number of components of MetS (per increment) and breast cancer was analysed according to obesity status. In addition, the numbers of MetS components were grouped into the following intervals: 0, 1–2, and ≥ 3 . The combination of the group number for MetS components and obesity status, and their association with breast cancer, were analysed. Finally, the associations between the combination of elevated FBG levels, obesity, abdominal obesity (WC ≥ 80 cm), and the risk of breast cancer were assessed against women with none of these conditions as a reference. A sensitivity analysis and repeated analysis were conducted after excluding incident breast cancer cases within the first 2 years of follow-up to minimise possible reverse causation. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

RESULTS

Table 1 shows the baseline characteristics of the study participants according to BMI categories and the presence of MetS at baseline. Of the 3,095,336 postmenopausal women, 1,159,536 (37.5%) were obese and 1,036,970 (33.5%) had MetS. Women with MHO and MUO status comprised 17.9% and 19.6% of the total participants and 47.7% and 52.3% of obese women, respectively.

Both obesity and MetS were associated with the risk of breast cancer, with an HR of 1.30 (95% CI = 1.26–1.33) and 1.16 (95% CI = 1.13–1.19), respectively (Table 2). When the effects of obesity and MetS were adjusted mutually, the associations were attenuated, especially for MetS; the HR for obesity was 1.26 (95% CI = 1.22–1.29) and that for MetS was 1.06 (95% CI = 1.03–1.09). Upon increasing the number of MetS components, the HR for the risk of breast cancer was 1.06 (95% CI = 1.05–1.07) before adjustment for obesity and 1.03 (95% CI = 1.02–1.04) after adjustment. All components of MetS significantly increased the risk of breast cancer by 3–21% (range of HR, 1.03–1.21). However, after adjusting for BMI, only FBG levels and WC showed an association with breast cancer (HR for elevated FBS levels: 1.08 [95% CI = 1.05–1.11]; HR for high WC: 1.06 [95% CI = 1.03–1.10]), while the other three components did not show a significant association.

The associations between metabolic obesity phenotypes (as a combination of MetS status, each component of MetS, and obesity) and breast cancer risk in postmenopausal women are presented in Table 3. With regard to MetS, compared with women

with MHNW status, women with MUNW, MHO, or MUO status had an increased risk of breast cancer, especially women with MUO status (HR = 1.05, 95% CI = 1.01–1.10 for women with MUNW status; HR = 1.25, 95% CI = 1.21–1.30 for women with MHO status; HR = 1.37, 95% CI = 1.32–1.42 for women with MUO). Regarding the presence of each component of MetS and obesity, compared with women with MHNW status, women with MHO or MUO status had an increased risk of breast cancer, with the highest risk occurring in women with MUO status. Regarding elevated BP, elevated TG, and reduced HDL, the risk of breast cancer in women with MUNW status was unchanged compared with that in women with MHNW status. However, regarding elevated FBG and elevated WC, compared with women with MHNW status, those with MUNW had a slightly higher risk of breast cancer (HR 1.08, 95% CI = 1.04–1.12 for FBG; HR 1.06, 95% CI = 1.02–1.10 for WC).

The HR for each increment in MetS components was similar in obese and non-obese women (HR 1.04, 95% CI = 1.02–1.05 in both groups, Table 4). Compared with non-obese women without any component of MetS, non-obese women with 1–2 components of MetS did not show increased risk of breast cancer, but non-obese women with ≥ 3 components of MetS showed a slightly increased risk of breast cancer (HR 1.08, 95% CI = 1.03–1.14). The HR of obese women without any MetS component was 1.17 (95% CI = 1.04–1.32), which was higher than that of non-obese women with ≥ 3 MetS components. The HRs of obese women with 1–2 components and ≥ 3 components of MetS were 1.29 (95% CI = 1.23–1.35) and 1.41 (95% CI = 1.34–1.47), respectively.

Based on the independent association between elevated FBG levels and high WC after adjusting for obesity (Table 2), we assessed the association between the combination of obesity, FBG, WC, and the risk of breast cancer (Table 5). Compared with non-obese women with normal FBG levels and WC, obese women with elevated FBG levels and WC had a higher risk of breast cancer (HR = 1.44, 95% CI = 1.38–1.50). The HR of women with obesity only was similar to that of non-obese women with elevated FBS levels and WC.

In sensitivity analysis excluding incident cases within the first two years of follow-up, none of the associations were changed, allowing for the exclusion of possible reverse causation (Supplementary Tables S1–S4).

DISCUSSION

In this large study, despite the association of both obesity and MetS with breast cancer risk in postmenopausal women, mutually adjusted results showed that the association with obesity persisted, but that the associations with MetS, number of MetS, and MetS components were attenuated. This suggests that the relationship between MetS and breast cancer appears to result from a partial association with BMI. However, the significantly increased HR of MetS after adjustment for BMI, the increased risk of breast cancer in postmenopausal women with MUNW, MHO, or MUO status compared with that in postmenopausal women with MHNW, and the highest risk in women with MUO may suggest independent contributions of both obesity and MetS to breast cancer development. Among MetS components, only elevated FBG levels and high WC were independently associated with the risk of breast cancer after adjusting for BMI. The combination of obesity status, FBG levels, and WC showed that women with all three components had a higher breast cancer risk, suggesting independent and combined effects. To the best of our knowledge, this is the first study to identify an independent association between metabolic obesity phenotype, in which the combined effect of obesity and MetS was considered, and the risk of breast cancer in Asian women.

The increased risk of breast cancer in postmenopausal women with MUO compared to that in women with MHNW status has been consistently observed in previous studies [15–17, 22, 23]. However, the observed risks of breast cancer in women with MHO

Table 1. Basic characteristics of study participants by body mass index categories and metabolic syndrome status.

	<25 kg/m ²		MetS: Yes		MetS: No		≥25 kg/m ²		MetS: Yes	
	MetS: No N	%	N	%	N	%	N	%	N	%
Age										
Mean (SD)	59.5	(8.2)	64.0	(8.2)	60.6	(7.6)	63.1	(7.8)		
Age at menarche										
<15 years	229,683	(15.3)	46,485	(10.8)	78,476	(14.2)	74,817	(12.3)		
15–16 years	594,328	(39.5)	155,914	(36.3)	213,783	(38.7)	224,133	(36.9)		
≥17 years	650,813	(43.2)	219,018	(50.9)	249,090	(45.1)	295,573	(48.7)		
Missing	30,930	(2.1)	8629	(2.0)	11,263	(2.0)	12,401	(2.0)		
Age at menopause										
<45 years	97,331	(6.5)	33,784	(7.9)	36,259	(6.6)	46,656	(7.7)		
45–52 years	985,542	(65.5)	275,496	(64.1)	344,114	(62.3)	374,685	(61.7)		
≥ 53 years	312,569	(20.8)	99,245	(23.1)	136,158	(24.6)	153,153	(25.2)		
Missing	110,312	(7.3)	21,521	(5.0)	36,081	(6.5)	32,430	(5.3)		
Hormone replacement therapy use after menopause										
Never use	1,168,767	(77.6)	357,901	(83.2)	445,628	(80.6)	511,163	(84.2)		
<5 years	224,672	(14.9)	43,914	(10.2)	67,859	(12.3)	56,801	(9.4)		
≥5 years	50,340	(3.3)	9483	(2.2)	15,302	(2.8)	11,810	(1.9)		
Missing	61,975	(4.1)	18,748	(4.4)	23,823	(4.3)	27,150	(4.5)		
Delivery										
Nullipara	50,246	(3.3)	10,117	(2.4)	14,254	(2.6)	14,428	(2.4)		
1 child	117,965	(7.8)	21,131	(4.9)	31,349	(5.7)	27,977	(4.6)		
≥2 children	1,333,804	(88.6)	397,934	(92.5)	505,479	(91.5)	563,138	(92.8)		
Missing	3739	(0.2)	864	(0.2)	1350	(0.2)	1381	(0.2)		
Duration of breastfeeding										
Never	132,234	(8.8)	24,088	(5.6)	34,800	(6.3)	32,426	(5.3)		
<1 year	431,137	(28.6)	86,213	(20.0)	125,071	(22.6)	114,203	(18.8)		
≥1 year	933,256	(62.0)	317,406	(73.8)	389,205	(70.4)	456,761	(75.3)		
Missing	9117	(0.6)	2339	(0.5)	3536	(0.6)	3534	(0.6)		
Oral contraceptive use										
Never	1,206,810	(80.2)	341,639	(79.4)	432,208	(78.2)	473,633	(78.0)		
Ever	215,041	(14.3)	63,310	(14.7)	88,096	(15.9)	97,740	(16.1)		
Missing	83,903	(5.6)	25,097	(5.8)	32308	(5.8)	35,551	(5.9)		
Family history of any cancer										
No	1,210,452	(80.4)	362,866	(84.4)	450,829	(81.6)	509,760	(84.0)		
Yes	295,302	(19.6)	67,180	(15.6)	101783	(18.4)	97,164	(16.0)		
Drinking frequency during the last 1 year										
No	1,280,493	(85.0)	382,158	(88.9)	471,562	(85.3)	534,210	(88.0)		
1 day/week	129,248	(8.6)	26,005	(6.1)	46,718	(8.5)	40,816	(6.7)		
≥2 day/week	83,814	(5.6)	18,546	(4.3)	29,965	(5.4)	27,355	(4.5)		
Missing	12,199	(0.8)	3337	(0.8)	4367	(0.8)	4543	(0.8)		
Smoking										
Never	1439103	(95.6)	410,656	(95.5)	533,131	(96.5)	582,242	(95.9)		
Ever	59859	(4.0)	17,678	(4.1)	16,878	(3.1)	22,141	(3.6)		
Missing	6792	(0.4)	1712	(0.4)	2603	(0.5)	2541	(0.4)		
Vigorous physical activity										
No	1049681	(69.7)	322,050	(74.9)	394,915	(71.5)	458,338	(75.5)		
1–2 day/week	220008	(14.6)	52,253	(12.2)	73,543	(13.3)	70,568	(11.6)		
≥3 day/week	227229	(15.1)	53,471	(12.4)	81,139	(14.7)	74,896	(12.3)		
Missing	8836	(0.6)	2272	(0.5)	3015	(0.6)	3122	(0.5)		
Moderate physical activity										

Table 1 continued

	<25 kg/m ²				≥25 kg/m ²			
	MetS: No		MetS: Yes		MetS: No		MetS: Yes	
	N	%	N	%	N	%	N	%
No	939474	(62.4)	290,625	(67.6)	356,405	(64.5)	414,701	(68.3)
1–2 day/week	243488	(16.2)	59,783	(13.9)	82,780	(15.0)	82,400	(13.6)
≥3 day/week	311141	(20.7)	76,065	(17.7)	109,071	(19.7)	104,774	(17.3)
Missing	11651	(0.8)	3573	(0.8)	4356	(0.8)	5049	(0.8)
Walking								
No	523887	(34.8)	162,895	(37.9)	205,264	(37.1)	238,072	(39.2)
1–3 days/week	453691	(30.1)	122,496	(28.5)	159,851	(28.9)	172,106	(28.4)
4–6 days/week	311160	(20.7)	79,162	(18.4)	106,325	(19.2)	106,941	(17.6)
7 days/week	208162	(13.8)	62,798	(14.6)	77,747	(14.1)	85,956	(14.2)
Missing	8854	(0.6)	2695	(0.6)	3425	(0.6)	3849	(0.6)

MetS metabolic syndrome, SD standard deviation.

Table 2. Associations between obesity, metabolic syndrome, and the risk of breast cancer in postmenopausal women who underwent a national Korean breast cancer screening program from 2009 to 2010.

BMI, metabolic phenotype	No. participants	Person-years	No. cases	Adjusted HR (95% CI) ^a	P-value	Adjusted HR (95% CI) ^b	P-value
BMI							
<25 kg/m ²	1,935,800	16,868,556.0	13,749	1.00		1	
≥25 kg/m ²	1,159,536	10,083,792.0	9835	1.30 (1.26–1.33)	<0.001	1.26 (1.22–1.29)	<0.001
MetS							
No	2,058,366	17,931,890.4	15,705	1.00		1	
Yes	1,036,970	9,020,457.7	7879	1.16 (1.13–1.19)	<0.001	1.06 (1.03–1.09)	<0.001
N of component of MetS							
Per 1 increment	–	–	–	1.06 (1.05–1.07)	<0.001	1.03 (1.02–1.04)	<0.001
Component of MetS							
Elevated BP							
No	1,697,774	14,787,997.2	13,324	1.00		1.00	
Yes	1,397,562	12,164,350.9	10,260	1.06 (1.03–1.09)	<0.001	1.01 (0.99–1.04)	0.405
Elevated FBG							
No	2,017,573	17,589,624.6	15,120	1.00		1.00	
Yes	1,077,763	9,362,723.5	8464	1.13 (1.10–1.16)	<0.001	1.08 (1.05–1.11)	<0.001
High WC							
No	1,512,909	13,185,877.7	11,264	1.00		1.00	
Yes	1,582,427	13,766,470.4	12,320	1.21 (1.18–1.24)	<0.001	1.06 (1.03–1.10)	0.001
Elevated TG							
No	2,176,753	18,948,154.5	16,737	1.00		1.00	
Yes	918,583	8,004,193.5	6847	1.06 (1.03–1.09)	<0.001	1.01 (0.98–1.04)	0.596
Reduced HDL							
No	2,042,142	17,775,976.8	15,748	1.00		1.00	
Yes	1,053,194	9,176,371.3	7,836	1.03 (1.00–1.06)	0.024	1.02 (0.99–1.05)	0.203

MetS metabolic syndrome, BP blood pressure, FBG fasting blood glucose, WC waist circumference, TG triglyceride, HDL high-density lipoprotein, HR hazard ratio, CI confidence interval.

^aAdjusted for age, age at menarche, age at menopause, hormone replacement therapy use after menopause, delivery, duration of breastfeeding, oral contraceptive use, family history of any cancer, drinking frequency per week during the last 1 year, smoking, and physical activity including vigorous physical activity, moderate physical activity, and walking per week.

^bAdjusted for the variables mentioned above^a and additionally mutually adjusted for BMI (<25 kg/m², ≥ 25 kg/m²) and MetS (no, yes).

and MUNW were inconsistent, followed by various conclusions regarding the association between metabolic obesity phenotypes, considered as a combination of MetS status and obesity, and breast cancer [24]. Several studies have shown an increased risk of breast cancer in postmenopausal women with MHO status, but

not in postmenopausal women with MUNW, and have proposed the contribution of metabolic health to the risk of breast cancer in only overweight/obese women [15, 16, 23]. A previous study showed an elevated risk of breast cancer in postmenopausal women with MUNW but not in postmenopausal women with

Table 3. Hazard ratio and 95% confidence interval of the combined effects of metabolic syndrome and obesity status on the risk of breast cancer in postmenopausal women who underwent a national Korean breast cancer screening program from 2009 to 2010.

Metabolic phenotype	No. participants	Person-years	No. cases	Adjusted HR ^a (95% CI)	P
<i>MeS</i>					
MHNW	1,505,754	13,122,024.1	10,996	1.00	
MHO	552,612	4,809,866.3	4709	1.25 (1.21–1.30)	<0.001
MUNW	430,046	3,746,531.9	2753	1.05 (1.01–1.10)	0.019
MUO	606,924	5,273,925.8	5126	1.37 (1.32–1.42)	<0.001
<i>Elevated BP</i>					
MHNW	1,175,139	10,239,426.2	8825	1.00	
MHO	522,635	4,548,571.0	4499	1.25 (1.21–1.30)	<0.001
MUNW	760,661	6,629,129.8	4924	1.00 (0.96–1.03)	0.808
MUO	636,901	5,535,221.1	5336	1.33 (1.29–1.38)	<0.001
<i>Elevated FBG</i>					
MHNW	1,346,303	11,740,805.9	9559	1.00	
MHO	671,270	5,848,818.7	5561	1.27 (1.23–1.32)	<0.001
MUNW	589,497	5,127,750.1	4190	1.08 (1.04–1.12)	<0.001
MUO	488,266	4,234,973.3	4274	1.41 (1.36–1.46)	<0.001
<i>High WC</i>					
MHNW	1,359,005	11,843,719.9	9944	1.00	
MHO	153,904	1,342,157.8	1320	1.19 (1.12–1.26)	<0.001
MUNW	576,795	5,024,836.1	3805	1.06 (1.02–1.10)	<0.001
MUO	1,005,632	8,741,634.3	8515	1.34 (1.30–1.38)	<0.001
<i>Elevated TG</i>					
MHNW	1,447,899	12,613,075.6	10,447	1.00	
MHO	728,854	6,335,078.9	6290	1.31 (1.26–1.35)	<0.001
MUNW	487,901	4,255,480.4	3302	1.04 (1.00–1.08)	0.067
MUO	430,682	3,748,713.2	3545	1.31 (1.26–1.36)	<0.001
<i>Reduced HDL</i>					
MHNW	1,331,239	11,595,263.0	9697	1.00	
MHO	710,903	6,180,713.9	6051	1.28 (1.24–1.32)	<0.001
MUNW	604,561	5,273,293.1	4052	1.00 (0.96–1.03)	0.871
MUO	448,633	3,903,078.1	3784	1.32 (1.27–1.37)	<0.001

MeS metabolic syndrome, *BP* blood pressure, *FBG* fasting blood glucose, *WC* waist circumference, *TG* triglyceride, *HDL* high-density lipoprotein, *HR* hazard ratio, *CI* confidence interval; MHNW (BMI < 25.0 kg/m² and no MetS or each component of MetS), MUNW (BMI < 25.0 kg/m² and presence of MetS or each component of MetS), MHO (BMI ≥ 25.0 kg/m² and no MetS) or each component of MetS, and MUO (BMI ≥ 25.0 kg/m² and presence of MetS or each component of MetS).

^aAdjusted for age, age at menarche, age at menopause, hormone replacement therapy use after menopause, delivery, duration of breastfeeding, oral contraceptive use, family history of any cancer, drinking frequency per week during the last 1 year, smoking, and physical activity including vigorous physical activity, moderate physical activity, and walking per week.

MHO status, suggesting that metabolic health would be more useful than adiposity for risk stratification [22]. Another study showed an increased risk of breast cancer in women with both MHO and MUNW status compared with that in women with MHNW status, suggesting an independent role of obesity and metabolic dysregulation [17]. In the present study, the independent association between MetS and obesity, and the increased risk in women with MUNW or MHO status compared with that in women with MHNW, support the result [17].

In previous studies, various definitions of metabolic health have been applied. Some studies have applied the definition of MetS using NECP-ATP III [15, 16] or the objective measurement of FBG [23]. Park et al. [17] defined metabolic abnormalities for type 2 diabetes or dyslipidemia based on self-reported medical history. In addition, being metabolically unhealthy was defined as having at least one of four factors, whereas the definition of NECP-ATP III criteria applies ≥3 factors. Gunter et al. [22] defined metabolic health using a homeostasis model assessment of insulin

resistance (HOMA-IR) and fasting insulin. Various definitions of metabolic health may be attributed to these inconsistent results.

Regarding each component of MetS, despite the possibility that the association between WC and postmenopausal breast cancer is a result of the correlation with BMI [25], a recent meta-analysis suggested that WC could be a predictor for breast cancer independent of BMI [6], which is consistent with our results. The increased risk of breast cancer in women with type 2 diabetes has been well established in a previous meta-analysis [26]. The association between hypertension and the risk of breast cancer has been inconsistent. A meta-analysis did not find a significant association between hypertension and postmenopausal breast cancer in five studies; however, when only two studies were considered for multiple adjustments, increased risk was observed and remained controversial [27]. Regarding dyslipidemia, the association between elevated TG and a decreased risk of total breast cancer and between elevated HDL and decreased risk of postmenopausal breast cancer was reported in a recent meta-

Table 4. Hazard ratio and 95% confidence interval of the combined effects of the number of components of metabolic syndrome and obesity status on the risk of breast cancer in postmenopausal women who underwent a national Korean breast cancer screening program from 2009 to 2010.

	BMI (kg/m ²)	No. participants	Person-years	No. cases	Adjusted HR ^a (95% CI)	P
Per 1 increment	<25	–	–	–	1.04 (1.02–1.05)	<0.001
	≥25	–	–	–	1.04 (1.02–1.05)	<0.001
0	<25	433,565	3,776,535.3	3,384	1.00	
	≥25	34,061	297,067.3	299	1.17 (1.04–1.32)	0.010
1–2	<25	1,072,189	9,345,488.8	7,612	1.04 (0.99–1.08)	0.083
	≥25	518,551	4,512,799.0	4,410	1.29 (1.23–1.35)	<0.001
>= 3	<25	430,046	3,746,531.9	2,753	1.08 (1.03–1.14)	0.003
	≥25	606,924	5,273,925.8	5,126	1.41 (1.34–1.47)	<0.001

BMI body mass index; HR hazard ratio; CI confidence interval.

^aAdjusted for age, age at menarche, age at menopause, hormone replacement therapy use after menopause, delivery, duration of breastfeeding, oral contraceptive use, family history of any cancer, drinking frequency per week during the last 1 year, smoking, and physical activity including vigorous physical activity, moderate physical activity, and walking per week.

Table 5. Hazard ratios and 95% confidence intervals for the combined effects of elevated fasting blood glucose levels, obesity, and central obesity on the risk of breast cancer in postmenopausal women who underwent a national Korean breast cancer screening program from 2009 to 2010.

Elevated FBG	BMI (kg/m ²)	High WC	No. participants	Person-years	No. cases	Adjusted HR ^a (95% CI)	P
No	<25	No	986,593	8,602,975.4	7203	1.00	
		Yes	359,710	3,137,830.6	2356	1.05 (1.00–1.10)	0.040
	≥25	No	104,324	911,094.3	862	1.15 (1.08–1.24)	<0.001
		Yes	566,946	4,937,724.4	4699	1.32 (1.27–1.37)	<0.001
Yes	<25	No	372,412	3,240,744.5	2741	1.08 (1.03–1.13)	0.001
		Yes	217,085	1,887,005.6	1449	1.13 (1.07–1.20)	<0.001
	≥25	No	49,580	431,063.5	458	1.34 (1.22–1.48)	<0.001
		Yes	438,686	3,803,909.9	3816	1.44 (1.38–1.50)	<0.001

FBG fasting blood glucose, WC waist circumference.

^aAdjusted for age, age at menarche, age at menopause, hormone replacement therapy use after menopause, delivery, duration of breastfeeding, oral contraceptive use, family history of any cancer, drinking frequency per week during the last 1 year, smoking, and physical activity including vigorous physical activity, moderate physical activity, and walking per week.

analysis [28]. However, this study assessed the relative risk of the highest vs. lowest risk category and did not consider certain thresholds, such as NECP-ATP or WHO [28]. The five components of MetS are largely and mutually affected by general obesity (BMI), but the consideration of BMI in previous studies varied. In this study, all MetS components increased postmenopausal risk of breast cancer, but when BMI was additionally adjusted, the associations were attenuated and statistical significance was maintained only for elevated FBG and WC, suggesting that the association could be at least partially attributed to BMI. Zhao et al. reported that central obesity and diabetes are essential components of MetS related to the risk of breast cancer [8], which supports our results after adjusting for BMI.

Despite the suggestion that central obesity is critical for the relationship between metabolic phenotype and breast cancer [17], among the independently associated metabolic obesity phenotypes, WC showed a smaller effect than that of both BMI and FBS in this study. A lower cut-off for abdominal obesity may explain the effect of WC. However, when we applied a WC cut-off of ≥85 cm, the results were comparable with those with a WC cut-off of ≥80 cm (results not shown). General obesity (based on the BMI) could affect postmenopausal breast cancer in two ways: overlapping pathogenesis with MetS [29] and increased oestrogen from the aromatisation of androgen in adipose tissue, thus showing a greater effect. Insulin resistance and central obesity are suggested to be the main factors in the pathogenesis of MetS [30, 31]. These findings may explain the independent and combined effects of BMI, FBS, and WC and their importance.

This study has several limitations. First, to define MetS, we did not consider treatment for hypertension, hyperglycaemia, or hyperlipidemia due to a lack of information on medication. Thus, medication-induced normal BP, FBG, HDL, or TG levels could be mixed in the normal group. Second, we did not consider changes in the MetS status and BMI during the follow-up period. As seen in the Reasons for Geographic and Racial Differences in Stroke cohort [32], we expected nondifferential changes in MetS status and BMI related to baseline estimates. Third, women who underwent health examinations were included in this study, and their characteristics might differ from those who did not undergo the examination. However, the participation rate in the NHIS health examination was ~70%, and we included all female examinees. Thus, the effect of selection bias on the associations observed in this study is expected to be minimal. Fourth, despite the various associations between obesity, MetS, and breast cancer subtypes, such as hormone receptor status [3], these factors were not considered in this study because the NHIS data did not have information on tumour characteristics. Fifth, some confounders such as diet could not be adjusted due to a lack of information, leaving possible residual confounding. Sixth, a follow-up period of 9 years may be considered a short timeframe for investigating the causal association between obesity, metabolic health, and breast cancer risk. Nevertheless, the follow-up period of this study is comparable to or longer than that in previous prospective studies [15, 17, 33].

In conclusion, obesity and MetS were independently associated with an increased risk of breast cancer in postmenopausal women. However, the contribution of MetS, independent of obesity, on

breast cancer risk was observed despite the fact that MetS and breast cancer appear to result from a partial association with BMI. Based on the increased postmenopausal risk of breast cancer in women with MUNW, MHO, and MUO, postmenopausal obese women should be encouraged to control their weight and metabolic health, especially FBG and WC.

DATA AVAILABILITY

The data that support the findings of this study are available on the website of the National Health Insurance Sharing Service (<https://nhiss.nhis.or.kr/>), and can be accessed by submitting a study protocol, document of IRB approval, and request form after being reviewed by the relevant committee.

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AUTHOR CONTRIBUTIONS

Conceptualisation, BP and MSC; Methodology, BP and CC; Formal analysis, BP and SK; Data curation, SK and HK; Writing—original draft preparation, BP and CC; Writing—review & editing, BP. and MSC; Project administration, SK and HK.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Before the health examination, consent for the transfer of results to the national health screening database was obtained from each participant. The Institutional Review Board (IRB) of Hanyang University College of Medicine approved the study protocol (IRB no. HYI-18-175-1). Before the health examination, consent for the transfer of results to the national health screening database was obtained from each participant.

CONSENT TO PUBLISH

Not applicable.

ADDITIONAL INFORMATION

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