Breast Cancer Res Treat (2017) 166:919–925
DOI 10.1007/s10549-017-4481-4

EPIDEMIOLOGY

BMI change and abdominal circumference are risk factors for breast cancer, even in Asian women

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Received: 18 August 2017 / Accepted: 22 August 2017 / Published online: 31 August 2017

Abstract
Purpose We investigated the association between breast cancer incidence and obesity among Asian women.
Methods We used data from 30,109 women who had undergone medical check-ups and opportunistic breast cancer screening at least twice at the St. Luke's International Hospital Affiliated Clinic, Center for Preventive Medicine, between April 1, 2005 and March 31, 2014. This study evaluated obesity through body mass index (BMI) at age 18–20 years (BMI18–20y), BMI at research entry (entry BMI), change of BMI from age 18–20 to research entry (ΔBMI), abdominal circumference at research entry (AC), and HbA1c [N] at research entry (HbA1c). We used a multivariate Cox proportional hazard model to evaluate hazard ratios (HRs) and 95% confidence intervals (95% CIs).
Results Of the 30,109 women, 325 were initially diagnosed with breast cancer over 131,657 person-years. Postmenopausal women whose BMI increased ≥+5.0 were significantly more likely to develop breast cancer (HR 1.902, 95% CI 1.202–3.009) than were the stable BMI group (ΔBMI: −2.5 to +2.5). Postmenopausal women with AC ≥90 cm were significantly likelier to develop breast cancer than were those with AC <70 cm (HR 2.500, 95% CI 1.091–5.730). Among postmenopausal women whose BMI18–20y was ≥20, those with high (≥6.5) HbA1c were more likely to develop breast cancer than those with low (<5.5) HbA1c (HR 3.325, 95% CI 1.307–8.460).
Conclusions Breast cancer incidence and obesity are positively associated in postmenopausal Asian women.

Keywords Breast cancer · Obesity · Body mass index · Abdominal circumference · Asian women · HbA1c

Background

Breast cancer has a high incidence among women worldwide [1–4]. Particularly in Japan, the morbidity and mortality of breast cancer has increased for a few decades [5]. Because breast cancer had been less common in Japan than Western countries, Westernized life styles (notably, diet and the consumption of much red meat and fat) are considered to be possible causes for this increased morbidity [6–13]. To prevent increased mortality, Japan began population-based mammography screening about 17 years ago. However, we cannot clearly show decreased breast cancer mortality in Japan yet [5].

Whereas associations among obesity, metabolic factors, weight gain, and breast cancer are widely reported in Western populations [14–30], Asian women tend to have lower body mass index (BMI) than Western women, and associations between breast cancer and BMI in Asian women have not been widely studied. We therefore investigated effects of obesity on breast cancer development in Asian women.

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Methods

Study population

We used the data from women who had each undergone at least two medical check-ups which included opportunistic breast cancer screening (ultrasonography, mammography or both) at St. Luke's International Hospital Affiliated Clinic, Center for Preventive Medicine between April 1, 2005 and March 31, 2014. We excluded women with histories of breast cancer, or who were diagnosed with breast cancer at their first examinations during this period. We also used written questionnaire data and measurements taken at subjects' first visits during this period as data at research entry.

Definitions

We evaluated obesity through body mass index (BMI) at age 18–20 years (BMI18–20y), BMI at research entry (entry BMI), change of BMI from age 18–20 to research entry (ΔBMI), abdominal circumference at research entry (AC), and HbA1c [N] at research entry (HbA1c).

Height and body weight at entry were defined as their measured values at the first medical check-up during the study period.

In calculating BMI18–20y, we assumed that height does not change after adulthood. We calculated BMI18–20y using height at research entry and the weight answered to the question "Body weight at age 18–20 years old" in the questionnaire. We excluded subjects who answered that their body weight at age 18–20 years old was less than 30 kg, because it seems to be erroneous. We classified BMI18–20y into 4 categories; BMI18–20y (kg/m^2): <18.5, 18.5 ≤ to < 20.0, 20.0 ≤ to < 24.0, and ≥24.0. These cut-off points were based on WHO classification and preceding studies [31, 32]. We evaluated hazard ratios (HRs) relative to the BMI18–20y: 20.0 ≤ to < 24.0 group.

We calculated entry BMI using height and body weight at entry. Entry BMI was classified into 4 categories: <20.0, 20.0 ≤ to < 22.0, 22.0 ≤ to < 24.0, 24.0≤. We evaluated HR relative to the 20.0 ≤ to < 22.0 group.

We calculated ΔBMI by subtracting BMI18–20y from entry BMI. ΔBMI was classified in 4 categories (loss: <−2.5, stable: −2.5 ≤ to < 2.5, gain: 2.5 ≤ to < 5.0, major gain: 5.0≤) as used in a preceding study [31]. We set the stable group as a reference in this analysis.

To assign abdominal circumference (AC), we used the data that were measured during medical check-up at entry. AC was classified to 3 categories: AC low: <70, AC norm: 70 ≤ to < 90, and AC high: ≥90. The cut-off point of 70 cm was based on the average measurement for Japanese women [33]; 90 cm is the reference value for metabolic syndrome screening in Japan. We calculated HR for the norm and obesity groups relative to the AC low group.

For HbA1c, we used HbA1c [N], which is used worldwide. Some women's data were taken as HbA1c [JDS], which had previously been used only in Japan. We converted the HbA1c [JDS] to HbA1c [N] with the formula "HbA1c [NGSP] % = 1.02 × HbA1c [JDS] +0.25%" [34]. The HbA1c was classified into 3 categories (<5.5, 5.5 ≤ to < 6.5, 6.5≤). These cut-off points came from a preceding study [35, 36]. We set the <5.5 group as a reference in this analysis.

Statistical analysis

We estimated HRs and 95% confidence intervals (CIs) using multivariate Cox proportional hazards regression model. We selected the 4 covariations: age at the first medical check-up during the study period, smoking habit (Never smokers, Past smokers, and Current smokers), alcohol consumption (Never drinkers, Opportunity drinkers, and Regular drinkers), and Family history (having breast cancer or ovarian cancer among primary or secondary family members). In the initial analysis, we divided women into premenopausal and postmenopausal groups, and analyzed their breast cancer incidence with regard to BMI18–20y, baseline BMI, ΔBMI, abdominal circumference, and HbA1c. In the secondary analysis, we divided women into two groups (BMI18–20y ≥ 20 or < 20). All analyses were performed using SPSS, version 21. All statistical tests were two-sided. $P < 0.05$ was considered significant.

Results

The subjects' characteristics are shown in Table 1. The average observation period was 52.5 months, which corresponded to 131,657 person-years. During the observation period, 325 initial breast cancers were identified among 30,109 women. The premenopausal group included more regular-drinkers ($P < 0.001$) and current-smokers ($P < 0.001$). Family history of breast cancer or ovarian cancer was not related to menopausal status. Premenopausal women tended to be leaner than postmenopausal women according to entry BMI ($P < 0.001$), BMI18–20y ($P < 0.001$), AC ($P < 0.001$), and HbA1c ($P < 0.001$).

In the analysis of ΔBMI, postmenopausal women in the major gain group had significantly higher risk for developing breast cancer than did the stable group (HR 1.902, 95% CI 1.202–3.009; Table 2). However, this association was observed in only women whose BMI18–20y was <20

Table 1 Subjects' characteristics and covariate states

Characteristics	All	Premenopausal	Postmenopausal	*P* value
Number of subjects	30,109	20,043	10,066	
Number of breast cancer	325	202	123	
Follow-up period, y, mean (SD)	52.5 (30.5)	51.0 (30.1)	55.4 (30.9)	
Person-years	131,657	85,219	46,437	
Age at entry, mean (SD)	46.9 (11.3)	40.5 (6.2)	59.8 (7.7)	
Smoking states				<0.001
Never smoker (%)	81.0	79.6	83.7	
Past smoker (%)	11.0	11.4	10.3	
Current smoker (%)	8.0	9.0	6.0	
Alcohol drinking states				<0.001
Non drinker (%)	51.1	45.7	62.0	
Occasional drinker (%)	19.6	21.4	15.9	
Regular drinker (%)	29.3	32.9	22.2	
Family history (%)	6.6	6.6	6.6	
BMI at entry, kg/m^2, mean (SD)	21.1 (3.0)	20.7 (2.9)	21.7 (3.0)	<0.001
BMI at age 18–20 (kg/m^2)	19.9 (2.1)	19.8 (2.1)	20.2 (2.1)	<0.001
BMI change	1.1 (2.7)	1.0 (2.5)	1.5 (3.0)	<0.001
Abdominal girth at entry, cm, mean (SD)	76.0 (8.5)	74.2 (7.8)	79.4 (8.8)	<0.001
HbA1c at entry, %, mean (SD)	5.4 (0.4)	5.3 (0.4)	5.7 (0.5)	<0.001

SD standard deviation

(BMI18–20y < 20—HR 2.048, 95% CI 1.114–3.765, whereas BMI18–20y ≥ 20—HR 0.974, 95% CI 0.469–2.024; Table 3) if analyzed separately for BMI18–20y.

Similarly, in analysis of AC, postmenopausal women in the large AC group were significantly more likely to develop breast cancer than those in the small AC group (HR 2.500, 95% CI 1.091–5.730; Table 2). However, this association was observed only among women whose BMI18–20y was <20 (BMI18–20y < 20—HR 0.360, 95% CI 0.049–2.625, whereas BMI18–20y ≥ 20—HR 3.259, 95% CI 1.208–8.786; Table 3) if analyzed separately by BMI18–20y.

HbA1c was not associated with breast cancer development if only menopausal status was considered. However, among women who were both postmenopausal and whose BMI18–20y was >20, those with high HbA1c were more likely to develop breast cancer than those with low HbA1c (HR 3.325, 95% CI 1.307–8.460; Table 3).

The entry BMI groups did not show significantly difference in breast cancer incidence. However, subgroup analysis showed that, among postmenopausal women with high entry BMI (>24), those whose BMI18–20y had been <20 had a high risk of developing breast cancer (HR 1.903, 95% CI 0.966–3.751, $P = 0.063$), whereas those whose BMI18–20 was ≥20 had a low risk of developing breast cancer (HR 2.267, 95% CI 0.903–5.689, $P = 0.081$; Table 3).

By itself, BMI18–20y did not affect breast cancer development.

Discussion

In this study, we evaluated the association between obesity and development of breast cancer in Asian women. We found that factors associated with developing breast cancer were large AC (≥90 cm), increased BMI ≥5 from 18 to 20 years old, and high HbA1c among postmenopausal women whose BMI18–20y was >20.

In analyzing entry BMI, we found that premenopausal women whose entry BMI was ≥24 kg/m^2 were less likely to develop breast cancer, and postmenopausal women whose entry BMI was ≥24 kg/m^2 were more likely to develop breast cancer.

In the previous study, postmenopausal obesity was reported to increase risk of breast cancer regardless of race, as also found in the current study [14, 37]. However, premenopausal obesity was reported to increase the risk of breast cancer for Asian women [14] and decrease it in non-Asian women [37]. This present study found that obesity in Asian and non-Asian women did not affect differently.

High BMI at 20 years old is reported to significantly decrease likelihood of premenopausal breast cancer [17, 31]. In our study, high BMI18–20y (≥24 kg/m^2) tended to decrease premenopausal breast cancer compared

Table 2 Hazard ratios (HR) and 95% confidence intervals (CI) for associations between obesity and breast cancer development for each menopausal status

	All		Premenopausal		Postmenopausal	
	$n = 30,109$		$n = 20,043$		$n = 10,066$	
	Event = 325		Event = 202		Event = 123	
	HR[a] (95% CI)	*P* value	HR[a] (95% CI)	*P* value	HR[a] (95% CI)	*P* value
BMI at entry						
<20	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
20–<22	0.888 (0.676–1.166)	0.392	0.830 (0.597–1.156)	0.271	1.014 (0.618–1.662)	0.958
22–<24	1.029 (0.752–1.409)	0.857	0.926 (0.615–1.394)	0.712	1.242 (0.743–2.076)	0.408
≥24	0.969 (0.692–1.356)	0.852	0.599 (0.356–1.008)	0.054	1.530 (0.930–2.516)	0.094
BMI18–20y						
<18.5	1.259 (0.958–1.654))	0.098	1.174 (0.835–1.651)	0.356	1.379 (0.877–2.168)	0.164
18.5–<20	1.068 (0.821–1.389)	0.624	0.981 (0.703–1.369)	0.911	1.185 (0.775–1.813)	0.433
20–<24	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
≥24	0.728 (0.356–1.489)	0.384	0.509 (0.160–1.615)	0.252	1.026 (0.408–2.580)	0.956
ΔBMI						
Loss: <−2.5	0.781 (0.462–1.322)	0.358	1.059 (0.541–2.076)	0.866	0.619 (0.268–1.429)	0.261
Stable:−2.5–<+2.5	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
Gain: +2.5–<+5.0	0.782 (0.571–1.072)	0.126	0.745 (0.490–1.133)	0.169	0.811 (0.502–1.310)	0.392
Major gain: ≥+5.0	1.335 (0.939–1.900)	0.108	0.805 (0.445–1.456)	0.473	1.902 (1.202–3.009)	0.006
Abdominal circumference						
<70	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
70–<90	0.974 (0.741–1.279)	0.847	0.826 (0.610–1.118)	0.216	1.871 (0.907–3.859)	0.09
≥90	1.034 (0.649–1.648)	0.888	0.533 (0.230–1.239)	0.144	2.500 (1.091–5.730)	0.03
HbA1c						
<5.5	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
5.5–<6.5	0.937 (0.731–1.200)	0.606	0.873 (0.623–1.222)	0.427	1.078 (0.739–1.572)	0.698
≥6.5	1.253 (0.578–2.717)	0.568	0.000 (0.000–3.981 × 10^{85})	0.931	1.739 (0.774–3.907)	0.180

[a] Estimated hazard ratio after adjustments for age at first medical check-ups, with regard to menstrual status, smoking states (never smokers, past smokers, and current smokers), alcohol consumption (never drinkers, opportunity drinkers, and regular drinkers), and Family history (patients with breast cancer or ovarian cancer among second-degree family members)

with average BMI18–20y (20 ≤ to < 24; HR 0.509, 95% CI 0.160–1.615; Table 2]. Therefore, high premenopausal BMI has been suggested to suppress premenopausal breast cancer.

In our study, large ΔBMI (≥5.0) increased postmenopausal breast cancer incidence. Other studies have shown similar results [17, 26, 28, 38, 39], indicating that a slender body habitus at adolescence is associated with postmenopausal breast cancer development [31]. In this study, significantly increased risks for breast cancer were associated with ΔBMI (major gain group compared with stable group) and AC (≥90 cm group compared with ≤70 cm group) were observed only among women whose BMI18–20y was <20, indicating that women who were slender or average at 18–20 years old and whose BMI or AC increased are significantly more likely to develop breast cancer. These findings also suggest that dramatic changes in lipid metabolism during menopause are associated with breast cancer. However, among women with high HbA1c, BMI18–20y ≥ 20 significantly increased breast cancer risk.

Although associations between HbA1c and cancer development have been reported [35, 36, 40], these relationships are controversial for each organ. Among studies of HbA1c and breast cancer, some support a relationship [35, 40] and some do not [36, 41, 42]. In this study, we had a new viewpoint from evaluating the relationship between breast cancer development and HbA1c with regard to BMI18–20y. A positive association between HbA1c and cancer incidence has been attributed to attenuated immunity against tumor cells caused by hyperglycemia [43]; thus, longer periods of hyperglycemia would correspond to

Table 3 Hazard ratios (HR) and 95% confidence intervals (CI) for associations between obesity and breast cancer development with respect to BMI18–20y

	BMI18–20y <20				BMI18–20y ≥20			
	Premenopausal		Postmenopausal		Premenopausal		Postmenopausal	
	$n = 12{,}023$		$n = 4962$		$n = 8020$		$n = 5104$	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
BMI at entry								
<20	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
20–<22	0.658 (0.421–1.029)	0.066	0.866 (0.471–1.589)	0.641	1.235 (0.680–2.241)	0.488	1.693 (0.650–4.406)	0.281
22–<24	0.792 (0.418–1.504)	0.477	0.916 (0.448–1.871)	0.809	1.199 (0.625–2.301)	0.584	2.399 (0.944–6.098)	0.066
≥24	0.971 (0.444–2.125)	0.941	1.903 (0.966–3.751)	0.063	0.558 (0.253–1.227)	0.147	2.267 (0.903–5.689)	0.081
ΔBMI								
Loss: <−2.5	1.682 (0.414–6.829)	0.467	0.723 (0.098–5.326)	0.750	1.001 (0.456–2.196)	0.997	0.593 (0.233–1.512)	0.274
Stable: −2.5–<+2.5	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
Gain: +2.5–<+5.0	0.807 (0.489–1.329)	0.399	1.073 (0.600–1.917)	0.813	0.609 (0.277–1.399)	0.217	0.390 (0.139–1.094)	0.074
Major gain: ≥+5.0	0.974 (0.469–2.024)	0.944	2.048 (1.114–3.765)	0.021	0.598 (0.216–1.657)	0.323	1.706 (0.823–3.535)	0.151
Abdominal girth at entry								
<70	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
70–<90	0.705 (0.490–1.015)	0.060	1.402 (0.632–3.111)	0.405	1.302 (0.683–2.484)	0.423	5.343 (0.735–38.828)	0.098
≥90	0.360 (0.049–2.625)	0.314	3.259 (1.208–8.786)	0.020	0.848 (0.292–2.463)	0.761	5.284 (0.673–41.504)	0.113
HbAlc at entry								
<5.5	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1	1.000 (ref.)	1
5.5–<6.5	0.924 (0.603–1.415)	0.715	1.139 (0.687–1.890)	0.614	0.803 (0.464–1.389)	0.433	1.001 (0.567–1.767)	0.998
≥6.5	0.000 (0.000–2.253 × 10^{149})	0.959	0.459 (0.062–3.426)	0.448	0.000 (0.000–3.723 × 10^{181})	0.963	3.325 (1.307–8.460)	0.012

[a] Estimated hazard ratio after adjustments for age at first medical check-ups, with regard to menstrual status, smoking states (Never smokers, Past smokers, and Current smokers), alcohol consumption (Never drinkers, Opportunity drinkers, and Regular drinkers), and family history (patients with breast cancer or ovarian cancer among second-degree family members)

increased risks for cancer. By considering obesity at 18–20 years old in this study, we may be able to evaluate the effect of high HbA1c on carcinogenesis more accurately.

Some studies have evaluated the relationship between waist size and breast cancer [29, 44], and found waist size to be positively associated with breast cancer risk; our results were similar to theirs. However, unlike most preceding studies, we both focused on Asian women, and used AC (which is the measurement method for Japanese figures), rather than waist measurement (which is obviously correlated, but not the same thing). The relationship between AC and breast cancer is interesting, because in recent years in Japan, AC measurement has become a standard part of medical check-ups, to help spot metabolic syndrome. Our results indicate that AC could also identify women with high breast cancer risk and thus lead to more effective breast cancer screening.

Our study has several limitations. First, all subjects had undergone opportunistic breast cancer screenings. Second, we used data from women who had at least two breast cancer screenings, which may have led to selective bias. Third, some data were obtained using questionnaires, and therefore must be affected by recall bias. Measurement error may also be included, although not inevitably.

In summary, this study showed that large BMI gain after adulthood and (among women whose BMI18–20y was greater than 20) large abdominal circumference and high HbA1c level are associated with greater postmenopausal breast cancer risk.

Compliance with ethical standards

Conflict of interest Neither author has any disclosures to report.

Ethical standards This study complies with the current laws of Japan.

Statement of human rights For this type of study, formal consent was not required.

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