Influence of Metabolic Syndrome on Risk of Breast Cancer: A Study Analyzing Nationwide Data from Korean National Health Insurance Service

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ABSTRACT

Background: To investigate the influence of metabolic syndrome and its components on the risk of breast cancer.

Methods: Retrospective nationwide cohort study analyzing data of 13,377,349 women older than 19 years from Korean National Health Insurance Service was performed. Cox proportional hazards model was used to calculate HR and 95% confidence interval (CI) of breast cancer risk.

Results: The presence of metabolic syndrome decreased the risk of all breast cancer types in all subjects (HR, 0.954; 95% CI, 0.939–0.970). In women with age ≤50 years, metabolic syndrome decreased the risk of all breast cancer types, with similar findings for all subject groups (HR, 0.915; 95% CI, 0.892–0.939). In women with age >50 years, metabolic syndrome increased the risk of all breast cancer types (HR, 1.146; 95% CI, 1.123–1.170), especially in age groups of more than 55 years. In women with age >50 years, HRs increased as the number of metabolic syndrome components increased, while HRs decreased as the number of metabolic syndrome components increased in women with age ≤50 years.

Conclusions: The presence of metabolic syndrome increased the risk of breast cancers in postmenopausal women, but decreased the risk in premenopausal women. Every metabolic syndrome component played similar roles on the risk of breast cancer as metabolic syndrome, and their effects became stronger when the number of components increased.

Impact: Metabolic syndrome is associated with the risk of breast cancer having different effect according to age groups.

Introduction

Metabolic syndrome is a constellation of interrelated risk factors of metabolic origin that appear to directly promote the development of cardiovascular disease and type 2 diabetes mellitus (1). The name of metabolic syndrome (2) has also been described in various terms such as Reaven syndrome (3), syndrome X (3), deadly quartet (4), insulin resistance syndrome (5), hypertriglyceridemic waist (6), and dysmetabolic syndrome. The most widely proposed metabolic risk factors are dyslipidemia, elevated blood pressure, elevated plasma glucose, and abdominal obesity. Criteria for clinical diagnosis of metabolic syndrome have been proposed by several expert groups. The World Health Organization (WHO) proposed the criteria of metabolic syndrome in 1998 (7). Since then, the European Group for Study of Insulin Resistance (EGIR; ref. 8), National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III; ref. 9), American Association of Clinical Endocrinologists (AACE; ref. 10), International Diabetes Foundation (IDF; ref. 11), and American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) have proposed their own criteria (1).

Metabolic syndrome has been reported to be associated with risks of various human cancers. A previous meta-analysis has shown that the presence of metabolic syndrome is associated with increased risk of liver, colorectal, and bladder cancers in men (12). It also found that increased risk of endometrial, pancreatic, colorectal, and postmenopausal breast cancer in women was associated with metabolic syndrome. Regarding breast cancer, previous studies have reported the association between metabolic syndrome and breast cancer, although results are inconsistent. Some studies have reported a positive association between metabolic syndrome and breast cancer (13–18), while other studies have reported no association (19–22). Furthermore, some studies have reported a negative association between them in premenopausal women (20). Currently, the association between metabolic syndrome and breast cancer remains largely unknown. Thus, more studies are needed to clarify this association.

The Republic of Korea (South) has a National Health Insurance system which is compulsory and required by the Korean law. The National Health Insurance Service (NHIS) is responsible for the management of National Health Insurance system. It covers all residents who are enrolled in the National Health Insurance system of Republic of Korea (South). The NHIS provides data of routine health checkups including information of metabolic syndrome and

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breast cancer. In this study, we investigated the association between metabolic syndrome and breast cancer risk in women using large nationwide data from the Korean NHIS.

Materials and Methods

Study subjects

This study is a retrospective cohort study utilizing data of routine health checkups provided by the NHIS. Target subjects of this study were women who received routine health checkups between 2009 and 2014 at the age of older than or equal to 20 years. The total number of subjects who had received routine health checkups between January 2009 and December 2014 was 27,155,170. Of these, subjects who met the exclusion criteria were sequentially excluded as follows: male subjects (n = 13,677,080), subjects younger than 20 years old (n = 32,339), subjects with incomplete information of metabolic syndrome (n = 28,723), and subjects who had been diagnosed with primary breast cancer at baseline, time of this study (n = 39,679). Primary cancers other than breast cancer were not considered at all. The final number of subjects included in this study was 13,377,349. End of follow-up of this study for all final subjects was December 31, 2015.

Definition of variables

Different definitions of metabolic syndrome have been proposed by WHO, EGIR, NCEP-ATP III, AACE, IDF, and AHA/NHLBI. Of these, this study adopted the AHA/NHLBI criteria (1). Metabolic syndrome was defined as having any three of the five metabolic syndrome components: elevated waist circumference (≥80 cm), elevated blood pressure (≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on antihypertensive drug), elevated fasting glucose (≥100 mg/dL or on drug treatment for elevated glucose), elevated triglyceride (≥150 mg/dL or on drug treatment for elevated triglyceride), and reduced high-density lipoprotein cholesterol (<50 mg/dL or on drug treatment for reduced high-density lipoprotein cholesterol). Although a subject could have repetitive data of metabolic syndrome during the enrollment period, we only utilized data of metabolic syndrome from the first routine health checkup as baseline information. The other information of metabolic syndrome except baseline information was not utilized. Age was defined as the baseline age when the subject was enrolled in this study. Body mass index (BMI) was defined as the ratio of body weight in kilograms to height in square meters. Smoking was classified into no smoker, ex-smoker, and current smoker. Alcohol drinking was classified into no drinker, moderate drinker (ethanol 0–30 g/day), and heavy drinker (ethanol >30 g/day). Exercise was classified into no (<3 days of vigorous intensity and <5 days of moderate intensity) and yes (≥3 days of vigorous intensity or ≥5 days of moderate intensity). Income was classified into four quartiles with Q1 as the lowest and Q4 as the highest. Breast cancer type was classified into two groups including invasive breast cancer and *in situ* breast cancer by pathologic diagnosis. Information of breast cancer type was acquired from claim data of NHIS.

Statistical analyses

Pearson χ^2 test was used to determine statistical differences in baseline characteristics between groups. Cox proportional hazards model was used to calculate HR and 95% confidence interval (CI) of breast cancer risk. All adjusted HRs were obtained by Cox proportional hazards model after adjusting for age, smoking, alcohol drinking, exercise, and income. In this study, we did not consider any competing risks or competing events. As data of metabolic syndrome was retrieved from the first routine health checkup without utilizing the other data of routine health checkups, time-dependent Cox regression was not performed. To assess differential effects of metabolic syndrome on the breast cancer risk according to the subgroup, Cox proportional hazards regression was conducted using factors such as metabolic syndrome, each subgroup, and interaction term between metabolic syndrome and each subgroup with adjustment for covariates. $P_{interaction}$ was calculated to interpret the effect of metabolic syndrome on the risk of breast cancer across subgroups, and it represents the overall significance for an interaction effect of metabolic syndrome and each subgroup. All statistical analyses were carried out using IBM SPSS Statistics, version 20.0 (IBM Corp.) and R software version 3.6.0 (R Foundation for Statistical Computing). All tests were two-sided. Statistical significance was considered when P value was less than 0.05.

Results

Baseline characteristics of study subjects according to metabolic syndrome

The total number of subjects was 13,377,349 (64,535,186 person-year). Numbers of subjects with and without metabolic syndrome were 3,578,546 (26.8%) and 9,798,803 (73.3%), respectively (**Table 1**). Women with metabolic syndrome showed higher proportions of all five metabolic syndrome components. Women with metabolic syndrome also showed higher proportions of age >50 years and BMI ≥25 kg/m^2. Women without metabolic syndrome showed higher proportions of smoking, alcohol drinking, exercise, and low income. Total numbers of subjects diagnosed as invasive breast cancer and *in situ* breast cancer, regardless of metabolic syndrome, were 79,447 and 8,300, respectively. Baseline characteristics of study subjects according to metabolic syndrome and breast cancer type are summarized in Supplementary Table S1.

Breast cancer risk according to metabolic syndrome

The presence of metabolic syndrome decreased the risk of all breast cancer types (HR, 0.954; 95% CI, 0.939–0.970; **Table 2**). In the subgroup with age ≤50 years, metabolic syndrome decreased the risk of all breast cancer types, with similar findings for all subject groups (HR, 0.915; 95% CI, 0.892–0.939). In the subgroup with age >50 years, metabolic syndrome increased the risk of all breast cancer types (HR, 1.146; 95% CI, 1.123–1.170). Each group with invasive breast cancer or *in situ* breast cancer showed similar findings to groups with all breast cancer types. Details for HR of breast cancer risk in each subgroup are described in **Table 2**.

Subgroup analysis of breast cancer risk according to metabolic syndrome

For the subgroup with age ≤50 years, metabolic syndrome decreased risks of breast cancers in most subgroups according to BMI, smoking, alcohol drinking, exercise, and income (**Table 3**). On the contrary, metabolic syndrome increased risks of breast cancers in most subgroups for the group with age >50 years. For the all subjects group, although metabolic syndrome decreased risks of breast cancers in the age subgroup with age ≤50 years, it increased risks of breast cancers in the age subgroup with age >50 years, regardless of breast cancer types. HRs of each age subgroup with 5-year interval are described in **Table 4**. In age groups of more than 55 years, metabolic syndrome increased risks of breast cancers. Furthermore, HRs increased as age increased until 80 years. HRs of invasive breast cancer showed similar findings with those of all breast cancer types. Subgroups with age less than

Table 1. Baseline characteristics of study subjects according to metabolic syndrome.

	All		Metabolic syndrome				
			No		Yes		
Subject characteristics	**Number**	**%**	**Number**	**%**	**Number**	**%**	***P***
Total	13,377,349	100.0	9,798,803	73.3	3,578,546	26.8	
Elevated waist circumference							<0.001
No	8,848,361	66.1	7,969,930	81.3	878,431	24.6	
Yes	4,528,988	33.9	1,828,873	18.7	2,700,115	75.5	
Elevated blood pressure							<0.001
No	8,553,448	63.9	7,814,183	79.8	739,265	20.7	
Yes	4,823,901	36.1	1,984,620	20.3	2,839,281	79.3	
Elevated fasting glucose							<0.001
No	9,830,971	73.5	8,427,435	86.0	1,403,536	39.2	
Yes	3,546,378	26.5	1,371,368	14.0	2,175,010	60.8	
Elevated triglyceride							<0.001
No	9,809,187	73.3	8,926,112	91.1	883,075	24.7	
Yes	3,568,162	26.7	872,691	8.9	2,695,471	75.3	
Reduced high-density lipoprotein							<0.001
No	8,741,957	65.4	8,002,636	81.7	739,321	20.7	
Yes	4,635,392	34.7	1,796,167	18.3	2,839,225	79.3	
Age (year)							<0.001
≤50	5,590,171	41.8	6,937,349	70.8	849,829	23.8	
>50	7,787,178	58.2	2,861,454	29.2	2,728,717	76.3	
BMI (kg/m^2)							<0.001
<25	3,514,121	26.3	8,231,236	84.0	1,631,992	45.6	
≥25	9,863,228	73.7	1,567,567	16.0	1,946,554	54.4	
Smoking							<0.001
No	12,485,305	93.3	9,113,151	93.0	3,372,154	94.2	
Former	296,045	2.2	236,857	2.4	59,188	1.7	
Current	595,999	4.5	448,795	4.6	147,204	4.1	
Alcohol drinking							<0.001
No	9,778,319	73.1	6,753,373	68.9	3,024,946	84.5	
Moderate (0–30 g/day)	3,450,394	25.8	2,925,291	29.9	525,103	14.7	
Heavy (>30 g/day)	148,636	1.1	120,139	1.2	28,497	0.8	
Exercise							<0.001
No	7,586,355	56.7	5,373,645	54.8	2,212,710	61.8	
Yes	5,790,994	43.3	4,425,158	45.2	1,365,836	38.2	
Income							<0.001
Q1	4,253,128	31.8	3,176,086	32.4	1,077,042	30.1	
Q2–Q4	9,124,221	68.2	6,622,717	67.6	2,501,504	69.9	
Invasive and *in situ* breast cancers							<0.001
No	13,289,602	99.3	9,736,409	99.4	3,553,193	99.3	
Yes	87,747	0.7	62,394	0.6	25,353	0.7	
Invasive breast cancer							<0.001
No	13,297,902	99.4	9,742,627	99.4	3,555,275	99.4	
Yes	79,447	0.6	56,176	0.6	23,271	0.7	
In situ breast cancer							<0.001
No	13,369,049	99.9	9,792,585	99.9	3,576,464	99.9	
Yes	8,300	0.1	6,218	0.1	2,082	0.1	

55 years showed weak or no significance regarding HRs for each type of breast cancer.

Breast cancer risk according to metabolic syndrome components

In the subgroup with age >50 years, HRs for all breast cancer types increased as the number of metabolic syndrome components increased except for the subgroup with only one metabolic syndrome component (**Table 5**). On the contrary, HRs for all breast cancer types decreased as the number of metabolic syndrome components increased in the subgroup with age ≤50 years, although the HR of the subgroup with five metabolic syndrome components was not lower than that of the subgroup with four components. As a whole, HRs for all breast cancer types lost their trends in all subject groups. However, subgroups with any of metabolic syndrome components showed increased risks of breast cancers except for the subgroup with four components. Invasive breast cancers showed similar patterns with all breast cancer types. HRs according to metabolic syndrome components in each breast cancer type are described in Supplementary Table S2. The presence of any metabolic syndrome component increased the risks of breast cancers in the subgroup with age >50 years in both all types of breast cancers and invasive breast cancer type. On the contrary, any metabolic syndrome component decreased the risks of breast cancers in the subgroup with age ≤50 years with several exceptions. The influence of metabolic syndrome components weakened in the all subjects group. HRs of breast cancer risk according to metabolic syndrome

Table 2. Adjusted HRs of breast cancer risk according to metabolic syndrome in each age group.

Age group (year)	Type of breast cancer	Metabolic syndrome	Number	Event	Rate	HR[a] (95% CI)
Total	Invasive and *in situ* breast cancers					
		No	9,798,803	62,394	1.333	Reference
		Yes	3,578,546	25,353	1.431	0.954 (0.939–0.970)
	Invasive breast cancer					
		No	9,798,803	56,176	1.199	Reference
		Yes	3,578,546	23,271	1.313	0.965 (0.949–0.982)
	In situ breast cancer					
		No	9,798,803	6,218	0.132	Reference
		Yes	3,578,546	2,082	0.117	0.849 (0.803–0.897)
Age ≤50	Invasive and *in situ* breast cancers					
		No	6,937,349	42,655	1.322	Reference
		Yes	849,829	6,915	1.751	0.915 (0.892–0.939)
	Invasive breast cancer					
		No	6,937,349	38,076	1.180	Reference
		Yes	849,829	6,300	1.595	0.932 (0.907–0.957)
	In situ breast cancer					
		No	6,937,349	4,579	0.141	Reference
		Yes	849,829	615	0.155	0.777 (0.714–0.847)
Age >50	Invasive and *in situ* breast cancers					
		No	2,861,454	19,739	1.356	Reference
		Yes	2,728,717	18,438	1.340	1.146 (1.123–1.170)
	Invasive breast cancer					
		No	2,861,454	18,100	1.243	Reference
		Yes	2,728,717	16,971	1.233	1.146 (1.122–1.171)
	In situ breast cancer					
		No	2,861,454	1,639	0.112	Reference
		Yes	2,728,717	1,467	0.106	1.143 (1.063–1.229)

[a]Adjusted HRs obtained by Cox proportional hazards model after being adjusted for age, smoking, alcohol drinking, exercise, and income.

components in each age group and breast cancer type are further described in Supplementary Table S3. The influence pattern of metabolic syndrome components distinctly changed with the cutoff value of age at 55 years. In the age subgroups with age of more than 60 years, positive correlation was prominent between HRs and total number of metabolic syndrome components (**Fig. 1A**). More prominent positive correlations were observed as the age of subgroups became older. BMI was strongly associated with breast cancer risk (**Fig. 1B**). HRs increased as BMI increased. These findings were more prominent as the age of subgroups became older.

Discussion

This study utilized nationwide data of 13,377,349 female subjects (64,535,186 person-year) older than 19 years from the Korean NHIS and investigated the influence of metabolic syndrome on the risk of breast cancer. This study showed that the presence of metabolic syndrome increased the risks of both invasive breast cancer and *in situ* breast cancer in the subgroup with age >50 years, but decreased the risks of both invasive and *in situ* breast cancers in the subgroup with age ≤50 years. As a whole, metabolic syndrome decreased the risks of both breast cancer types in all subjects.

The prevalence of metabolic syndrome has been reported to have broad ranges according to definitions of metabolic syndrome and study populations (23–25). Rochlani and colleagues (23) have performed a literature review and reported that prevalence rates of metabolic syndrome in women in the United States and Republic of Korea (South) are 21.8%–37.4% and 21.3% (NCEP-ATP III), respectively. O'Neill and O'Driscoll (24) have reported that prevalence rates of metabolic syndromes in females in the United States and Republic of Korea (South) are 38.1% (IDF criteria) and 9.1% (NCEP-ATP III), respectively. Agnoli and colleagues (13) have used the same definition as in our study (AHA/NHLBI) and reported a prevalence of 29.8% in Italian postmenopausal women. In our study, the prevalence rate of metabolic syndrome in Korean women older than 19 years was 26.8%.

For postmenopausal women, previous studies have reported the influence of metabolic syndrome on the risk of breast cancer, although results are inconsistent. Some studies have insisted no association (19–22), while others have reported a positive association (13–18). Kabat and colleagues (19) have analyzed data of 4,888 postmenopausal women [6% of subjects in the Women's Health Initiative (WHI) clinical trial and 1% of women in the observational study] during 1993–1998. They reported that the presence of the metabolic syndrome had no significant association with altered risk of postmenopausal breast cancer [HR (95% CI), 1.12 (0.78–1.62) for all breast cancers and HR (95% CI), 1.19 (0.79–1.79) for invasive breast cancer]. Bjørge and colleagues (20) have analyzed data of 287,320 women enrolled in the Me-Can study during 1974–2005. They also reported no significant association between metabolic syndrome and the risk of breast cancer in postmenopausal women [RR (95% CI), 0.95 (0.87–1.01) for age 50–59 years and RR (95% CI), 1.04 (0.97–1.12) for age ≥60 years]. Agnoli and colleagues (13) have analyzed data of 3,966 postmenopausal women enrolled in the ORDET study during 1987–1992. They reported that the presence of metabolic syndrome was significantly associated with increased postmenopausal breast cancer risk (rate ratio, 1.58; 95% CI, 1.07–2.33). Rosato and colleagues (15) have analyzed data of 3,869 postmenopausal women with breast

Table 3. Adjusted HRs of breast cancer risk for groups with metabolic syndrome in each subgroup according to age group and breast cancer type.

Age group (year)	Subgroup	Invasive and *in situ* breast cancers		Invasive breast cancer		*In situ* breast cancer	
		HR[a] (95% CI)	$P_{interaction}$	HR[a] (95% CI)	$P_{interaction}$	HR[a] (95% CI)	$P_{interaction}$
Total	Age (year)						
	≤50	0.915 (0.892–0.939)	<0.001	0.932 (0.907–0.957)	<0.001	0.777 (0.714–0.847)	0.048
	>50	1.146 (1.123–1.170)		1.146 (1.122–1.171)		1.143 (1.063–1.229)	
	BMI (kg/m^2)						
	<25	0.830 (0.811–0.849)	<0.001	0.837 (0.817–0.858)	<0.001	0.763 (0.707–0.823)	<0.001
	≥25	1.056 (1.028–1.084)		1.054 (1.026–1.084)		1.071 (0.975–1.176)	
	Smoking						
	No	0.961 (0.945–0.977)	<0.001	0.971 (0.954–0.989)	<0.001	0.859 (0.812–0.909)	0.393
	Former	0.823 (0.727–0.932)		0.833 (0.732–0.948)		0.728 (0.473–1.121)	
	Current	0.905 (0.836–0.981)		0.925 (0.852–1.005)		0.657 (0.475–0.910)	
	Alcohol drinking						
	No	1.000 (0.982–1.018)	<0.001	1.010 (0.991–1.030)	<0.001	0.899 (0.845–0.956)	<0.001
	Moderate (0–30 g/day)	0.837 (0.806–0.870)		0.850 (0.817–0.885)		0.720 (0.632–0.820)	
	Heavy (>30 g/day)	0.941 (0.790–1.121)		0.933 (0.777–1.120)		1.038 (0.564–1.910)	
	Exercise						
	No	0.981 (0.960–1.003)	<0.001	0.992 (0.970–1.015)	<0.001	0.871 (0.807–0.940)	0.031
	Yes	0.923 (0.900–0.946)		0.934 (0.910–0.958)		0.828 (0.764–0.897)	
	Income						
	Q1	0.954 (0.926–0.983)	<0.001	0.960 (0.931–0.991)	<0.001	0.888 (0.800–0.986)	0.002
	Q2–Q4	0.957 (0.938–0.976)		0.970 (0.905–0.990)		0.837 (0.784–0.893)	
Age ≤50	BMI (kg/m^2)						
	<25	0.882 (0.849–0.918)	0.001	0.898 (0.861–0.935)	0.007	0.758 (0.668–0.861)	0.004
	≥25	1.008 (0.969–1.049)		1.006 (0.965–1.049)		1.027 (0.897–1.175)	
	Smoking						
	No	0.923 (0.898–0.948)	0.635	0.939 (0.913–0.966)	0.646	0.786 (0.720–0.859)	0.796
	Former	0.839 (0.707–0.995)		0.863 (0.723–1.031)		0.613 (0.326–1.152)	
	Current	0.824 (0.737–0.921)		0.837 (0.746–0.940)		0.677 (0.444–1.031)	
	Alcohol drinking						
	No	0.928 (0.900–0.957)	0.813	0.944 (0.915–0.975)	0.832	0.791 (0.716–0.875)	0.960
	Moderate (0–30 g/day)	0.889 (0.846–0.934)		0.905 (0.859–0.954)		0.752 (0.637–0.888)	
	Heavy (>30 g/day)	0.880 (0.706–1.098)		0.903 (0.717–1.136)		0.657 (0.289–1.494)	
	Exercise						
	No	0.897 (0.866–0.929)	0.080	0.910 (0.877–0.944)	0.045	0.786 (0.699–0.884)	0.744
	Yes	0.938 (0.903–0.974)		0.959 (0.921–0.998)		0.767 (0.677–0.869)	
	Income						
	Q1	0.945 (0.903–0.988)	0.037	0.951 (0.907–0.997)	0.145	0.885 (0.760–1.030)	0.044
	Q2–Q4	0.902 (0.874–0.931)		0.923 (0.893–0.954)		0.735 (0.663–0.815)	
Age >50	BMI (kg/m^2)						
	<25	1.094 (1.064–1.125)	0.006	1.089 (1.057–1.122)	0.007	1.149 (1.043–1.266)	0.567
	≥25	1.097 (1.059–1.135)		1.095 (1.056–1.135)		1.120 (0.988–1.271)	
	Smoking						
	No	1.149 (1.125–1.173)	0.247	1.149 (1.123–1.174)	0.380	1.151 (1.069–1.239)	0.186
	Former	1.091 (0.918–1.296)		1.077 (0.900–1.289)		1.279 (0.682–2.397)	
	Current	1.079 (0.965–1.206)		1.098 (0.979–1.231)		0.798 (0.488–1.303)	
	Alcohol drinking						
	No	1.158 (1.133–1.184)	0.035	1.159 (1.132–1.186)	0.034	1.150 (1.064–1.243)	0.344
	Moderate (0–30 g/day)	1.068 (1.008–1.131)		1.068 (1.006–1.134)		1.063 (0.865–1.306)	
	Heavy (>30 g/day)	1.103 (0.836–1.455)		1.033 (0.775–1.378)		2.626 (0.891–7.741)	
	Exercise						
	No	1.172 (1.140–1.204)	0.116	1.173 (1.140–1.207)	0.090	1.156 (1.047–1.277)	0.794
	Yes	1.110 (1.075–1.146)		1.108 (1.072–1.146)		1.125 (1.012–1.251)	
	Income						
	Q1	1.134 (1.090–1.180)	0.500	1.136 (1.091–1.184)	0.561	1.107 (0.962–1.274)	0.667
	Q2–Q4	1.150 (1.123–1.179)		1.150 (1.121–1.179)		1.157 (1.063–1.259)	

[a]HRs of breast cancer risk for the groups with metabolic syndrome with reference of the group without metabolic syndrome.

cancer and 4,082 postmenopausal controls during 1983–2007. They reported that the presence of metabolic syndrome significantly increased the risk of postmenopausal breast cancer (OR, 1.75; 95% CI, 1.37–2.22). Esposito and colleagues (18) have analyzed results of meta-analysis using nine articles with 6,417 postmenopausal breast cancer cases and 371,545 control subjects. They also reported that the presence of metabolic syndrome increased 52% of breast cancer risk in postmenopausal women (risk ratio, 1.52; 95%

Table 4. Adjusted HRs of breast cancer risk according to metabolic syndrome in each age subgroup and breast cancer type.

Age group (year)	Metabolic syndrome	Invasive and *in situ* breast cancers				Invasive breast cancer				*In situ* breast cancer			
		Number	Event	Rate	HR[a] (95% CI)	Number	Event	Rate	HR[a] (95% CI)	Number	Event	Rate	HR[a] (95% CI)
20≤ Age <25	No	667,290	193	0.070	Reference	667,290	169	0.062	Reference	667,290	24	0.009	Reference
	Yes	15,557	5	0.081	1.169 (0.480–2.845)	15,557	3	0.048	0.803 (0.256–2.519)	15,557	2	0.032	3.707 (0.869–15.822)
25≤ Age <30	No	1,079,352	1,098	0.217	Reference	1,079,352	977	0.193	Reference	1,079,352	121	0.024	Reference
	Yes	29,112	28	0.210	0.950 (0.652–1.383)	29,112	27	0.202	1.031 (0.703–1.513)	29,112	1	0.007	0.303 (0.042–2.167)
30≤ Age <35	No	776,829	2,074	0.564	Reference	776,829	1,841	0.500	Reference	776,829	233	0.063	Reference
	Yes	40,769	107	0.585	1.029 (0.847–1.250)	40,769	97	0.530	1.047 (0.853–1.285)	40,769	10	0.055	0.882 (0.468–1.664)
35≤ Age <40	No	703,295	4,047	1.223	Reference	703,295	3,618	1.093	Reference	703,295	429	0.129	Reference
	Yes	56,596	275	1.083	0.898 (0.794–1.015)	56,596	253	0.997	0.922 (0.812–1.048)	56,596	22	0.086	0.688 (0.448–1.057)
40≤ Age <45	No	2,060,090	17,737	1.919	Reference	2,060,090	15,748	1.703	Reference	2,060,090	1,989	0.214	Reference
	Yes	284,406	2,341	1.862	0.959 (0.918–1.001)	284,406	2,117	1.683	0.974 (0.931–1.020)	284,406	224	0.177	0.834 (0.726–0.957)
45≤ Age <50	No	1,215,106	13,273	2.191	Reference	1,215,106	11,907	1.964	Reference	1,215,106	1,366	0.224	Reference
	Yes	278,894	2,890	2.134	0.978 (0.939–1.018)	278,894	2,629	1.940	0.991 (0.950–1.034)	278,894	261	0.192	0.864 (0.757–0.987)
50≤ Age <55	No	1,364,707	12,415	1.818	Reference	1,364,707	11,308	1.655	Reference	1,364,707	1,107	0.161	Reference
	Yes	568,113	4,986	1.776	0.984 (0.952–1.017)	568,113	4,587	1.633	0.993 (0.959–1.028)	568,113	399	0.141	0.897 (0.800–1.006)
55≤ Age <60	No	645,519	5,014	1.535	Reference	645,519	4,594	1.406	Reference	645,519	420	0.128	Reference
	Yes	467,700	3,919	1.662	1.088 (1.043–1.134)	467,700	3,582	1.518	1.084 (1.038–1.133)	467,700	337	0.142	1.127 (0.976–1.301)
60≤ Age <65	No	528,596	3,601	1.310	Reference	528,596	3,287	1.195	Reference	528,596	314	0.114	Reference
	Yes	583,110	4,559	1.521	1.168 (1.118–1.221)	583,110	4,184	1.395	1.173 (1.121–1.228)	583,110	375	0.125	1.117 (0.961–1.298)
65≤ Age <70	No	294,580	1,529	0.972	Reference	294,580	1,403	0.892	Reference	294,580	126	0.080	Reference
	Yes	440,045	2,924	1.259	1.298 (1.220–1.381)	440,045	2,671	1.149	1.291 (1.210–1.378)	440,045	253	0.109	1.367 (1.104–1.693)
70≤ Age <75	No	257,092	976	0.721	Reference	257,092	909	0.672	Reference	257,092	67	0.049	Reference
	Yes	456,284	2,285	0.973	1.346 (1.249–1.451)	456,284	2,138	0.910	1.352 (1.251–1.462)	456,284	147	0.062	1.264 (0.947–1.688)
75≤ Age <80	No	113,866	290	0.512	Reference	113,866	272	0.480	Reference	113,866	18	0.032	Reference
	Yes	208,341	714	0.708	1.373 (1.197–1.573)	208,341	680	0.674	1.392 (1.210–1.603)	208,341	34	0.034	1.071 (0.605–1.898)
80≤ Age	No	92,481	147	0.383	Reference	92,481	143	0.373	Reference	92,481	4	0.010	Reference
	Yes	149,619	320	0.513	1.298 (1.067–1.578)	149,619	303	0.485	1.262 (1.034–1.541)	149,619	17	0.027	2.564 (0.861–7.633)

[a]Adjusted HRs obtained by Cox proportional hazards model after being adjusted for age, smoking, alcohol drinking, exercise, and income.

Table 5. Adjusted HRs of breast cancer risk according to number of metabolic syndrome components in each age group and breast cancer type.

Age group (year)	Component number of metabolic syndrome	Invasive and *in situ* breast cancers			Invasive breast cancer			*In situ* breast cancer		
		Event	Rate	HR[a] (95% CI)	Event	Rate	HR[a] (95% CI)	Event	Rate	HR[a] (95% CI)
Total	0	24,121	1.213	Reference	21,437	1.077	Reference	2,684	0.135	Reference
	1	21,835	1.404	1.103 (1.083–1.124)	19,721	1.268	1.118 (1.096–1.141)	2,114	0.136	0.981 (0.925–1.040)
	2	16,438	1.444	1.080 (1.057–1.103)	15,018	1.319	1.105 (1.081–1.130)	1,420	0.124	0.875 (0.817–0.937)
	3	12,069	1.422	1.028 (1.004–1.053)	11,039	1.301	1.052 (1.026–1.079)	1,030	0.121	0.835 (0.772–0.904)
	4	8,527	1.407	0.992 (0.965–1.020)	7,845	1.294	1.020 (0.991–1.050)	682	0.112	0.763 (0.696–0.837)
	5	4,757	1.502	1.042 (1.008–1.078)	4,387	1.385	1.073 (1.036–1.111)	370	0.116	0.787 (0.700–0.884)
Age ≤50	0	19,642	1.170	Reference	17,386	1.035	Reference	2,256	0.134	Reference
	1	14,754	1.429	0.976 (0.956–0.998)	13,233	1.281	0.988 (0.966–1.011)	1,521	0.147	0.885 (0.828–0.945)
	2	8,259	1.605	0.933 (0.909–0.958)	7,457	1.449	0.950 (0.924–0.977)	802	0.155	0.802 (0.739–0.871)
	3	4,306	1.738	0.914 (0.884–0.946)	3,917	1.581	0.937 (0.905–0.971)	389	0.156	0.736 (0.660–0.821)
	4	1,921	1.736	0.854 (0.814–0.895)	1,751	1.582	0.876 (0.834–0.921)	170	0.153	0.676 (0.578–0.792)
	5	688	1.887	0.879 (0.815–0.949)	632	1.732	0.909 (0.839–0.985)	56	0.153	0.644 (0.493–0.840)
Age >50	0	4,479	1.446	Reference	4,051	1.307	Reference	428	0.138	Reference
	1	7,081	1.356	1.022 (0.985–1.062)	6,488	1.242	1.034 (0.994–1.076)	593	0.113	0.912 (0.805–1.033)
	2	8,179	1.311	1.062 (1.024–1.102)	7,561	1.211	1.082 (1.041–1.125)	618	0.099	0.869 (0.767–0.984)
	3	7,763	1.292	1.106 (1.065–1.148)	7,122	1.185	1.117 (1.074–1.162)	641	0.106	1.001 (0.884–1.134)
	4	6,606	1.333	1.199 (1.153–1.246)	6,094	1.230	1.216 (1.168–1.267)	512	0.103	1.032 (0.905–1.177)
	5	4,069	1.452	1.361 (1.303–1.421)	3,755	1.340	1.380 (1.318–1.444)	314	0.112	1.182 (1.018–1.373)

[a]Adjusted HRs obtained by Cox proportional hazards model after being adjusted for age, smoking, alcohol drinking, exercise, and income.

CI, 1.20–1.93). This study showed that the presence of metabolic syndrome increased the risk of all breast cancer types by 14.6% in postmenopausal women. Age subgroup analysis showed that this finding was prominent in subgroups with age more than 55 years. The effect of metabolic syndrome on the risk of postmenopausal breast cancer increased as the age of subgroups became older.

For premenopausal women, less evidence for the influence of metabolic syndrome on the risk of breast cancer has been reported compared with that for postmenopausal women. The Me-Can study reported that metabolic syndrome reduced the risk of premenopausal breast cancer (RR, 0.83; 95% CI, 0.76–0.90; ref. 20). A previous study reported no association between metabolic syndrome and premenopausal breast cancer (22). This study showed similar results to the Me-Can study, revealing that metabolic syndrome decreased the risk of premenopausal breast cancer by 8.5%. For all subjects, including both premenopausal and postmenopausal women, this study showed that the presence of metabolic syndrome decreased the risk of breast cancer. The effect of metabolic syndrome was less prominent compared with that of each subgroup possibly due to the summation effect of results in premenopausal and postmenopausal women. A previous study has performed a meta-analysis using nine independent cohorts with 97,277 women aged 18 years and older (26). It reported that there was a modest positive association between metabolic syndrome and breast cancer risk (RR, 1.47; 95% CI, 1.15–1.87).

Previous studies have reported the association between each component of metabolic syndrome and the risk breast cancer. Results were highly inconsistent across studies. The WHI clinical trial reported that only elevated diastolic blood pressure showed a borderline positive association with the increased risk of breast cancer in postmenopausal women (19). The Me-Can study reported that high BMI, blood pressure, cholesterol, and triglyceride were associated with decreased risk of breast cancer in age <50 years (20). Only high BMI and glucose were associated with increased risk of breast cancer in age ≥60 years (20). The ORDET study reported that the increased risk of breast cancer was only associated with high triglyceride and low high-density lipoprotein cholesterol in postmenopausal women (13). Rosato and colleagues (15) reported that increased risk of breast cancer was significantly associated with diabetes, hypertension, BMI, and waist circumference, but not with hyperlipidemia. Esposito and colleagues (18) reported that high glucose, high blood pressure, and low high-density lipoprotein cholesterol were associated with high risk of breast cancer in postmenopausal women. This study showed that every metabolic syndrome component increased the risks of breast cancers in postmenopausal women, but decreased the risks of breast cancers in premenopausal women. Waist circumference in postmenopausal women and triglyceride in premenopausal women were the strongest risk factors.

The Me-Can study reported the influence of metabolic syndrome on breast cancer according to BMI. It reported that postmenopausal women showed no association between metabolic syndrome and risk of breast cancer in low or high BMI subgroup (20). In premenopausal women, the presence of metabolic syndrome decreased the risk of breast cancer in only high BMI subgroups (RR, 0.67; 95% CI, 0.57–0.78). However, there was no association in low BMI subgroups (20). This study showed different results from those of the Me-Can study. The presence of metabolic syndrome increased the risks of breast cancers regardless of BMI status in postmenopausal women. In premenopausal women, the presence of metabolic syndrome decreased the risk of breast cancer in only low BMI subgroups. Further studies are needed to clarify the relationship between metabolic syndrome and BMI in breast cancers.

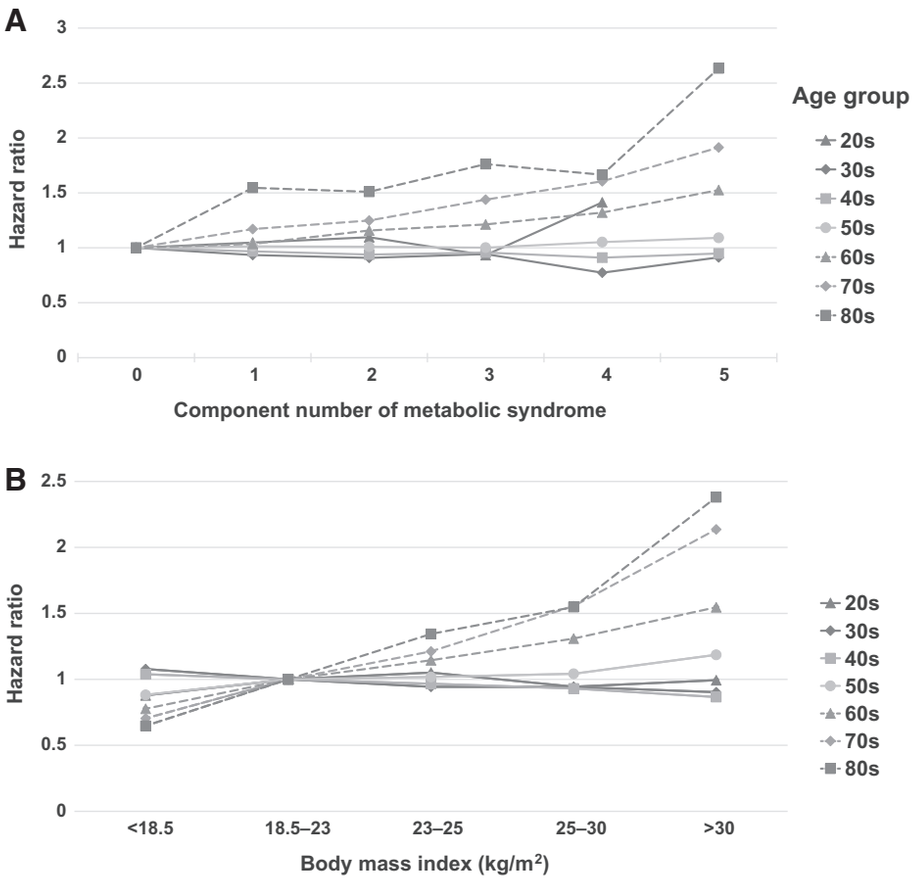

Figure 1.
Adjusted HRs of each age group according to the total number of metabolic syndrome components (**A**) and BMI (**B**) regarding all breast cancer types.

As most previous studies have reported the influence of metabolic syndrome on invasive breast cancer, little is unveiled for *in situ* breast cancer. This study showed that the presence of metabolic syndrome increased the risk of *in situ* breast cancer in postmenopausal women, but decreased the risk in premenopausal women. As a whole, metabolic syndrome increased the risk of *in situ* breast cancer in all subjects. These findings were largely the same as those of invasive breast cancer. The risk reduction effect of metabolic syndrome was more prominent for *in situ* breast cancer compared with that for invasive breast cancer in premenopausal and all subject groups. All metabolic syndrome components decreased the risk of *in situ* breast cancer in premenopausal women, but only triglyceride and high-density lipoprotein significantly increased the risk of *in situ* breast cancer in postmenopausal women.

Underlying mechanisms that link metabolic syndrome and breast cancer risk have been under active investigation, but still are not sufficiently revealed (12, 27–29). Metabolic syndrome could be a surrogate marker for cancer risk factors such as obesity, unhealthy diet, decreased physical activity, aging process, and so on (12, 30). Obesity is supposed to lead a chronic subclinical inflammatory state inducing proinflammatory cytokine production and infiltration of immune cells, and consequently to promote a protumorigenic environment (28, 31, 32). Adipose tissue could play a key role in the pathophysiology of metabolic syndrome as an active endocrine organ to secrete various adipocytokines, which mediate systemic metabolism (28). In breast cancer, obesity plays different roles in cancer risk according to menopausal status and estrogen receptor status. Obesity is associated with decreased risk of estrogen receptor–positive breast cancer in premenopausal women, but it is closely related with increased risk of estrogen receptor–positive breast cancer in postmenopausal women (32). Metabolic syndrome could be linked with other cancer risk factors such as unhealthy diet (33), decreased physical activity (32, 34), and aging process (30). Insulin and insulin-like growth factor (IGF) system are crucial factors in pathophysiology of metabolic syndrome that are mainly characterized as insulin resistance and hyperinsulinemia (27, 28). The insulin receptor and the IGF-1 receptor are overstimulated in metabolic syndrome. Dysregulated insulin and IGF system could activate growth hormones and associated signal pathways to promote apoptosis reduction, cellular proliferation, and cell survival, which increase the risks of cancer development and progression. Previous investigations proposed that each component of the metabolic syndrome is connected with systemic alterations, such as insulin resistance, proinflammatory cytokine production, oxidative stress, and angiogenesis, which potentiate the risk of cancer (16, 28, 35, 36). Common soil hypothesis is proposed to explain the association between metabolic syndrome and cancer risk, as both of them share many common risk factors such as age, genetic factors, obesity, physical inactivity, unhealthy diet, and so on (30, 33).

This study analyzed nationwide data of 13,377,349 women (64,535,186 person-year). It had the largest number of subjects regarding studies on metabolic syndrome. Nonetheless, this study has several limitations. First, this study was a retrospective cohort study. Prospective cohort study could provide more solid evidences on the association between metabolic syndrome and the risk of breast cancers. Second, this study did not analyze the association between the duration of metabolic syndrome and the risk of breast cancers. This study did

not deal with the association between metabolic syndrome and breast cancer–related mortality either. Finally, as this study utilized only baseline data of metabolic syndrome, time-dependent exposures during the follow-up period were not analyzed. Change of metabolic syndrome status or new development of metabolic syndrome components over time might influence the breast cancer risk, and it is worth to be investigated in the subsequent studies. Further studies are needed to reveal more evidences regarding the influence of metabolic syndrome on breast cancer.

In conclusion, the presence of metabolic syndrome increased the risks of breast cancers in postmenopausal women, but decreased the risks in premenopausal women. The effect of metabolic syndrome on the risks of breast cancers was more prominent as age of subgroups became older, especially in postmenopausal women. The effect also became stronger as the number of metabolic syndrome components increased. Each component of metabolic syndrome and metabolic syndrome as a whole played similar roles on the risks of breast cancers. Further studies are needed to validate the relationship between metabolic syndrome and breast cancer risk. Clinicians need to assess breast cancer risks for women with metabolic syndrome.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

K.-T. Hwang: Conceptualization, formal analysis, supervision, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **K.-D. Han:** Data curation, formal analysis, investigation, methodology, writing–review and editing. **S. Oh:** Formal analysis, investigation, methodology, writing–review and editing. **B.K. Koo:** Conceptualization, investigation, methodology, writing–review and editing. **S.K. Lee:** Investigation, writing–review and editing. **J. Kim:** Formal analysis, investigation, writing–review and editing. **H.J. Seo:** Investigation, writing–review and editing. **J. Jung:** Investigation, writing–review and editing. **B.H. Kim:** Investigation, methodology, writing–review and editing. **H. Hur:** Resources, formal analysis, investigation, writing–review and editing.

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