The Clinical Impact of Body Mass Index on Breast Cancer in Korea: A Nationwide Population-Based Cohort Study

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Purpose: Although increasing body mass index (BMI) is regarded as a potential risk factor for breast cancer (BC) in postmenopausal women, research on premenopausal women has produced conflicting results. We investigated the association between BMI and BC according to menopausal status in Korean. **Methods:** We analyzed clinical data from 186,835 women aged 20 years or older between 2003 and 2008 using a sample cohort from the national database in Korea. We identified women newly diagnosed with BC and estimated the risk of BC according to BMI (kg/m²). Subjects were categorized into five groups according to World Health Organization recommendations for Asians: underweight, < 18.5 kg/m²; normal weight, 18.5–22.9 kg/m²; overweight, 23.0–24.9 kg/m²; obese class I, 25.0–29.9 kg/m²; and obese class II, ≥ 30.0 kg/m². **Results:** 1,372 women in the cohort were newly diagnosed with BC. A positive relationship between BMI and BC was detected and the hazard ratio in each group compared with the normal weight group was 0.57 (95% CI, 0.42–0.78), 1.27 (1.11–1.45), 1.25 (1.09–1.44), and 1.28 (0.95–1.73), respectively. BMI was determined to be an important risk factor for BC in postmenopausal women (*p* for trend was 0.015). We failed to find a significant correlation between BMI and BC in premenopausal women. **Conclusion:** BMI is positively associated with BC in postmenopausal Korean women.

Key Words: Body mass index, Breast neoplasms, Incidence, Obesity

INTRODUCTION

Breast cancer (BC) is the second most common cancer in Korean women, and its incidence has significantly increased in recent years [1,2]. The crude incidence rate (IR) of Korean women with BC in 2012 was 70.7 cases per 100,000 women, which was more than three times the rate in 1999. This increasing trend seems to be associated with westernization of lifestyle and diet, that is, excessive nutritional intake and lower physical activity are increasing as Korea's economy develops [2].

Consistent with the rapid socioeconomic development, the obesity rate has been increasing rapidly in Korea [3]. The overall prevalence of obesity, as defined by a body mass index (BMI) ≥ 25.0 kg/m², in Korean women increased from 18.0% in 1995 to 29.4% in 2001. Obesity is a major health problem in several countries including Korea because it

contributes to increasing rates of not only obesity-related morbidities, such as cardiovascular disease, but also various types of cancers [4].

An association between obesity and BC has been demonstrated in several studies and it is generally accepted that obesity is a risk factor for BC in postmenopausal women [5]. However, some studies have provided conflicting results regarding obesity as a risk factor for BC in premenopausal women [6,7]. Korean women exhibit more distinctive demographic differences compared with Western women, including a lower obesity rate and relatively dense breasts. Additionally, approximately half of all BC in Korea are observed in premenopausal women; hence, the effects of obesity in the development of BC in Korean women have been paid careful attention. We investigated the association between BMI and BC in Korean women according to menopausal status using a nationwide population-based cohort.

METHODS

In the present study, we used the National Health Insurance Service (NHIS) National Sample Cohort, a population-based retrospective cohort in South Korea. The NHIS is a single-payer organization that

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provides medical services for all residents in Korea. It maintains national records, including patient demographics, medical use/transaction information, insurers' payment coverage, and a patient deduction and claim database, which covers diagnosis, prescriptions, and consultation statements [8]. The NHIS constructed a representative sample database with a substantial volume of representative information that is exempted from privacy regulations for research and policy development [9]. From the target population, a representative sample cohort of 1,025,340 subjects was randomly selected. Members of the cohort, which represented 2.2% of the total eligible Korean population in 2002, were followed up for 11 years until 2013, unless a subject was disqualified due to death or emigration. From this cohort, we selected women aged at least 20 years who had received at least one regular medical checkup between 2003 and 2008. We excluded patients who reported a diagnosis of BC before 2003. As a result, 186,835 subjects were included in the present study.

BMI was calculated as the subject's weight (kg) divided by the square of her height (m^2) measured at regular medical checkups. Subjects were categorized into one of five groups according to BMI following the World Health Organization recommendations for Asians: underweight, $< 18.5 \text{ kg/m}^2$; normal weight, $18.5\text{--}22.9 \text{ kg/m}^2$; overweight, $23.0\text{--}24.9 \text{ kg/m}^2$; obese class I, $25.0\text{--}29.9 \text{ kg/m}^2$; and obese class II, $\geq 30.0 \text{ kg/m}^2$ [10,11]. Laboratory examinations with serum samples were also performed during weight measurement. Detailed histories of smoking habits, alcohol consumption, and physical activity (including amount and frequency) were obtained using questionnaires. We performed statistical analyses using the simplified status classifications of smoking (current, ex-smoker, or non-smoker), alcohol consumption (drinker or non-drinker), and regular exercise, which was defined as strenuous physical activity that was performed for at least 20 min per day (yes or no). A subject's socioeconomic status was dichotomized at the lower 20%. Blood samples were drawn after an overnight fast and measured to assess the serum levels of glucose and total cholesterol. Hospitals where these health examinations were performed were certified by the NHIS and subjected to regular quality controls. The primary endpoint of this study was BC development, defined in those who were registered with a C50 code according to the International Classification of Disease, 10th Revision, within 30 days of a breast biopsy. Individuals were followed up from baseline to the date of death or until December 31, 2013, whichever came first. The

baseline was the first date the individuals received a standardized regular medical checkup. All subjects provided informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Catholic Kwandong University of Korea (IRB No. IS16RISI0034).

The association between BMI and BC risk was analyzed using a Cox proportional hazard regression model. Variables used for the multivariate models included age, smoking habits, alcohol consumption, exercise, and patient's income. Interactions between variables were tested. Kaplan–Meier curves were plotted and compared using a log-rank test. Statistical analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC, USA). A two-sided p -value < 0.05 was considered statistically significant.

RESULTS

Of the study's 186,835 subjects, 11,983 (6.4%), 86,803 (46.5%), 39,996 (21.4%), 42,377 (22.7%), and 5,676 (3.0%) women were classified as underweight, normal weight, overweight, obese class I, and obese class II, respectively. The baseline characteristics of each group are shown in Table 1. Only approximately 16% of the underweight group was aged 50 years or older, compared with greater than 50% of the overweight or obesity group. Blood pressure and fasting glucose and blood cholesterol level increased proportionally with BMI. Higher incidences of hypertension (HTN), diabetes mellitus (DM), and dyslipidemia were observed in women with higher BMIs than in women with lower BMIs. The underweight group was associated with a high frequency of smoking, low alcohol uptake, and low exercise.

During an 84-month follow-up period, 1,372 women were newly diagnosed with BC. The incidence of BC in each group is shown in Table 2. The IR of BC per 1,000 subjects during the follow-up duration increased with increasing BMI: 0.45 in the underweight, 0.84 in the normal weight, 1.11 in the overweight, 1.10 in the obese class I, and 1.10 in the obese class II. This association was observed in both premenopausal and postmenopausal women (IR, 0.45, 0.82, 1.24, 1.23, and 1.04 in each group of premenopausal women and 0.45, 0.86, 0.98, 1.02, and 1.15 in each group of postmenopausal women, respectively).

A Cox regression analysis also showed that increasing BMI was positively associated with BC development (Table 3, Figure 1). Com-

Table 1. Baseline characteristics of the study population

Characteristic	Underweight ($< 18.5 \text{ kg/m}^2$) n = 11,983 No. (%)	Normal weight ($18.5\text{--}22.9 \text{ kg/m}^2$) n = 86,803 No. (%)	Overweight ($23\text{--}24.9 \text{ kg/m}^2$) n = 39,996 No. (%)	Obese, class I ($25\text{--}29.9 \text{ kg/m}^2$) n = 42,377 No. (%)	Obese, class II ($\geq 30 \text{ kg/m}^2$) n = 5,676 No. (%)	p-value
Age (yr)						< 0.001
< 50	10,012 (83.5)	60,714 (69.9)	19,317 (48.3)	15,971 (37.7)	2,286 (40.3)	
≥ 50	1,971 (16.5)	26,089 (30.1)	20,679 (51.7)	26,406 (62.3)	3,390 (59.7)	
Mean age (yr)*	35.3 ± 15.9	42.8 ± 15.0	50.3 ± 13.2	53.3 ± 12.7	52.0 ± 13.7	
Height (cm)*	159.2 ± 6.5	157.3 ± 6.2	155.4 ± 5.9	154.5 ± 5.9	154.3 ± 6.5	< 0.001
Weight (kg)*	44.6 ± 4.1	52 ± 4.7	58 ± 4.5	64.1 ± 5.7	76.6 ± 9.0	< 0.001
Mean BMI (kg/m^2)*	17.6 ± 0.8	21 ± 1.2	24 ± 0.6	26.8 ± 1.3	32.1 ± 2.8	< 0.001
Systolic blood pressure (mmHg)*	112 ± 14.5	116.7 ± 15.8	123.1 ± 17.1	128 ± 17.8	133.1 ± 17.7	< 0.001
Diastolic blood pressure (mmHg)*	70.3 ± 9.5	72.8 ± 10.3	76.3 ± 10.9	79 ± 11.2	82.2 ± 11.3	< 0.001
Hypertension (yes)	966 (8.1)	13,516 (15.6)	11,810 (29.5)	18,088 (42.7)	3,223 (56.8)	< 0.001
Fasting glucose (mmol/L)*	87.7 ± 17.9	90.6 ± 21.4	94.9 ± 25.4	98.6 ± 29.1	103.1 ± 31.0	< 0.001
Diabetes Mellitus (yes)	258 (2.2)	3,169 (3.7)	2,993 (7.5)	4,850 (11.4)	978 (17.2)	< 0.001
Cholesterol (mmol/L)*	175.2 ± 31.4	186.2 ± 35.4	198.7 ± 38.4	204.9 ± 39.3	208.1 ± 39.1	< 0.001
Dyslipidemia (yes)	467 (3.9)	8,080 (9.3)	7,066 (17.7)	10,133 (23.9)	1,607 (28.3)	< 0.001
Smoking status						< 0.001
None	11,239 (93.8)	82,745 (95.3)	38,615 (96.6)	40,875 (96.5)	5,366 (94.5)	
Ex-smoker	139 (1.2)	705 (0.8)	236 (0.6)	235 (0.5)	40 (0.7)	
Current smoker	605 (5.0)	3,353 (3.9)	1,145 (2.8)	1,267 (3.0)	270 (4.8)	
Alcohol drinking						< 0.001
None	7,494 (62.5)	59,592 (68.7)	30,526 (76.3)	33,583 (79.3)	4,379 (77.2)	
1-2 times/week	2,775 (23.2)	15,827 (18.2)	5,350 (13.4)	4,790 (11.3)	670 (11.8)	
≥ 3 times/week	1,714 (14.3)	11,384 (13.1)	4,120 (10.3)	4,004 (9.4)	627 (11.0)	
Regular exercise [†] (yes)	2,572 (21.5)	30,171 (34.8)	15,789 (39.5)	16,050 (37.9)	1,979 (34.9)	< 0.001
Income (lower 20%)	2,486 (20.8)	18,005 (20.7)	8,066 (20.2)	8,696 (20.5)	1,243 (21.9)	0.019

BMI = body mass index.

*Mean $\pm$ SD; [†]Strenuous physical activity that was performed for at least 20 min per day.**Table 2.** Development and incidence of breast cancer rates according to body mass index group

Variable	Total			Age < 50			Age ≥ 50		
	Event	Duration (yr)*	IR [†]	Event	Duration (yr)*	IR [†]	Event	Duration (yr)*	IR [†]
Underweight	42	93,178.11	0.45	35	77,773.18	0.45	7	15,404.93	0.45
Normal weight	569	680,023.08	0.84	394	475,761.73	0.83	175	204,261.35	0.86
Overweight	348	314,688.43	1.10	188	152,129.93	1.24	160	162,558.49	0.98
Obese, class I	365	332,391.29	1.10	154	125,112.63	1.23	211	207,278.66	1.02
Obese, class II	48	43,459.18	1.10	18	17,380.08	1.04	30	26,079.10	1.15

*Person-years of observation (number of case $\times$ follow up period); [†]Incidence rate (per 1000) during follow-up period.

pared with the normal weight, the unadjusted hazard ratio (HR) of BC was 0.54 (95% confidence interval [CI], 0.39–0.74) in the underweight, 1.32 (95% CI, 1.16–1.51) in the overweight, 1.31 (95% CI, 1.15–1.50) in the obese class I, and 1.32 (95% CI, 0.99–1.78) in the obese class II (p for trend < 0.001). When adjusting for age, smoking, drinking, exercise, and income, similar patterns were observed in all models (p for trend < 0.001). The more detailed the BMI section was, the more closely an association between BMI and BC was observed (p for trend

< 0.001 , Figure 2).

According to Cox regression analysis, premenopausal women showed significantly increased unadjusted HR of BC according to increasing BMI (Table 3). Compared with the normal weight, the unadjusted HR was 0.54 (95% CI, 0.39–0.77) in the underweight, 1.49 (95% CI, 1.25–1.77) in the overweight, 1.49 (95% CI, 1.23–1.79) in the obese class I, and 1.26 (95% CI, 0.78–2.01) in the obese class II (p for trend < 0.001). However, adjusted HRs showed no statistically significant

Table 3. Hazard ratios for development of breast cancer according to body mass index group

Variable	Group	Hazard ratio (95% CI)		
		Model 1*	Model 2†	Model 3‡
Total	Underweight	0.54 (0.39–0.74)	0.56 (0.41–0.76)	0.57 (0.42–0.78)
	Normal weight	Reference	Reference	Reference
	Overweight	1.32 (1.16–1.51)	1.28 (1.12–1.47)	1.27 (1.11–1.45)
	Obese, class I	1.31 (1.15–1.50)	1.26 (1.10–1.44)	1.25 (1.09–1.44)
	Obese, class II	1.32 (0.99–1.78)	1.27 (0.95–1.71)	1.28 (0.95–1.73)
	<i>p</i> for trend	< 0.001	< 0.001	< 0.001
Age < 50	Underweight	0.54 (0.39–0.77)	0.87 (0.61–1.23)	0.87 (0.61–1.23)
	Normal weight	Reference	Reference	Reference
	Overweight	1.49 (1.25–1.77)	1.13 (0.94–1.34)	1.13 (0.94–1.34)
	Obese, class I	1.49 (1.23–1.79)	1.06 (0.88–1.28)	1.06 (0.88–1.29)
	Obese, class II	1.26 (0.78–2.01)	0.98 (0.61–1.57)	0.99 (0.62–1.59)
	<i>p</i> for trend	< 0.001	0.337	0.311
Age ≥ 50	Underweight	0.53 (0.25–1.13)	0.66 (0.31–1.40)	0.67 (0.32–1.43)
	Normal weight	Reference	Reference	Reference
	Overweight	1.15 (0.93–1.42)	1.13 (0.91–1.39)	1.12 (0.90–1.39)
	Obese, class I	1.19 (0.97–1.45)	1.20 (0.98–1.47)	1.20 (0.98–1.47)
	Obese, class II	1.34 (0.91–1.98)	1.37 (0.93–2.01)	1.38 (0.94–2.03)
	<i>p</i> for trend	0.012	0.015	0.015

*Cox proportional hazards model unadjusted; †Cox proportional hazards model adjusted for age, income; ‡Cox proportional hazards model adjusted for age, income, DM, hypertension, and dyslipidemia.

# at risk	1	2	3	4	5	6
1	11,983	11,974	11,968	10,001	6,750	2,612
2	86,803	86,674	86,524	73,881	50,040	19,234
3	39,996	39,912	39,840	34,520	23,358	9,152
4	42,377	42,302	42,197	36,528	24,395	9,602
5	5,676	5,663	5,651	4,707	2,994	1,208

Figure 1. Breast cancer free-survival in each group of body mass index.

differences according to BMI (*p* for trend = 0.3371 and 0.3107, respectively). Although neither unadjusted and adjusted HRs of BC in postmenopausal women were statistically significant, the *p* for trend was

Figure 2. The relationship between body mass index and breast cancer risk.

statistically significant in each model (0.012, 0.015, and 0.015, respectively, Table 3).

Further examination regarding the association between other clinical variables, such as DM, HTN, and hypercholesterolemia, and BC development was conducted (Table 4). The results showed that pre-existing DM was inversely associated with BC, corresponding to the adjusted HR of 0.70 (95% CI 0.52–0.94) for the pre-existing DM group, compared with those without DM. HTN also showed an inverse association with BC, and comparison of the non-HTN group with the new HTN group and pre-existing HTN group produced an adjusted HR of 0.84 (95% CI, 0.71–0.99) and 0.82 (95% CI, 0.69–0.97), respectively. There was no significant association between hypercholesterol-

Table 4. Cox regression analysis for association between breast cancer and DM*, hypertension, and hypercholesterolemia

Variable	Event	Duration (yr)*	IR [†]	Model 1 [‡]	Model 2 [‡]	Model 3 [§]
DM						
No	1,289	1,369,137.48	0.94	Reference	Reference	Reference
New	35	34,431.77	1.02	1.08 (0.77–1.51)	0.98 (0.70–1.37)	0.96 (0.68–1.34)
Pre-existing	48	60,170.83	0.80	0.85 (0.64–1.13)	0.74 (0.56–0.99)	0.70 (0.52–0.94)
Hypertension						
No	1,014	185,499.92	0.93	Reference	Reference	Reference
New	159	174,900.98	0.91	0.97 (0.82–1.15)	0.86 (0.73–1.03)	0.84 (0.71–0.99)
Pre-existing	199	203,339.18	0.98	1.05 (0.90–1.22)	0.88 (0.75–1.04)	0.82 (0.69–0.97)
Hypercholesterolemia						
No	1,168	1,251,585.84	0.93	Reference	Reference	Reference
New	129	138,780.95	0.93	0.99 (0.83–1.19)	0.92 (0.76–1.11)	0.89 (0.74–1.07)
Pre-existing	75	73,373.30	1.02	1.10 (0.87–1.39)	0.98 (0.77–1.25)	0.91 (0.72–1.16)

DM = diabetes mellitus.

*Person-years of observation (number of case × follow up period); [†]Incidence rate (per 1000) during follow-up period; [‡]Cox proportional hazards model adjusted for age, income; [§]Cox proportional hazards model adjusted for age, income, DM, hypertension, and dyslipidemia.

emia and BC.

DISCUSSION

In this large cohort study, we investigated the association between obesity and BC risk in Korean women. Although the rate of obesity has increased in Korea, a majority of Korean women remain non-obese, and the prevalence of obesity is low in young women [3]. Considering that BC is observed in approximately 50% of premenopausal Korean women, the effect of obesity on BC in Korean women may be different from that in Western women. However, the results of this study were similar to the previous studies, showing a positive association between BMI and BC, even in Korean women.

The effect of obesity on BC in postmenopausal women is not subject to significant debate. We confirmed a positive association between obesity and BC in postmenopausal women. Hypercholesterolemia associated with obesity increases the risk of BC through the production of estrogen via aromatization and through the effect of 27-hydroxycholesterol in postmenopausal women [12]. Obesity also dysregulates multiple biological pathways, including those related to inflammation, insulin resistance, and endogenous sex hormone synthesis [13,14]. Obesity-induced free insulin-like growth factor 1 is associated with increased risk of premenopausal and postmenopausal BC [15]. The potential mechanisms responsible for obesity suggest that obesity can increase the risk of BC development, even in premenopausal women. However, our study failed to show the association be-

tween obesity and BC risk for Korean women.

Multiple inconsistent studies have been conducted to assess the association between obesity and BC risk in premenopausal women. Several studies show that obesity reduces the risk of BC [16,17], whereas others claim that obesity increases the risk of BC in premenopausal women [18–22]. It is difficult to explain the discrepancies in these findings because race, weight change, medication, and several other clinical factors can influence the results. A possible influence of medication was indirectly observed in the present study. Although DM is generally associated with BC [23], the results of the present study showed that pre-existing DM, but not newly diagnosed DM, was inversely associated with BC, suggesting that DM medications such as metformin, which can reduce BC development, may have influenced the results.

Previous studies have demonstrated the importance of weight change on the risk of BC. Weight gain among women in their 40s increased the risk of pre- and postmenopausal BC [24]. In the Nurses' Health Study, recent weight gain over four years was associated with an increased risk of premenopausal BC, and the risk was greater for estrogen receptor (ER)-negative/progesterone receptor (PR)-negative and ER-positive/PR-negative disease than for ER-positive/PR-positive disease [25]. Although we could not confirm the change in weight for individual women or medications in the present study, we determined the potential risk of obesity associated with premenopausal BC using an unadjusted HR in the Cox regression analysis. However, the number of BC events in the present study was small, most notably in the

obese groups, a limitation that could have influenced the results. Our definition of menopause is also a limitation of the present study. Although we defined premenopausal status as beginning at the age of 50, several Korean women become menopausal in their 40s, and the average age at natural menopause in Koreans is approximately 49 years [26-29]. Further study using a larger population and more accurate measurements of menopause is required to determine the effect of obesity on premenopausal BC.

We demonstrated that increasing BMI is positively associated with BC in postmenopausal women using a Korean large cohort, although we failed to show the association between obesity and BC in premenopausal women. We suggest that a reduction in BMI may decrease the risk of BC in overweight or obese Korean women.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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