Body mass index and breast cancer risk in Japan: a pooled analysis of eight population-based cohort studies

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Received 11 August 2013; revised 1 November 2013; accepted 4 November 2013

Background: A positive association between body mass index (BMI) and breast cancer risk among postmenopausal women has been reported, and a weak inverse association has been suggested among premenopausal women from studies in the Western population. The effects of BMI on breast cancer have remained unclear among the Asian population, especially in premenopausal women.

Methods: We assessed the associations between BMI and breast cancer incidence by a pooled analysis from eight representative large-scale cohort studies in Japan. Cancer incidence was mainly confirmed through regional population-based cancer registries and/or through active patient notification from major local hospitals. Breast cancer was defined as code C50 according to ICD10. Pooled estimates of the hazard ratios (HRs) and 95% confidence interval (CIs) for breast cancer were calculated using random-effects models.

Results: Analytic subjects were 183,940 women, 1783 of whom had breast cancer during 2,194,211 person-years of follow-up. A positive association between BMI and the risk of postmenopausal breast cancer was observed (trend P < 0.001). The HRs for premenopausal breast cancer were 1.05 (95% CI 0.56-1.99), 1.07 (95% CI 0.76-1.52), 0.91 (95% CI 0.64-1.30), 1.15 (95% CI 0.76-1.73), 1.45 (95% CI 0.71-2.94), and 2.25 (95% CI 1.10-4.60), respectively, in BMIs of <19, 19 to <21, 21 to <23, 25 to <27, 27 to <30, and ≥30 kg/m². These results were not substantially altered after excluding the patients who were diagnosed with breast cancer in the first 2 years of follow-up.

Conclusions: The increased risk of postmenopausal breast cancer among women with higher BMIs was confirmed in Japanese. A borderline-significant positive association between BMI and premenopausal breast cancer was observed, suggesting that body mass in Asian women might have opposite effects on breast cancer compared with Western women.

Key words: body mass index, breast cancer, cohort study, pooled analysis

Introduction

Although the incidence of breast cancer in the Asian population still remains lower than that in the Western population, it has recently seen a rapid increase [1] concurrent with change in body size.
among premenopausal women increased in Asian women and decreased in North American white women. In addition, many cohort studies analyzed the association between BMI and breast cancer risk by menopause at the baseline [10–12, 20–23], whereas few studies focused on menopausal status at the time of diagnosis of breast cancer [24–27]. In the analyses of premenopausal women, whether or not the breast cancer at diagnosis is a premenopausal or postmenopausal tumor might have implications for understanding the mechanism of developing breast cancer.

In this study, we conducted a pooled analysis of more than 180 000 women from eight prospective studies in Japan and analyzed the association between BMI and breast cancer by menopausal status.

**methods**

**study population**

Subjects in this study were from eight representative large-scale cohort studies in Japan: (i) the Japan Public Health Center-based Prospective Study (JPHC-I), (ii) JPHC-II, (iii) the Japan Collaborative Cohort Study (JACC), (iv) the Ohsaki National Health Insurance Cohort Study (OHSAKI), (v) the Miyagi Cohort Study (MIYAGI-I), (vi) the Three-Prefecture Cohort Study in Miyagi (MIYAGI-II), (vii) the Three-Prefecture Cohort study in Aichi (AICHI), and (viii) the Takayama Study (TAKAYAMA). Each study was approved by the relevant institutional ethical review board. All of these studies satisfied the following criteria: (i) a population-based cohort study conducted in Japan, (ii) started in the mid-1980s to mid-1990s, (iii) included more than 30 000 participants, (iv) obtained information on anthropometric characteristics in the baseline questionnaire, and (v) determined the incidence of all cancers during the follow-up period. Five of these studies (JPHC-I and -II, JACC, MIYAGI-I and -II) have already had published results on the association between BMI and breast cancer risk [9–12]. For the present analysis, we updated the data files of each study and extended the follow-up period. Women who reported a positive history of any cancers and/or did not reveal their height and weight in the baseline questionnaire were excluded.

**assessment of exposure**

Subjects’ height and weight were obtained by self-administered questionnaires at baseline in each study. BMI was calculated as (weight in kg)/(height in m)². Women with a BMI of <14 or >40 kg/m² was excluded from the analysis. Seven categories of BMI using identical cut points across the studies were created: <19, 19 to <21, 21 to <23, 23 to <25, 25 to <27, 27 to <30, and ≥30 kg/m². Correlation coefficients between BMI estimated from the questionnaire and BMI from actually measured weight and height were 0.90 in women for JPHC-I and -II and 0.91 in both sexes for MIYAGI-I. The corresponding values for height and weight in both sexes were 0.93 and 0.97 for TAKAYAMA, and 0.97 and 0.85 for MIYAGI-I, respectively. Although the information was not available for the other four studies, JACC and OHSAKI used the same questions on weight and height as MIYAGI-I, and MIYAGI-II and AICHI used questions similar to those of JPHC-I and -II.

**outcome and follow-up**

Subjects were followed from the baseline survey to the last follow-up in each study. Information on migration and death was obtained from the residential registry. The incidence of cancer was mainly confirmed through the regional population-based cancer registries and/or through active patient notification from major local hospitals. Breast cancer was defined as code C50 according to the International Classification of Diseases and Health Related Problems, 10th Revision.

**statistical analysis**

We started with conducting the study-specific analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) by a two-sided test were estimated for each BMI category using the Cox proportional hazards regression model. The end of follow-up was determined as the date of breast cancer diagnosis, the date of emigration from the study area, the date of death, or the end of the study, whichever came first. BMI of 23 to <25 kg/m² was considered as the reference category. Tests for a linear trend were conducted by treating BMIs as continuous variables, which would provide HRs by a 1-kg/m² increase of BMI. The analyses were conducted using SAS (Version 9.1 or 9.2; SAS Institute, Inc., Cary, NC) or STATA (Version 10.1; Stata Corporation, College Station, TX) statistical software.

We took two approaches to the analyses stratified by menopausal status. First, the association between BMI and incidence of breast cancer was tested by menopausal status obtained from the questionnaire at baseline. Next, we focused on the menopausal status at the time of diagnosis (the censored date). Since no study had direct information on menopausal status after the start of follow-up, 51 years of age, the time at which ~50% of the women had become postmenopausal [30], was used as a proxy cut point. Postmenopausal breast cancer was defined as those who reported being postmenopausal at baseline, and/or were 51 years or older at the time of diagnosis. All other breast cancers were defined as premenopausal. The years of observation were considered as the postmenopausal period when participants were 51 years or older and/or reported being postmenopausal at baseline. When participants who reported not to be postmenopausal at baseline were younger than 51 years old at the censored date, the years of observation were considered as the premenopausal period. When participants who reported not to be postmenopausal at baseline passed their 51st birthday during the study period, the years of observation were split into pre- and postmenopausal periods by their 51st birthday [28, 29].

For all studies, the estimations of HRs were carried out after adjustments for age and area (within each study for JPHC-I, -II, and JACC) (model 1), and after adjustments for age, area, smoking status (never, past, current smoker), alcohol consumption (non drinker, <1 week/day, current by <23 g/day, current by ≥23 g/day), age at menarche (<13, 13 to <15, 15 to <17, ≥17 years), age at first delivery (no, <21, 21 to <26, 26 to <31, ≥31 years), and parity number (0, 1, 2, ≥3) (model 2). Only for some studies, additional adjustments for other potential confounders were supplementally done in model 3 and 4: the HRs after adjustments for physical activity (<almost daily, <almost daily) and history of hormone replacement therapy (yes, no), in addition to the variable included in model 2 were estimated for JPHC-I, JPHC-II, JACC, OHSAKI, MIYAGI-I, and Takayama (model 3). The HRs after additional adjustments for years of education (<9, 9 to <12, 12 to <15, ≥15 years) were estimated only for JPHC-I, JACC, OHSAKI, and Takayama (model 4). Indicator terms were specifically created for missing data of categorical covariates.

To obtain a single pooled estimate of the HR from the individual studies for each category, we applied a random-effects model [31]. The ‘metan’ command for STATA was used for meta-analysis. A P value of <0.05 was considered statistically significant in the analyses. Categories that included no cases were not included in the pooled estimates. The extent of heterogeneity for each category was indicated by Cochran’s Q-statistic, which was considered statistically significant when P < 0.10. The I²-statistic was also reported to describe the percentage of total variation in the study-specific HRs which was due to heterogeneity [32].

**results**

Our analyses included 183 940 women, 1783 of whom had breast cancer during a mean 11.93 years of follow-up (2 194 211...
person-years) (supplementary Table S1, available at Annals of Oncology online). Breast cancers were divided into 301 premenopausal and 1482 postmenopausal tumors. The characteristics of subjects according to the information of menopausal status at baseline were shown in supplementary Table S2, available at Annals of Oncology online.

As shown in Table 1, higher BMI was significantly associated with increased relative risk of breast cancer among premenopausal and postmenopausal women at baseline; HR per 1 kg/m² increase of BMI: 1.03 (P = 0.03) in premenopausal and 1.06 (P < 0.001) in postmenopausal women (model 2).

When we analyzed by premenopausal and postmenopausal breast cancer (Table 2), significant increase of risk (HR = 2.25) for premenopausal breast cancer was found among the highest BMI group (≥30 kg/m²) (model 2). BMI was positively associated with the risk of postmenopausal breast cancer (trend P < 0.001).

Additional adjustments for other potential confounders (model 3 or 4) did not substantially change the results. When we repeated the analyses after excluding patients who were diagnosed with breast cancer in the first 2 years of follow-up, none of the results was substantially altered (supplementary Tables S3 and S4, available at Annals of Oncology online).

**Discussion**

The observed positive association between BMI and breast cancer after menopause was consistent with the results from numerous previous reports [4, 5, 7, 10–12, 16, 18–24, 26, 27]. The risk increase was monotinous, similar to the results from another pooled analysis in an Asian population (the estimated HRs for breast cancer among women aged 60 years or older: 0.71, 1.13, and 1.63, respectively, in BMIs of 12.0–18.4, 25.0–29.9, and 30.0–60.0 (the reference category: 18.5–24.9 kg/m²)) [3]. The 5–6% risk increase per 1 kg/m² increase in BMI was compatible with a result of a meta-analysis by Renihan et al. showing 31% increase of postmenopausal breast cancer per 5 kg/m² increase of BMI in five Asia-Pacific studies [7]. In a pooled analysis of Western cohort studies, Brandt et al. stated that the positive association between BMI and postmenopausal breast cancer was nonlinear and that the risks did not increase further above BMI of more than 28 kg/m² [4]. Patterns of the risk increment of postmenopausal breast cancer with the increase in BMI in Asian people might be different from those in Western people.

The convincing evidence that higher BMI is a cause of postmenopausal breast cancer should be explained by a sex hormone-related mechanism, because adipose tissue may be the main source of estrogen biosynthesis, rather than the ovary, among obese postmenopausal women [10]. Several studies have shown that the substantial positive association of postmenopausal BMI and breast cancer risk was confined to estrogen-receptor-positive (ER+) and progesterone-receptor-positive (PR+) tumors [6, 10].

On the other hand, we observed the borderline-significant positive association between BMI and premenopausal breast cancer. The risks seemed to increase especially in BMI of more than 27 kg/m². So far, among four cohort studies in premenopausal Asian women [9–11, 15], three Japanese studies [9–11] included in this pooled analysis reported non-significant associations, and one Taiwanese study [15] reported the significant increase of breast cancer risk in BMI of more than 26.2 kg/m² (multivariate-adjusted HR was 1.9). These results contradict the major findings from Western studies [4, 5, 7, 8, 21, 22, 25, 27], showing a significant inverse association. In two studies of them [21, 25], the statistically significant risk reduction of breast cancer seemed to emerge among women with a BMI of more than 30 kg/m². Also, in a pooled analysis by Brandt et al., the risk reduction was only observed among women in the highest BMI categories [4].

The lack of an inverse association between BMI and premenopausal breast cancer may be due to the lower prevalence of overweight women in Asia. Since women who are obese or overweight tend to develop anovulation or to have lower estrogen levels [33], they were supposed to have a decreased risk for breast cancer. However, in this study, the group with BMI of more than 30 kg/m² included much fewer women who were severe obese compared with their Western studies counterparts, making the absolute gap of BMI between lean and obese women smaller, attenuating a protective effect of higher BMI on premenopausal breast cancer. In addition, Japanese women might be less likely than Caucasians to have ER+ or PR+ breast cancer [6, 10], which is suggested to involve the risk reduction of breast cancer in premenopausal women. Finally, it is possible that the effect of BMI on breast cancer is mediated by some mechanisms other than the estrogen pathway. Percentage of body fat was positively associated with serum IGF-1 [34], whereas BMI was negatively associated with plasma estrogen levels [35] in premenopausal Japanese women. Higher levels of IGF-1 have been reported to be positively associated with risk for breast cancer among premenopausal women [36–38]. The effects of body mass through the IGF-1 pathway might surpass the effects through the estrogen pathway on premenopausal breast cancer in Japanese.

One of the strengths in this study is the large number of participants gathered from large-scale prospective cohorts in Japan. Each study had a good participation rate, a long follow-up, and information on several confounders. Because this is a pooled analysis with identical categories for BMI and covariates across studies, the possibility of publication bias or the use of a heterogeneous source is small. As the information on height, weight, and confounders was collected before the diagnosis of breast cancer, the recall bias of exposure should be minimal. The validation of self-reported height, weight, and BMI was high among four cohorts that assessed it. Although BMI at baseline might have changed due to preclinical signs, the exclusion of cases during the first 2 years of follow-up did not change the results.

There are several limitations. We did not obtain any direct information on menopausal status after the start of follow-up. To make up for the absence of information, we used 51 years of age as a proxy cutoff-point, but some misclassification might have occurred. As the information on height, weight, and confounders was also based only on the baseline questionnaire, we were unable to consider changes over time of those in the analysis. Another limitation was the lack of information on the estrogen-receptor status of tumors, which could modify the association between BMI and breast cancer risk.

This pooled analysis from large prospective studies in Japan confirmed the increased risk of postmenopausal breast cancer among women with higher BMIs. The borderline-significant positive association between BMI and premenopausal breast cancer was also observed among Japanese women.
Table 1. Pooled analyses for associations between body mass index and breast cancer risk by menopausal status at baseline in Japan

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|                        | Premenopausal women | | | | | | | | |
| Number of subjects     | 4511                | 12 800                  | 17 683                  | 14 226                  | 7700                  | 4434                  | 1335                  | | |
| Person-years           | 54 993               | 159 482                 | 222 884                 | 180 551                 | 98 267                 | 56 341                 | 16 870                 | | |
| Crude rate (per 100 000) | 87.28              | 84.65                   | 91.08                   | 89.73                   | 87.52                  | 115.37                 | 130.41                 | | |
| Age- and area-adjusted (HR1) | 1.06 (0.71–1.59) | 0.97 (0.77–1.23) | 1.03 (0.81–1.30) | 1.00 (Reference) | 1.00 (0.77–1.30) | 1.32 (0.91–1.93) | 1.71 (1.08–2.69) | 1.02 (1.00–1.05) | 0.11 | 0.0 | 0.93 | 19.3 | 0.28 |
| Multivariate-adjusted (HR2) | 1.03 (0.71–1.49) | 0.94 (0.74–1.18) | 1.01 (0.80–1.28) | 1.00 (Reference) | 1.03 (0.79–1.34) | 1.36 (0.93–2.01) | 1.72 (1.09–2.72) | 1.03 (1.00–1.06) | 0.03 | 0.0 | 0.93 | 14.8 | 0.31 |
| Multivariate-adjusted (HR3) | 1.11 (0.73–1.67) | 0.96 (0.75–1.24) | 1.06 (0.85–1.33) | 1.00 (Reference) | 1.07 (0.81–1.42) | 1.34 (0.83–2.15) | 1.75 (1.10–2.80) | 1.03 (1.00–1.06) | 0.03 | 0.0 | 0.84 | 17.1 | 0.30 |
| Multivariate-adjusted (HR4) | 0.79 (0.47–1.33) | 0.93 (0.67–1.27) | 0.95 (0.72–1.27) | 1.00 (Reference) | 1.12 (0.79–1.58) | 0.99 (0.63–1.54) | 1.76 (0.94–3.28) | 1.04 (0.99–1.09) | 0.16 | 0.0 | 0.60 | 43.9 | 0.15 |

|                        | Postmenopausal women | | | | | | | | |
| Number of subjects     | 9298                | 18 263                  | 28 226                  | 25 880                  | 16 378                  | 10 301                  | 3100                  | | |
| Person-years           | 99 284               | 210 622                 | 312 277                 | 306 978                 | 193 743                 | 122 598                 | 36 374                 | | |
| Crude rate (per 100 000) | 49.35              | 54.13                   | 73.73                   | 89.91                   | 89.29                   | 85.65                   | 93.47                   | | |
| Age- and area-adjusted (HR1) | 0.57 (0.42–0.78) | 0.61 (0.48–0.87) | 0.82 (0.69–0.98) | 1.00 (Reference) | 1.02 (0.77–1.36) | 0.99 (0.78–1.24) | 1.27 (0.88–1.83) | 1.06 (1.04–1.08) | <0.001 | 0.0 | 0.44 | 26.2 | 0.22 |
| Multivariate-adjusted (HR2) | 0.54 (0.39–0.74) | 0.59 (0.47–0.76) | 0.81 (0.68–0.97) | 1.00 (Reference) | 1.03 (0.78–1.37) | 0.99 (0.79–1.25) | 1.27 (0.88–1.83) | 1.06 (1.04–1.09) | <0.001 | 0.0 | 0.46 | 27.2 | 0.21 |
| Multivariate-adjusted (HR3) | 0.58 (0.41–0.83) | 0.60 (0.45–0.80) | 0.82 (0.68–0.99) | 1.00 (Reference) | 0.92 (0.68–1.24) | 0.95 (0.74–1.22) | 1.14 (0.77–1.69) | 1.05 (1.03–1.07) | <0.001 | 0.0 | 0.58 | 0.0 | 0.50 |
| Multivariate-adjusted (HR4) | 0.46 (0.30–0.72) | 0.50 (0.36–0.68) | 0.79 (0.63–0.99) | 1.00 (Reference) | 0.77 (0.58–1.01) | 0.90 (0.60–1.33) | 1.20 (0.75–1.92) | 1.07 (1.04–1.10) | <0.001 | 0.0 | 0.79 | 0.0 | 0.41 |

RR, relative risk.

*Estimated hazard ratio after adjustments for age, area, smoking status (never, past, current smoker), alcohol consumption (nondrinker, <1 week/day, current by <23 g/day, current by ≥23 g/day), age at menarche (<13, 13 to <15, 15 to <17, 17 years), age at first delivery (no, <21, 21 to <26, 26 to <31, ≥31 years), and parity number (0, 1, 2, ≥3).

bEstimated hazard ratio after adjustments for physical activity (<almost daily, almost daily) and history of hormone replacement therapy (yes, no), in addition to adjustment in the variable included in HR2. This model is only for JPHC-I, JPHC-II, JACC, OHSAKI, MIYAGI-I, and Takayama.

cEstimated hazard ratio after adjustments for years of education (<9, 9 to <12, 12 to <15, ≥15 years), in addition to the variable included in HR3. This model is only for JPHC-I, JACC, OHSAKI, and Takayama.

dEstimated hazard ratio after adjustments for age, area, smoking status (never, past, current smoker), alcohol consumption (nondrinker, <1 week/day, current by <23 g/day, current by ≥23 g/day), age at menarche (<13, 13 to <15, 15 to <17, 17 years), age at menopause (<45, 45 to <50, 50 to <55, ≥55 years), age at first delivery (no, <21, 21 to <26, 26 to <31, ≥31 years), and parity number (0, 1, 2, ≥3).

eEstimated hazard ratio after adjustments for physical activity (<almost daily, almost daily) and history of hormone replacement therapy (yes, no), in addition to adjustment in the variable included in HR2. This model is only for JPHC-I, JPHC-II, JACC, OHSAKI, MIYAGI-I, and Takayama.

fEstimated hazard ratio after adjustments for years of education (<9, 9 to <12, 12 to <15, ≥15 years), in addition to the variable included in HR3. This model is only for JPHC-I, JACC, OHSAKI, and Takayama.
### Table 2. Pooled analyses for associations of body mass index with premenopausal and postmenopausal breast cancer risk in Japan

<table>
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<th>Body mass index</th>
<th>Premenopausal cancer</th>
<th>Postmenopausal cancer</th>
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<td>RR (95% CI)</td>
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<td>Trend (per 1 kg/m²) for the highest category</td>
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**RR**, relative risk.

*Estimated hazard ratio after adjustments for age, area, smoking status (never, past, current smoker), alcohol consumption (nondrinker, <1 week/day, current by <23 g/day, current by ≥23 g/day), age at menarche (<13, 13 to <15, 15 to ≤17 ≥17 years), age at first delivery (no, <21, 21 to <26, 26 to <31, ≥31 years), and parity number (0, 1, 2, ≥3).

*bEstimated hazard ratio after adjustments for physical activity (<almost daily, almost daily) and history of hormone replacement therapy (yes, no), in addition to adjustment in the variable included in HR2. This model is only for JPHC-I, JPHC-II, JACC, OHSAKI, MIYAGI-I, and Takayama.

*cEstimated hazard ratio after adjustments for years of education (<9, 9 to <12, 12 to <15, ≥15 years), in addition to the variable included in HR3. This model is only for JPHC-I, JACC, OHS KI, and Takayama.

*dEstimated hazard ratio after adjustments for age, area, smoking status (never, past, current smoker), alcohol consumption (nondrinker, <1 week/day, current by <23 g/day, current by ≥23 g/day), age at menarche (<13, 13 to <15, 15 to ≤17 ≥17 years), menopausal status (premenopausal, postmenopausal <45 years, postmenopausal 45 to <50 years, postmenopausal 50 to <55 years, postmenopausal ≥55 years), age at first delivery (no, <21, 21 to <26, 26 to <31, ≥31 years), and parity number (0, 1, 2, ≥3).

*eEstimated hazard ratio after adjustments for physical activity (<almost daily, almost daily) and history of hormone replacement therapy (yes, no), in addition to adjustment in the variable included in HR2. This model is only for JPHC-I, JPHC-II, JACC, OHS KI, MIYAGI-I, and Takayama.

*fEstimated hazard ratio after adjustments for years of education (<9, 9 to <12, 12 to <15, ≥15 years), in addition to the variable included in HR3. This model is only for JPHC-I, JACC, OHS KI, and Takayama.
cancer observed suggested that body mass in Asian women might have opposite effects on breast cancer compared with Western women.

funding
This work was supported in part by the National Cancer Center Research and Development Fund (24-A-3).

disclosure
The authors have declared no conflicts of interest.

references