RESEARCH ARTICLE

Weight Gain and Alcohol Drinking Associations with Breast Cancer Risk in Japanese Postmenopausal Women - Results from the Japan Collaborative Cohort (JACC) Study

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Abstract

Background: We investigated four factors, height, weight gain since age 20, physical activity, and alcohol drinking, for associations with risk of breast cancer (BC) according to menopausal status, using the latest data of the Japan Collaborative Cohort Study (JACC Study). Materials and Methods: We confined the analysis to 24 areas available of cancer incidence information, excluding women with a previous diagnosis of BC. Baseline data were collected from 38,610 (9,367 premenopausal, and 29,243 postmenopausal) women during 1988 and 1990. The study subjects were followed-up at the end of 2009, and 273 (84 premenopausal, and 189 postmenopausal) cases of BC were newly diagnosed in 501,907 person-years. The Cox model was used to estimate a hazards ratio (HR) and its 95% confidence interval (CI) of BC risk. Results: As a result of the multivariate analysis adjusting for age at baseline survey, age at menarche, number of live births, and, age at first delivery, weight gain since age 20 of 6.7 kg-9.9 kg, and ≥10.0 kg were significantly associated with increased risk for postmenopausal BC (HR=2.48, 95% CI 1.40-4.41, and, HR=2.94, 95% CI 1.84-4.70, respectively). Significantly increased trend of BC risk was also observed in weight gain since age 20 (p for trend, p<0.001). Amount of ethanol intake per day≥15.0 g was significantly associated with increased risk for postmenopausal BC in the multivariable-adjusted analysis (HR=2.74, 95% CI 1.32-5.70). Conclusions: Higher weight gain in adulthood and larger amounts of ethanol intake were significantly associated with increased risk of BC in Japanese postmenopausal women. None of the investigated factors were significantly associated with BC risk in Japanese premenopausal women.

Keywords: Breast cancer - cohort study - menopausal status - weight gain - alcohol drinking

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Introduction

Breast cancer (BC) is the most common cancer among Japanese women. The incidence rate of BC is the highest among cancers in females, followed by colon cancer (Matsuda et al., 2013). The mortality rate of BC is also high, and 13,148 women died of BC in 2013. (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, 2015). Accordingly, BC remains a great menace to Japanese women.

According to a review by Colditz et al. (2006), risk factors for BC were summarized as follows: younger age at menarche, smaller number of live births, older age at the first full-term pregnancy, older age at menopause, taller in body height, larger weight gain during adulthood, higher BMI, lower physical activity, smoking and drinking habits, family history of BC in first-degree relatives, and various dietary factors. Ovarian hormones, and estrogens, in particular, play an important role in etiology of BC (Henderson and Feigelson, 2000). Both endogenous and exogenous hormones increase cellular proliferation in the breast, thereby the likelihood of random genetic errors during cell proliferation (Henderson and Feigelson, 2000).

Hormonal milieus of postmenopausal women are different from premenopausal women in terms of amount of estrogen through reduction by menopause. For example, body fat has been suggested to be associated with increased risk of BC in postmenopausal women,

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but, in contrast, has been suggested to be associated with decreased risk of BC in premenopausal women (World Cancer Research Fund/ American Institute for Cancer Research, 2007). Hastert et al. (2013) examined six prevention recommendations such as body fatness, physical activity, energy density in foods, plant foods, red meat, and alcohol, for postmenopausal BC, according to the report by the World Cancer Research Fund and the American Institute for Cancer Research (2007). They concluded that adherence to recommendations, especially two recommendations for body fat and alcohol, could substantially reduce postmenopausal BC risk in U.S. women (Hastert et al. 2013).

In order to examine some of the above-mentioned recommendations in Japanese women, we conducted a cohort study on association of body height, weight gain since age 20, physical activity, and ethanol intake with BC risk according to menopausal status, using the latest data of the Japan Collaborative Cohort (JACC) study.

Materials and Methods

Details of the study subjects have been described elsewhere (Tamakoshi et al., 2013). Briefly, the baseline data of the JACC Study were collected from 1988 to 1990, and 110,585 individuals (46,395 men and 64,190 women) aged 40 to 79 years in 45 study areas throughout Japan participated in the study. The follow-up survey for cancer mortality was conducted from the baseline, and finalized at the end of the 2009 year (Tamakoshi et al., 2013). In 24 of the 45 study areas, data on cancer incidence, such as date of diagnosis and primary site, were also collected simultaneously through population-based cancer registries or by reviewing the records of local major hospitals. We confined the analysis to these 24 areas available of cancer incidence information, excluding data of all the male subjects and women with previous diagnosis of BC.

Thus, data from the 38,610 (9,367 premenopausal, and 29,243 postmenopausal) women were used for analysis, and 273 (84 premenopausal, and 189 postmenopausal) cases of BC were newly diagnosed in 501,907 person-years. Because a part of the study areas discontinued the follow-up survey regarding cancer before 2009, the mean and median follow-up period of the incidence survey was 13.0 and 13.3 years, respectively, which were shorter than those of the mortality survey.

Among the variables in the baseline data, four explanatory variables, body height, weight gain since age 20, physical activity, and amount of ethanol intake per day, were selected for risk assessment for BC by menopausal status. Categorization of body height was referred to in two previous case-control studies of BC for Japanese women (Hirose et al., 2001; Kawai et al., 2013). Weight gain since age 20 was calculated as weight at baseline survey minus weight at age 20, and categorized referring to an article by Suzuki et al. (2013).

Physical activity was categorized referring to an article by Suzuki et al. (2008). Namely, the most physically active women were defined as those whose time spent exercising per week was longer than or equal to one hour, and time spent walking per day was longer than or equal to one hour. Excluding the most physically active women, physically active women who exercised was defined as those whose time spent per week doing physical exercise was longer than or equal to one hour, and physically active women who walked was defined as those whose time spent walking per day was longer than or equal to one hour. Residual subjects were categorized as inactive women (Suzuki et al., 2008).

Amount of ethanol intake per day was defined as total amount per opportunity multiplied by frequency of consumption in a week, divided by seven, and then categorized referring to an article by Lin et al. (2005). If information of the subjects' menopausal status was missing in the administrated questionnaire, and if her age at baseline survey was 55 years or older, she was designated as a postmenopausal women.

The Cox proportional hazards regression model (the Cox model) was used to estimate hazards ratio (HR) and its 95% confidence interval (CI) of the explanatory variables for BC risk. For multivariable-adjusted analysis with the Cox model, age at the baseline survey (continuous variable), age at menarche (categorical variable), number of live births (categorical variable), and age at the first delivery (categorical variable), were involved in the model as potentially confounding factors. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), and is a modified version of an R commander designed to add statistical functions frequently used in biostatistics (Kanda, 2013). Significance level was set up to a level of 5%. This study was approved by the Ethics Boards at Hokkaido University Graduate School of Medicine, and Sapporo Medical University.

Results

Table 1 shows baseline characteristics of premenopausal and postmenopausal women in the JACC Study. Information of the four selected explanatory variables, body height, weight gain since age 20, physical activity, and amount of ethanol intake per day, and the four chosen potential confounding factors in the multivariable-adjusted analysis, age at baseline survey, age at menarche, number of live births, and age at the first delivery, were included in Table 1 by menopausal status.

Table 2 shows the results from the age-adjusted and the multivariable-adjusted analyses with the Cox model in premenopausal women. Amount of ethanol intake per day ≥15.0 g was significantly associated with increased risk of BC in the age-adjusted analysis (HR=2.38, 95% CI 1.02-5.45), however, a significant association was not observed in the multivariable-adjusted analysis (HR=2.30, 95% CI 0.97-5.45). A significant trend of BC risk was not observed in amount of ethanol intake per day in neither the age-adjusted analysis (p for trend, p=0.101), nor in the multivariable-adjusted analysis (p for trend, p=0.162). Although the most physically active lifestyle was shown as about 40% reduction of BC risk in premenopausal women, it was not significant (multivariable-adjusted,

Table 1. Baseline Characteristics of Premenopausal and Postmenopausal Women in the JACC Study

Variables	Premenopausal women	Postmenopausal women
Number of individuals	9,367	29,243
Age at baseline survey, mean (SD), in year	45.5 (3.8)	62.4 (7.8)
Body height, mean(SD), in cm	153.6 (51.7)	150.2 (59.3)
Body weight at age 20, mean (SD), in kg	49.7 (59.3)	49.7 (65.3)
Body weight, mean (SD), in kg	53.8 (72.7)	51.6 (78.9)
Weight gain since age 20≥10g (%)	20.9	19.3
Most physically active $ (%)	11.4	14.1
Amount of ethanol intake per day≥15.0g (%)	4.1	2.6
Age at menarche, mean (SD), in year	14.0 (1.5)	15.3 (1.8)
Age at menopause mean (SD), in year	#	48.7 (4.7)
Number of live births, mean (SD)	2.3 (0.9)	2.8 (1.4)
Age at the first delivery, mean (SD), in year	25.2 (3.1)	25.0 (3.1)

SD: Standard deviation #: Not applicable; $: The most physically active lifestyle was defined as those for whom time spent on physical exercise per week was longer than or equal to one hour, and time spent walking per day was longer than or equal to one hour

Table 2. Hazard ratios (HRs) and their 95% confidence intervals (CIs) of the four variables for premenopausal breast cancer risk by age-adjusted and multivariable-adjusted analysis with the Cox model.

Variables	Contents	Number of subjects	Person-years	Breast cancer	Incidence rate#	Age-adjusted			Multivariable-adjusted &		
						HR	95% CI	P value	HR&	95% CI	P value
Body height	<149.0cm	1,394	20,098	13	6.5	1.00			1.00		
	149.0-152.9cm	2,467	36,528	20	5.5	0.84	0.42-1.70	0.633	0.94	0.37-2.36	0.895
	153.0-156.9cm	2,783	41,111	25	6.1	0.93	0.48-1.83	0.842	1.44	0.61-3.36	0.405
	≥157.0cm	2,535	38,172	26	6.8	1.03	0.53-2.03	0.917	1.16	0.48-2.80	0.748
	Total	9,179	135,909	84	6.2		P for trend	0.724		P for trend	0.476
Weight gain since age 20	<3.3kg	3,881	58,824	35	5.9	1.00			1.00		
	3.3-6.6kg	1,542	23,421	11	4.7	0.80	0.40-1.56	0.506	0.89	0.42-1.89	0.753
	6.7-9.9kg	1,098	16,169	13	8.0	1.36	0.72-2.57	0.348	1.27	0.59-2.70	0.543
	≥10.0kg	1,727	25,083	22	8.8	1.48	0.87-2.53	0.149	1.46	0.78-2.73	0.643
	Total	8,248	123,497	81	6.6		P for trend	0.109		P for trend	0.221
Physical activity	Inactive	3,236	46,280	30	6.5	1.00			1.00		
	Active with exercising	840	12,014	12	10.0	1.54	0.79-3.01	0.207	1.63	0.78-3.43	0.197
	Active with walking	2,991	45,085	26	5.8	0.90	0.53-1.52	0.685	1.15	0.64-2.04	0.643
	Most physically active$	913	13,679	5	3.7	0.57	0.22-1.46	0.238	0.60	0.21-1.74	0.348
	Total	7,980	117,058	73	6.2		P for trend	0.282		P for trend	0.731
Amount of ethano intakel per day	0.0g	6,372	94,181	49	5.2	1.00			1.00		
	0.1-4.9g	723	10,418	10	9.6	1.81	0.92-3.58	0.086	1.77	0.86-3.64	0.122
	5.0-14.9g	697	10,436	5	4.8	0.92	0.37-2.32	0.866	0.84	0.30-2.34	0.732
	≥15.0g	334	4,877	6	12.3	2.38	1.02-5.45	0.046	2.30	0.97-5.45	0.060
	Total	8,126	119,912	70	5.8		P for trend	0.101		P for trend	0.162

#: Incidence rate per 10,000 person-years; $: See Table 1; &: For the multivariable-adjusted analysis, four variables in Table 2 were involved in the model as categorical variables, in addition to age at the baseline survey (continuous variable), age at menarche (categorical variable), number of live births (categorical variable), and age at the first delivery (categorical variable)

Table 3. Hazard Ratios (HRs) and their 95% Confidence intervals (CIs) of the four Variables for Postmenopausal Breast Cancer Risk by Age-adjusted and Multivariable-adjusted & Analysis with the Cox Model

Variables	Contents	Number of subjects	Person-years	Breast cancer	Incidence rate#	Age-adjusted			Multivariable-adjusted		
						HR	95%CI	P value	HR	95%CI	P value
Body height	<149.0cm	10,139	126,994	56	4.4	1.00			1.00		
	149.0-152.9cm	8,224	102,565	44	4.3	0.96	0.65-1.43	0.847	1.13	0.67-1.91	0.655
	153.0-156.9cm	5,652	70,765	49	6.9	1.54	1.04-2.28	0.032	1.27	0.74-2.20	0.385
	≥157.0cm	3,411	41,719	31	7.4	1.64	1.04-2.58	0.032	1.51	0.83-2.74	0.181
	Total	27,426	342,043	180	5.3		P for trend	0.007		P for trend	0.165
Weight gain since age 20	<3.3kg	12,113	153,494	52	3.4	1.00			1.00		
	3.3-6.6kg	3,244	42,156	22	5.2	1.53	0.93-2.53	0.096	1.45	0.78-2.70	0.246
	6.7-9.9kg	2,333	29,560	27	9.1	2.67	1.67-4.26	<0.001	2.48	1.40-4.41	0.002
	≥10.0kg	4,220	52,912	52	9.8	2.88	1.96-4.24	<0.001	2.94	1.84-4.70	<0.001
	Total	21,910	278,122	153	5.5		P for trend	<0.001		P for trend	<0.001
Physical activity	Inactive	8,700	99,519	68	6.8	1.00			1.00		
	Active with exercising	2,597	30,443	22	7.2	1.08	0.67-1.75	0.745	1.15	0.65-2.04	0.635
	Active with walking	7,867	100,728	44	4.4	0.64	0.43-0.94	0.021	0.79	0.50-1.23	0.291
	Most physically active $	3,154	39,337	13	3.3	0.50	0.28-0.91	0.024	0.53	0.26-1.10	0.087
	Total	22,318	270,027	147	5.4		P for trend	0.003		P for trend	0.067
Amount of ethanol intake per day	0.0g	21,123	270,090	131	4.9	1.00			1.00		
	0.1-4.9g	1,650	19,616	13	6.6	1.35	0.76-2.39	0.309	1.25	0.64-2.41	0.515
	5.0-14.9g	1,411	15,890	7	4.4	0.89	0.42-1.91	0.771	0.49	0.15-1.56	0.227
	≥15.0g	633	6,697	9	13.4	2.72	1.38-5.36	0.004	2.74	1.32-5.70	0.007
	Total	24,817	312,293	160	5.1		P for trend	0.041		P for trend	0.174

#: Incidence rate per 10,000 person-years; $: See Table 1; &: For the multivariable-adjusted analysis, four variables in Table 3 were involved in the model as categorical variables, in addition to age at the baseline survey (continuous variable), age at menarche (categorical variable), number of live births (categorical variable), and age at the first delivery (categorical variable)

HR=0.60, 95% CI 0.21-1.74). None of the other variables were associated with risk of BC in premenopausal women, either.

Table 3 shows the results from the age-adjusted and the multivariable-adjusted analyses with the Cox model in postmenopausal women. Body height of 153.0 cm-156.9 cm, and ≥157.0 cm was significantly associated with increased risk of BC in the age-adjusted analysis (HR=1.54, 95% CI 1.04-2.28, and HR=1.64, 95% CI 1.04-2.58, respectively), and significantly increased trend of BC risk was also observed in body height in the age-adjusted analysis (p for trend, p=0.007). However, the multivariable-adjusted analysis revealed that body height was not significantly associated with risk of BC (p for trend, p=0.165).

Weight gain since age 20 of 6.7 kg-9.9 kg, and ≥10.0 kg were significantly associated with increased risk of BC, even in the multivariable-adjusted analysis (HR=2.48, 95% CI 1.40-4.41, and HR=2.94, 95% CI 1.84-4.70, respectively). Significantly increased trend of BC risk was also observed in weight gain since age 20, even in the multivariable-adjusted analysis (p for trend, p<0.001).

Being physically active by walking and being the most physically active was significantly associated with reduced risk of BC in the age-adjusted analysis (HR=0.64, 95% CI 0.43-0.94, and HR=0.50, 95% CI 0.28-0.91, respectively), and significantly decreased trend of BC risk was also observed in physical activity level in the age-adjusted analysis (p for trend, p=0.003). However, the multivariable-adjusted analysis showed that being the most physically active was not significantly associated with reduced risk of BC (HR=0.53, 95% CI 0.26-1.10), and a significant trend was not observed in the physical activity level (p=0.067).

Amount of ethanol intake per day ≥15.0 g was significantly associated with increased risk of BC, even in the multivariable-adjusted analysis (HR=2.74, 95% CI

1.32-5.70), although an increased trend of BC risk was not observed in amount of ethanol intake per day in the multivariable-adjusted analysis (p for trend, p=0.174).

Discussion

We investigated the four risk factors of BC by menopausal status, using the latest data from the JACC Study. Firstly, body height had never been assessed with regard to risk of BC in the JACC Study, and we found that taller body height was not associated with increased risk of BC if multivariable adjustment was performed. Secondly, consistent with the previous report from the JACC Study (Suzuki et al., 2013), higher weight gain since age 20 was significantly associated with increased risk of BC only in postmenopausal women. Thirdly, inconsistent with the previous report from JACC Study (Suzuki et al., 2008), level of physical activity was not associated with risk of BC, although some risk reduction was noted in a higher level of physical activity. Fourthly, ethanol intake had never been shown as being related to BC risk by menopausal status in the JACC Study, and we found that ethanol intake per day≥15g was associated with increased risk of BC in postmenopausal women. It is thought that similar results for Japanese women were noted compared with those for U. S. women reported by Hastert et al. (2013), because they showed that adherence to two recommendations for body fat and alcohol intake was significantly associated with decreased risk for postmenopausal BC.

As stated by Vrieling et al (2010), weight gain is thought to be a better measure to assess adiposity and its metabolic consequences than BMI, and this is the reason why we chose it for analysis. According to a review (World Cancer Research Fund/ American Institute for Cancer Research, 2007), there is a substantial amount of epidemiological evidence showing an inverse relationship between greater body fat and risk of premenopausal BC, especially, among women in western countries. However, Emaus et al. (2014) recently reported from a pooled analysis of European cohort studies that a positive relationship between weight gain in adulthood and risk of BC was observed in women before or at age 50. Furthermore, pooled analysis in Japanese cohort studies (Wada et al., 2014) revealed that higher BMI was significantly associated with increased risk of BC, not only in postmenopausal women, but also, in premenopausal women. Our findings on positive, but, insignificant association of weight gain since age 20 with risk of premenopausal BC have indicated that body fat is not inversely associated with BC risk in Japanese premenopausal women.

According to a meta-analysis by Vrieling et al. (2010), the association between adult weight gain and postmenopausal BC risk was stronger for estrogen-receptor positive BC than the other type. Their findings suggested that higher weight gain in adulthood may increase risk of BC via elevated estrogen exposure. Another possible mechanism is, as indicated from the results of the prospective study conducted by Muti et al. (2002), increased levels of insulin-like growth factor (IGF)-I which is observed in high weight-gain women.

High alcohol consumption has been reported to increase risk of BC in premenopausal (Petri et al., 2004; Suzuki et al., 2009) and postmenopausal women (Petri et al., 2004; Tjonneland et al., 2004; Suzuki et al., 2009). Suzuki et al. (2009) reported from the results of another cohort study in Japan called the JPHC Study that the relationship between alcohol consumption and risk of BC was found not only in premenopausal women, but also in postmenopausal women. Petri et al. (2004) reported that a large intake of alcohol was associated with increased risk both in premenopausal women and postmenopausal women older than 70 years. Tjonneland et al. (2004) showed that alcohol intake in the fifties increased risk of postmenopausal BC.

Although a U-shaped relationship of ethanol intake with BC risk was observed in postmenopausal women of our study, there are few reports which have suggested the U-shaped relationship, to our knowledge. Therefore, more evidence would be necessary to substantiate the U-shaped relationship, if any. According to a review of the mechanism of alcohol mediated mammary carcinogenesis by Seitz et al. (2012) alcohol increased estrogen levels, and estrogen may exert its carcinogenetic effect on breast tissue either via the estrogen receptor or directly. Other mechanisms may include acetaldehyde, oxidative stress, and epigenetic changes caused by alcohol consumption (Seitz et al., 2012).

Several cohort studies indicated that taller body height was associated with increased risk of BC in premenopausal (Kabat et al., 2013) and postmenopausal (Iwasaki et al., 2007; Fagherazzi et al., 2012; Kabat et al., 2013; Stenndof et al., 2013) women, even if potential confounding factors were adjusted. Unlike these studies, we found that taller body height was not associated with risk of BC in the multivariable-adjusted analysis. There are at least two case-control studies of body height for BC risk in Japanese women (Hirose et al., 2001; Kawai et al., 2013), and one study showed a significant positive association only in postmenopausal women (Hirose et al., 2001), but, another study did not show the association either in premenopausal or in postmenopausal women (Kawai et al., 2013). Further study is necessary to clarify the association between body height and BC risk in Japanese women.

A higher level of physical activity has been reported to reduce risk of BC in premenopausal (Maruti et al., 2008) and postmenopausal women (Maruti et al., 2008; Peters et al., 2009) even if potential confounding factors were adjusted. The mechanism of the inverse relationship between physical activity level and BC risk has been explained by lower endogenous estradiol concentration in women with higher regular physical activity levels (Chan et al., 2007). However, our study did not suggest a significant inverse association of higher physical activity with BC risk. Since level of physical activity was defined using only two items in the questionnaire in our study, a more precise definition might have induced a validating result of the association between physical activity and BC risk.

Some limitations in this study should be considered for interpreting our results. First, because we collected information about menopausal status at the baseline survey,

but, not at BC onset, the possibility of misclassification of menopausal status at BC onset should be considered. Second, our data analyses relied on self-reported information at baseline, and that information was not updated during follow-up. However, Zhu et al. (2002) reported high short-term and long-term reliability for 440 participants who were selected from the JACC Study. Third, the cohort population of the JACC Study was not established by random sampling. However, it was shown that they were similar to the Japanese general population in light of several demographic and lifestyle features (Ohno et al., 2001).

In conclusion, higher weight gain in adulthood, and higher ethanol intake were significantly associated with increased risk of BC in Japanese postmenopausal women. None of the investigated factors were significantly associated with BC risk in Japanese premenopausal women. Further study is required to provide valid recommendations for preventing BC in Japanese premenopausal and postmenopausal women.

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