Breast Cancer Research

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Body mass index and breast cancer risk in premenopausal and postmenopausal East Asian women: a pooled analysis of 13 cohort studies

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Abstract

Background It has been suggested that the association between body mass index and breast cancer risk differs between Asian women and Western women. We aimed to assess the associations between body mass index and breast cancer incidence in East Asian women.

Methods Pooled analyses were performed using individual participant data of 319,189 women from 13 cohort studies in Japan, Korea, and China. Participants' height and weight were obtained by measurement or self-reports at cohort baseline. Breast cancer was defined as code C50.0-C50.9 according to the International Classification. Using a Cox proportional hazards model, hazard ratios of breast cancer were estimated for each body mass index category, with the reference group set as the group with a body mass index of 21 to < 23 kg/m^2. The hazard ratio for a 5 kg/m^2 increase in body mass index was also calculated.

Results During a mean 16.6 years of follow-up, 4819 women developed breast cancer. Similar to Westerners, a steady increase in breast cancer risk with increasing body mass index was observed in postmenopausal women, but the slope of the risk increase appeared to slow at a body mass index of 26–28 kg/m^2. In premenopausal women, the inverse association seen in Westerners was not observed. The risk of developing breast cancer after 50 years of age increased slightly with increasing body mass index, which was more pronounced in the older birth cohort. There was no significant association between body mass index and the risk of developing breast cancer before 50 years of age, but the risk estimates changed from positive to negative as the birth cohort got younger.

Conclusions In East Asia, the role of body mass index in breast cancer in premenopausal women may be changing along with the increase in obesity and breast cancer. The increased risk of postmenopausal breast cancer with a higher body mass index was as robust as that of Western women.

Keywords Body mass index, Breast cancer, Pooled analysis, Asians

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Background

Breast cancer is the most common female cancer worldwide [1]. The incidence of breast cancer has been increasing in Asian countries, especially China, Korea, and Japan, although it remains lower than that in Western countries [2, 3]. The prevalence of overweight and obesity has also increased over the same period, but the burden of postmenopausal breast cancer attributable to overweight is not thought to be high, with estimates of 0.4–2.9% in Japan, 8.2% in Korea, and 5.9–8.8% in China [4–7]. The burden of premenopausal breast cancer is unknown.

Obesity is known to be a main risk factor for postmenopausal breast cancer. Numerous cohort studies have universally and consistently revealed a positive association between body mass index (BMI) and breast cancer risk in postmenopausal women [8–24], which has been confirmed in several meta-analyses [25–28]. This is presumed to be due primarily to the estrogenic effects of adipose tissue rather than the ovaries in postmenopausal women [29]. A nonlinear positive association with a plateau in increasing breast cancer risk at higher BMIs has been suggested in Western women [28], whereas a linear association has been observed among Asian women, for whom severe obesity is less common [26].

It has been suggested that the effect of BMI on premenopausal breast cancer differs between Asian women and Western women [27, 30, 31]; BMI has been inversely associated with breast cancer incidence in premenopausal women in most Western cohort studies [21, 27, 28, 32–34], but such an association has scarcely been observed in Asian studies [9–11, 15, 16, 18–20, 26]. A 2014 pooled analysis of 0.2 million women from eight population-based prospective cohort studies in Japan suggested a possible positive association between BMI and breast cancer risk in premenopausal women [26]. However, a 2022 Japanese cohort study of 0.8 million women and a 2021 Korean cohort study of 6.6 million women based on data from a health checkup database managed by the National Health Insurance Service retrospectively revealed an inverse association between BMI and breast cancer incidence in premenopausal women [14, 35].

Thus, it is necessary to determine whether the positive association between BMI and breast cancer in postmenopausal Asian women is linear or nonlinear and whether BMI is positively or inversely associated with breast cancer in premenopausal women. The aim of this study was to investigate the role of BMI in the incidence of breast cancer in premenopausal and postmenopausal East Asian women using more than 300,000 individual-level data pooled through the collaboration of several cohort studies.

Methods

Study population

This project was conducted by the Asia Cohort Consortium (ACC), an international collaboration involving more than a million participants across Asia aimed at elucidating the etiology of various diseases [36, 37]. The present pooled analysis included twelve population-based cohorts and one hospital-based cohort, all from Japan, Korea, and China (Supplementary Table 1). To pool the data, the relevant cohort investigators provided the following individual participant data: age, sex, height, weight, and other confounders such as smoking status and alcohol consumption at baseline as well as breast cancer incidence during the follow-up period. The ACC's coordinating center harmonized the data.

Women who reported no history of any cancers and/or had data on height, weight, and menopausal status were included in the analysis (Supplementary Fig. 1). After women with a BMI of < 14 kg/m^2 or > 50 kg/m^2 were excluded, a total of 319 189 participants were included in the analysis.

Assessment of exposure

Participants' height and weight were obtained by either measurement or self-administered questionnaires at baseline in each study. BMI was calculated as (weight in kg)/(height in m)^2. In some cohorts with self-reports, the correlation coefficients between the responses reported on the questionnaire and the actual measurements were 0.93–0.97 for height, 0.85–0.97 for weight, and 0.90–0.91 for BMI [38–40]. Other studies for which validation was unavailable used questions similar to those for cohorts for which validation was available. Identical cutoff points for BMI were used for the pooled data. To examine the association with breast cancer in finer BMI categories, BMI was divided into the following seven categories: < 18.5 kg/m^2, 18.5 to < 21 kg/m^2, 21 to < 23 kg/m^2, 23 to < 25 kg/m^2, 25 to < 27.5 kg/m^2, 27.5 to < 30 kg/m^2, and ≥ 30 kg/m^2, using the cutoff points recommended by the World Health Organization [41].

Menopausal status data were obtained from the questionnaire at baseline. Smoking status, alcohol consumption, age at menarche and menopause, parity number, and age at first delivery were also obtained from the baseline questionnaire. Details of the definitions of reproductive factors were described previously [42].

Outcomes and follow-up

Information on migration and death was obtained from the residential registry and death certificates. The incidence of cancer was confirmed mainly with reference to local cancer registries and/or through active patient notification from major local hospitals. The causes of cancer were coded according to the International Classification of Diseases for Oncology (ICD-O-2 or -3) or the International Classification of Diseases and Health Related Problems, 10th Revision (ICD-10). Breast cancer was defined as code C50, and the first primary cancer was included in this study.

Statistical analyses

Hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer incidence were estimated for each BMI category using a Cox proportional hazards model. Follow-up periods were calculated as the time from baseline to the date of breast cancer diagnosis, date of death, date of moving out of the study area, or the end of follow-up, whichever came first. The reference group was defined as the group with a BMI ranging from 21 to < 23 kg/m^2. Tests for a linear trend were performed using the Cox model with BMIs treated as continuous variables, thereby providing HRs for every 5-kg/m^2 increase in BMI.

Because some premenopausal women undergo menopause during the follow-up period, additional analyses focused on breast cancer that developed before or after menopause among premenopausal women at baseline. Because no study collected information on menopausal status after the start of follow-up, 50 years of age, when approximately 50% of the participants were reported to be postmenopausal, was used as a proxy cutoff point; breast cancer was divided into breast cancer that developed before 50 years of age (early-onset) and breast cancer that developed after 50 years of age (later-onset). Then, the HRs for early-onset breast cancer were estimated by censoring the years of observation when participants reached 50 years of age. The HRs for later-onset breast cancer were estimated by using the years of observation thereafter. Sensitivity analysis was performed when 45 years of age, at which 16% of the participants were reported to be postmenopausal, was used as a cutoff point.

In addition, restricted cubic splines [43] with four knots placed at the 5th, 35th, 65th, and 95th percentiles of the BMI were used to delineate the dose–response relationship between BMI and breast cancer and to test the nonlinear associations. A BMI of 22 kg/m^2 was used as the spline reference.

After potential risk factors for breast cancer were identified through a literature review, the confounding factors included cohort (13 cohorts), age at enrollment (years, continuous), smoking status (never, former, or current smoker), alcohol consumption (non-drinkers or current drinkers), age at menarche (≤ 10 years, 11–12 years, 13–14 years, 15–16 years, or ≥ 17 years), nulliparity (yes or no), age at first delivery (≤ 20 years, 21–25 years, 26–30 years, or ≥ 31 years), and age at menopause (≤ 44 years, 45–49 years, 50–54 years, or ≥ 55 years; postmenopausal women only). All analyses were adjusted for these confounders. Dummy variables were created for missing categorical covariate data.

To evaluate the cohort effect by birth year on the associations, the analysis was repeated with the participants divided into three groups by birth year tertile. Country-specific associations were also evaluated.

Sensitivity analysis was performed after excluding patients who were diagnosed with breast cancer in the first three years because they might have had latent cancer at baseline, as well as after excluding one hospital-based study (Korean National Cancer Center cohort).

All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC). *P* values were calculated by a two-sided test.

Results

Among 118,786 premenopausal and 200,403 postmenopausal women at baseline, 2,202 and 2,617 had developed breast cancer, respectively, during the mean 16.6 years of follow-up (Supplementary Table 1).

The mean age and BMI at baseline were 43.7 years and 23.0 kg/m^2, respectively, for premenopausal women and 60.6 years and 23.5 kg/m^2, respectively, for postmenopausal women (Table 1). More than 90% of the premenopausal and postmenopausal women were never smokers and/or had ever given birth.

A higher BMI was associated with an increased risk for breast cancer among both premenopausal and postmenopausal women at baseline (Table 2). In postmenopausal women, spline regression analysis revealed a steady increase in breast cancer risk with increasing BMI, but the slope of the increase in risk appeared to decrease as BMI reached approximately 26–28 kg/m^2 (p for nonlinearity = 0.01) (Fig. 1b). In premenopausal women, BMI at baseline was not associated with the risk of developing breast cancer before 50 years of age, whereas a slight increase in the risk of developing breast cancer after 50 years of age was observed with increasing BMI (Table 3 and Fig. 1a). The results were essentially unaltered when 45 years of age was used as a cutoff point; the fully multivariate adjusted HRs per 5-kg/m^2 increase in BMI were 1.00 (95% CI 0.80–1.25) and 1.11 (95% CI 1.03–1.19) for breast cancer developed before and after 45 years of age, respectively.

Table 1 Characteristics of women at baseline by menopausal status

n	Premenopausal women		Postmenopausal women	
	118,786		**200,403**	
Age at enrollment, mean, s.d	43.7	5.1	60.6	8.1
Body mass index, mean, s.d	23.0	3.1	23.5	3.5
Body mass index, n, %				
< 18.5	5,862	4.9%	11,885	5.9%
18.5- < 21	27,243	22.9%	34,326	17.1%
21- < 23	32,295	27.2%	46,852	23.4%
23- < 25	26,556	22.4%	45,963	22.9%
25- < 27.5	17,294	14.6%	37,651	18.8%
27.5- < 30	6,566	5.5%	16,091	8.0%
30-	2,970	2.5%	7,635	3.8%
Smoking status, n, %				
Never	104,385	91.9%	164,467	91.2%
Former	1567	1.4%	3678	2.0%
Current	7598	6.7%	12,198	6.8%
Alcohol consumption, n, %				
Non-drinkers	87,553	76.1%	150,976	81.5%
Current drinkers	27,444	23.9%	34,300	18.5%
Age at menarche (years), n, %				
≤ 10	257	0.2%	157	0.1%
11–12	12,330	11.1%	7778	4.4%
13–14	52,410	47.3%	52,241	29.5%
15–16	35,427	32.0%	71,843	40.5%
≥ 17	10,330	9.3%	45,165	25.5%
Nulliparity, n, %				
No	108,760	94.0%	174,919	92.3%
Yes	6961	6.0%	14,623	7.7%
Age at first delivery (years), n, %				
≤ 20	4992	4.7%	23,160	13.6%
21–25	49,110	45.8%	93,919	55.3%
26–30	43,940	41.0%	43,971	25.9%
≥ 31	9134	8.5%	8786	5.2%
Age at menopause (years), n, %				
≤ 44			27,861	16.0%
45–49			62,059	35.5%
50–54			75,850	43.4%
≥ 55			8818	5.1%

s.d. standard deviation

When patients diagnosed with breast cancer during the first 3 years of follow-up were excluded, none of the results were substantially altered (Tables 2 and 3). The exclusion of one hospital-based study also did not change the associations; the fully multivariate adjusted HRs of breast cancer for the lowest (< 18.5 kg/m^2) and highest (≥ 30 kg/m^2) BMIs were 0.80 (95% CI 0.64–1.00) and 1.71 (95% CI 1.42–2.05), respectively, in postmenopausal women. The corresponding HRs were 0.90 (95% CI 0.57–1.43) and 1.23 (95% CI 0.71–2.13), respectively, for breast cancer before 50 years of age, and 0.91 (95% CI 0.70–1.18) and 1.12 (95% CI 0.82–1.52), respectively, for breast cancer after 50 years of age in premenopausal women.

In premenopausal women, a significant positive association between BMI at baseline and the risk of developing breast cancer after 50 years of age was observed in the oldest birth cohort, but not in the younger birth cohorts (Table 4). There was no significant association between BMI at baseline and the risk of developing breast cancer before 50 years of age in all birth cohorts, but the risk estimates changed from positive to negative as the birth cohort got younger; the HR per 5-kg/m^2 increase in BMI was 1.25 (95% CI 0.85–1.84) in women with a birth year of 1944 or earlier and 0.92 (95% CI 0.76–1.12) in women with a birth year of 1953 or after. BMI at baseline was positively associated with the risk of developing breast cancer after 50 years of age in the Japanese cohorts, while an inverse association was observed between BMI at baseline and the risk of developing breast cancer before 50 years of age in the Korean cohorts. A positive association between BMI and breast cancer in postmenopausal women was observed across all birth cohorts and countries, although the association was weaker in the Korean cohorts. The oldest cohort was predominantly Japanese, while the youngest birth cohort consisted mainly of Korean and Chinese participants.

Discussion

This pooled analysis, including 13 ongoing prospective cohorts in East Asia, showed that BMI was positively associated with subsequent risk of breast cancer in both premenopausal and postmenopausal women.

A 2021 pooled analysis of 20 prospective studies, consisting mainly of Western studies and one Japanese study, reported a nonlinear positive association with a plateau in increasing postmenopausal breast cancer risk at a BMI > 30 kg/cm^2 [28]. The present pooled analysis of Asians revealed a steady increase in breast cancer risk with increasing BMI in postmenopausal women, but the slope of the increase in risk appeared to decrease at a BMI of approximately 26–28 kg/m^2. Although nonlinear, the overall risk increase of 32% per 5-kg/m^2 increase in BMI was compatible with the results of previous meta-analyses in Asians [26, 27, 30]. As has been suggested, the magnitude of risk increase may be greater in Asian women than in Western women [27, 30]. One reason may be that Asian women are less likely to use hormone replacement therapy (HRT) than Western women are. It was reported that only approximately 3% of Asian women had received HRT [42], whereas approximately 30% of European women had [44]. The positive

Table 2 The association between body mass index and breast cancer risk in Asian women by menopausal status at baseline

	Body mass index at baseline (kg/m²)								
	< 18.5	18.5– < 21	21– < 23	23– < 25	25– < 27.5	27.5– < 30	30-	Trend (per 5 kg/m²)	
	HR (95% CI)	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	*p*
Premenopausal women									
Number of participants	5,862	27,243	32,295	26,556	17,294	6,566	2,970		
Person-years	115,078	509,956	589,871	483,623	315,679	119,619	53,686		
Number of cases	92	470	578	496	370	135	61		
Crude rate (per 100,000)	79.95	92.16	97.99	102.56	117.21	112.86	113.62		
Age- and study-adjusted (HR1)	0.86 (0.69–1.07)	0.97 (0.86–1.10)	1 (ref.)	1.01 (0.89–1.14)	1.12 (0.99–1.28)	1.07 (0.89–1.29)	1.11 (0.85–1.44)	1.08 (1.01–1.16)	0.02
Multivariate-adjusted (HR2)[a]	0.86 (0.69–1.07)	0.97 (0.86–1.10)	1 (ref.)	1.01 (0.90–1.14)	1.13 (0.99–1.28)	1.07 (0.89–1.29)	1.11 (0.85–1.44)	1.08 (1.01–1.16)	0.02
Multivariate-adjusted (HR3)[b]	0.83 (0.67–1.04)	0.96 (0.85–1.08)	1 (ref.)	1.01 (0.90–1.14)	1.13 (0.99–1.29)	1.08 (0.89–1.30)	1.11 (0.85–1.44)	1.09 (1.02–1.17)	0.01
(Excluding cases within 3 years)									
Multivariate-adjusted (HR2)[a]	0.85 (0.66–1.08)	0.93 (0.81–1.07)	1 (ref.)	1.01 (0.89–1.16)	1.13 (0.98–1.30)	1.13 (0.93–1.38)	1.03 (0.77–1.39)	1.10 (1.02–1.18)	0.01
Multivariate-adjusted (HR3)[b]	0.82 (0.64–1.05)	0.92 (0.80–1.05)	1 (ref.)	1.01 (0.89–1.16)	1.14 (0.99–1.31)	1.15 (0.94–1.40)	1.03 (0.77–1.39)	1.11 (1.03–1.20)	0.005
Postmenopausal women									
Number of participants	11,885	34,326	46,852	45,963	37,651	16,091	7,635		
Person-years	167,878	526,765	734,224	727,835	595,491	254,248	117,526		
Number of cases	98	331	526	669	564	276	153		
Crude rate (per 100,000)	58.38	62.84	71.64	91.92	94.71	108.56	130.18		
Age- and study-adjusted (HR1)	0.83 (0.67–1.03)	0.89 (0.77–1.02)	1 (ref.)	1.26 (1.12–1.41)	1.27 (1.13–1.43)	1.40 (1.21–1.62)	1.64 (1.37–1.96)	1.28 (1.21–1.35)	< 0.001
Multivariate-adjusted (HR2)[a]	0.83 (0.67–1.03)	0.89 (0.77–1.02)	1 (ref.)	1.26 (1.12–1.41)	1.27 (1.13–1.44)	1.40 (1.21–1.62)	1.64 (1.37–1.97)	1.28 (1.22–1.35)	< 0.001
Multivariate-adjusted (HR4)[c]	0.80 (0.64–1.00)	0.87 (0.76–1.00)	1 (ref.)	1.27 (1.13–1.42)	1.30 (1.15–1.46)	1.43 (1.24–1.66)	1.72 (1.43–2.06)	1.32 (1.25–1.39)	< 0.001
(Excluding cases within 3 years)									
Multivariate-adjusted (HR2)[a]	0.80 (0.63–1.02)	0.87 (0.75–1.02)	1 (ref.)	1.22 (1.08–1.39)	1.28 (1.12–1.46)	1.46 (1.24–1.71)	1.72 (1.42–2.10)	1.31 (1.24–1.39)	< 0.001
Multivariate-adjusted (HR4)[c]	0.77 (0.60–0.99)	0.85 (0.73–1.00)	1 (ref.)	1.23 (1.08–1.40)	1.31 (1.14–1.49)	1.50 (1.28–1.75)	1.80 (1.48–2.19)	1.35 (1.27–1.43)	< 0.001

HR hazard ratio, *CI* confident interval, *ref* reference

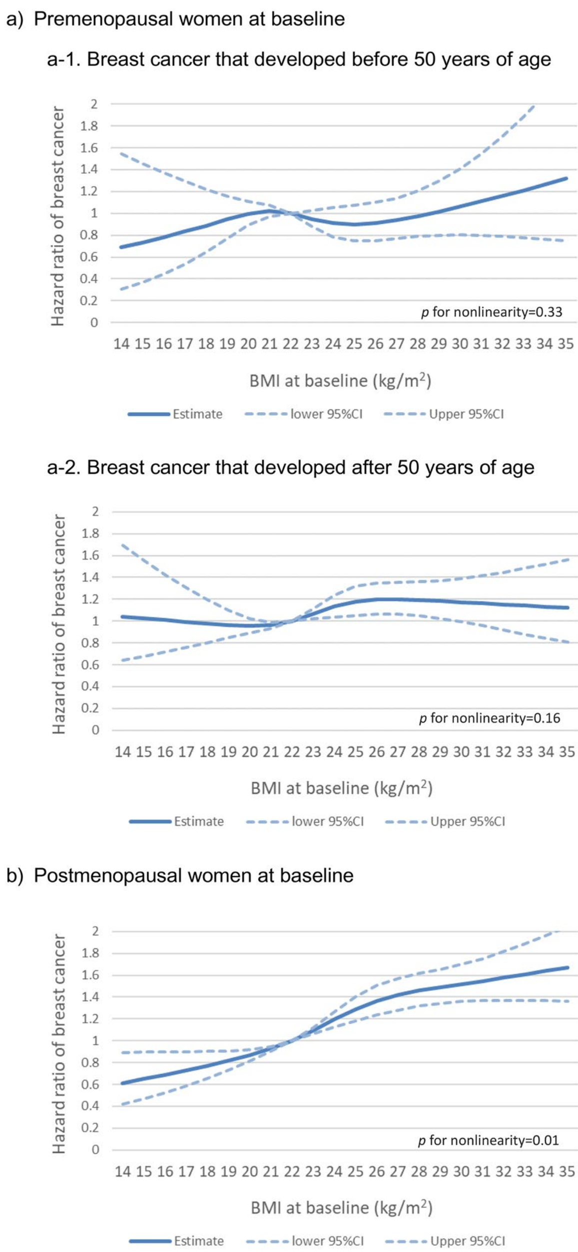
[a] Estimated hazard ratio after adjustments for age at enrollment (continuous), study (13 cohorts), smoking status (never, former, current smokers), and alcohol consumption (non-drinkers or current drinkers)

[b] Estimated hazard ratio after adjustments for age at enrollment (continuous), study (13 cohorts), smoking status (never, former, current smokers), alcohol consumption (non-drinkers or current drinkers), age at menarche (≤ 10 y, 11–12 y, 13–14 y, 15–16 y, ≥ 17 y), nulliparity (yes, no), and age at first delivery (≤ 20 y, 21–25 y, 26–30 y, ≥ 31 y)

[c] Estimated hazard ratio after adjustments for age at enrollment (continuous), study (13 cohorts), smoking status (never, former, current smokers), alcohol consumption (non-drinkers or current drinkers), age at menarche (≤ 10 y, 11–12 y, 13–14 y, 15–16 y, ≥ 17 y), nulliparity (yes, no), age at first delivery (≤ 20 y, 21–25 y, 26–30 y, ≥ 31 y), and age at menopause (≤ 44 y, 45–49 y, 50–54 y, ≥ 55 y)

association between BMI and breast cancer in postmenopausal women has been reported to be stronger among never HRT users than ever HRT users [22, 23, 25, 27, 28].

The potential biological mechanism underlying this association may be related to estrogen. After estrogen production in the ovary decreases, adipose tissue



CI: confidence interval.

Fig. 1 Spline regression curves for the association between body mass index and breast cancer risk by menopausal status at baseline and age at diagnosis.

becomes the primary source of estrogen in postmenopausal women [29]. The positive association between BMI and breast cancer risk in postmenopausal women has been shown to be more pronounced for estrogen receptor-positive (ER+) and progesterone receptor-positive (PR+) tumors [16, 24, 25, 28].

In contrast with the inverse association between BMI and breast cancer risk observed mainly in premenopausal Western women [34], this pooled analysis of premenopausal Asian women revealed a positive association, similar to the results of a previous pooled analysis in Japan (eight studies in our analyses overlapped with the pooled analysis) [26]. This positive association was attributed to an increase in the risk of breast cancer that developed after 50 years of age, suggesting that this may be due primarily to the effect of BMI carried over after menopause. The positive association with BMI was weaker compared with postmenopausal women. This may be because the postmenopausal period before breast cancer diagnosis was shorter in premenopausal women (average age at diagnosis: 60 years) than in postmenopausal women (average age at diagnosis: 70 years). The association between BMI and breast cancer risk has been reported to become stronger with increasing age [27, 45].

There was no significant association between BMI and breast cancer that developed before 50 years of age. The reason for the lack of an inverse association in Asian women is unclear. One possible explanation may be the lower prevalence of overweight or obese Asian women [46, 47], especially severely obese women, who are more prone to anovulation and result in lower exposure to estrogen [48, 49]. However, in Western women, the inverse association was observed even in the range of BMI less than 30 kg/cm^2. The difference in risk between Western and Asian women with the same BMI may be due to BMI in young adulthood in the twenties or earlier. Lower early-adult BMI has been reported to be associated with an increased risk of breast cancer in Asian and Western women [17, 28, 33, 34, 50]. It is likely that the Asian women included in this pooled analysis had much lower early-adult BMI than Western women. Another possibility is that Asian women might have a lower incidence of ER+or PR+breast cancer [51], which has been implicated in the reduced risk associated with a higher BMI in premenopausal women [16, 25, 28, 33, 51]. Other factors might include race, ethnicity, and obesity-related lifestyles.

Moreover, the current pooled analysis suggested a positive association between BMI and breast cancer in premenopausal women among Japanese and an inverse association among Koreans. All the Japanese cohorts were population-based studies, whereas the Koreans included one hospital-based study. The Japanese cohorts had a baseline in the 1980s and the early 1990s, whereas the Korean cohorts included data of the 2000s or later. In addition, two larger-scale retrospective cohort studies in Japan and Korea, conducted in the 2000s to the 2010s with shorter follow-up periods and likely composed of health-conscious participants, suggested an inverse association [14, 35]. Furthermore, the current study revealed that a positive association between BMI and the risk of

Table 3 The association between body mass index and breast cancer by age at diagnosis in premenopausal women at baseline

	Body mass index at baseline (kg/m²)								
	< 18.5	18.5– < 21	21– < 23	23– < 25	25– < 27.5	27.5- < 30	30-	Trend (per 5 kg/m²)	
	HR (95% CI)	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	*p*
Breast cancer that developed before 50 years of age									
Number of participants	5,571	25,518	29,294	23,556	14,804	5,566	2,484		
Person-years	48,597	194,531	197,523	146,036	86,777	31,975	14,699		
Number of cases	24	160	161	122	91	26	15		
Crude rate (per 100,000)	49.39	82.25	81.51	83.54	104.87	81.31	102.05		
Age- and study-adjusted (HR1)	0.85 (0.55–1.31)	1.15 (0.92–1.43)	1 (ref.)	0.97 (0.77–1.23)	1.19 (0.92–1.54)	0.92 (0.61–1.39)	1.19 (0.70–2.02)	1.02 (0.89–1.17)	0.80
Multivariate-adjusted (HR2)[a]	0.84 (0.55–1.29)	1.14 (0.92–1.42)	1 (ref.)	0.97 (0.77–1.23)	1.19 (0.92–1.54)	0.91 (0.60–1.38)	1.18 (0.69–2.00)	1.02 (0.89–1.17)	0.78
Multivariate-adjusted (HR3)[b]	0.84 (0.55–1.30)	1.15 (0.92–1.43)	1 (ref.)	0.97 (0.77–1.23)	1.19 (0.92–1.54)	0.91 (0.60–1.37)	1.18 (0.69–2.00)	1.02 (0.89–1.16)	0.81
(Excluding cases within 3 years)									
Multivariate-adjusted (HR2)[a]	0.80 (0.44–1.48)	1.02 (0.75–1.40)	1 (ref.)	0.93 (0.67–1.30)	1.09 (0.75–1.59)	1.13 (0.66–1.93)	0.65 (0.24–1.77)	1.02 (0.84–1.23)	0.86
Multivariate-adjusted (HR3)[b]	0.80 (0.44–1.48)	1.02 (0.75–1.40)	1 (ref.)	0.93 (0.67–1.30)	1.10 (0.76–1.60)	1.13 (0.66–1.93)	0.66 (0.24–1.80)	1.02 (0.84–1.24)	0.84
Breast cancer that developed after 50 years of age									
Number of participants	5147	24,698	29,973	25,109	16,544	6263	2806		
Person-years[c]	66,481	315,425	392,348	337,587	228,903	87,644	38,987		
Number of cases	68	310	417	374	279	109	46		
Crude rate (per 100,000)	102.28	98.28	106.28	110.79	121.89	124.37	117.99		
Age- and study-adjusted (HR1)	0.94 (0.72–1.22)	0.91 (0.79–1.06)	1 (ref.)	1.03 (0.90–1.19)	1.14 (0.98–1.32)	1.15 (0.93–1.42)	1.09 (0.80–1.48)	1.10 (1.02–1.19)	0.02
Multivariate-adjusted (HR2)[a]	0.94 (0.73–1.23)	0.92 (0.79–1.06)	1 (ref.)	1.03 (0.90–1.19)	1.14 (0.98–1.33)	1.15 (0.93–1.42)	1.10 (0.81–1.49)	1.10 (1.02–1.19)	0.02
Multivariate-adjusted (HR3)[b]	0.90 (0.69–1.16)	0.90 (0.78–1.04)	1 (ref.)	1.04 (0.91–1.20)	1.16 (0.99–1.35)	1.17 (0.94–1.44)	1.10 (0.81–1.49)	1.12 (1.04–1.21)	0.004
(Excluding cases within 3 years)									
Multivariate-adjusted (HR2)[a]	0.94 (0.72–1.22)	0.93 (0.80–1.08)	1 (ref.)	1.04 (0.90–1.20)	1.17 (1.01–1.37)	1.18 (0.95–1.46)	1.11 (0.81–1.52)	1.11 (1.03–1.20)	0.009
Multivariate-adjusted (HR3)[b]	0.89 (0.68–1.16)	0.91 (0.79–1.06)	1 (ref.)	1.05 (0.91–1.21)	1.19 (1.02–1.39)	1.19 (0.96–1.48)	1.11 (0.81–1.52)	1.13 (1.05–1.22)	0.002

HR hazard ratio, *CI* confident interval

[a] Estimated hazard ratio after adjustments for age at enrollment (continuous), study (13 cohorts), smoking status (never, former, current smokers), and alcohol consumption (non-drinkers or current drinkers)

[b] Estimated hazard ratio after adjustments for age at enrollment (continuous), study (13 cohorts), smoking status (never, former, current smokers), alcohol consumption (non-drinkers or current drinkers), age at menarche (≤ 10 y, 11–12 y, 13–14 y, 15–16 y, ≥ 17 y), nulliparity (yes, no), and age at first delivery (≤ 20 y, 21–25 y, 26–30 y, ≥ 31 y)

[c] Follow-up period after 50 years of age

developing breast cancer after 50 years of age was more pronounced in the older birth cohort, and the association between BMI and the risk of developing breast cancer before 50 years of age changed from positive to inverse as the birth cohort became younger. Although we were unable to distinguish the effect by birth cohort or country, the association between BMI and breast cancer in premenopausal Asian women might be moving towards an inverse association like that in Western women, given that newer Asian generations show a greater prevalence of obesity starting in childhood with Westernization. Further investigations will be needed in the form

Table 4 The association between body mass index and breast cancer risk according to birth year and country

	n	Body mass index at baseline (kg/m²)									
		< 18.5	18.5– < 21	21– < 23	23– < 25	25– < 27.5	27.5– < 30	30-	Trend (per 5 kg/m²)		*p* for interaction
		HR (95% CI)	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	*p*	
Birth year											
Premenopausal women at baseline											
Breast cancer that developed before 50 years of age											
1944 or before	32,654	1.03 (0.29–3.66)	1.35 (0.66–2.76)	1 (ref.)	1.22 (0.57–2.60)	1.96 (0.92–4.19)	0.43 (0.06–3.31)	4.53 (1.47–13.96)	1.25 (0.85–1.84)	0.27	0.69
1945–1952	39,693	0.88 (0.44–1.76)	0.99 (0.69–1.42)	1 (ref.)	0.84 (0.57–1.23)	1.16 (0.77–1.75)	1.13 (0.62–2.05)	1.18 (0.51–2.73)	1.12 (0.90–1.38)	0.32	
1953 or after	34,446	0.82 (0.44–1.51)	1.23 (0.91–1.67)	1 (ref.)	1.07 (0.77–1.49)	1.11 (0.76–1.62)	0.85 (0.46–1.56)	0.75 (0.30–1.86)	0.92 (0.76–1.12)	0.40	
Breast cancer that developed after 50 years of age											
1944 or before	38,518	0.85 (0.58–1.24)	0.94 (0.74–1.20)	1 (ref.)	1.03 (0.81–1.31)	1.26 (0.97–1.64)	1.33 (0.93–1.90)	1.18 (0.69–2.01)	1.15 (1.02–1.30)	0.03	0.98
1945–1952	41,962	1.02 (0.65–1.60)	0.81 (0.63–1.05)	1 (ref.)	1.10 (0.88–1.36)	1.11 (0.88–1.41)	1.09 (0.79–1.51)	1.05 (0.67–1.64)	1.10 (0.97–1.24)	0.13	
1953 or after	30,060	0.74 (0.40–1.38)	0.92 (0.68–1.23)	1 (ref.)	0.94 (0.70–1.24)	1.03 (0.75–1.41)	0.99 (0.63–1.57)	0.98 (0.49–1.93)	1.08 (0.91–1.28)	0.39	
Postmenopausal women at baseline											
1928 or earlier	68,886	0.66 (0.48–0.92)	0.68 (0.53–0.87)	1 (ref.)	1.17 (0.94–1.46)	1.23 (0.97–1.55)	1.69 (1.27–2.24)	1.81(1.24-.62)	1.44(1.31–1.58)	< 0.001	0.24
1929–1936	71,600	0.99 (0.67–1.46)	0.79 (0.62–1.01)	1 (ref.)	1.32 (1.10–1.59)	1.26 (1.04–1.53)	1.23 (0.96–1.56)	1.45 (1.07-	1.23 (1.12–1.35)	< 0.001	
1937 or later	59,917	0.80 (0.51–1.27)	1.17 (0.93–1.46)	1 (ref.)	1.31 (1.08–1.59)	1.42 (1.16–1.73)	1.55 (1.21–1.99)	2.03 (1.52–2.72)	1.30 (1.19–1.43)	< 0.001	
Country											
Premenopausal women at baseline											
Breast cancer that developed before 50 years of age											
Japan	63,588	0.86 (0.48–1.55)	1.10 (0.81–1.50)	1 (ref.)	0.97 (0.70–1.35)	1.36 (0.95–1.94)	1.08 (0.61–1.91)	1.81 (0.94–3.49)	1.17 (0.97–1.41)	0.09	0.04
Korea	10,229	1.14 (0.46–2.80)	1.43 (0.85–2.39)	1 (ref.)	1.04 (0.57–1.88)	0.78 (0.36–1.67)	0.21 (0.03–1.58)	0.74 (0.17–3.13)	0.63 (0.43–0.92)	0.02	
China	32,976	0.67 (0.27–1.69)	1.09 (0.73–1.63)	1 (ref.)	0.95 (0.63–1.42)	1.16 (0.75–1.80)	1.01 (0.53–1.94)	0.67 (0.21–2.13)	1.02 (0.80–1.29)	0.88	
Breast cancer that developed after 50 years of age											
Japan	67,282	0.96 (0.70–1.32)	0.93 (0.76–1.12)	1 (ref.)	1.12 (0.92–1.35)	1.19 (0.96–1.47)	1.45 (1.10–1.92)	1.19 (0.77–1.83)	1.16 (1.05–1.28)	0.005	0.82
Korea	6794	0.61 (0.08–4.60)	0.63 (0.28–1.45)	1 (ref.)	0.92 (0.46–1.83)	0.61 (0.25–1.47)	0.45 (0.10–1.99)	0.40 (0.05–3.05)	0.86 (0.53–1.39)	0.53	
China	36,464	0.77 (0.47–1.27)	0.89 (0.70–1.13)	1 (ref.)	0.96 (0.77–1.19)	1.13 (0.90–1.42)	0.90 (0.64–1.26)	1.04 (0.66–1.62)	1.08 (0.95–1.22)	0.25	

Table 4 (continued)

	n	Body mass index at baseline (kg/m²)									
		< 18.5	18.5– < 21	21– < 23	23– < 25	25– < 27.5	27.5– < 30	30-	Trend (per 5 kg/m²)		*p* for interaction
		HR (95% CI)	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	*p*	
Postmenopausal women at baseline											
Japan	141,822	0.74 (0.57–0.94)	0.76 (0.64–0.90)	1 (ref.)	1.27 (1.11–1.45)	1.22 (1.05–1.41)	1.42 (1.18–1.71)	1.45 (1.11–1.88)	1.33 (1.24–1.42)	< 0.001	0.15
Korea	22,050	0.59 (0.14–2.45)	1.43 (0.89–2.31)	1 (ref.)	1.30 (0.85–1.99)	0.98 (0.60–1.59)	1.10 (0.58–2.09)	1.95 (0.96–3.94)	1.05 (0.82–1.34)	0.70	
China	36,531	1.11 (0.69–1.80)	1.12 (0.83–1.51)	1 (ref.)	1.31 (1.03–1.67)	1.60 (1.27–2.03)	1.61 (1.23–2.12)	2.17 (1.61–2.92)	1.33 (1.21–1.47)	< 0.001	

HR hazard ratio, *CI* confident interval

Estimated hazard ratio after adjustments for age at enrollment (continuous), study (13 cohorts), smoking status (never, former, current smokers), alcohol consumption (non-drinkers or current drinkers), age at menarche (≤ 10 y, 11–12 y, 13–14 y, 15–16 y, ≥ 17 y), nulliparity (yes, no), age at first delivery (≤ 20 y, 21–25 y, 26–30 y, ≥ 31 y), and age at menopause (≤ 44 y, 45–49 y, 50–54 y, ≥ 55 y)(postmenopausal women only) of prospective Asian studies of these newer generations with longer follow-up periods.

The strengths of this study include the large number of participants from Japan, Korea, and China. Each study had a long follow-up period as well as information on several confounders. Because only cohort studies were included in the pooled analysis, the recall bias of exposure should be minimal. Unlike with meta-analyses of published studies, common approaches for exposures, outcomes, covariates, and statistical models were applied to the pooled data, and publication bias is considered limited because of the inclusion of studies that have not previously been published on the association. Although self-reported height and weight data were used in the Japanese cohort studies, the validity was high, and Japanese people are suggested to be more accurate in reporting their weight and height compared with other populations [52]. Although BMI at baseline might have changed due to preclinical signs, the exclusion of patients during the first three years of follow-up did not change the results.

Several limitations should be considered. None of the analyzed studies obtained information on menopausal status after the start of follow-up. Although 50 years of age was used as a proxy cutoff point, some misclassification might have occurred. However, sensitivity analyses using another cutoff point did not substantially change the results. Because information on exposures and confounders was obtained only at baseline, changes during follow-up were not considered. The lack of information on tumor subtypes, including ER, PR, and human epidermal growth factor receptor 2 (HER2), as well as experience with HRT, was also a limitation because these factors might modify the association between BMI and breast cancer risk. The possibility of residual confounding could not be fully ruled out even after accounting for several factors.

Conclusions

This pooled analysis of prospective studies in Japan, Korea, and China confirmed increased risks of breast cancer among postmenopausal women with higher BMIs. In premenopausal women, the association between BMI and the risk of breast cancer tended to be positive in the older birth cohorts and inverse in the younger cohorts. In Asia, the role of BMI in breast cancer in premenopausal women may be changing along with the increase in obesity and breast cancer. New-generation prospective Asian studies with longer follow-up periods warrant further investigation. Understanding changes in the association over time will help to elucidate the mechanism by which obesity contributes to the etiology of breast cancer.

Abbreviations

BMI	Body mass index
ACC	The Asia Cohort Consortium
ICD-O	The International Classification of Diseases for Oncology
ICD-10	The International Classification of Diseases and Health Related Problems, 10th Revision
HR	Hazard ratio
CI	Confidence interval
HRT	Hormone replacement therapy
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-024-01907-5.

Additional file1

Acknowledgements
We appreciate all participants of the Asia Cohort Consortium and the staff of the Coordinating Center.

Author contributions
KW designed the research, analyzed and interpreted the data, drafted the original manuscript, and took responsibility for the integrity of the data and the accuracy of the data analysis; KK analyzed and interpreted the data and critically revised the draft; CN supervised the study, assisted in data interpretation, and critically revised the draft; NS, AT, XOS, RS, AH, SK, HI, YS, SKP, SK, AO, TK, WW, IO, and MHS provided data and critically reviewed the draft; SKA, MSR, MRI, and ES provided administrative, technical, or material support and critically reviewed the draft; AS, JK, JEL, KM, NR, YLQ, WZ, PB, and MI. supervised the study and critically reviewed the draft.

Funding
The Asia Cohort Consortium Coordinating Center, National Cancer Center Japan Research and Development Fund; Japan Public Health Center-Based Prospective Study (1 and 2), National Cancer Center Japan Research and Development Fund (since 2011) and a grant-in-aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (from 1989 to 2010); the Japan Collaborative Cohort Study, National Cancer Center Japan Research and Development Fund, grants for health service and comprehensive research on cardiovascular and lifestyle related diseases from the Ministry of Health, Labour and Welfare, Japan, and a grant for scientific research from the Ministry of Education, Culture, Sports, Science and Technology, Japan; Life Span Study Cohort, Radiation Effects Research Foundation, the Japanese Ministry of Health, Labour and Welfare and the US Department of Energy; Miyagi Cohort Study, National Cancer Center Japan Research and Development Fund; Ohsaki National Health Insurance Cohort Study, National Cancer Center Japan Research and Development Fund; Three Prefecture Cohort Study Aichi, The Japanese Ministry of the Environment (former Environment Agency); Three Prefecture Cohort Study Miyagi, National Cancer Center Japan Research and Development Fund; Takayama Study, National Cancer Center Japan Research and Development Fund; Korea Multi-Center Cancer Cohort Study, the Frontier Functional Human Genome Project from the Ministry of Science and Technology of Korea, the National Research Foundation of Korea grant funded by the Korea government (MSIP), the Korean Foundation for Cancer Research, a research grant from the National Cancer Center, Korea, partly by grant from the Seoul National University Hospital Research Fund; Korea National Cancer Center Cohort, National Cancer Center Korea Research Grant; The Namwon Study, Chonnam National University Hwasun Hospital Research grant; The Shanghai Women's Health Study, the US National Cancer Institute. The study funders had no role in the design or execution of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the Declaration of Helsinki. Each participating study was approved by the relevant institutional ethical review boards. The protocol for the ACC analysis was approved by the institutional review board of the National Cancer Center, Japan. The requirement for consent from several cohort studies was waived due to the justification for lack of consent at the time of the survey, the difficulty in obtaining new consent, and the public necessity of the research.

Consent for publication
All authors reviewed and approved the final version for submission.

Competing interests
The authors declare no competing interests.

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Received: 19 April 2024 Accepted: 19 October 2024
Published online: 14 November 2024

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