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Reproductive and lifestyle factors related to breast cancer among Japanese women

An observational cohort study

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Abstract

The incidence of breast cancer among Japanese women is substantially increasing. This study evaluated the effects of reproductive and lifestyle factors with respect to breast cancer overall and separately among pre- and postmenopausal women using data from the Three-Prefecture Cohort Study of Japan.

A total of 33,410 women aged 40 to 79 years completed a self-administered questionnaire, which included items about menstrual and reproductive history and other lifestyle factors. The follow-up period was from 1984 to 1992 in Miyagi and 1985 to 2000 in Aichi Prefectures. We used Cox proportional hazards regression models to estimate hazards ratios (HRs) and 95% confidence intervals (CIs) after adjusting for confounding factors.

After 9.8 mean years of follow-up, 287 cases of breast cancer were recorded. In the overall analysis, later menarche (≥16 years) and parity were significantly associated with a decreased risk of breast cancer, with HRs of 0.69 (95% CI 0.48–0.99) and 0.72 (95% CI 0.52–0.99), respectively. Further, there was a significant decline in the risk of breast cancer with increasing number of birth among parous women (*P* for trend = .010). On the contrary, a family history of breast cancer in the mother was significantly associated with an increased risk of breast cancer (HR 3.22, 95% CI 1.52–6.84). Analyses based on menopausal status at baseline indicated that height (≥160 cm) and weight (≥65 kg) were significantly associated with an increased risk of postmenopausal breast cancer, with HRs of 1.34 (95% CI 0.72–2.50) and 3.13 (95% CI 1.75–5.60), respectively. Risk associated with BMI significantly differs by menopausal status.

Our findings suggest the important role of reproductive factors in the development of breast cancer in Japanese women; however, body mass index (BMI) may have different effects on breast cancer in Japanese women compared with western women.

Abbreviations: BMI = body mass index, CI = confidence interval, HR = hazard ratio, ICD = International Classification of Disease, IGF-1 = insulin-like growth factor, RR = relative risk.

Keywords: body mass index, breast cancer, cohort, epidemiology, reproductive factors

1. Introduction

Breast cancer is the most common cancer among women worldwide, accounting for 25% of all cancer cases among women.[1] Although Japanese women have a relatively low risk of breast cancer compared with women in Western countries,[2] the incidence rate has been increasing rapidly,[3] and breast cancer is

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currently the leading cancer among Japanese women. The incidence rate of breast cancer among Japanese women increases with increasing age but decreases or flattens after 50 years of age, whereas it increases irrespective of age among women in Western countries.[4]

A number of epidemiological studies from Western countries with high incidence rates of breast cancer have been reported. Early age at menarche, null parity, later age at menopause, late age at first birth, less experience of breastfeeding, and family history of breast cancer were important risk factors for the development of breast cancer.[5–9] A meta-analysis of 8 case–control studies conducted from 1948 to 1993 in Japan revealed that reproductive factors for breast cancer risk were similar to those in Western countries.[10] However, different effects of body mass index (BMI) on breast cancer have been observed between women in Japan and Western countries.[11] For Japanese women, higher BMI was associated with an increased risk of breast cancer in both pre- and postmenopausal women.[12] In contrast, higher BMI in Western countries was associated with an increased risk of breast cancer in postmenopausal women and a decreased risk in premenopausal women.[13]

Lifestyle and reproductive patterns have changed among women in Japan. Although several Japanese cohort studies examined the association between known and suspected risk factors and breast cancer incidence,[14–16] a large-scale, population-based prospective survey (The Three-Prefecture Cohort Study)[17] enabled us to provide further evidence for the association between several risk factors and the risk of breast cancer among Japanese women. Using this dataset, we evaluated the effects of reproductive and lifestyle factors related to breast cancer to investigate differences in these associations between women in Japan and Western countries.

2. Methods

2.1. Study cohort

The present study was based on the Three-Prefecture Cohort Study, and its study design was previously reported in detail.[17] Briefly, a self-administered questionnaire regarding demographic factors and lifestyle characteristics was administered to participants living in Miyagi, Aichi, and Osaka Prefectures. This study did not include data from residents in Osaka Prefecture because information on reproductive factors was lacking. Of 35,136 women, 9 were excluded after the beginning date of follow-up was unified. In addition, 1411 elderly women aged ≥80 years and 306 women with cancer history were excluded. Finally, 33,410 women aged ≥40 years and without histories of cancer were eligible for our analyses (Fig. 1).

2.2. Baseline questionnaire survey

The Three-Prefecture Cohort Study conducted baseline questionnaire surveys from February 1, 1983 to November 1, 1985.[17] A self-administered questionnaire in a sealed envelope was distributed by hand to participants. The questionnaire covered personal information as follows: area of residence, sex, height, weight, frequency of food intake, smoking, alcohol drinking status, family history of breast cancer in mother, age at menarche, menopausal status at baseline, age at menopause, parity history, parity number, and age at first birth. The agreement or permission of baseline survey for municipality residents was obtained from the municipal government with collaborators. The response to the questionnaire by participant was thought to be the agreement to the survey. The study was approved by the institutional review board of the National Cancer Center and the Ethics Committee of Osaka University School of Medicine.

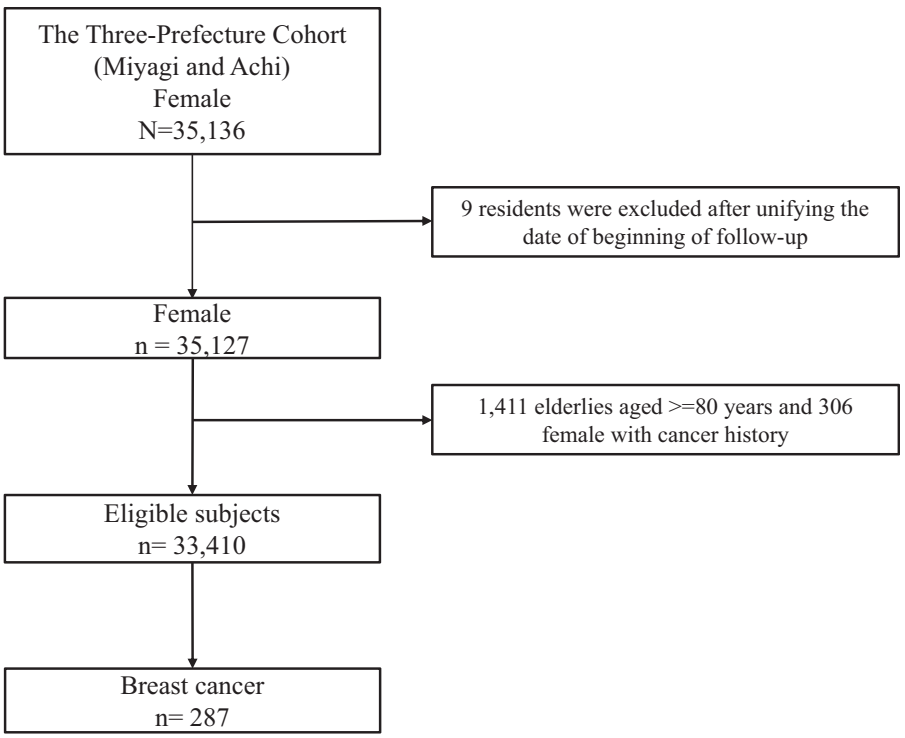

Figure 1. Participants from the Three-Prefecture Cohort study who were included in the current analysis.

2.3. Follow-up and identification of cancer cases

The study participants were followed from the start of the study, and the follow-up periods of cancer incidence were 9 years for Miyagi Prefecture (1984–1992) and 15 years for Aichi Prefecture (1985–2000). Vital status and dates of death and relocation were confirmed by the local government using residence certificates. During the study period, 7427 (22.2%) women moved out of the study area and 3201 (9.6%) died. Cancer incidence data were collected only for participants living in the study area. Cancer incidence and the date of diagnosis were obtained from local population-based cancer registries. The endpoint of this analysis was the incidence of breast cancer, defined as the International Classification of Disease 9th version (ICD9) codes 174 to 175.9 and 10th version (ICD10), codes C50 to C50.9. Up to the end of the cancer incidence follow-up period, 287 new breast cancer cases were identified in this population (Fig. 1).

2.4. Statistical analysis

The person-years of follow-up were calculated from the baseline survey for each participants until the date of diagnosis of breast cancer, or the date of emigration from the study area, or the date of death, or the end of follow-up (Miyagi, December 31, 1992; Aichi, December 31, 2000). The exposure variables analyzed in the present study were age at menarche, menopausal status, age at menopause, parity history, parity number, age at first birth, and family history of breast cancer in the mother. The crude incidence rate per 100,000 for breast cancer was calculated by dividing the number of breast cancer cases by the number of person-years. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer incidence by the exposure variables using STATA version 13 MP (Stata Corp., College Station, TX).

The following variables were used for adjustment as potential confounders: age, area, region (urban/rural), BMI, alcohol consumption, smoking status, green-yellow vegetables consumption, other vegetables consumption, packed vegetables consumption, fruit consumption, miso soup consumption. Different sets of exposure variables were used for adjustment in respective estimated models (see footnotes in Tables 1–3). In our analyses, missing values in confounders were treated as an additional category and included in the models. Linear trends were assessed using the Cox proportional hazards models by treating each exposure category as a continuous variable. In the subgroup analyses, we excluded women without menopausal information at baseline. According to menopausal status (pre or post), we assessed breast cancer risk by reproductive factors and other variables, including height (<148, 148–151, 152–155, 156–159, or ≥160 cm), weight (<50, 50–54, 55–59, 60–64, or ≥65 kg), BMI (<18.5, 18.5–24.9, 25.0–26.9, or ≥27.0 kg/m^2), smoking category (never, former, or current), and drinking category (never, former, sometimes, or almost daily). In addition, chi-square tests were used to determine differences the distributions of categorical variables of the baseline characteristics. All *P* values reported are 2-sided, and the significance level was set at $P < .05$.

3. Results

The demographic and lifestyle characteristics of the study participants at baseline with respect to menopausal status are presented in Table 1. Among the 33,410 participants, 10,861 (32.5%) were premenopausal and 20,831 (62.4%) were postmenopausal; the menopausal status was undefined in 1718 participants (5.1%). Compared with postmenopausal women, premenopausal women tended to be taller and thinner. Most of women were never smokers, and approximately half of women had never consumed alcohol.

Table 2 shows the reproductive characteristics of participants at baseline by menopausal status. The proportions of those aged ≤13 years at menarche was 31.8% in premenopausal women and 18.5% in postmenopausal women. The proportion of postmenopausal women with no parous experience (11.7%) was higher than that among premenopausal women (8.3%). Among parous

Table 1

Demographic and lifestyle characteristics of participants at baseline.

	All	Premenopausal women	Postmenopausal women	*P*-value*
Number of participants	33,410	10,861	20,831	
Area (%)				
Miyagi Prefecture	48.9	46.2	49.5	<.001
Aichi Prefecture	51.1	53.8	50.5	
Region (%)				
Rural	40.5	38.4	40.3	.001
Urban	59.5	61.6	59.7	
Age group (%)				
40–49	32.2	81.6	8.0	<.001
50–59	31.8	14.2	41.7	
60–69	22.7	2.7	32.5	
70–79	13.3	1.5	17.9	
Height (%)				
<148	16.0	8.2	19.7	<.001
148–151	29.4	25.5	31.9	
152–155	25.8	29.8	24.4	
156–159	15.3	20.8	12.9	
160+	9.0	13.9	6.7	
Missing	4.5	1.8	4.4	
Weight (%)				
<50	35.1	30.9	37.2	<.001
50–54	25.7	28.8	24.7	
55–59	18.1	19.7	17.7	
60–64	11.0	11.4	11.0	
65+	7.2	7.6	6.9	
Missing	2.9	1.6	2.5	
Body mass index (%)				
<18.5	7.7	5.9	8.6	<.001
18.5–24.9	66.8	73.9	64.7	
25.0–26.9	11.4	10.7	11.8	
≥27.0	9.0	7.3	9.9	
Missing	5.1	2.31	5.0	
Smoking status (%)				
Never	66.2	71.4	65.9	<.001
Former	3.0	2.0	3.6	
Current	9.0	8.5	9.5	
Missing	21.8	18.1	21.1	
Drinking status (%)				
Never	44.8	41.0	48.4	<.001
Former	2.2	1.7	2.6	
Sometimes	24.9	33.6	21.3	
Almost daily	5.1	6.1	4.8	
Missing	23.0	17.7	23.0	

Excluding 1718 women without information on menopausal status at baseline.
* Chi-square test for categorical variables.

Table 2

Reproductive characteristics of participants at baseline.

	All	Premenopausal women	Postmenopausal women	*P*-value*
Age at menarche (%)				
≤13	22.1	31.8	18.5	<.001
14	20.9	27.8	18.7	
15	21.1	21.4	22.0	
≥16	28.7	16.5	36.2	
Missing	7.3	2.5	4.5	
Age at menopause (%) n = 20,831				
≤47	26.9		26.9	
48–50	30.0		30.0	
51–53	17.9		17.9	
≥54	6.6		6.6	
Missing	18.6		18.6	
Parity (%)				
Nulliparous	11.6	8.3	11.7	<.001
Parous	86.8	91.5	87.8	
Missing	1.6	0.2	0.6	
Number of births (%) n = 28,986				
1	7.0	7.0	7.0	<.001
2	24.2	34.1	19.2	
3	17.7	17.8	17.6	
4	7.8	3.8	9.9	
≥5	10.1	2.3	13.3	
Missing	33.2	35.0	33.0	
Age at 1st-birth (%) n = 28,986				
≤21	16.3	9.7	19.6	<.001
22–25	50.2	52.1	49.5	
26–29	22.9	27.6	20.7	
≥30	8.1	8.2	8.1	
Missing	2.5	2.4	2.2	
Family history of breast cancer in mother (%)				
Other	99.2	98.9	99.3	
Yes	0.8	1.1	0.7	<.001

Excluding 1718 women without information on menopausal status at baseline.
* Chi-square test for categorical variables.

women, only 7.0% had 1 child no matter the menopause status. In addition, the proportion of women who had a first birth younger than 21 years was higher among postmenopausal women (19.6%) than that among premenopausal women (9.7%). Only 0.8% of women overall had a family history of breast cancer.

Of 325,840 person-years for 33,410 study participants (average follow-up period: 9.8 years), 94, 183, and 10 cases of breast cancer were recorded among premenopausal, postmenopausal, and undefined women at baseline, respectively. The HRs and 95% CIs of breast cancer according to menstrual and reproductive factors among the women overall are shown in Table 3. Compared with women with earlier menarche (≤13 years), women with later age at menarche (≥16 years) had a significant risk reduction of breast cancer incidence (HR 0.69; 95% CI 0.48–0.99). Relative to nulliparous women, the multi-adjusted HR for parous women was 0.72 (95% CI 0.52–0.99). Among parous women, the risk decreased significantly with an increasing number of births (*P* for trend = .010), even after adjusting for age at first birth. The risk of breast cancer incidence was significantly reduced for women with ≥5 births relative to those with 1 birth (HR 0.43; 95% CI 0.19–0.97). Women whose mother had a history of breast cancer had a significantly increased risk of breast cancer (HR 3.22; 95% CI 1.52–6.84).

After excluding 1718 women whose information of menopausal status were missing at baseline, the HRs of breast cancer by menopausal status were showed in Table 4. Compared with an age of 13 at menarche, the risk of breast cancer incidence decreased marginally for those ≥16 years in postmenopausal women (HR 0.66; 95% CI 0.43–1.02). Women with a later age at menopause (≥54 years) had a higher risk of breast cancer (HR 1.72; 95% CI 0.98–3.02) compared with those with age at menopause ≤47 years. Regardless of the menopausal status, the risk of breast cancer incidence was significantly reduced for parous women (HR 0.54; 95% CI 0.30–0.99 among premenopausal women and HR 0.64; 95% CI 0.43–0.94 among postmenopausal women). Although the risk of breast cancer incidence among parous women decreased with increasing number of births in both pre- and postmenopausal women, only the risk for premenopausal women was statistically significant (*P* for trend = .010). Women whose mother had breast cancer had increased risks for the disease, although a significant association was observed only among postmenopausal women (HR: 4.49; 95% CI 1.83–11.00).

Table 5 shows the HRs of breast cancer incidence by height, weight, BMI, smoking status, and drinking category according to menopausal status. Overall, a positive association between height and breast cancer risk was observed for both pre- and postmenopausal women (*P* for trend = .340 and .009, respectively). Weight was also associated with an increased risk of breast cancer in both pre- and postmenopausal women, but the association was more evident in postmenopausal women (*P* for trend < .001). Among postmenopausal women, a high BMI was associated with high HRs of breast cancer incidence compared with that in women with a low BMI (*P* for trend = .002), while it was not associated in premenopausal women with breast cancer. In contrast, smoking and drinking category were not associated with the risk of breast cancer incidence irrespective of the menopausal status.

4. Discussion

This population-based prospective cohort study from 3 prefectures in Japan demonstrated that several menstrual and reproductive factors; family history of breast cancer in the mother; height; weight; and high BMI were associated with an increased risk of breast cancer.

Estrogen plays an important role in the development of breast cancer.[18] Women who start menstruating early in life have an increased risk of developing breast cancer.[19] Early menarche was associated with the early onset and increased frequency of ovulatory circles. Women with an early age of menarche are earlier exposed to increased ovarian hormone levels and have higher estrogen levels for several years longer. Several years of exposure to high-level estrogen stimulus increased the risk of breast cancer.[20,21] In other words, an older age of menarche is associated with a lower risk of breast cancer. For every year delay in menarche, the risk decreases by around 5%.[22] In the present study, a risk decrement was observed among women with later age at menarche (women aged ≥16 years, HR, 0.69; 95% CI 0.48–0.99) and the risk decreased nearly 6% for each 1-year delay in menarche (data not shown).

Pregnancy promotes the differentiation of mammary gland epithelium, and the differentiated cells are not susceptible to undergo neoplastic transformation. Therefore, when the early first full pregnancy occurs early, the early differentiation of

Table 3

HR of breast cancer incidence according to reproductive factors.

	No. of cases	Person-years	Incidence rate per 100,000	Age and area-adjusted			Multivariable-adjusted		
				HR1	(95% CI)	*P* for trend	HR2	(95% CI)	*P* for trend
Menopausal status									
Premenopausal women	94	107221	87.7	1.00			1.00[*]		
Postmenopausal women	183	202877	90.2	0.95	(0.68–1.32)		0.92	(0.66–1.29)	
Age at menarche									
≤13	75	73925	101.5	1.00		.010	1.00[†]		.136
14	57	69044	82.6	0.79	(0.56–1.12)		0.84	(0.59–1.18)	
15	71	68959	103.0	0.96	(0.69–1.33)		1.06	(0.76–1.47)	
≥16	59	91023	64.8	0.58	(0.41–0.83)		0.69	(0.48–0.99)	
Parity									
Nulliparous	47	38122	123.3	1.00			1.00[‡]		
Parous	239	283679	84.3	0.67	(0.49–0.91)		0.72	(0.52–0.99)	
No. of birth									
1	22	18008	122.2	1.00		.001	1.00[§]		.010
2	57	66708	85.4	0.72	(0.44–1.18)		0.70	(0.42–1.17)	
3	33	48581	67.9	0.55	(0.32–0.94)		0.57	(0.33–1.00)	
4	9	20724	43.4	0.33	(0.15–0.73)		0.37	(0.16–0.83)	
≥5	12	24320	49.3	0.35	(0.17–0.74)		0.43	(0.19–0.97)	
Age at first-birth									
≤21	30	44677	67.1	1.00		.008	1.00[‖]		.177
22–25	111	144724	76.7	1.17	(0.78–1.76)		1.07	(0.71–1.61)	
26–29	67	65507	102.3	1.58	(1.02–2.46)		1.30	(0.83–2.04)	
≥30	25	22495	111.1	1.71	(1.00–2.92)		1.27	(0.73–2.21)	
Family history of breast cancer in mother (%)									
Other	280	323338	86.6	1.00			1.00[¶]		
Yes	7	2503	279.7	3.26	(1.54–6.92)		3.22	(1.52–6.84)	

CI = confidence interval; HR = hazard ratio.

HR1: adjusted for age (continuous) and area (Miyagi and Aichi).

HR2: adjusted for age (continuous), area (Miyagi and Aichi), region (urban and rural), BMI (–18.5, 18.5–24.9, 25.0–26.9, 27.0+, missing), drinking (never, former, sometimes, almost daily, missing), smoking (never, former, current, missing), green-yellow vegetables consumption (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), non-green and yellow vegetable consumption (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), fruit (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), miso (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), packed vegetables (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), and family history of breast cancer in mother (other, yes).

[*] Adjusted for age at menarche (–13, 14, 15, 16+, missing), parity (nulliparous, parous, missing), age at 1st-birth (–21, 22–25, 26–29, 30+, missing) plus HR2.

[†] Adjusted for menopausal status (premenopausal women, age at menopause for postmenopausal women [–47, 48–50, 51–53, 54+, missing]), parity (nulliparous, parous, missing), age at 1st-birth (–21, 22–25, 26–29, 30+, missing) plus HR2.

[‡] Adjusted for age at menarche (–13, 14, 15, 16+, missing), menopausal status (premenopausal women, age at menopause for postmenopausal women [–47, 48–50, 51–53, 54+, missing]) plus HR2.

[§] (Parous) adjusted for age at menarche (–13, 14, 15, 16+, missing), menopausal status (premenopausal women, age at menopause for postmenopausal women [–47, 48–50, 51–53, 54+, missing]), age at 1st-birth (–21, 22–25, 26–29, 30+, missing) plus HR2.

[‖] (Parous) adjusted for age at menarche (–13, 14, 15, 16+, missing), menopausal status (premenopausal women, age at menopause for postmenopausal women [–47, 48–50, 51–53, 54+, missing]), no. of birth (1, 2, 3, 4, 5+, missing) plus HR2.

[¶] Adjusted for age at menarche (–13, 14, 15, 16+, missing), menopausal status (premenopausal women, age at menopause for postmenopausal women [–47, 48–50, 51–53, 54+, missing]), parity (nulliparous, –22, 22–25, 26–29, 30+, missing) plus HR2 but excluding family history of breast cancer in mother.

mammary gland cells are induced.[23] In addition, the first full pregnancy changes the long-term hormonal levels including decreased prolactin, higher sex hormone-binding globulin, and lower estrogen, which may be associated with the decreased of breast cancer.[16] Compared with nulliparous women, women who have had at least one full-term pregnancy have an approximately 25% reduction in breast cancer risk.[6,7] In addition, a younger age at first birth was associated with greater protection against breast cancer.[22,24] A previous study showed that women with first delivery after 35 years of age had a risk about 40% higher than that in those with a first birth before 20 years.[7] In addition, women with multi-parity had a lower risk of breast cancer than that in women with low parity. The risk of breast cancer significantly declined with increasing number of birth even after controlling for the influence of various risk factors related to breast cancer. Our result was similar to one from other previous studies[5–10,14,16] and would reinforce the importance of the association between high parity and the decreased risk of breast cancer. In addition, this phenomenon would be partially explained by the long-lasting protective effect which has been enhanced by every new full-term pregnancy after the first. The diminution in breast cancer risk with increasing parity may be related to changes in plasma prolactin levels, and high parity was associated with low prolactin concentration both in pre- and postmenopausal women.[22] Our results were similar to those of other studies in which parous women had a 28% reduction in breast cancer risk relative to nulliparous women. Women with >5 children had exceedingly lower risks than those of women with only 1 child. Furthermore, women with a later age at first birth tended to have a higher risk of breast cancer, although the results were not statistically significant.

The results of this study underscored that women with a family history of breast cancer were at an increased risk of the disease, which could be explained partially by shared genes. Mutations in *BRCA1*, *BRCA2*, *P53*, *PTEN*, and *ATM* are associated with breast cancer risk, especially those in *BRCA1* and *BRCA2*.[22]*BRCA2* plays a more important role than *BRCA1* in Japanese familial breast cancers.[25,26] The pooled estimate of

Table 4

HR of breast cancer incidence according to reproductive factors by menopausal status.

	Premenopausal women				Postmenopausal women			
	No. of cases	HR	(95% CI)	*P* for trend	No. of cases	HR	(95% CI)	*P* for trend
Age at menarche								
≤13	33	1.00[*]		.629	42	1.00[*]		.148
14	23	0.83	(0.48–1.42)		34	0.85	(0.54–1.35)	
15	16	0.77	(0.42–1.43)		53	1.18	(0.78–1.78)	
≥16	13	0.93	(0.47–1.85)		45	0.66	(0.43–1.02)	
Age at menopause								
≤47					42	1.00[†]		.125
48–50					55	1.18	(0.79–1.77)	
51–53					34	1.14	(0.72–1.81)	
≥54					18	1.72	(0.98–3.02)	
Parity								
Nulliparous	13	1.00[‡]			32	1.00[‡]		
Parous	81	0.54	(0.30–0.99)		151	0.64	(0.43–0.94)	
No. of birth								
1	8	1.00[§]		.010	13	1.00[§]		.210
2	30	0.67	(0.29–1.51)		24	0.64	(0.32–1.30)	
3	8	0.35	(0.13–0.98)		23	0.70	(0.34–1.44)	
4	1	0.20	(0.02–1.71)		7	0.41	(0.16–1.10)	
≥5	0				12	0.58	(0.23–1.46)	
Age at first-birth								
≤21	4	1.00[‖]		.871	25	1.00[‖]		.105
22–25	42	1.57	(0.56–4.45)		65	0.95	(0.60–1.52)	
26–29	25	1.63	(0.56–4.81)		41	1.34	(0.80–2.24)	
≥30	6	1.23	(0.33–4.52)		18	1.40	(0.74–2.64)	
Family history of breast cancer in mother								
Other	92	1.00[¶]			178	1.00[¶]		
Yes	2	2.21	(0.54–9.05)		5	4.49	(1.83–11.00)	

Excluding 1718 women without information on menopausal status at baseline.

CI = confidence interval; HR = hazard ratio.

HR: adjusted for age (continuous), area (Miyagi and Aichi), region (urban and rural), BMI (–18.5, 18.5–24.9, 25.0–26.9, 27.0+, missing), drinking (never, former, sometimes, almost daily, missing), smoking (never, former, current, missing), green-yellow vegetables, non-green and yellow vegetable consumption (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), fruit (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing) consumption (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), miso (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), and packed vegetables (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing) and family history of breast cancer in mother (other, yes).

[*] Adjusted for parity (nulliparous, parous, missing), age at 1st-birth (–21, 22–25, 26–29, 30+, missing), age at menopause for postmenopausal women (–47, 48–50, 51–53, 54+, missing) plus HR.

[†] Adjusted for age at menarche (–13, 14, 15, 16+, missing), parity (nulliparous, parous, missing), age at 1st-birth (–21, 22–25, 26–29, 30+, missing) plus HR.

[‡] Adjusted for age at menarche (–13, 14, 15, 16+, missing), age at menopause for postmenopausal women (–47, 48–50, 51–53, 54+, missing) plus HR.

[§] (Parous) adjusted for age at menarche (–13, 14, 15, 16+, missing), age at 1st-birth (–21, 22–25, 26–29, 30+, missing), age at menopause for postmenopausal women (–47, 48–50, 51–53, 54+, missing) plus HR.

[‖] (Parous) adjusted for age at menarche (–13, 14, 15, 16+, missing), no. of birth (1, 2, 3, 4, 5+, missing), age at menopause for postmenopausal women (–47, 48–50, 51–53, 54+, missing) plus HR.

[¶] Adjusted for age at menarche (–13, 14, 15, 16+, missing), age at menopause for postmenopausal women (–47, 48-50, 51–53, 54+, missing)], parity (nulliparous, –22, 22–25, 26–29, 30+, missing) plus HR but excluding family history of breast cancer in mother.

relative risk (RR) of women with a single affected first-degree relative (mother, sister, or daughter) was 2.1 (95% CI: 2.0–2.2).[27] In the present study, the HR of women with a family history of breast cancer in mother was about 3 times, which was similar to that in previous study in Japan (HR: 2.79, 95% CI 1.59–4.87).[15]

Obesity increased the risk of breast cancer in postmenopausal women.[22,27] After menopause, instead of ovarian, aromatization of adrenal androgens to estrogens in adipose tissue become the main estrogen source.[28,29] As BMI increases, estradiol increases and sex hormone-binding globulin concentration deceases in postmenopausal women. Therefore, obese postmenopausal women have higher levels of bioavailable estrogens, resulting in increased risks of breast cancer.[30] A meta-analysis showed that a 5 kg/m^2 increase in BMI was positively associated with postmenopausal breast cancer (RR: 1.12, 95% CI 1.08–1.16).[13] In this study, HR per 5 kg/m^2 increased of BMI: 1.07 (95% CI: 1.03–1.10) in postmenopausal women (data not shown in Table).

Circulating insulin-like growth factor (IGF)-1 concentration was also positively related to the risk of premenopausal breast cancer. IGF-1 concentration is low among women with low BMI and increases with increasing BMI but decreases again with obesity.[31] In addition, obese premenopausal women tend to have an increased frequency of anovulatory menstrual cycles and lower estrogen level.[30] These might be associated with an inverse association between increased BMI and premenopausal breast cancer. A significant inverse association was observed among women with BMI ≥31 kg/m^2.[11] However, a previous study suggested an inverse association between increased BMI and premenopausal breast cancer in North American, European, and Australian but a positive association in Asian women.[13] Compared with Western women, Japanese women have a low prevalence of obesity (BMI ≥30 kg/m^2), at ~3%,[32] compared with ~33% in the United States,[33] and ~19% in the European Union.[34] This may be one reason for the lack of inverse association in Japan.

Table 5

HR of breast cancer incidence by height, weight, body mass index, smoking, and drinking category according to the menopausal status.

	Premenopausal women				Postmenopausal women			
	No. of cases	HR	(95% CI)	*P* for trend	No. of cases	HR	(95% CI)	*P* for trend
Height								
<148	4	1.00*		.340	31	1.00*		.009
148–151	20	1.52	(0.52–4.46)		43	0.81	(0.50–1.28)	
152–155	36	2.34	(0.83–6.63)		49	1.16	(0.73–1.85)	
156–159	18	1.65	(0.55–4.93)		39	1.74	(1.06–2.83)	
160+	15	1.99	(0.65–6.07)		16	1.34	(0.72–2.50)	
Weight								
<50	22	1.00†		.336	38	1.00†		<.001
50–54	37	1.76	(1.02–3.03)		50	2.06	(1.33–3.17)	
55–59	14	0.99	(0.50–1.99)		42	2.52	(1.60–3.98)	
60–64	12	1.64	(0.79–3.43)		33	3.22	(1.96–5.27)	
65+	8	1.76	(0.75–4.16)		19	3.13	(1.75–5.60)	
Body mass index								
<18.5	4	0.60	(0.22–1.67)	.322	11	0.69	(0.37–1.30)	.002
18.5–24.9	73	1.00*			112	1.00*		
25.0–26.9	8	0.88	(0.42–1.84)		34	1.88	(1.28–2.78)	
≥27.0	8	1.38	(0.65–2.92)		21	1.50	(0.93–2.41)	
Smoking status								
Never	75	1.00‡		.209	126	1.00‡		.711
Former	1	0.47	(0.06–3.42)		5	0.76	(0.31–1.88)	
Current	4	0.55	(0.20–1.55)		18	1.18	(0.70–1.98)	
Drinking status								
Never	39	1.00§		.952	94	1.00§		.699
Former		–			3	0.65	(0.20–2.08)	
Sometimes	33	1.08	(0.67–1.74)		37	0.84	(0.57–1.25)	
Almost daily	4	0.80	(0.28–2.30)		11	1.17	(0.61–2.22)	

Excluding 1718 women without information on menopausal status at baseline.

CI = confidence interval; HR = hazard ratio.

HR: adjusted for age (continuous), area (Miyagi and Aichi), region (urban and rural), green-yellow vegetables consumption (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), non-green and yellow vegetable consumption (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), fruit (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), miso (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), packed vegetables (≤1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost daily, missing), family history of breast cancer in mother, age at menarche (–13, 14, 15, 16+, missing), parity (nulliparous, –22, 22–25, 26–29, 30+, missing), and age at menopause for postmenopausal women (–47, 48–50, 51–53, 54+, missing).

* Adjusted for drinking (never, former, sometimes, almost daily, missing), smoking (never, former, current, missing) plus HR.

† Adjusted for height (–148, 148–151, 152–155, 156–159, 160+, missing), drinking (never, former, sometimes, almost daily, missing), smoking (never, former, current, missing) plus HR.

‡ Adjusted for body mass index (–18.5, 18.5–24.9, 25.0+, missing), drinking (never, former, sometimes, almost daily, missing) plus HR.

§ Adjusted for body mass index (–18.5, 18.5–24.9, 25.0+, missing), smoking (never, former, current, missing) plus HR.

The mechanisms underlying the association between height and breast cancer risk are not completely understood. Height is primarily determined by genetic factors. However, early energy and nutrition restriction, resulting in short height, may inhibit cell proliferation and early events in tumorigenesis.[11] Women in this study born between 1905 and 1945 might have been experienced nutritional inadequacy in childhood and adolescence during World War II, resulting in sufficient variation in energy intake, which has been proposed as an explanation for the positive association between height and breast cancer risk.[35] Pooled analysis of Western countries[11] showed a significant positive association between height and the risk of postmenopausal breast cancer, while the association was not significant for premenopausal women. One study from Japan also indicated that the positive association was more evident in postmenopausal women.[35]

This study had several limitations. First, the follow-up period of the cohort study was 1984 to 1992 in Miyagi Prefecture and 1985 to 2000 in Achi Prefecture, and the reproductive and life style patterns of this study might differ from the present situation in 2019. Further, we did not have information on menopausal status after the start of follow-up. In addition, the information on BMI and other confounders were also based on the baseline questionnaire; thus, we were unable to consider changes over time of those confounders. Second, this study obtained information about family history of breast cancer, however, since our questionnaire could not differentiate between "no," "unknown," or "missing" responses, we treated these as 1 item. Therefore, this study likely underestimated the effect of a family history of breast cancer. Third, reproductive information such as breastfeeding, and the information on exogenous female hormone use were lacking. In addition, we could not evaluate the association of menstrual and reproductive factors with hormone receptor-defined breast cancer.[17]

In conclusion, in this large-scale prospective cohort study among Japanese women, we showed that multi-parity was associated with a decreased risk of breast cancer. Early age at menarche (≤13 years) and family history of breast cancer in the mother were related to an increased risk of breast cancer. Height, weight, and BMI ≥25.0 kg/m^2 were also associated with an increased risk of breast cancer in postmenopausal women.

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