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EPIDEMIOLOGY

Obesity and breast cancer risk for pre- and postmenopausal women among over 6 million Korean women

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Abstract

Purpose To examine the association between obesity measured by body mass index (BMI) and waist circumference (WC) according to menopausal status in Korean women.

Methods We identified 6,467,388 women, using the Korean National Health Insurance System Cohort. Cox-proportional hazard models were used to generate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for breast cancer risk in relation to BMI and WC.

Results In postmenopausal women, the risk of breast cancer increased with BMI. Compared to women with a BMI of 18.5–23 kg/m two, the risk of invasive breast cancer was lower in patients with BMI < 18.5 (aHR 0.82, 95% CI 0.75–0.89), while it increased linearly in those with BMI 23–25 (1.11, 1.08–1.14), BMI 25–30 (1.28, 1.25–1.32), and BMI ≥ 30 (1.54,1.47–1.62). In contrast, the risk of breast cancer decreased with BMI in premenopausal women. Compared to women with a BMI of 18.5–23, the risk of IBC was similar in those with a BMI < 18.5 (1.02, 0.94–1.11) and BMI 23–25 (1.01, 0.97–1.05), but was significantly lower in those with a BMI 25–30 (0.95, 0.91–0.98) and BMI ≥ 30 (0.90, 0.82–0.98). A relative increase with BMI was less profound for carcinoma in situ in postmenopausal women, and a relative decrease was more profound in premenopausal women. An analysis using WC showed almost identical results.

Conclusions There was a positive relationship between obesity and breast cancer in postmenopausal women, and an inverse association in premenopausal women.

Keywords Breast cancer · Obesity · Waist circumference · Body mass index · Menopause

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Introduction

Breast cancer is one of the most prevalent cancers and a leading cause of cancer mortality in females worldwide. As of 2018, 2.09 million new breast cancer cases were diagnosed worldwide, and 0.62 million women died from breast cancer, contributing to 24.2% of cancer incidence and 15.0% of cancer mortality in the female population [1].

The association between obesity and the risk of breast cancer has been investigated in many studies. Breast cancer was found to be associated with obesity and this association was related to the estrogenic effect of obesity [2]. Therefore, it can be hypothesized that the association between obesity and breast cancer risk is modified by menopausal status [3].

Most studies consistently found a positive association between body mass index (BMI) [4–8] and waist circumference (WC) [9, 10] with breast cancer incidence, and recent meta-analyses confirming such overall positive associations [11, 12] in postmenopausal women. However, for premenopausal women, results are inconsistent. Many studies performed in the Western population showed a negative association [13–15]. Asian studies showed null associations between BMI and breast cancer [7, 16, 17]. However, a recent pooled analysis showed a negative association [18] and several meta-analyses showed a positive association in Asian women [11, 19]. This discrepancy suggests that there may be ethnic or racial differences in the correlation between obesity and breast cancer. However, previous studies in Asia had relatively small sample sizes and so, had insufficient statistical power to draw definite conclusions [18], which suggested the need for an additional study to be carried out in an Asian population.

In addition, previous studies had the following limitations. First, they generally used a single obesity parameter. Most studies used only BMI as the obesity indicator to assess obesity's association with breast cancer risk [4, 8, 9, 11, 12, 15, 17], while others only used WC [20, 21] which has the advantage of reflecting abdominal obesity and metabolic syndrome [22]. Only a few studies have used both parameters [6, 23, 24]. Second, some studies included only invasive breast cancer (IBC) cases, and did not include carcinoma in situ (CIS) [25, 26]. Although it is unclear whether CIS develops into invasive breast cancer or not [27], both types of breast cancer (IBC and CIS), should be considered at the same time in studies done to investigate the risk of breast cancer.

Therefore, we sought to examine the association between obesity and breast cancer risk according to menopausal status in Korean women. We evaluated obesity using both BMI and WC, and considered IBC and CIS as separate outcomes.

Methods

Study setting and data source

We used data from the Korean National Health Insurance Service (NHIS). As the single government insurer, the NHIS provides comprehensive medical insurance to most of the Korean population (over 97%) and provides the administration of medical aid assistance to 3% of the vulnerable population. The NHIS database contains data on the characteristics of the enrollees (age, sex, income status, place of residence, etc.), diagnosis code by the International Classification of Disease 10th revision (ICD-10), and information about medical treatment based on medical expenditure claims and prescription data [28].

The NHIS provides biennial general health screening programs for people ≥ 40 years [29], including anthropometric measurements (BMI, WC, etc.), lifestyle questionnaires (smoking, alcohol consumption, physical activities, etc.), and laboratory testing (blood glucose, lipid levels, etc.). In addition, the NHIS runs breast cancer Screening Programs for all Korean women ≥ 40 years every two years. Before breast cancer screening examination, women are required to answer a questionnaire, which includes menopausal status and reproductive history [30]. This data is also registered on the NHIS database. The NHIS database offers useful and relevant data as a massive epidemiological study pool to medical researchers. More details of the NHIS database are described elsewhere [31].

Study population

We included women ≥ 40 years who had undergone both the general health screening and breast cancer screening at the same time from January 1, 2009 to December 31, 2014 (Fig. 1). Even though there were individuals who were screened two or more times during the enrollment period, the measurement of the first screening was considered as baseline. Data were collected at the study enrollment, which was the first health screening participation during the study period Table1.

Among 6,467,388 eligible subjects, we excluded participants who had previously undergone a hysterectomy ($n = 14{,}926$), were diagnosed with any previous malignancy ($n = 167{,}585$) and those with missing data for a key variable ($n = 12{,}510$). As a result, a total of 6,272,367 women (1,418,180 premenopausal and 4,854,187 postmenopausal women) were included in this study. Our study was approved by the Institutional Review Board of Samsung Medical Center (IRB File No. SMC 2019–01-050), and individual informed consent was waived because this study used only de-identified data.

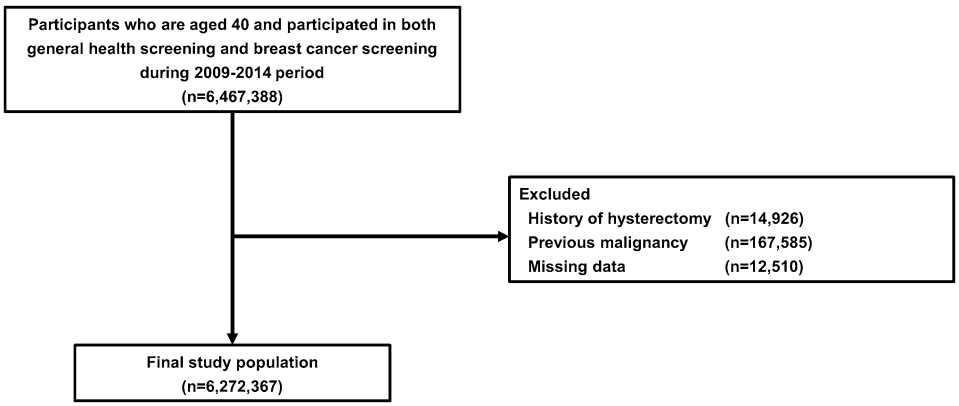

Fig. 1 Study participants

Data collection

All data collection, including anthropometric measurement and questionnaires, were made at the date of health screening. BMI was calculated using weight (kg) divided by the square of the height (m^2), and classified into five levels as low (< 18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), obese (25–29.9 kg/m^2), or severely obese (≥ 30 kg/m^2) according to the World Health Organization/International Association for the Study of Obesity/International Obesity Task Force obesity guidelines [32]. WC was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. WC was divided into 5 levels as low (< 65 cm), normal (65–74.9 cm), overweight (75–84.9 cm), obese (85–94.9 cm), and severely obese (≥ 90 cm) according to the Korean Society for the Study of Obesity guidelines [33].

Information about health-related behaviors and menstrual and reproductive histories were obtained using a self-administered questionnaire. Before the general health examination, women were asked about their smoking history (classified as never, former and current smoker), alcohol consumption (divided into three levels: none, < 30 g/day, and ≥ 30 g/day), regularity of exercise (defined as moderate physical activity for more than 30 min daily and more than 5 days per week over the past week), and comorbidities. Before taking the breast cancer screening examination, women were asked about their age at menarche, age at menopause, parity (0, 1, or ≥ 2 children), breast feeding history (never, < 6, 6–12, and ≥ 12 total months), use of hormone replacement therapy (HRT; never, < 2, 2–5, ≥ 5 years) and oral contraceptive use (never, < 1, ≥ 1 year, and unknown).

Study outcomes and follow-up

The primary endpoint of this study was newly diagnosed IBC cases, defined as new claims for inpatient or outpatient care with the diagnosis code of C50 (malignant neoplasm of the breast) with registration in the special co-payment reduction program for critical illnesses. CIS (D05, carcinoma in situ of the breast) was defined in the same manner. All breast cancer was defined as either being IBC or CIS. The patients were followed up from their health check-up date to the date of incident breast cancer, death, or until the end of the study period (December 31, 2016), whichever came first.

Statistical analysis

The incidence rates for breast cancer were calculated by dividing the number of incident cases by the total follow-up period. Hazard ratios (HRs) and 95% confidence interval (CI) according to BMI and WC categories were analyzed using Cox proportional hazards models. Covariates for adjustment were selected based on their previous association with breast cancer incidence in the literature [34–37], and were added serially into the models: (1) Model 1 was non-adjusted; (2) Model two was adjusted for age, income, smoking [34], alcohol drinking [35], and physical activity [36]; (3) Model three was further adjusted for age at menarche, parity, breast feeding, oral contraceptive use in premenopausal women, and additionally for age at menopause and HRT in postmenopausal women [37]. Statistical analyses were performed using the Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA), and a p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The mean age of the participants was 43.7 years in the premenopausal women and 59.9 years in the postmenopausal women. The mean BMI and WC was 23.1 kg/m^2 and 75.0 cm, respectively in the premenopausal women and 24.1 kg/m^2 and 79.6 cm, respectively in the postmenopausal women. Reproductive factors differed by menopausal

status: postmenopausal women had later menarche (16.3 vs. 14.8 years), more parity (90.1 vs. 78.6%), longer breastfeeding history (91.8% vs. 78.4% for any, 65.8 vs. 27.8 for ≥ 1 year), and more oral contraceptive use (19.2% vs 16.0%) (Table 1).

Association between BMI and the risk of breast cancer by menopausal status

During a mean follow-up of 6.2 years, 18,141 premenopausal women and 39,485 postmenopausal women were diagnosed with breast cancer. In postmenopausal women, the risk of breast cancer increased with BMI (Table 2, Fig. 2). Compared with the BMI reference group (BMI 18.5–23), the risk of invasive breast cancer (IBC) was lower in the underweight group (aHR 0.82, 95% CI 0.75–0.89), while it increased linearly in the overweight (1.11, 1.08–1.14), obese (1.28,1.25–1.32), and severely obese groups (1.54,1.47–1.62). In contrast, IBC decreased with BMI in premenopausal women. Compared with the BMI reference group (BMI 18.5–23), the risk of IBC was similar in the underweight (1.02, 0.94–1.11) and overweight groups (1.01, 0.97–1.05), but was significantly lower in the obese (0.95, 0.91–0.98), and severely obese groups (0.90, 0.82–0.98) (Fig. 2a). But the relative risk increased less with BMI in the postmenopausal women with CIS [e.g., aHR, 95% CI for the severely obese group was 1.26 (1.14–1.40) in CIS compared to 1.54 (1.47–1.62) for IBC] and it decreased more in the premenopausal women with CIS [e.g., aHR, 95% CI for the severely obese group was 0.68 (0.56–0.82) in CIS compared to 0.82 (0.75–0.89) for IBC] (Fig. 2b).

Association between WC and the risk of breast cancer by menopausal status

In postmenopausal women, the risk of breast cancer increased with WC (Table 3, Fig. 2). Compared with the reference group (WC: 65–75), the relative risk (aHR, 95% CI) for IBC was lower in the underweight group (0.92, 0.85–0.98), while it increased linearly in the overweight (1.15, 1.12–1.18), obese (1.32, 1.28–1.37), and severely obese groups (1.49, 1.42–1.57). In contrast, the risk of breast cancer decreased with WC in premenopausal women. Compared with the WC reference group (WC 65–75), the relative risk of IBC was similar in the underweight (1.01, 0.95–1.08) and overweight groups (1.00, 0.97–1.04), but was significantly lower in the obese (0.94, 0.89–0.99), and severely obese groups (0.93, 0.83–1.05) (Fig. 2d). The relative risk increased less with WC in postmenopausal women with CIS women [e.g., aHR and 95% CI for the severely obese group was 1.22 (1.09–1.36) in CIS compared to 1.49 (1.42–1.67) for IBC], and decreased more with WC in premenopausal women with CIS [e.g., aHR, 95% CI for the severely obese group was 0.70 (0.55–0.89) in CIS compared to 0.93 (0.83–1.05) for IBC] (Fig. 2e).

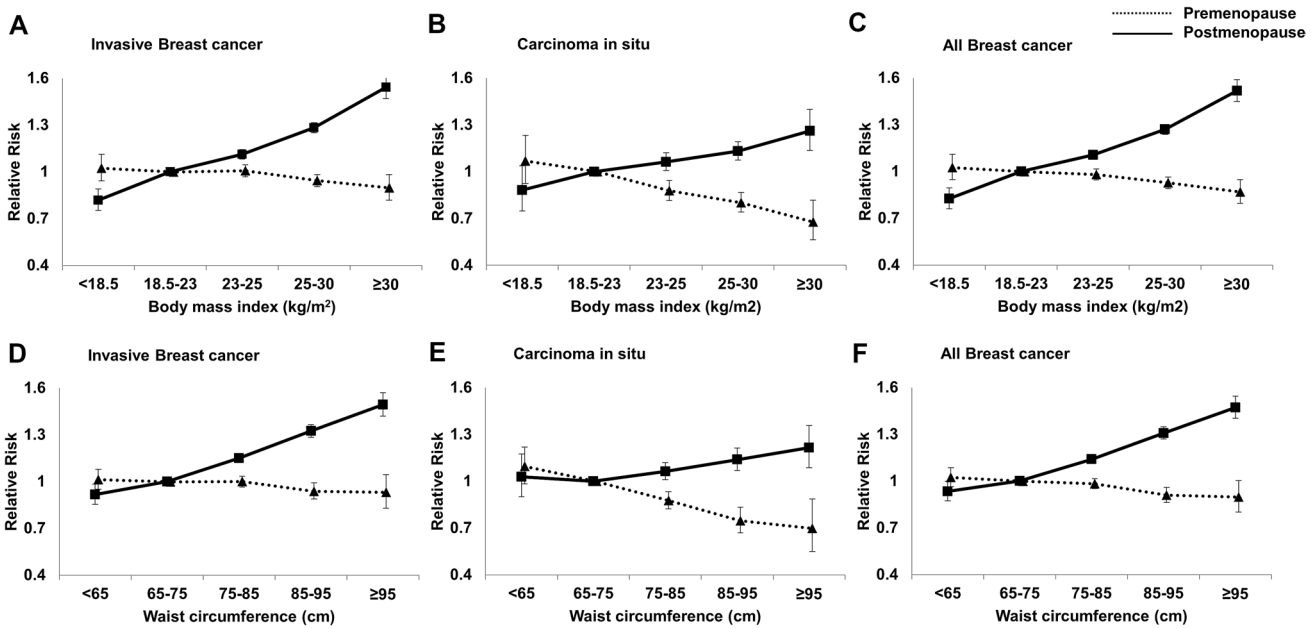

Fig. 2 Breast cancer incidence according to body mass index (**A**, **B**, **C**) and waist circumference (**D**, **E**, **F**) by menopausal status

Table 1 Selected baseline characteristics of the study population

	Premenopausal (n = 1,418,180) N (%)	Postmenopausal (n = 4,854,187) N (%)	p value
Age, year, mean (SD)	43.7 (±3.6)	59.9 (±9.0)	< .0001
40–49	1,291,146 (91.0)	472,492 (9.7)	–
50–59	127,027 (9.0)	2,060,510 (42.5)	–
60–69	–	1,459,097 (30.1)	–
≥ 70	–	862,088 (17.8)	–
Body mass index, kg/m^2, mean (SD)	23.1 (±3.2)	24.1 (±3.2)	< .0001
< 18.5	51,540 (3.6)	106,434 (2.2)	–
18.5–22.9	719,899 (50.8)	1,743,980 (35.9)	–
23–24.9	311,800 (22.0)	1,273,411 (26.2)	–
25–29.9	286,908 (20.2)	1,517,419 (31.3)	–
≥ 30	48,033 (3.4)	212,943 (4.4)	–
Waist circumference, cm, mean (SD)	75.0 (±8.0)	79.6 (±8.4)	< .0001
< 65	96,735 (6.8)	119,397 (2.5)	–
65–74.9	645,214 (45.5)	1,258,799 (25.9)	–
75–84.9	508,444 (35.9)	2,186,858(45.1)	–
85–94.9	139,332 (9.8)	1,061,378 (21.9)	–
≥ 95	28,455 (2.0)	227,755 (4.7)	–
Age at menarche, years, mean (SD)	14.8 (±1.6)	16.3 (±1.9)	< .0001
> 13	1,129,924 (79.7)	4,568,698 (94.1)	–
≤ 13	288,256 (20.3)	285,489 (5.9)	–
Age at menopause, years, mean (SD)	–	50.3 (±4.0)	< .0001
40–44	–	321,874 (6.6)	–
45–49	–	1,222,126 (25.2)	–
50–54	–	2,700,822 (55.6)	–
≥ 55	–	609,365 (12.6)	–
Income	–	–	< .0001
1st quartile (lowest)	440,323 (31.1)	1,403,913 (28.9)	–
2nd quartile	295,925 (20.9)	1,073,281 (22.1)	–
3rd quartile	330,672 (23.3)	1,115,959 (23.0)	–
4th quartile (highest)	351,260 (24.8)	1,261,034 (26.0)	–
Smoking status	–	–	< .0001
Never	1,328,311 (93.7)	4,639,439 (95.6)	–
Ex-smoker	30,097 (2.1)	58,824 (1.2)	–
Current	59,772 (4.2)	155,924 (3.2)	–
Alcohol drinking	–	–	< .0001
None	979,518 (69.1)	4,150,329 (85.5)	–
Mild	419,628 (29.6)	670,917 (13.8)	–
Heavy	19,034 (1.3)	32,941 (0.7)	–
Regular physical activity, yes	233,555 (16.5)	862,147 (17.8)	< .0001
Comorbid condition	–	–	–
Hypertension	156,742 (11.2)	1,957,793 (40.3)	< .0001
Diabetes	47,075 (3.3)	620,895 (12.8)	< .0001
Hyperlipidemia	1,39,289 (9.8)	1,636,125 (33.7)	< .0001
Parity	–	–	< .0001
Nullipara	96,386 (6.8)	94,792 (2.0)	–

Table 1 (continued)

	Premenopausal (n = 1,418,180) N (%)	Postmenopausal (n = 4,854,187) N (%)	p value
1	206,513 (14.6)	384,672 (7.9)	–
≥ 2	1,115,281 (78.6)	4,374,723 (90.1)	–
Duration of breastfeeding, months	–	–	< .0001
< 6	380,893 (26.9)	405,186 (8.4)	–
6–12	335,912 (23.7)	854,644 (17.6)	–
≥ 12	394,402 (27.8)	3,194,685 (65.8)	–
Never	306,973 (21.7)	399,672 (8.2)	–
Duration of oral contraceptive use, years	–	–	< .0001
Never	1,191,585 (84.0)	3,924,021 (80.8)	–
< 1	133,598 (9.4)	422,632 (8.7)	–
≥ 1	47,181 (3.3)	280,017 (5.8)	–
Unknown	45,816 (3.2)	227,517 (4.7)	–
Duration of HRT, years	–	–	< .0001
Never	–	3,963,453 (81.7)	–
< 2	–	411,623 (8.5)	–
2–5	–	162,651 (3.4)	–
≥ 5	–	133,515 (2.8)	–
Unknown	–	182,945 (3.8)	–

HRT Hormone replacement therapy

Discussion

In this large-scale prospective cohort of Korean women, we found a significant positive association between obesity and IBC in postmenopausal women, but a significant inverse association in premenopausal women. CIS showed a less positive association in postmenopausal women, and an inverse association with obesity in premenopausal women. The patterns were not different, whether they were measured by BMI or WC. The strengths of our study are as follows; it was a single ethnic Asian cohort which is representative of the entire Korean population, had a large sample size with a sufficient number of breast cancer events, a simultaneous evaluation of BMI and WC in a single study, and a low number of lost to follow-up cases.

In postmenopausal women, we confirmed a positive association between obesity and IBC, which was consistent with numerous previous studies [10, 38–41]. Obesity induces oncogenic environments by multiple biological pathways including endogenous sex hormone synthesis, inflammation, and insulin resistance [2, 42] An obese woman has large amounts of adipose cells, which act as primary sources of estrogen production after menopause; for example, androgens originating from the adrenal glands are converted to estrogen by aromatization in adipose cells [2]. Therefore, women with higher amounts of body fat tend to have higher levels of circulating estrogen, and this stimulates more estrogen-sensitive breast tissues that may already have a propensity for hyperstimulation, ultimately promoting the formation and development of tumors [43]. In addition, adipose tissue produces various cytokines, growth factors, and inflammatory factors, which may in turn trigger sex hormone aromatization. Moreover, insulin resistance, adipocytokines, and leptin, are also important factors for the formation and development of breast cancer stimulated in the obese state [43–46].

In contrast, we found an inverse association between obesity and breast cancer in premenopausal women. In premenopausal women unlike postmenopausal women, estrogen is mainly produced in the ovaries. Estrogen production in premenopausal women is less affected by obesity. Estrogen levels are lower in obese premenopausal women, which is explained by the substantial uptake of estradiol into fat and the higher liver clearance rate of estrogen [47].

In comparison with other studies, while obesity and breast cancer had an inverse association in premenopausal women in most Western studies [14, 48], several Asian studies showed inconsistent results. Several Japanese studies showed a null association between obesity and breast cancer [7, 16, 17]. A Pooled analysis of eight Japanese studies by Wada et al. (the number for premenopausal breast cancer patients in the meta-analyses was only about

Table 2 Associations between body mass index (BMI) and breast cancer risk by menopausal status

	Body mass index	Subjects (N)	Event (n)	Duration (person-years)	Incidence rate (per 1,000 person-years)	Model 1	Model 2	Model 3
Invasive breast cancer								
Pre-menopause	< 18.5	51,527	205	297,160.2	1.98	1.02 (0.94,1.11)	1.06 (0.98,1.15)	1.02 (0.94,1.11)
	18.5–22.9	719,786	3097	4,319,121.6	1.95	1 (ref.)	1 (ref.)	1 (ref.)
	23–24.9	311,771	1447	1,896,652.6	1.99	1.02 (0.98,1.06)	0.99 (0.95,1.03)	1.01 (0.97,1.05)
	25–29.9	286,877	1283	1,728,982.7	1.88	0.97 (0.93,1.01)	0.93 (0.89,0.97)	0.95 (0.91,0.98)
	≥ 30	48,025	218	279,813.1	1.79	0.92 (0.84,1.01)	0.89 (0.82,0.98)	0.90 (0.82,0.98)
	p for trend	–	–	–	–	0.0391	< .0001	0.0013
Post -menopause	< 18.5	106,421	567	640,439.0	0.89	0.79 (0.72,0.86)	0.83 (0.76,0.90)	0.82 (0.75,0.89)
	18.5–22.9	1,743,609	12,278	10,911,154.8	1.13	1 (ref.)	1 (ref.)	1 (ref.)
	23–24.9	1,273,179	9,541	8,042,745.3	1.19	1.06 (1.03,1.08)	1.09 (1.06,1.12)	1.11 (1.08,1.14)
	25–29.9	1,517,196	12,408	9,539,587.5	1.30	1.16 (1.13,1.19)	1.23 (1.20,1.26)	1.28 (1.25,1.32)
	≥ 30	212,920	2,019	1,304,680.0	1.55	1.38 (1.31,1.44)	1.46 (1.40,1.53)	1.54 (1.47,1.62)
	p for trend	–	–	–	–	< .0001	< .0001	< .0001
Carcinoma in situ								
Pre-menopause	18.5–22.9	719,786	2,657	4,319,120.6	0.62	1 (ref.)	1 (ref.)	1 (ref.)
	23–24.9	311,771	1,017	1,896,652.6	0.54	0.87 (0.81,0.94)	0.85 (0.79,0.92)	0.88 (0.82,0.94)
	25–29.9	286,877	845	1,728,982.7	0.49	0.79 (0.74,0.86)	0.78 (0.72,0.84)	0.80 (0.74,0.87)
	≥ 30	48,025	116	279,813.1	0.41	0.68 (0.70,0.82)	0.67 (0.55,0.80)	0.68 (0.56,0.82)
	p for trend	–	–	–	–	< .0001	< .0001	< .0001
	< 18.5	106,421	150	640,439.0	0.23	0.82 (0.70,0.97)	0.89 (0.75,1.05)	0.88 (0.75,1.04)
Post -menopause	18.5–22.9	1,743,609	3,103	10,911,154.8	0.28	1 (ref.)	1 (ref.)	1 (ref.)
	23–24.9	1,273,179	2,286	8,042,745.4	0.28	1.00 (0.95,1.06)	1.04 (0.98,1.10)	1.06 (1.01,1.12)
	25–29.9	1,517,196	2,706	9,539,587.5	0.28	1.00 (0.95,1.05)	1.08 (1.03,1.14)	1.13 (1.08,1.19)
	≥ 30	212,920	404	1,304,680.0	0.31	1.09 (0.98,1.21)	1.18 (1.07,1.31)	1.26 (1.14,1.40)
	p for trend	–	–	–	–	0.1613	< .0001	< .0001
	< 18.5	51,527	201	297,160.2	0.68	1.10 (0.96,1.27)	1.13 (0.98,1.31)	1.07 (0.93,1.24)
All breast cancer								
Pre-menopause	< 18.5	51,527	660	297,160.2	2.22	1.03 (0.95,1,11)	1.07 (0.99,1.15)	1.03 (0.95,1.11)
	18.5–22.9	719,786	9,343	4,319,121.6	2.16	1 (ref.)	1 (ref.)	1 (ref.)
	23–24.9	311,771	4,072	1,896,652.6	2.15	0.99 (0.96,1.03)	0.96 (0.93,1.00)	0.98 (0.95,1.02)
	25–29.9	286,877	3,530	1,728,982.6	2.04	0.94 (0.91,0.98)	0.91 (0.87,0.95)	0.93 (0.89,0.97)
	≥ 30	48,025	536	279,813.1	1.92	0.89 (0.81,0.97)	0.87 (0.79,0.94)	0.87 (0.80,0.95)
	p for trend	–	–	–	–	< .0001	< .0001	< .0001
Post -menopause	< 18.5	106,421	616	640,439.0	0.96	0.79 (0.73,0.86)	0.83 (0.77,0.90)	0.83 (0.76,0.90)
	18.5–22.9	1,743,609	13,248	10,911,154.8	1.21	1 (ref.)	1 (ref.)	1 (ref.)
	23–24.9	1,273,179	10,241	8,042,745.3	1.27	1.05 (1.02,1.08)	1.08 (1.06,1.11)	1.11 (1.08,1.14)
	25–29.9	1,517,196	13,242	9,539,587.5	1.39	1.14 (1.12,1.17)	1.22 (1.19,1.25)	1.27 (1.24,1.30)
	≥ 30	212,920	2,138	1,304,680.0	1.64	1.35 (1.29,1.41)	1.44 (1.37,1.50)	1.52 (1.45,1.59)
	p for trend	–	–	–	–	< .0001	< .0001	< .0001

Model 1 non-adjusted

Model 2 adjusted for age, income, smoking status, alcohol drinking, regular physical activity

Model 3 (premenopausal) adjusted for age, income, smoking status, alcohol drinking, regular physical activity, parity, duration of breastfeeding, duration of oral contraceptive use, age at menarche

Model 3 (postmenopausal) adjusted for age, income, smoking status, alcohol drinking, regular physical activity, parity, duration of breastfeeding, duration of oral contraceptive use, age at menarche, age at menopause, duration of hormonal replacement therapy

Table 3 Associations between waist circumference (WC) and breast cancer risk by menopausal status

	Waist circumference (cm)	Subjects (N)	Event (n)	Duration (person-years)	Incidence rate (per 1,000 person-years)	Model1	Model2	Model3
Invasive breast cancer								
Pre-menopause	< 65	96,719	1,109	567,811.8	1.95	1.01 (0.94,1.08)	1.04 (0.98,1.11)	1.01 (0.95,1.08)
	65–74.9	645,118	7,514	3,892,876.0	1.93	1 (ref.)	1 (ref.)	1 (ref.)
	75–84.9	508,376	6,047	3,070,487.7	1.97	1.02 (0.98,1.06)	0.99 (0.95,1.02)	1.00 (0.97,1.04)
	85–94.9	139,319	1,542	827,212.5	1.86	0.97 (0.92,1.02)	0.92 (0.88,0.98)	0.94 (0.89,0.99)
	≥ 95	28,454	303	163,341.3	1.86	0.96 (0.86,1.08)	0.93 (0.83,1.04)	0.93 (0.83,1.05)
	p for trend	–	–	–	–	0.4981	0.0012	0.0414
Post -menopause	< 65	119,371	828	731,680.0	1.13	0.97 (0.90,1.04)	0.94 (0.88,1.01)	0.92 (0.85,0.98)
	65–74.9	1,258,531	9,231	7,890,588.3	1.17	1 (ref.)	1 (ref.)	1 (ref.)
	75–84.9	2,186,471	16,512	13,783,262.7	1.20	1.03 (1.00,1.05)	1.12 (1.09,1.14)	1.15 (1.12,1.18)
	85–94.9	1,061,226	8,343	6,643,184.6	1.26	1.07 (1.04,1.11)	1.25 (1.22,1.29)	1.32 (1.28,1.37)
	≥ 95	227,726	1,899	1,389,891.1	1.37	1.17 (1.11,1.23)	1.40 (1.33,1.47)	1.49 (1.42,1.57)
	p for trend	–	–	–	–	< .0001	< .0001	< .0001
Carcinoma in situ								
Pre-menopause	< 65	96,719	61	666,609.0	0.68	1.13 (1.01,1.25)	1.15 (1.03,1.28)	1.10 (0.98,1.22)
	65–74.9	645,118	611	4,552,139.4	0.61	1 (ref.)	1 (ref.)	1 (ref.)
	75–84.9	508,376	545	3,589,342.5	0.53	0.88 (0.82,0.93)	0.86 (0.80,0.91)	0.88 (0.82,0.94)
	85–94.9	139,319	173	968,524.6	0.45	0.74 (0.67,0.83)	0.73 (0.65,0.81)	0.75 (0.67,0.83)
	≥ 95	28,454	28	192,078.8	0.42	0.70 (0.55,0.89)	0.69 (0.54,0.87)	0.70 (0.55,0.89)
	p for trend	–	–	–	–	< .0001	< .0001	< .0001
Post -menopause	< 65	119,371	293	847,005.6	0.33	1.08 (0.95,1.24)	1.06 (0.92,1.21)	1.03 (0.9,1.17)
	65–74.9	1,258,531	3102	9,116,821.4	0.30	1 (ref.)	1 (ref.)	1 (ref.)
	75–84.9	2,186,471	6903	15,887,585.8	0.28	0.93 (0.88,0.98)	1.03 (0.98,1.08)	1.06 (1.01,1.12)
	85–94.9	1,061,226	3835	7,648,061.1	0.27	0.88 (0.83,0.94)	1.07 (1.00,1.14)	1.14 (1.07,1.21)
	≥ 95	227,726	922	1,602,340.1	0.27	0.90 (0.80,1.00)	1.12 (1.00,1.25)	1.22 (1.09,1.36)
	p for trend	–	–	–	–	1.13 (1.01,1.25)	1.15 (1.03,1.28)	1.10 (0.98,1.22)
All breast cancer								
Pre-menopause	< 65	96,719	1,249	567,812.8	2.20	1.03 (0.97,1.09)	1.06 (1.00,1.12)	1.03 (0.97,1.09)
	65–74.9	645,118	8,340	3,892,876.0	2.14	1 (ref.)	1 (ref.)	1 (ref.)
	75–84.9	508,376	6,578	3,070,487.7	2.14	1.00 (0.97,1.03)	0.97 (0.94,1.00)	0.98 (0.95,1.02)
	85–94.9	139,319	1,652	827,212.5	2.00	0.93 (0.89,0.98)	0.90 (0.85,0.94)	0.91 (0.86,0.96)
	≥ 95	28,454	322	163,341.3	1.97	0.92 (0.83,1.03)	0.89 (0.80,1.00)	0.90 (0.80,1.00)
	p for trend	–	–	–	–	0.0098	< .0001	0.0002
Post -menopause	< 65	119,371	912	731,680.0	1.25	0.98 (0.92,1.05)	0.96 (0.90,1.03)	0.93 (0.87,1.00)
	65–74.9	1,258,531	9,983	7,890,588.3	1.27	1(ref.)	1 (ref.)	1 (ref.)
	75–84.9	2,186,471	17,688	13,783,262.7	1.28	1.02 (0.99,1.04)	1.10 (1.08,1.13)	1.14 (1.11,1.17)
	85–94.9	1,061,226	8,887	6,643,184.6	1.34	1.06 (1.03,1.09)	1.24 (1.20,1.27)	1.31 (1.27,1.35)
	≥ 95	227,726	2,015	1,389,891.1	1.45	1.15 (1.09,1.20)	1.37 (1.30,1.44)	1.47 (1.40,1.55)
	p for trend					< .0001	< .0001	< .0001

Model 1: non-adjusted

Model 2: adjusted for age, income, smoking status, alcohol drinking, regular physical activity

Model 3 (premenopausal) adjusted for age, income, smoking status, alcohol drinking, regular physical activity, parity, duration of breastfeeding, duration of oral contraceptive use, age at menarche

Model 3 (postmenopausal) adjusted for age, income, smoking status, alcohol drinking, regular physical activity, parity, duration of breastfeeding, duration of oral contraceptive use, age at menarche, age at menopause, duration of hormonal replacement therapy

300) found a positive association between BMI and breast cancer [49]. Ethnic and/or racial difference can explain this, as the epidemiology of breast cancer is much different between Asian and Western countries (e.g., much leaner body composition in Asian countries, earlier age of breast cancer diagnosis [50, 51] and smaller proportion of estrogen receptor-positive (ER +) cancer cases [52]). However, our large-scale study (n for premenopausal breast cancer = 18,141) showed an inverse association which is rather similar to that of the Western population.

Our study shows that CIS has a somewhat different association with obesity compared to IBC. The positive association in postmenopausal women was weaker, and the inverse association in premenopausal women was stronger than those observed for IBC. This is consistent with previous studies which showed a different direction of association for obesity between CIS and IBC [53]. This suggests that CIS may have a distinct pathophysiology from IBC. Though its etiology is still not clear, there is some evidence suggesting that CIS has a different pathogenesis. First, though CIS is suggested as a precursor of IBC, its progression to IBC is not absolute [27]. Second, in relation to HRT especially in estrogen and breast cancer patients, several studies showed that CIS has no relationship with HRT use [54, 55], while IBC has a positive relationship [56, 57]. This suggests that CIS has a weak association with estrogen in terms of etiology. So, obesity has been shown to be less influential in the development of CIS than in IBC, regardless of menopausal status [58]. An alternative explanation to differences in tumor biology could be the effect of screening, as CIS is mostly detected by breast cancer screening. It is possible that the attenuation of effect estimates can occur as a result of misclassification in CIS-specific analysis, but the stronger association observed for CIS in premenopausal women cannot be explained in this way. In addition, a previous study that investigated CIS and IBC did not expect differential misclassification of mode of detection by CIS or IBC [53]. Overall, we think our results are more suggestive of a different tumor biology between IBC and CIS, rather than a difference in screening pattern.

WC is a simple and convenient way to measure obesity, and it reflects abdominal and central obesity more exactly than BMI [22]. Many studies showed that WC is better for predicting type 2 diabetes [59], myocardial infarction [60], and all causes of mortality [61] than BMI but the results between WC and BMI did not show any significant difference in the risk of breast cancer incidence.

Although menopause does not directly increase BMI, the decrease in ovary-related hormones promotes an increase in adipose tissue mass especially in the early postmenopausal period [62]. Our findings suggest that obesity in postmenopausal women results in an increased breast cancer incidence; so, controlling obesity in postmenopausal women is important for the prevention of breast cancer.

This study had several limitations. First, we did not have information on the hormonal receptor status of the breast cancer cases. As ER + breast cancers in Asians is a growing trend [52], future studies will need to investigate whether ER receptors are expressed in Korean women in order to correlate ER + status with obesity and menopausal status. Analyses according to receptor status would have been helpful to better elucidate their relationship with obesity, estrogen, and breast cancer. Second, obesity measurement was only done once at the time of enrollment, so, it did not reflect changes in obesity patterns. There could be a bias in evaluating dose-dependent effects. Third, menopausal status was evaluated at baseline only. However, premenopausal women at baseline can become menopausal during follow up. Breast cancer in premenopausal women may not necessarily be premenopausal breast cancer. Finally, our study findings cannot be generalized as it was carried out only in the Korean population. However, our data is supplementary to current knowledge on the risk factors for breast cancer in the Asian population.

In conclusion, we demonstrated that the association between obesity and breast cancer risk is modified by menopausal status. There was a positive relationship between obesity and breast cancer in postmenopausal women, and an inverse association in premenopausal women. Our study suggests the need to manage obesity in breast cancer prevention especially in postmenopausal women.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

Ethical approval All procedures performed in this study which involved human participants were in accordance with the ethical standards of institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participats included in the study.

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