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BRIEF REPORT

Metabolic syndrome and incidence of breast cancer in middle-aged Korean women: a nationwide cohort study

Jung Ah Lee[1] · Jung Eun Yoo[1] · Hye Soon Park[1]

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Abstract
Purpose To evaluate the risk of breast cancer in middle-aged women with metabolic syndrome using the National Health Insurance Service-National Sample Cohort (NHIS-NSC).
Methods We analyzed 23,820 women aged 50–64 years who participated in the NHIS-NCS in 2008 and 2009. We excluded subjects with any previous history of cancer or with inadequate information regarding metabolic syndrome. Participated subjects underwent anthropometric measurements and provided fasting blood samples for the assessment of glucose and lipid profiles, and answered a lifestyle questionnaire. Cox regression analysis was performed to evaluate relative risks (RRs) and 95% confidence intervals (CIs) for the association between metabolic syndrome and breast cancer.
Results During the 5-year follow-up, 131 subjects were newly diagnosed with breast cancer (incidence, 10.86 per 10,000 person years). After adjusting for age and body mass index, the RR for incident breast cancer in participants with metabolic syndrome versus those without it was 1.47 (95% CI 1.01–2.13). For those individuals of metabolic syndrome, hyperglycemia was most primarily related with the incidence of breast cancer (RR 1.44, 95% CI 1.02–2.04).
Conclusions Among the study individuals who were middle-aged Korean women, metabolic syndrome is highly related with the risk of breast cancer. Therefore, it needs to be managed or prevented to reduce the incidence of breast cancer.

Jung Ah Lee and Jung Eun Yoo have contributed equally to this work.

✉ Hye Soon Park
hyesoon@amc.seoul.kr

[1] Department of Family Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul, South Korea

Keywords Metabolic syndrome · Hyperglyceridemia · Breast cancer · Middle-aged · Korean women

Introduction

Metabolic syndrome is a cluster of metabolic abnormalities associated with insulin resistance, which includes central obesity, elevated blood pressure, impaired glucose tolerance, elevated triglyceride levels, and decreased high-density lipoprotein (HDL) cholesterol levels [1]. It is linked with the strong possibility of cardiovascular morbidity and mortality [2, 3], and also has been related to certain types of cancers [4, 5].

According to previous studies, it has been proven that metabolic syndrome in women increases with age [6, 7]. In women, the prevalence increases abruptly after middle age. The reason for this is somewhat unclear, but certain factors such as deficiency in sex hormones and the development of insulin resistance in older populations may play a role [8].

There are inconsistent results regarding metabolic syndrome and breast cancer, but researches have generally been conducted in Western countries. In an Italian community-based, case–control study, metabolic syndrome increased the risk of breast cancer by almost 60% in postmenopausal women [9]. In addition, cancer occurrence was also increased in postmenopausal women in a Women's Health Initiative clinical trial in US [10]. This may be because women with diabetes at baseline were excluded from that study.

Very few studies have involved Asian ethnicity. Asian women usually carry greater abdominal and visceral fat than Caucasian women with a similar body mass index (BMI) [11]. As a result, Asian women have a propensity for developing diseases associated with this. This may result a

higher risk for metabolic syndrome and related diseases, including cancers [11]. In this present study, we evaluated the breast cancer risk in middle-aged women having metabolic syndrome, using a national representative sample of Korea.

Materials and methods

Study population

This study was based on the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort established by the Korean NHIS. The NHIS-NSC cohort is described in a previous report [12]. This cohort comprised 2.2% of the total eligible Korean population in 2002 and was followed for 11 years until 2013. In 2008, waist circumference was measured for the first time in the national health examination. In consideration of the fact that the national health examination in Korea was performed once every 2 years, we included women who were administered the national health examination from 2008 to 2009 and followed it until 2013. In total, 153,712 women older than 20 years were administered the examination in 2008 and 2009. Of these, we included 74,347 women in whom we could determine the existence of metabolic syndrome, and we selected 23,820 women between whose age was 50–64 years old without any previous history of cancer.

Measurement of variables

In the Korean national health examination, waist circumference, BMI, and systolic and diastolic pressure were measured. In addition, the levels of fasting plasma glucose, triglycerides, total cholesterol, and HDL were obtained. Lifestyle factors like smoking status, alcohol consumption, and physical activity were obtained by filling out a self-reported questionnaire. Smoking status was categorized as current, former, and never smokers. Alcohol intake was assessed by the frequency of ingestion and average consumption of alcohol each time. Heavy drinking was defined as drinking one bottle of Korean hard liquor, soju, or seven standard drinks each week. Physical activity was measured by questionnaire determining the number of exercises per week in 2008. Exercising less than three times per week was defined as lacking physical activity.

Definition of metabolic syndrome and development of breast cancer

The definition of metabolic syndrome was based on the definition of the joint interim statement of the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention [13]. According to this institution, metabolic syndrome would have three or more of the following five components which are: abdominal obesity based on population- or country-specific definitions (WC $\geq$ 85 cm [19]); elevated BP (systolic $\geq$ 130 and/or diastolic $\geq$ 85 mmHg); hyperglycemia (fasting plasma glucose $\geq$ 100 mg/dL); hypertriglyceridemia (triglycerides $\geq$ 150 mg/dL); and low HDL-cholesterol levels (<40 mg/dL).

The development of breast cancer was detected using ICD-10 codes, which included invasive breast cancer (C50) and ductal carcinoma in situ of the breast (D051). Participants were defined as having breast cancer if they had admissions records for breast cancer in their national health insurance data from 2010 to 2013.

Statistical analysis

The follow-up duration was measured as the interval of the national health examination and the diagnosis of breast cancer or the date of last follow-up through December 2013. Cox regression analysis was used to examine the relation between different variables and the incidence of breast cancer, after the adjustment for age and BMI. The outcome from the Cox regressions are presented with RRs and 95% CIs. A P value < 0.05 was accepted as statistically significant. All data were analyzed using STATA version 14 (StataCorp LP, College Station, TX).

Results

Basic characteristics of the study population

The characteristics of the study population are indicated in Table 1. The average BMI of the study participants at baseline was 24.5 kg/m^2. The prevalence of metabolic syndrome as defined by IDF at baseline was 24.6%. Among metabolic components, elevated BP was the most common component (52.5%), followed by hyperglycemia (39.5%). The percentage of subjects that reported being a current smoker, being a high-risk drinker, and lacking physical activity were 2.8, 5.9, and 49.9%, respectively.

Incidence of breast cancer and the lifestyle factors related to them

Table 2 shows lifestyle factors and metabolic components according to the development of breast cancer at follow-up. During the 5-year follow-up period, 131 subjects were newly diagnosed with breast cancer, and the incidence of breast cancer per 10,000 person years was 10.86. For those

Table 1 Baseline characteristics of the study population of women who received the Korean national health examination in 2008 and 2009 ($n = 23,820$)

Characteristics	Mean (SD) or *n* (%)
	Mean (SD)
Metabolic risk factors	
Body mass index (kg/m^2)	24.5 (3.2)
Waist circumference (cm)	80.0 (8.5)
Systolic blood pressure (mmHg)	124.7 (15.9)
Diastolic blood pressure (mmHg)	76.9 (10.3)
Fasting glucose (mg/dL)	100.8 (26.0)
Total cholesterol (mg/dL)	209.3 (38.7)
Triglycerides (mg/dL)	128.2 (79.3)
LDL-cholesterol (mg/dL)	127.0 (39.4)
HDL-cholesterol (mg/dL)	58.3 (32.3)
	n (%)
Age (yrs)	
50–54	10,350 (43.5)
55–59	6342 (26.6)
60–64	7128 (29.9)
BMI (kg/m^2)	
<25	14,414 (60.5)
≥25	9404 (39.5)
Lifestyle factors	
Current smoking	665 (2.8)
High-risk alcohol use	1415 (5.9)
Lack of physical activity	11,893 (49.9)
Metabolic components	
Metabolic syndrome	5867 (24.6)
Abdominal obesity	6962 (29.2)
Elevated blood pressure	12,507 (52.5)
Hyperglycemia	9416 (39.5)
Hypertriglyceridemia	5939 (24.9)
Low HDL-cholesterol	1769 (7.4)

SD standard deviation, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *BMI* body mass index

participants with metabolic syndrome, the incidence of breast cancer per 10,000 person years was 13.82. Among the components of metabolic syndrome, hyperglycemia significantly increased the incidence of breast cancer (13.11 per 10,000 person years).

Cox regression analysis was applied to assess the adjusted relative risk of breast cancer according to lifestyle factors and metabolic syndrome. After the adjustment for age and BMI, the RR for the incidence of breast cancer in individuals without the metabolic syndrome was 1.47 (95% CI 1.01–2.13). Among the participants of metabolic syndrome, hyperglycemia was primarily related to incidence of breast cancer (RR 1.44; 95% CI 1.02–2.04).

Discussion

We showed that the existence of metabolic syndrome at baseline was a substantial risk factor for the breast cancer to develop among middle-aged Korean women. Among participants of metabolic syndrome, hyperglycemia was the significant factor that increased the risk of breast cancer.

Both in the developed and less-developed world, breast cancer is the most common cancer in women even though its incidence rates may differ considerably worldwide. According to GLOBOCAN 2012, which presented global and region-specific cancer estimates, the prevalence of breast cancer in Western Europe was 96 per 100,000, while it was 52.1 per 100,000 in Korean women [14]. We found an incidence rate of 10.86 per 10,000, which is somewhat higher than in other studies. One reason may be that we only included middle-aged women aged 50–64 years who normally have a high risk for cancer, and thus this study would be expected to show a higher incidence of breast cancer than other studies that targeted whole populations.

Although the underlying component related with metabolic syndrome and cancer risk requires further understanding, there are several possible mechanisms where the syndrome could encourage to develop breast cancer. Insulin resistance may influence both metabolic syndrome and breast cancer, which could affect the sex hormones, growth factors, and the bioavailability of inflammatory cytokines [15, 16]. The altered balance between pro-inflammatory and anti-inflammatory cytokines driven by central obesity may contribute to insulin resistance, a core component of metabolic syndrome. Asian populations in particular have a propensity to develop such diseases. Excess adiposity, in particular visceral obesity, results in a state of chronic systemic low-grade inflammation, attributed to the production of inflammatory cytokines by both adipocytes and infiltrating immune cells, creating a pro-tumorigenic environment [17].

Insulin resistance, recently recognized as a strong predictor of disease in adults, has become a leading element of metabolic syndrome. This condition exists when insulin levels are higher than expected relative to the level of glucose [18]. Hyperinsulinemia and the insulin growth factor-1 (IGF-1) axis have also been implied in the progress of breast cancer as well. Circulating insulin levels can influence the levels of IGF-1, and higher insulin levels could lead to decreased levels of IGF-binding proteins, thus increasing the bioavailability of IGF [19]. An analysis which included 17 prospective studies indicated that insulin growth factor-1 was accompanied with a greater chance of breast cancer in both premenopausal and postmenopausal women [20].

Among the individuals that suffered from metabolic syndrome, we observed that hyperglycemia was a

Table 2 Relative risks and 95% CIs for metabolic syndrome and its individual components affecting the development of breast cancer in Korean middle-aged women

Characteristics	No. of subjects	Person years	No. of breast cancer	Incidence of 10,000 person years	RR (95% CI)*	*P* value
Total	23,820	120,651	131	10.86		
Lifestyle factors						
Current smoking						
No	22,838	115,681	124	10.72	1	
Yes	665	3363	4	11.89	1.12 (0.41–3.04)	0.821
Heavy drinking						
No	21,864	110,741	117	1057	1	
Yes	1415	7197	10	13.89	1.34 (0.70–2.56)	0.383
Lack of physical activity						
No	11,693	58,789	60	10.21	1	
Yes	11,893	60,683	71	11.70	1.16 (0.82–1.63)	0.407
Metabolic components						
Metabolic syndrome						
No	17,953	89,531	88	9.83	1	
Yes	5867	31,120	43	13.82	1.52 (1.01–2.28)	0.045
Abdominal obesity						
No	16,858	84,060	88	10.47	1	
Yes	6962	36,591	43	11.75	1.15 (0.73–1.82)	0.542
Elevated blood pressure						
No	11,313	56,423	54	9.58	1	
Yes	12,507	64,228	77	11.99	1.26 (0.88–1.81)	0.213
Hyperglycemia						
No	14,404	71,845	67	9.32	1	
Yes	9416	48,806	64	13.11	1.44 (1.02–2.05)	0.041
Hypertriglyceridemia						
No	15,996	79,774	79	9.90	1	
Yes	5939	29,613	34	11.48	1.16 (0.77–1.74)	0.478
Low HDL-cholesterol						
No	20,166	100,554	107	10.64	1	
Yes	1769	8833	6	6.79	0.63 (0.28–1.45)	0.278

* Adjusted for age and body mass index

RR relative risk, *CI* confidence interval, *HDL* high-density lipoprotein

significant risk factor for breast cancer. Although we did not measure insulin levels, this indicates that insulin resistance is highly related to breast cancer. Other previous prospective studies have reported that serum levels of glucose, HDL-cholesterol, triglycerides, and diastolic blood pressure have a positive impact on breast cancer [9, 10]. On the other hand, in our current study, other components of metabolic syndrome did not seem powerful enough to influence the individual development of breast cancers. It is possible that different molecular pathways need to be vitalized to derive breast cancer tumorigenesis [21]. Additionally, our follow-up period was too short to show an association. Because our study population seems to be concerned about their health, they may lead a healthier lifestyle, thus resulting in the prevention of disease progression or complications if they have higher cardiovascular risk factors. This might weaken the relation between metabolic syndrome and the incidence of breast cancer. Thus, a long-term study is needed to determine the relationship.

There were several limitations to this study of note. One limitation was a potential selection bias. This cohort could have probably included healthier individuals or those who are more attentive about their well-being since the NHIS in Korea recommends all health insurance subscribers to take a health examination at least biennially. Another limitation

was the lack of confounders for breast cancer, such as high-fat diets and histories of menarche, menopause, or hormonal therapy. The initial questionnaire did not include this information. As breast cancer is affected by hormonal status and is different between premenopausal and postmenopausal women [22, 23], further studies including menopausal status should be included in the future.

In conclusion, metabolic syndrome is accompanied with increased possibility for breast cancer in middle-aged Korean women. This syndrome should be prevented or managed to reduce the incidence of breast cancer.

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Compliance with ethical standards

Conflicts of interest Nothing to declare.

Research involving human participants and animals Human participants were involved.

Informed consent This study was approved by Institutional Review Board of Asan Medical Center (2015-1299). The need for informed consent was waived since the NHIS-NSC cohort was provided anonymous data to researchers.

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