Age-specific interval breast cancers in Japan: estimation of the proper sensitivity of screening using a population-based cancer registry

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The age-specific sensitivity of a screening program was investigated using a population-based cancer registry as a source of false-negative cancer cases. A population-based screening program for breast cancer was run using either clinical breast examinations (CBE) alone or mammography combined with CBE in the Miyagi Prefecture from 1997 to 2002. Interval cancers were newly identified by linking the screening records to the population-based cancer registry to estimate the number of false-negative cases of screening program. Among 112 071 women screened by mammography combined with CBE, the number of detected cancers, false-negative cases and the sensitivity were 289, 22 and 92.9%, respectively, based on the reports from participating municipalities. The number of newly found false-negative cases and corrected sensitivity when using the registry were 34 and 83.8%, respectively. In detected cancers, the sensitivity of screening by mammography combined with CBE in women ranging from 40 to 49 years of age based on a population-based cancer registry was much lower than that in women 50–59 and 60–69 years of age (40–49: 18, 71.4%, 50–59: 19, 85.8%, 60–69: 19, 87.2%). These data suggest that the accurate outcome of an evaluation of breast cancer screening must include the use of a population-based cancer registry for detecting false-negative cases. Screening by mammography combined with CBE may therefore not be sufficiently sensitive for women ranging from 40 to 49 years of age. (*Cancer Sci* 2008; 99: 2264–2267)

Breast cancer is the most common cancer among women in Japan.[1] A great deal of effort has been made to improve surgical and radiotherapeutic techniques as well as chemo-endocrine therapies for the management of breast cancer, although the mortality rate from breast cancer still remains high. The early detection of breast cancer is believed to be the best means of reducing this mortality and mammography is the only evidence-based screening technology currently available for this purpose. To reduce the mortality of breast cancer, Japan's Ministry of Health, Labor and Welfare declared in 2004 that mammography should be introduced for breast cancer screening in women 40 years of age or older. In addition, Japan's *National Cancer Act*, namely the law to promote cancer prevention and improve the quality of cancer screening, was also enforced in April 2007. Therefore, assessment of not only the screening modality, but also the accuracy of such screening programs has become increasingly important.

Although mammography is useful for detecting breast cancer in early stages, it is thought that the effectiveness of mammography screening in women from 40 to 49 years of age is lower than that in women 50 years of age and over.[2,3] The dense parenchyma in women before menopause can obscure tumor shadows and this results in the lower sensitivity of mammography screening in women 40–49 years of age.[4]

To calculate the proper sensitivity of the screening program, it is necessary to get hold of false-negative cases. A reporting system for false-negative cases from participating municipalities was established in Miyagi Prefecture. However, the report was not a legal duty for the municipalities, so the true number of false-negative cases was difficult to determine.

Interval cancers are cases that are diagnosed with no evidence of cancer in the primary screening, but they are diagnosed as breast cancer until further screening can be conducted. Generally speaking, interval cancer does not always indicate a false-negative case. However, determining the precise number of cases of interval cancer is worthwhile for estimating the proper sensitivity of mammography screening.[5] The present study compared the list of all women screened at Miyagi Cancer Screening Center with a population-based cancer registry covering the study areas to determine the precise number of cases of interval cancer. These data were used to calculate the proper sensitivity of breast cancer screening based on the age of the patient and screening method.

The purpose of the present study is to estimate age-specific sensitivity using a population-based cancer registry in Japan. Organizing a cancer registry takes a lot of time and effort, but it is almost impossible to obtain accurate statistics regarding cancer screening without using a cancer registry. When Japan's *National Cancer Act* came into force in April 2007, assessment of the screening task became of primary importance. However, there have been no reports evaluating the precise sensitivity of breast cancer screening using the cancer registry. With the use of a population-based cancer registry in Miyagi Prefecture, we investigated age-specific interval cancers to estimate precise sensitivity of mammography screening conducted in women aged not only 50–69 years, but also 40–49 years. The present study indicates that mammography screening may not be sufficiently sensitive for women aged 40–49 years. This study will help us to establish an optimal breast cancer screening system on the basis of proper sensitivity of mammographic screening in Japan.

Subjects and Methods

Study subjects. Biennial clinical breast examinations (CBE) alone or CBE combined with mammography were performed

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for all participants requesting screening in Miyagi Prefecture[6] from January 1997 to December 2002. There were 112 071 eligible women in the mammography combined with CBE group (20 587 women aged 40–49, 47 728 women aged 50–59 and 43 756 women aged 60–69) and 236 839 women in the CBE alone group (103 926 women aged 40–49, 65 529 women aged 50–59 and 67 384 women aged 60–69). On the basis of screening history, 13% of the participants were 'initial', or without screening history, and 87% were 'subsequent', or were previous participants in the screening program.

Screening methods. The screening system included mediolateral oblique imaging of both breasts performed in mobile vans equipped with the mammography system. CBE were conducted simultaneously with interpretation of the mammograms. The mammograms were subsequently re-evaluated by two authorized screeners at Miyagi Cancer Screening Center. The findings of the CBE and mammograms were classified into five categories: Category 1, negative; Category 2, benign finding(s); Category 3, probably benign finding(s); Category 4, suspicious abnormality; Category 5, malignancy. The women who were rated in Category 3 or higher by the CBE and/or mammography were referred for diagnostic examinations.

Breast density was later graded by a single examiner according to criteria for Breast Imaging Reporting and Data System (BI-RADS) mammography density categories:[7,8] < 25% dense for almost entirely fatty (Category 1), 25–50% dense for scattered fibroglandular densities that could obscure a lesion on a mammogram (Category 2), 51–75% for heterogeneously dense, which may lower the sensitivity of mammography (Category 3), and > 75% dense for the extremely dense breast, which lowers the sensitivity of mammography (Category 4).

Identification of cancer cases. All results of diagnostic examinations were reported by the hospitals that performed the diagnostic mammography and/or ultrasonography (biopsy and/or surgical operation if necessary). Screen-detected cancer was defined as a case diagnosed pathologically within 6 months after a positive screening test (detected cases). Interval cancers are defined as cases that were diagnosed as no malignancy in the primary screening, but were clinically diagnosed as breast cancer during the screening interval (2 years) until the subsequent screening was conducted. We regarded interval cancers as false-negative cases in this study. Therefore, the false-negative rate was defined as the proportion of interval cancers in 2 years after screening out of the sum of interval cancers and all screen-detected cancers. Information was obtained on false-negative cases using the reports from participating municipalities. When the reports were received, they were referred to the hospital to obtain information concerning the cases (reported cases).

Interval cancers were newly identified in this study by linking the screening records to the population-based cancer registry data for incident breast cancers in Miyagi Prefecture (registered cases). The death certificate only (DCO) rate is an important factor to confirm the reliability of the cancer registry. The DCO rate in Miyagi Prefecture is 2.7%, indicating that the data for registered cases are of relatively high reliability.[9] The matching of records from the screening database with the cancer registry was carried out with the aid of registry officials. Name, address and date of birth were used to identify individuals. This study was conducted in accordance with the principles specified in the Declaration of Helsinki. All procedures and analyses of the individual records were evaluated and approved by the ethical committee of Tohoku University.

Sensitivity of mammography and CBE. Screening sensitivity is defined as the number of screen-detected cancers expressed as a proportion of the total cancer incidence (screen detected plus interval cancers) in women screened. The sensitivity was calculated for all age groups (40–49, 50–59, and 60–69) for each method; i.e. mammography based screening and CBE alone.

Table 1. Recall rate, detected cancers and detection rates for the two screening and three age groups

	Subject	Recall rate	Detected cancers	Detection rate
MMG with CBE				
40–49	20 587	11.6%	45	0.22%
50–59	47 728	9.5%	115	0.24%
60–69	43 756	7.2%	129	0.29%
CBE alone				
40–49	103 926	8.1%	131	0.13%
50–59	65 529	4.9%	68	0.10%
60–69	67 384	3.6%	82	0.12%

MMG, mammography; CBE, clinical breast examination.

Results

Table 1 compares the recall rates for the diagnostic examinations and detection rates of breast cancer, according to the two screening groups and the three age groups. Among women aged 40–49 years screened by mammography combined with a CBE, the recall rate and detection rate were 11.6% and 0.22%, respectively. In women aged 50–59 years, the respective recall and detection rates were 9.5%, 0.24%. In women aged 60–69 years, the respective recall and detection rates were 7.2% and 0.29%. Over 99% of patients had visited hospitals for further examination in all age groups. The recall rate in screening generally declined with increasing age. Among women screened by CBE alone, the recall rate of women aged 40–49 years was significantly higher than that of women aged 50 and over, but detection rate of cancer was almost the same in the three groups.

Thirty-five interval cancer cases were newly identified in the mammography with CBE group, and 137 cases in the CBE alone group based on the population-based cancer registry. There were 2, 9 and 10 reported interval cancer cases for age 40–49, 50–59 and 60–69 groups, respectively, in the mammography with CBE group. The total number of interval cancers was therefore 18, 19 and 19, respectively, for each group. Similarly, 21, 11, 15, interval cancer cases were revised to 79, 47 and 58 in the CBE alone group for women aged 40–49, 50–59 and 60–69 groups, respectively (Table 2). The proportion of early breast cancer in the mammography with CBE group was 81.4% in the screening detected group and 58.5% in the interval cancer group. On the other hand, early breast cancer rate in the CBE alone group was 69.2% in the screening detected group, and 47.5% in the interval cancer group. Among the mammography combined with CBE group, the lowest sensitivity (71.4%) was observed in the 40–49 years group. The sensitivity in the 50–59 and 60–69 groups were 85.8% and 87.2%, respectively. According to the results of χ^2 test, the sensitivity in the 40–49 years group was statistically significantly lower than other older groups. In contrast, the sensitivity of CBE alone was almost the same value in the three age groups, and these values were much lower than that of the 40–49 years group with mammography. There was no statistical significance of age in CBE alone groups. On the other hand, mammography with CBE groups were significantly more sensitive than CBE alone groups in 50–59 and 60–69 years of age. However, there was no significant difference between the mammography with CBE group and CBE alone group for women 40–49 years of age.

Table 3 shows the sensitivity of mammography in association with different breast densities and ages. Among women 40–49 years of age, the sensitivities in extremely dense and dense breasts were 50.0% and 60.0%, respectively. In women 50–59 years of age, the sensitivities in extremely dense and dense breasts were 50.0% and 66.7%, respectively. In women 60–69 years of

Table 2. Sensitivity, specificity and positive predictive value according to the two screening groups and three age groups

Methods and age groups	MMG with CBE			CBE alone		
	40–49	50–59	60–69	40–49	50–59	60–69
Detected cancer	45	115	129	131	68	82
Reported interval cancers	2	9	10	21	11	15
Provisional sensitivity	95.7%	92.0%	92.8%	86.2%	86.1%	84.5%
Specificity	88.6%	90.7%	93.1%	92.0%	95.2%	96.5%
PPV	1.9	2.5	4.1	1.6	2.1	3.4
Interval cancers from population-based cancer registry	16	10	9	58	36	43
Total interval cancers	18	19	19	79	47	58
Proper sensitivity	71.4%	85.8%	87.2%	62.4%	59.1%	59.9%

CBE: clinical breast examination, MMG: mammography, PPV: positive predictive value.

Table 3. Sensitivity of mammography in association with different breast densities and ages

Age group (years)	Breast density (BI-RADS‡ category)			
	1	2	3	4
40–49†	100.0% (1/1)	69.2% (9/13)	60.0% (15/25)	50.0% (10/20)
50–59	87.5% (7/8)	80.7% (46/57)	66.7% (34/51)	50.0% (9/18)
60–69	91.2% (31/34)	79.7% (63/79)	78.6% (22/28)	57.1% (4/7)
Total	90.7% (39/43)	79.2% (118/143)	68.3% (71/104)	51.1% (23/45)

†Four data are lacking because of missed mammography.
‡BI-RADS: Breast Imaging Reporting and Data System.

age, the sensitivities in extremely dense and dense breasts were 57.1% and 78.6%, respectively. Sensitivity according to BI-RADS category was statistically significant (p-value < 0.001, x^2 test).

Discussion

Breast screening has been an important means of decreasing breast cancer mortality and mammography is the only evidence-based screening technology currently available for this purpose. Several randomized trials of mammography screening showed that the usefulness of mammography screening in women aged 50 and over is statistically obvious; however, the effectiveness in women aged 40–49 is controversial.[2,3] The purpose of this study is to estimate age-specific sensitivity using a population-based cancer registry in Japan.

Reducing mortality from specific cancer is the most important index of the cancer screening, but it will take several decades to show the true effectiveness of screening. In the present study, we adopted interval cancers as an important indicator of the quality of a breast cancer screening program and as a predictor for its success in reducing breast cancer mortality.[5] In general, interval cancer does not always indicate a false-negative case. However, we regarded interval cancers as false-negative cases in this study because a population-based screening program should be responsible for a participant's health until further screening. The number of interval cancer cases from participating municipalities was very small. The provisional sensitivity of screening using mammography with CBE in woman 40–49 years of age is 95.8% based on the data from the participating municipalities. After using the cancer registry, the sensitivity went down to 71.4% in women 40–49 years of age. In the Age Trial[10] a randomized controlled trial that was designed specifically to study the benefit of starting mammography screening from age 40, the sensitivity of first screening was reported as 73.6%. Fracheboud *et al.*[11] reported observation of 1002 interval cancers within 2 years of screening whereas the number of screening-detected cancers was 3639 cases. This means that of all breast cancers diagnosed in regular participants, 64% will be detected by screening and 34% will emerge as interval cancers. Our results are in line with previous studies.

The sensitivity in the 40–49 years group was significantly lower than other older groups as shown in Table 2. Several factors were discussed as the reason for this. The first of those factors is the dense parenchyma in women before menopause. Breast masses are indicated by their density in the mammography, so that the masses are often hidden in a dense breast. A previous study by Kolb[12] showed a low sensitivity, 47.8% and 58.0%, in dense breast screening and in women under 50. These types of interval cancers are true false negatives. A great deal of effort has been made to decrease this type of interval cancer; digital mammography may be one of the useful candidates for overcoming this problem. Pisano *et al.*[13] showed that the overall diagnostic accuracy of digital and film mammography as a means of screening for breast cancer is similar, but digital mammography is more accurate in women under the age of 50 years, women with radiographically dense breasts and premenopausal or perimenopausal women. Further technological improvement is expected in this field.

The second factor is the unexpected, rapid, aggressive growth of tumors in younger women. Weedon-Fekjær *et al.*[14] reported a large variation in breast cancer tumor growth, with faster growth among younger women. This type of interval cancer may not be a false-negative case, but this type of cancer often results in a bad end. Further study on the suitable interval of screening program in younger women may be needed.

Although the sensitivity of screening using mammography with CBE in the 40–49 years of age group was lower than older groups, the sensitivity was relatively higher than screening with CBE alone in the 40–49 years of age group. Among the older groups, the sensitivities were statistically significantly higher in the mammography with CBE groups than CBE alone groups. The effectiveness of mammography is beyond doubt from the viewpoint of sensitivity in the 50–69 years of age group. On the other hand, we may need to consider introducing new modality

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to the screening program for younger women in order to find cancers at an earlier stage.

Ultrasonography is one of the candidates for this purpose because it is able to detect breast cancer at early stage based on the mass shape even in the dense parenchyma of women before menopause. In a study of 374 women using a state cancer registry, Moy *et al.*[15] reported only six (2.6%) women that had cancer that was not detected by either mammography or ultrasonography. The accuracy of ultrasonography tends to depend on the experience of the screener, so that it is important to provide training systems and diagnostic lexicons in breast cancer screening.

The American College of Radiology Imaging Network (ACRIN), a multicenter protocol to assess the efficacy of screening breast ultrasonography, began enrollment for high-risk asymptomatic women with dense breasts for three annual screening mammograms and ultrasonography independently in April, 2004, to determine the true measures of the performance of screening ultrasonography.[16] It is anticipated that mammography and ultrasonography will complement each other.

The Ministry of Health, Labor and Welfare of Japan launched a national priority research program, entitled 'Randomized controlled trial on effectiveness of ultrasonography for breast cancer screening' in 2007. To verify the quality and effectiveness of ultrasonograohy for breast cancer screening, 120 000 women aged 40–49 years will be enrolled, with randomization into two groups, mammography with ultrasonography and mammography alone. The first endpoints of this trial are sensitivity and specificity, and the secondary endpoint is the cumulative rate of advanced breast cancer in the two groups. Using a cancer registry is necessary to identify the false-negative cancer cases and accurately estimate the sensitivity of screening. This trial, designated the Japan Strategic Anticancer Randomized Trial (J-START), is the first large-scale RCT of cancer screening in Japan, following enforcement of the *National Cancer Act* in 2007.

In conclusion, mammography is considered to be an effective screening method in comparison with CBE, especially in the 50–69 years of age group. However, screening by mammography combined with CBE may not be sufficiently sensitive for women between 40 and 49 years of age. Adding other screening modalities should therefore be further discussed to establish an optimal sensitive screening protocol.

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Effect of screening mammography on breast cancer survival in comparison to other detection methods: A retrospective cohort study

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The effectiveness of screening mammography (SMG) on mortality has been established in randomized controlled trials in Western countries, but not in Japan. This study evaluated the effectiveness by comparing the survival based on detection methods. The survivals were estimated by the Kaplan–Meier method. Breast cancer patients diagnosed from 1 January 1989 to 31 December 2000 were determined using the Miyagi Prefectural Cancer Registry and follow-up was performed from the date of the diagnosis until the date of death or the end of follow-up, 31 December 2005. The hazard ratios (HR) and 95% confidence interval (CI) of breast cancer death based on the detection methods were estimated by the Cox proportional-hazard regression model. The mean age of the 7513 patients was 55.7 years (range, 15.0–99.3). The 5-year survival associated with the SMG group, the clinical breast examination (CBE) group, and the self-detection group was 98.3%, 94.3%, and 84.8%, respectively. The HR (95% CI) of deaths from breast cancer was 2.50 (1.10–5.69) for patients in the CBE group and 6.57 (2.94–14.64) for the self-detection group in comparison to the SMG group. In women aged 50–59, the HRs were 1.64 (0.58–4.62) among the CBE group and 3.74 (1.39–10.03) among the self-detection group, and the HRs for the CBE and self-detection groups in women aged 60–69 were 2.96 (0.68–12.83) and 9.51 (2.36–38.26), respectively. After adjusting for stage, the HRs dropped remarkably. Screening mammography may be more effective in the elderly group and be able to reduce the mortality of breast cancer in Japan. (*Cancer Sci* 2009; 100: 1479–1484)

Breast cancer is one of the most common cancers worldwide. The trend in the mortality of breast cancer is declining in Western countries in spite of the growing morbidity. Secondary and tertiary prevention, such as SMG and adjuvant therapy, have greatly contributed to this trend.[1] On the contrary, in Japanese women, breast cancer has now risen to first place in terms of age-standardized incidence among all cancers, and it is increasing rapidly.[2] Furthermore, the age-specific mortality rate of breast cancer among Japanese females aged 30 to 64 years was the highest of all cancers. Therefore, reducing the mortality rate is considered to be an important public health concern.

Western countries with national healthcare systems have state-sponsored breast cancer screening programs by mammography. Currently, only 12.9% (2005)[3] of Japanese women are screened by mammography for breast cancer as opposed to 60.8% (2003) in the United States, 69.5% (2005) in the United Kingdom, and 81.9% (2005) in the Netherlands.[4] The reason for this low screening rate in Japan is that SMG was only introduced in 2000 for those aged over 50 and in 2004 for those aged over 40, and it is conducted according to guidelines which are not legally binding from the Ministry of Health, Labour and Welfare. The assured effectiveness of SMG must be the presupposition of the declining mortality of breast cancer before addressing the problem of the low screening rate.

Randomized controlled trials (RCTs) for SMG have been carried out in Western countries during the 1960s; some of them determined its effectiveness[5,6]. In Japan, breast cancer screening by CBE has been introduced for women 30 years of age and over under the Health and Medical Services Law for the Aged in 1987 without any evidence regarding the effectiveness of breast cancer screening with CBE.[7] Studies to evaluate efficacy of SMG compared with CBE in Japan revealed that SMG was proven to be superior to CBE for breast cancer screening in regards to sensitivity, specificity, and detection rate.[8,9] Based on the results of these studies, SMG was endorsed in Japan. However, in regards to the effectiveness of SMG on the mortality of breast cancer, the introduction of SMG was mainly based on the scientific background of the RCTs in Western countries, not in Japan.

The efficacy of SMG for Japanese women was further examined using cost-effectiveness analysis with the actual screening data of Japan,[10] and by validation study of the precise false-negative rate of SMG, referencing the Miyagi Prefectural Cancer Registry.[11] These studies showed the superiority of SMG to CBE, but there is still no data on the effectiveness of SMG on breast cancer mortality in Japan. We need an evaluation of the effectiveness of SMG in Japan because of the following reasons: there is a difference in the age-specific incidence of breast cancer between Western and Japanese women; and Japanese women tend to have more mammographically dense breasts than Western women, which inhibit the depiction of lesions.[11]

To evaluate the effectiveness of SMG, RCTs provide evidence of the highest quality according to the hierarchical ranking of studies based on 'evidence level',[12] but planning an RCT for verifying the effectiveness of SMG for Japan is not realistic because of budget problems and the scale of the trial.

Therefore, the current study clarified the efficacy of SMG for Japanese women by investigating the survival rates of breast cancer by their detection methods in this retrospective cohort study. The effect of improving the survival rate of breast cancer by SMG in comparison to CBE and self-detected breast cancer was evaluated by referencing the Miyagi Prefectural Cancer Registry, one of the oldest and most reliable population-based cancer registries in Japan.[13]

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Table 1. Age distribution of breast cancer patients according to detection modalities

		Age group						Mean age, years (SD)
		Under 40 (%)	40 to 49 (%)	50 to 59 (%)	60 to 69 (%)	70 and over (%)	Total	
Modality								
	Screening mammography	1 (0.5)	33 (16.8)	62 (31.5)	94 (47.7)	7 (3.6)	197	58.9 (8.3)
	Clinical breast examination	93 (7.5)	490 (39.7)	324 (26.3)	236 (19.1)	91 (7.4)	1234	53.1 (10.7)
	Self-detection	585 (10.7)	1575 (28.9)	1222 (22.4)	1100 (20.2)	963 (17.7)	5445	55.9 (13.5)
	Unknown	68 (10.7)	212 (33.3)	138 (21.7)	135 (21.2)	84 (13.2)	637	54.7 (12.9)
Total		747 (9.9)	2310 (30.7)	1746 (23.2)	1565 (20.8)	1145 (15.2)	7513	55.7 (13.2)

Materials and Methods

The end-point of this analysis was the survival of breast cancer detected by SMG, CBE, and self-detection defined as the topography code C50.0–C50.9 according to the International Classification of Disease for Oncology, Second Edition (ICD-O-2).[14] Breast cancer patients were identified from the Miyagi Prefectural Cancer Registry. In this registry, the relevant patients were abstracted from medical records of hospitals by a medical doctor or trained medical record reviewer, except for patients reported directly from an institution to the registry. The percentage registered by DCO for breast cancer was 2.7% for women from 1998–2002.[13]

A total of 7701 breast cancer patients, diagnosed from 1 January 1989 to 31 December 2000, were extracted from the Miyagi Prefectural Cancer Registry. Of them, 188 DCO patients were excluded from this analysis. Finally, 7513 (97.4%) patients, with a mean age of 55.7 years (range, 15.0–99.3), were entered into this analysis. The exact number of women who were under 40 years of age, 40–49 years, 50–59 years, 60–69 years, and over 70 years were 747, 2310, 1746, 1565, and 1145, respectively. The detection methods (SMG, CBE, and self-detection) for each cancer patient were confirmed by comparing these data to the breast cancer database in the Miyagi Cancer Society. This society performs breast cancer screening for women in Miyagi prefecture. CBE is defined as the inspection and palpation of breasts and regional lymph nodes done by the attending physician at the screening. Self-detection is defined as the patients' findings of lesions by themselves, which are later diagnosed as breast cancer. This study conducted follow-up for each of the subjects from the date of diagnosis of breast cancer until the date of death or the end of follow-up (31 December 2005), whichever occurred first. Patients without any information on death were regarded as alive at 31 December 2005. Based on these data, the relationship between the detection method and prognosis of the breast cancer patient was analyzed. A Kaplan–Meier survival analysis was performed according to the detection method by excluding any patients whose detection method was unknown, and patients who died from other types of cancer, other sicknesses, and other causes in 7513 patients to estimate the effectiveness of SMG only on breast cancer survival. The survival rates between two of the three groups were statistically assessed by the log-rank test. The Cox proportional-hazard regression model was used to estimate the HR and 95% CI of relative mortality risk according to the detection method and to adjust for age and clinical stage. The analysis used the clinical staging system developed by the Research Group for Population-Based Cancer Registration in Japan for adjusting clinical progression between the detection methods. The lesions were classified into four stages (*in situ* or localized, lymph node metastasis, regional invasion, distant metastasis) based on information regarding tumor extension and metastasis to lymph nodes and distant sites.[15] All statistical analyses were performed using SAS version 9.1 statistical software (SAS, Cary, NC, USA). All reported *P*-values were considered statistically significant if they were less than 0.05.

The study protocol was approved by the institutional review board of Tohoku University Graduate School of Medicine and the committee of the Miyagi Prefectural Cancer Registry. This study was conducted in accordance with the principles specified in the Declaration of Helsinki.

Results

Prognosis and survival analysis according to diagnostic method. In 7513 breast cancer patients, a total of 197 patients were detected by SMG. In these patients, one (0.5%) patient was 40 and under, 33 (16.8%) were 40–49, 62 (31.5%) were 50–59, 94 (47.7%) were 60–69, and seven (3.6%) were 70 years and over. In 1234 patients detected by CBE, 93 (7.5%), 490 (39.7%), 324 (26.3%), 236 (19.1%), and 91 (7.4%) were 40 and under, 40–49, 50–59, 60–69, and 70 years and over, respectively. In 5445 self-detected patients, 585 (10.7%), 1575 (28.9%), 1222 (22.4%), 1100 (20.2%), and 963 (17.7%) were 40 and under, 40–49, 50–59, 60–69, and 70 years and over, respectively. In 637 patients whose detection methods were unknown, 68 (10.7%), 212 (33.3%), 138 (21.7%), 135 (21.2%), and 84 (13.2%) were 40 and under, 40–49, 50–59, 60–69, and 70 and over, respectively (Table 1).

Stages of 4822 (64.2%) patients were ascertained from the Miyagi Prefectural Cancer Registry in 7513 breast cancer patients. Stages of 152 (77.2%) patients were identified in patients detected by SMG. In these patients, 128 (84.2%) were *in situ* or localized, 23 (15.1%) were lymph node metastasis, one (0.7%) was regional invasion, and the stages of 45 patients were unknown. In patients detected by CBE, stages of 846 (68.6%) patients were verified. In these patients, 609 (72%) were *in situ* or localized, 200 (23.6%) were lymph node metastasis, 20 (2.4%) were regional invasion, 17 (2%) were distant metastasis, and the stages of 388 patients were unknown. Stages of 3444 (63.3%) patients were identified in self-detection patients. In these patients, 1898 (55.1%) were *in situ* or localized, 1076 (31.2%) were lymph node metastasis, 237 (6.9%) were regional invasion, 233 (6.8%) were distant metastasis, and the stages of 2001 patients were unknown. In patients whose detection methods were unknown, stages of 380 (59.7%) patients were ascertained. In these patients, 210 (55.3%) were *in situ* or localized, 121 (31.8%) were lymph node metastasis, 24 (6.3%) were regional invasion, 25 (6.6%) were distant metastasis, and the stages of 257 were unknown (Table 2).

In SMG-detected cancers, 173 (87.8%) were alive, and 24 (12.2%) were dead. In 1234 patients detected by CBE, 1069 (86.6%) were alive, and 165 (13.4%) were dead. A total of 5445 self-detection patients, 3851 (70.7%) were alive, and 1594 (29.3%) were dead. In 637 patients whose detection methods were unknown, 453 (71.1%) patients were alive, and 184 (28.9%) were dead (Table 3).

An analysis of the causes of death revealed that six patients (25%) died from breast cancer of 24 death patients of SMG, 104 patients (63%) of 165 death patients of CBE, 1073 patients (67.3%) of 1594 death patients of self-detection, and 135 patients

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Table 2. Stages of breast cancer patients according to detection modalities

		Stage					Stage unknown (2)	Total (1) + (2)
		In situ or localized (%)	Lymph node metastasis (%)	Regional invasion (%)	Distant metastasis (%)	Total (1)		
Modality								
	Screening mammography	128 (84.2)	23 (15.1)	1 (0.7)	0 (0)	152	45	197
	Clinical breast examination	609 (72.9)	200 (23.6)	20 (2.4)	17 (2.0)	846	388	1234
	Self-detection	1898 (55.1)	1076 (31.2)	237 (6.9)	233 (6.8)	3444	2001	5445
	Unknown	210 (55.3)	121 (31.8)	24 (6.3)	25 (6.6)	380	257	637
Total		2845 (73.8)	1420 (29.4)	282 (5.8)	275 (5.7)	4822	2691	7513

Table 3. Status of breast cancer patients according to detection modalities

		Status			Average observation period, days
		Alive (%)	Dead (%)	Total	
Modality					
	Screening mammography	173 (87.8)	24 (12.2)	197	3012.7
	Clinical breast examination	1069 (86.6)	165 (13.4)	1234	3508.4
	Self-detection	3851 (70.7)	1594 (29.3)	5445	3208.4
	Unknown	453 (71.1)	184 (28.9)	637	2643.9
Total		5546 (73.8)	1967 (26.2)	7513	

Table 4. Cause of the death of breast cancer patients according to detection modalities

		Cause of death				
		Breast cancer (%)	Other cancer (%)	Other disease (%)	Unknown (%)	Total
Modality						
	Screening mammography	6 (25.0)	8 (33.3)	8 (33.3)	2 (8.3)	24
	Clinical breast examination	104 (63.0)	32 (19.4)	26 (15.8)	3 (1.8)	165
	Self-detection	1073 (67.3)	164 (10.3)	326 (20.5)	31 (1.9)	1594
	Unknown	135 (73.4)	22 (12.0)	26 (14.1)	1 (0.5)	184
	DCO	158 (84.0)	2 (1.1)	27 (14.4)	1 (0.5)	188
Total		1476 (68.5)	228 (10.6)	413 (19.2)	38 (1.8)	2155

DCO, Death certificate only.

Table 5. Survival of breast cancer patients according to detection modalities

		Number of patients	5-year survival
Modality			
	Screening mammography	179	98.3%
	Clinical breast examination	1173	94.3%
	Self-detection	4924	84.8%

(73.4%) of 184 death patients whose detection methods were unknown (Table 4).

The 5-year survival rates of breast cancer by SMG, CBE, and self-detection were 98.3%, 94.3%, and 84.8%, respectively (Table 5). Statistically significant differences were thus observed between SMG and self-detection ($P < 0.0001$, log-rank test), CBE and self-detection ($P < 0.0001$, log-rank test), and SMG and CBE ($P = 0.023$, log-rank test) (Fig. 1).

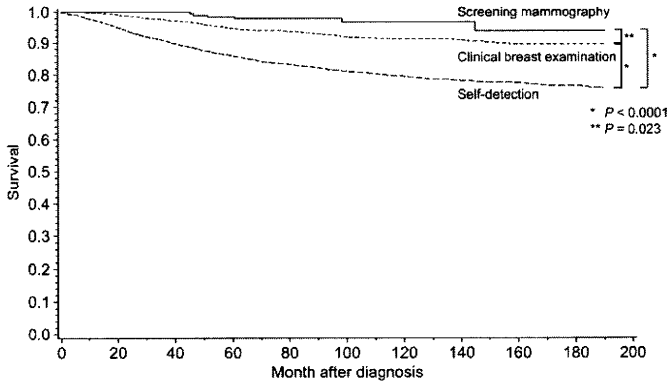

Fig. 1. Kaplan–Meier survival curves for screening mammography (SMG) (179 patients), clinical breast examination (CBE) (1173 patients), and self-detection (4924 patients) (*,**log-rank test). Statistically significant differences were thus observed between SMG and self-detection ($P < 0.0001$), CBE and self-detection ($P < 0.0001$), and SMG and CBE ($P = 0.023$).

Table 6. Hazard ratio of the mortality risk for each of the modalities compared by screening mammography adjusted by each confounding factor

		Adjustment					
		None		Age		Stage	
		HR	95% CI	HR	95% CI	HR	95% CI
Modality							
	Screening mammography	1.00 (reference)		1.00 (reference)		1.00 (reference)	
	Clinical breast examination	2.50	1.10–5.69	2.64	1.16–6.00	2.01	0.88–4.57
	Self-detection	6.57	2.94–14.64	6.80	3.05–15.17	3.92	1.76–8.76

CI, confidence interval; HR, hazard ratio.

Table 7. Hazard ratio of the mortality risk for each of the modalities compared by screening mammography and stratified by age

		Age group			
		50–59		60–69	
		HR	95% CI	HR	95% CI
Modality					
	Screening mammography	1.00 (reference)		1.00 (reference)	
	Clinical breast examination	1.64	0.58–4.62	2.96	0.68–12.83
	Self-detection	3.74	1.39–10.03	9.51	2.36–38.26

CI, confidence interval; HR, hazard ratio.

Mortality risk analysis according to detection method. The mortality risk of the CBE was 2.5 times (95% CI, 1.10–5.69) and of the self-detection was 6.57 times (95% CI, 2.94–14.64) higher than that of SMG. Age-adjusted risk analysis, which was performed because the screening methods were mainly determined by age group, of the CBE was 2.64 times (95% CI, 1.16–6.00) and self-detection was 6.8 times (95% CI, 3.05–15.17) higher than that of SMG. The mortality risk of CBE adjusted by the clinical stage of the breast cancer at detection was 2.01 times (95% CI, 0.88–4.57) and that of self-detection was 3.92 times (95% CI, 1.76–8.76) higher than that of SMG. The differences of the mortality risk became much lower by this adjustment (Table 6).

The subjects were stratified into two age groups (50–59 and 60–69) to conduct a statistical analysis of the mortality according to the detection method. The analysis of SMG in women aged 40–49 could not be evaluated because there was no death among the 33 patients detected by SMG. In the age group of 50–59, the mortality risk of the CBE group was 1.64 times (95% CI, 0.58–4.62) and self-detection was 3.74 times (95% CI, 1.39–10.03) higher than that of SMG. On the contrary, in age group of 60–69, the mortality risk of the CBE was 2.96 times (95% CI, 0.68–12.83) and self-detection was 9.51 times (95% CI, 2.36–38.26) higher than that of SMG (Table 7).

Discussion

Numerous trials for evaluating the effectiveness of SMG have been carried out in several countries on the basis of the relative risk of death. The meta-analysis of major mammographic trials by the US Preventative Services Task Force[16] showed the effectiveness of SMG more than control group in all age groups, especially those aged 50 and over. The current results showed that SMG would be more effective than self-detection for reducing mortality of breast cancer in those aged 50 and over. This retrospective trial has some limitations in its ability to demonstrate the effectiveness of breast cancer screening on mortality due to the possibility of biases, such as self-selection (healthy-screenee) and lead-time biases. From this point of view, RCTs, as in Western countries, are required for evaluating the effectiveness of SMG, but that is not realistic because many women were included in the SMG program in Japan through studies to evaluate efficacy of SMG[8–11] and endorsement by the Ministry of Health, Labour and Welfare in 2000. Therefore, this retrospective cohort study is one of the best efforts to clarify whether SMG has the possibility to reduce the mortality of breast cancer for the first time in Japan by using the population-based cancer registry in Miyagi.

The survival rates of SMG and CBE were over 90% in 5 years in this study, but the analysis of the cause of death in each group revealed that the proportion of other causes of death was higher in SMG (75%) than in CBE (37%) and self-detection (32.7%), which resulted in the differences of the mortality by breast cancer. The proportion of *in situ* or localized breast cancer was higher in the SMG group than for the other two methods. On the other hand, the CBE and self-detection groups had a higher proportion of advanced breast cancer, such as lymph node metastasis, regional invasion, and distant metastasis, which were directly related to breast cancer death. The age distribution of the cancer patients in SMG is higher than that for CBE and self-detection, and therefore other causes of death are higher in the SMG group. These differences result in the lower proportion of breast cancer death in the SMG group.

The present study has some limitations. First, the effectiveness of SMG in women aged 40–49 whose incidence and mortality should be a major factor in Japan could not be evaluated by an analysis of mortality risk by age groups because there was no death in patients detected by SMG and the number of patients was small. In women over 50, the efficacy of the SMG increased proportionally by the screened age; in other words, the breast density gets lower.[11] The efficacy of the SMG may decline in women aged 40–49 whose breast density is higher. Therefore, further investigation of the effectiveness of SMG is required in women aged 40–49. An approach for complementing this weakness of SMG has been evaluated by the study named 'The Japan Strategic Anti-cancer Randomized Trial (J-START)' as a strategic outcome study (a project in the 3rd Term Comprehensive Strategy for Cancer Control). The Ministry of Health, Labour and Welfare Study Group on Cancer Screening pointed out the lack of evidence supporting the effectiveness of ultrasound screening

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in reducing the mortality rate of the breast cancer. J-START evaluates the effectiveness of SMG with ultrasound breast cancer screening compared to mammography alone in women aged 40–49. The planned number is 120 000 persons in total, with 60 000 persons in each group.[17]

A second limitation is that this study is vulnerable to various biases due to comparison of survival rates. Breast cancer screening presumably reduces mortality by detecting breast cancer and allowing the patient to be appropriately treated at an earlier stage. The differences in the mortality risk between SMG and CBE, and SMG and self-detection were presumably caused by the effect of SMG on reducing mortality and biases, such as self-selection bias (healthy-screenee bias). However, the HRs of CBE and self-detection dropped remarkably after adjustment for stage; this indicates that SMG is better able to reduce the mortality of breast cancer than CBE and self-detection. Other factors which could cause this difference are thought to be the lead time bias. However, the Kaplan–Meier survival curve of these three methods does not crossover in spite of the long observational period of this study, and it is therefore assumed that the influence of this bias on survival is too small to have negatively affected the results.

A third limitation is that we can only use the limited data on clinical cancer stage from the cancer registry, which resulted in significant differences in the mortality risk after performing the stage-adjusted analysis. From the cancer registry which we used, four categories have been established to express the clinical extent of breast cancer, but the precise risk of breast cancer is expressed by such clinical features as age, the histological maximum invasive diameter, vessel invasion, the number of lymph node metastases, and the hormonal receptor status.[18] CBE-detected and self-detected cancer would have more advanced lymph node metastatic breast cancer than SMG-detected cancer. These specific clinical features were not precisely expressed in the cancer registry, and therefore we consider that these differences may have occurred after adjusting for various factors.

The current study had several strengths. First, the quality of CBE and reading of SMG were controlled. The screening program was done by registered surgeons who were approved by the committee of breast cancer screening in the Miyagi Cancer Society to have sufficient experience in general surgery, including the treatment of breast cancer. Statistically significant differences of survival were observed between self-detection and CBE, and self-detection and SMG (Fig. 1). In comparison to self-detection, CBE and SMG showed statistically better survival. The difference in survival between self-detection and CBE is larger than for between CBE and SMG. This implies that the quality of CBE by the registered physician was well controlled. It can be said that SMG is better than quality controlled CBE, although CBE is, of course, better than self-detection. Second, the Miyagi Prefectural Cancer Registry is one of the earliest and most accurate population-based cancer registries in Japan, with a low rate of DCO patients with breast cancer.[13] Therefore, the quality of the data is considered to be sufficiently reliable in Japan.

In conclusion, using the population-based cancer registry in Miyagi, Japan, this analysis revealed for the first time in Japan that SMG has the possibility to reduce the mortality of breast cancer in women over 50, although it is necessary to investigate the effectiveness of SMG in women age 40–49. Many countries in Europe and the United States are carrying out SMG as a national policy, and the screening rate is much higher than Japan.[4] In Miyagi Prefecture, the prevalence of SMG is 32.1% (2005) which is better than almost all of the other prefectures in Japan.[3] However, in order to reduce the mortality of breast cancer in Japan in the future, the national screening rate should be increased, while examining various expedients to increase the screening rate, such as education and invitations to the public to raise awareness for the efficacy of SMG.

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Abbreviations

CBE	clinical breast examination
CI	confidence interval
DCO	death certificate only
HR	hazard ratio
RCT	randomized controlled trial
SMG	screening mammography

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ORIGINAL PAPER

Reproductive factors, exogenous female hormone use and breast cancer risk in Japanese: the Miyagi Cohort Study

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Abstract The incidence of breast cancer among Japanese women is substantially increasing. This population-based prospective cohort study in Japan evaluated the associations of reproductive factors and exogenous female hormone use with breast cancer risk, both overall and separately among premenopausal and postmenopausal women. A total of 24,064 women aged 40–64 were followed from 1990 to 2003. During 309,424 person-years of follow-up, 285 breast cancer cases were documented. In overall evaluation, nulliparity was significantly associated with an increased risk of breast cancer. There was a significant decrease in risk with increasing parity number among parous women (trend $P = 0.008$). No association was observed between age at menarche or age at first birth and breast cancer risk. Neither oral contraceptive (OC) use nor the use of exogenous female hormones other than OC was associated with breast cancer risk. The evaluation according to menopausal status revealed that nulliparity and parity number were significantly related to breast cancer risk only among postmenopausal women. Later age at natural menopause was associated with an increased risk of breast cancer among postmenopausal women (trend $P = 0.02$). Our findings suggest that parity number and age at menopause have great effects on breast cancer risk among Japanese women.

Keywords Breast Cancer · Cohort studies · Menopause · Oral contraceptives · Reproductive factors

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Abbreviations

OC	Oral contraceptive
HRT	Hormone replacement therapy
HR	Hazard ratio
CI	Confidence interval

Introduction

Breast cancer is one of the most common cancers worldwide. However, there is a variation in the incidence between countries [1]. Although Japan has a lower risk of breast cancer in comparison with Western countries, the incidence of breast cancer is first in terms of age-standardized

incidence rates among all female cancers in Japan, and it is continuously increasing [2, 3]. Furthermore, the age-specific incidence curve shows a unique pattern: the age-specific incidence rate after the age of natural menopause either decreases or flattens with aging.

During past several decades, numerous epidemiologic studies of breast cancer have been conducted in a large number of populations throughout the world. Especially, the associations between menstrual and reproductive factors and breast cancer risk have been extensively investigated [4–7]. In Japan, several studies have clarified such associations. A meta-analysis including eight Japanese case–control studies conducted during 1948–1993 showed the significant associations of early age at menarche, late age at first birth and low parity with breast cancer risk [8]. These reproductive factors have been recognized as risk factors of breast cancer. However, there have been changes in the socioeconomic environment in Japan during subsequent period. Lifestyles and reproductive patterns in Japanese women are changing [3, 9–11]. The data on sales of hormones indicate that users of exogenous female hormones such as oral contraceptives (OC) are gradually increasing [12]. We need to reevaluate the association of menstrual and reproductive factors with breast cancer risk and to elucidate the effect of exogenous hormone use on breast cancer risk. In Europe and United States, exogenous female hormone use has been regarded as an important risk factor of breast cancer [13–15], whereas the association of the use of exogenous hormones with breast cancer risk has been unclear in Japan.

Meanwhile, the unique pattern of age-specific incidence rate in Japanese women suggests the possibility that the etiology of breast cancer may differ between premenopausal and postmenopausal breast cancer. There has been considerable interest in the differences of risk factors between pre- and post menopausal breast cancer not only in Japan but also in Western countries [16–19].

In the present study, the data obtained from a large sample of Japanese women participating in the Miyagi Cohort Study were analyzed. This study first evaluated the association of known and suspected risk factors such as age at menarche, age at menopause, parity number, age at first birth, breast feeding and family history of breast cancer with the risk of breast cancer. Second, after controlling for these risk factors, the association of exogenous female hormone use with breast cancer risk was examined. The examination for exogenous female hormone use included the history of OC use, duration of OC use and the history of using exogenous female hormones other than OC. The analyses were done separately in premenopausal and postmenopausal women separately, as well as in overall women.

Materials and methods

Study cohort

The present study was based on the Miyagi Cohort Study, whose study design has been described in detail elsewhere [20, 21]. Briefly, 25,279 men and 26,642 women aged 40–64 years living in 14 municipalities, which were randomly selected from 62 municipalities in Miyagi Prefecture, Northeastern Japan, were entered into a cohort of subjects in June 1, 1990. A self-administered questionnaire on various health habits was delivered to these subjects between June and August, 1990. The questionnaires were collected by members of health-promotion committees appointed by the municipal governments. Usable questionnaires were returned from 22,836 men and 24,769 women, and the response rate was 91.7, 90.3 and 93.0% for all, men and women, respectively. All the residents in study area were entered into the cohort, and the response rate of questionnaires was very high; thus, the subjects were thought to be sufficiently representative of this area.

In the present study, of the 24,769 women who responded to the above questionnaire survey, 705 who were diagnosed to have cancer before the start of the baseline survey were excluded. Consequently, 24,064 women were entered into the analytic cohort. The study protocol was approved by the institutional review board of Tohoku University School of Medicine. This study was conducted in accordance with the principles specified in the Declaration of Helsinki. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

Questionnaire at the baseline survey

The questionnaire covered personal history including age, educational level, height, weight, family history including family history of breast cancer in mother or sisters, general lifestyles including cigarette smoking, alcohol drinking, walking status, menstrual and reproductive histories and history of exogenous female hormone use. The questions on menstrual and reproductive histories included age at menarche, menopausal status, age at menopause, parity history, parity number, age at first birth and history of breast feeding. Regarding history of exogenous female hormone use, items on OC use, duration of OC use and use of exogenous female hormones other than OC were included. At the time of the baseline survey, it was assumed that Japanese women would rarely use exogenous female hormones and had no detailed knowledge about the hormones; therefore, only basic questions were listed in the questionnaire.

Ascertainment of cases and follow-up

Study subjects were followed from the start of the study (June 1, 1990) to December 31, 2003. The end point of our analysis was incidence of breast cancer defined as the topography code C50.0–C50.9 according to the International Classification of Disease for Oncology, Second Edition (ICD-O-2). The incidence of breast cancer was confirmed by the Miyagi Prefecture Cancer Registry, which is one of the oldest and most accurate population-based cancer registries in Japan [1, 22]. The relevant cases were abstracted from the medical records of hospitals by a medical doctor or trained medical record reviewer, except for the cases reported from an institution to the registry. The percentage registered by death certificates only (DCO) for breast cancer was 2.5% for women during 1991–2003. In this point of view, this study has the highest quality of epidemiological surveillance of breast cancer incidence in Japan. A total of 285 cases with breast cancer were identified among the 24,064 subjects during the follow-up period.

A Follow-up Committee was established consisting of the Miyagi Cancer Society, the Divisions of Community Health of all 14 municipalities, the Department of Health and Welfare, Miyagi Prefectural Government, and Division of Epidemiology, Tohoku University School of Medicine. The Committee periodically reviewed the Residential Registration Record of each municipality. This checkup identified subjects who had either died or emigrated during the observation period. The follow-up of subjects who had moved from the study municipalities was discontinued because the Committee could not review the Residential Registration Record from outside the study area. During the study period, 1,382 women (5.7%) were lost to follow-up.

Statistical analysis

The person-years of follow-up were counted for each of the subjects from the start of the study (June 1, 1990) 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 (December 31, 2003), whichever occurred first. The mean follow-up period was 12.8 years. The exposure variables analyzed in the present study were menstrual and reproductive factors (age at menarche, menopausal status, age at menopause, parity history, parity number, age at first birth and history of breast feeding) and family history of breast cancer in mother or sisters, most of which are known to be a breast cancer risk factor in Japan, and exogenous female hormone use: history of OC use (ever, never), duration of OC use and history of the use of exogenous female hormones other than OC (ever, never). All these exposures were asked at baseline.

The Cox proportional-hazard regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the incidence of breast cancer according to category of exposure variable and to adjust for confounding variables [23]. Linear trends were tested in the Cox model by treating each exposure category as a continuous variable. We considered the following variables as potential confounders: age, educational level, cigarette smoking, alcohol drinking, walking status and body mass index, which were known or suspected risk factors of breast cancer. Menstrual and reproductive factors and family history of breast cancer in mother or sisters were also considered to be adjusted each other. Walking status was regarded as an indicator of physical activity. In the analysis, missing values in confounders were treated as an additional category in the variable and were included in the model.

The analysis first estimated HRs for menstrual and reproductive factors and family history of breast cancer. Second, after controlling for these factors, HRs were estimated for histories of OC use and other female hormone use and duration of OC use.

Separate analyses were conducted after dividing the subjects into premenopausal and postmenopausal status, along with the analysis for overall women. Menopause was defined as the cessation of menstrual periods due to natural or other reasons including surgery at baseline. The mean age at natural menopause was 49.5 years in this cohort. Regarding menopause due to other reasons, we could not obtain any information on the history of oophorectomy. Therefore, women under 50 years with menopause due to other reasons, who were regarded to have an undefined menopausal status, were not considered in the analyses according to menopausal status. Updated data regarding menopause were not available in our study.

The results were regarded as significant if the two-sided P values were <0.05. All statistical analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC).

Results

The characteristics of the study subjects at baseline are presented in Table 1. Among the 24,064 subjects, 9,131 are premenopausal and 11, 364 are postmenopausal. The menopausal status was undefined for 3,569 subjects (642 subjects under 50 years with menopause due to other reasons and 2,927 subjects with missing data regarding menopausal status). During 309,424 person-years of follow-up from the 24,064 subjects, 285 breast cancer cases (127 cases among premenopausal women, 123 cases among postmenopausal women and 35 cases among undefined

women) were documented. The data on smoking and alcohol drinking were missing in about 20–30% of subjects.

The HRs and 95% CIs r for menstrual and reproductive factors and family history of breast cancer among overall women are presented in Table 2. Although a slight risk reduction was observed among women with later age at menarche (16 y.o.≤: HR 0.89), a linear association between age at menarche and breast cancer risk was not statistically significant (P for trend = 0.65). Natural menopausal women tended to have a lower breast cancer risk in comparison with premenopausal women or women with menopause due to other reasons. Nulliparity was significantly associated with an increased risk of breast cancer (multivariate-adjusted HR 2.23, 95% CI 1.30–3.84). There was a significant decrease in risk with increasing parity number among parous women (multivariate-adjusted P for trend = 0.008). An older age at first birth was significantly associated with an increased risk of breast cancer in the age-adjusted model (P for trend = 0.04); however, this association turned out to be insignificance in the multivariate model (P for trend = 0.28). The association with

Table 1 Characteristics of study population at baseline

Factor	All subjects	Menopausal status[a]	
		Premenopausal	Postmenopausal
Number of subjects (n)	24064	9131	11364[b]
Age group (%)			
40–44	21.7	52.2	0.2
45–49	16.0	31.8	3.2
50–54	18.5	14.3	23.5
55–59	21.6	1.3	36.8
60–64	22.2	0.4	36.3
Age (mean, years)	52.3 ± 7.4	45.1 ± 4.1	56.7 ± 5.0
Body mass index (%)			
<20	9.0	10.7	8.2
20≤ <23	31.9	37.3	29.7
23≤ <25	23.7	23.8	25.0
25≤	29.7	25.8	32.9
Missing	5.7	2.4	4.2
Educational level (%)			
Junior high school or less	36.7	29.5	41.9
High School	43.3	51.1	40.8
College/university or higher	11.5	13.9	11.2
Missing	8.5	5.5	6.1
Smoking (%)			
Current smoker	6.8	8.7	5.1
Past smoker	1.5	1.8	1.4
Never smoker	65.0	73.3	65.4
Missing	26.7	16.2	28.1
Alcohol drinking (%)			
Current drinker	20.8	28.4	15.5
Past drinker	3.2	3.5	3.1
Never drinker	55.9	56.2	60.4
Missing	20.1	11.9	21.0
Walking status (%)			
Longer than 1 h per day	40.7	38.8	43.9
Less than 1 h per day	48.5	56.0	45.6
Missing	10.8	5.2	10.5

[a] Menopause was defined as the cessation of menstrual periods due to natural or other reasons including surgery

[b] Natural menopause, n = 9545; Menopause due to other reasons including surgery, n = 1819

history of breast feeding was unity (multivariate-adjusted HR 1.00, 95% CI 0.72–1.39). A family history of breast cancer in mother or sisters was significantly associated with an increased risk of breast cancer (multivariate-adjusted HR 2.79, 95% CI 1.59–4.87).

Table 3 shows the results by menopausal status at baseline. The HRs in the table were adjusted for confounders including menstrual and reproductive factors and family history of breast cancer. In the analysis limited to postmenopausal women, no association for age at menarche was observed, whereas later age at natural menopause was significantly associated with an increased risk of breast cancer (P for trend = 0.02). A significantly positive association was also observed between the duration of menstruation (period from age at menarche to age at natural menopause) and breast cancer risk (P for trend = 0.006). Nulliparity was associated with an increased risk (HR 3.40, 95% CI 1.64–7.04). Among parous women, the risk decreased significantly with increasing parity number (P for trend = 0.006). There was no association between age at first birth and breast cancer risk (P for trend = 0.47). A history of breast feeding tended to be inversely related to the risk of breast cancer; however, statistical test showed non significance ($P = 0.15$). A family history of breast cancer doubled the risk of breast cancer (HR 2.43, 95% CI 1.07–5.54). Among premenopausal women, none of the reproductive factors was significantly associated with the risk of breast cancer, which was in contrast to the findings among postmenopausal women. Meanwhile, a significant higher risk of breast cancer was found among premenopausal women with family history of breast cancer (HR 3.40, 95% CI 1.49–7.76).

The HRs and 95% CIs for exogenous female hormone use among overall women are presented in Table 4. The multivariate models controlled for the known reproductive risk factors of breast cancer, including age at menarche and parity number, and family history of breast cancer, although the associations with some of the factors were insignificant in this study (shown in Table 2). The HRs for OC use and the use of the exogenous female hormones other than OC were less than one in both age-adjusted and multivariate models; however, statistical test showed insignificance. An inverse association between duration of OC use and breast cancer was observed; however, this association was also insignificant.

Table 5 presents HRs and 95% CIs for exogenous female hormone use by menopausal status at baseline. The HR of breast cancer for OC use was 0.54 (95% CI 0.22–1.34) for premenopausal women, which was in contrast to that for postmenopausal women (HR 1.49, 95% CI 0.69–3.21). In premenopausal women, an inverse association with duration of OC use was also suggested (P for trend = 0.09), although it was hard to evaluate the trend because of the small numbers of breast cancer cases. The use of exogenous female hormones other than OC was not significantly associated with breast cancer risk among either premenopausal or postmenopausal women.

Discussion

This population-based prospective cohort study in Japan confirmed the associations of some menstrual and reproductive factors and family history of breast cancer in mother and sisters, which have been described as risk factors of breast cancer, with the risk of breast cancer. No significant association was found between the use of OC and other exogenous female hormones other than OC and overall breast cancer risk. The analysis according to menopausal status revealed different epidemiologic characteristics between the premenopausal and postmenopausal status.

The analysis for overall women showed that multiparity was associated with a decreased risk of breast cancer and that family history of breast cancer was related to an increased risk, which was similar to those described in studies previously conducted in Western and Asian countries and Japan [4–8, 24, 25]. The association for multiparity has also been described in two population-based cohort studies recently conducted in Japan [19, 26]. However, our study did not find any significant associations for age at menarche and age at first birth, which have been recognized as risk factors in Japan and other countries [5, 8, 19, 26]. Although the reason for the inconsistency in the results among the studies is unclear, different distributions in exposure variables among study areas and times of study might partly contribute to this. For example, our study was conducted in confined rural area, i.e., 14 municipalities in Miyagi prefecture; therefore, the background status of study subjects would be homogenous. The distributions of menstrual and reproductive factors, such as age at menarche and age at first birth, were similar among the municipalities [20, 27]. On the other hand, the two recent population-based cohort studies cover multiple areas in Japan [19, 26]; therefore, the associations between menstrual and reproductive factors and breast cancer risk might have been influenced by some area-related factors. The correlations among the reproductive factors may also contribute to this inconsistency. In our cohort, the age at first birth was inversely correlated with the parity number (correlation coefficient = −0.29; $P = 0.0001$), which may make it difficult to identify the independent effect of age at first birth. Furthermore, changes in the socioeconomic environment and improvement in nutrition, which might have accelerated menarche in the recent generation, may modify the effect of age at menarche on breast cancer risk [3]. In the present study, a slight risk reduction was

Table 2 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to menstrual and reproductive factors and family history of breast cancer

	Number of cases	Person-years	Age-adjusted			Multivariate-adjusted		
			HR	95% CI	*P* for trend	HR	95% CI	*P* for trend
Age at menarche (years)								
≤13	69	66211	1.00		0.46	1.00	[a]	0.65
14	66	64547	1.02	0.73–1.43		1.03	0.73–1.45	
15	58	58406	1.03	0.72–1.48		1.06	0.74–1.52	
16≤	56	73495	0.84	0.57–1.25		0.89	0.61–1.32	
Menopausal status[f]								
Premenopause	127	117591	1.00			1.00	[b]	
Natural menopause	95	122703	0.80	0.51–1.26		0.74	0.46–1.18	
Menopause due to other reasons	28	23359	1.24	0.72–2.12		1.12	0.64–1.96	
Parity								
Parous	241	278832	1.00			1.00	[c]	
Nulliparous	14	6863	2.33	1.36–3.99		2.23	1.30–3.84	
Parity number[g]								
1	25	20317	1.00		0.001	1.00	[d]	0.008
2	116	117058	0.79	0.51–1.21		0.80	0.51–1.26	
3	80	99686	0.66	0.42–1.03		0.70	0.43–1.12	
4	16	30648	0.45	0.24–0.84		0.50	0.26–0.96	
5≤	4	11124	0.32	0.11–0.92		0.35	0.12–1.04	
Age at first birth (years)[g]								
≤21	27	46518	1.00		0.04	1.00	[d]	0.28
22≤ ≤25	142	160129	1.51	1.00–2.28		1.43	0.94–2.16	
26≤ ≤29	58	56433	1.77	1.12–2.79		1.53	0.96–2.44	
30≤	13	13859	1.59	0.82–3.08		1.21	0.61–2.44	
Breast feeding[g]								
No	49	49992	1.00			1.00	[e]	
Yes	186	220281	0.94	0.68–1.30		1.00	0.72–1.39	
Family history of breast cancer in mother or sisters								
No	272	304417	1.00			1.00	[a]	
Yes	13	5007	2.92	1.67–5.10		2.79	1.59–4.87	

[a] Adjusted for age (continuous variable), smoking (ever, never), alcohol drinking (ever, never), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), body mass index (<20, 20≤ <23, 23≤ <25, 25≤), age at menarche (≤13, 14, 15, 16<), parity number (0, 1, 2, 3, 4, 5≤) and family history of breast cancer (present, absent) each other

[b] Adjusted for age, smoking, alcohol drinking, walking, educational level, body mass index, age at menarche, parity number and family history of breast cancer

[c] Adjusted for age, smoking, alcohol drinking, walking, educational level, body mass index, age at menarche and family history of breast cancer

[d] Adjusted for age, smoking, alcohol drinking, walking, educational level, body mass index, age at menarche, parity number (1, 2, 3, 4, 5≤), age at first birth (≤21, 22≤ ≤25, 26≤ ≤29, 30≤) and family history of breast cancer each other

[e] Adjusted for age, smoking, alcohol drinking, walking, educational level, body mass index, age at menarche, parity number, age at first birth and family history of breast cancer

[f] Women with undefined menopausal state were excluded from the analysis

[g] Analyzed for parous women only

observed for women with late age at menarche (16 y.o.≤). Only women with extremely late menarche may have a low risk of breast cancer.

The analyses according to menopausal status at baseline showed different associations for reproductive factors and family history of breast cancer between premenopausal and postmenopausal women. Menstrual and reproductive factors, including parity number, age at menopause and duration of menstruation, were significantly related to breast cancer risk only among postmenopausal women, while family history of breast cancer was strongly associated with an increased risk among premenopausal women.

Table 3 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to menstrual and reproductive factors and family history of breast cancer by menopausal status at baseline

	Premenopausal					Postmenopausal				
	Number of cases	Person-years	Multivariate-adjusted[a]			Number of cases	Person-years	Multivariate-adjusted		
			HR	95% CI	*P* for trend			HR	95% CI	*P* for trend
Age at menarche (years)										
≤13	47	41769	1.00		0.69	18	20135	1.00	[b]	0.96
14	42	32587	1.17	0.77–1.78		18	27520	0.76	0.40–1.46	
15	23	21125	1.03	0.62–1.72		34	32643	1.16	0.65–2.06	
16≤	11	13820	0.80	0.41–1.60		40	51357	0.90	0.51–1.58	
Age at natural menopause (years)										
≤47	–					10	22914	1.00	[c]	0.02
48≤ ≤50	–					28	40518	1.40	0.67–2.93	
51≤ ≤53	–					31	29193	2.46	1.19–5.08	
54≤	–					8	8939	1.96	0.73–5.27	
Duration of menstruation (years)										
≤32						15	26268	1.00	[e]	0.006
33≤ ≤35						17	30387	0.97	0.49–1.95	
36≤ ≤38						27	26666	1.77	0.94–3.34	
39≤						14	10753	2.43	1.15–5.11	
Parity										
Parous	115	111526	1.00			104	137557	1.00	[b]	
Nulliparous	5	2984	1.61	0.65–3.95		8	3193	3.40	1.64–7.04	
Parity number[f]										
1	11	8029	1.00		0.68	13	10506	1.00	[b]	0.006
2	58	54253	0.83	0.43–1.63		47	51850	0.73	0.38–1.38	
3	36	39223	0.75	0.37–1.52		34	49697	0.55	0.27–1.10	
4	8	8014	0.88	0.34–2.26		8	18065	0.37	0.15–0.93	
5≤	2	2006	0.92	0.20–4.27		2	7439	0.23	0.05–1.06	
Age at first birth (years)[f]										
≤21	14	17790	1.00		0.39	10	23445	1.00	[b]	0.47
22≤ ≤25	66	64870	1.26	0.70–2.26		63	77617	1.76	0.90–3.45	
26≤ ≤29	28	22299	1.50	0.77–2.91		25	29116	1.66	0.78–3.51	
30≤	7	6144	1.19	0.46–3.10		6	6538	1.47	0.51–4.29	
Breast feeding[f]										
No	26	28069	1.00			19	17221	1.00	[b]	
Yes	85	79505	1.22	0.78–1.91		84	118062	0.68	0.40–1.15	
Family history of breast cancer in mother or sisters										
No	121	115941	1.00			117	143269	1.00	[b]	
Yes	6	1649	3.40	1.49–7.76		6	2793	2.43	1.07–5.54	

[a] See the footnote of Table 2

[b] Additionally adjusted for type of menopause (natural, other reasons) and age at menopause (≤47, 48≤ <50, 51≤ ≤53, 54≤)

[c] Adjusted for age, smoking, alcohol drinking, walking, educational level, body mass index, age at menarche, parity number (0, 1, 2, 3, 4, 5≤) and family history of breast cancer

[d] Period from age at menarche to age at natural menopause

[e] Adjusted for age, smoking, alcohol drinking, walking, educational level, body mass index, parity number and family history of breast cancer

[f] Analyzed for parous women only

Table 4 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to exogenous hormone use

	Number of cases	Person-years	Age-adjusted			Multivariate-adjusted[a]		
			HR	95% CI	*P* for trend	HR	95% CI	*P* for trend
OC[b] use								
Never	236	243319	1.00			1.00		
Ever	12	15418	0.77	0.43–1.38		0.80	0.45–1.44	
Duration of OC use (years)								
Never	236	243319	1.00		0.18	1.00		0.21
<1	5	4965	0.96	0.39–2.33		1.00	0.41–2.45	
1≤ <5	4	5934	0.67	0.25–1.80		0.70	0.26–1.89	
5≤	1	3234	0.33	0.05–2.32		0.33	0.05–2.33	
Use of exogenous female hormones other than OC								
Never	231	246214	1.00			1.00		
Ever	15	18226	0.87	0.52–1.46		0.84	0.50–1.42	

[a] Adjusted for age (continuous variable), smoking (ever, never), alcohol drinking (ever, never), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), body mass index (<20, 20≤ <23, 23≤ <25, 25≤), age at menarche (≤13, 14, 15, 16≤), parity number (0, 1, 2, 3, 4, 5≤) and family history of breast cancer (present, absent)

[b] *OC* Oral contraceptive

Table 5 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to exogenous female hormone use by menopausal status at baseline

	Premenopausal					Postmenopausal				
	Number of cases	Person-years	Multivariate-adjusted[a]			Number of cases	Person-years	Multivariate-adjusted[b]		
			HR	95% CI	*P* for trend			HR	95% CI	*P* for trend
OC[d] use										
Never	114	97399	1.00			105	124610	1.00		
Ever	5	7744	0.54	0.22–1.34		7	6226	1.49	0.69–3.21	
Duration of OC use (years)										
Never	114	97399	1.00		0.09	105	124610	1.00		0.66
<1	3	3340	0.77	0.24–2.44		2	1199	2.16	0.53–8.82	
1≤ <5	1	2932	0.28	0.04–2.02		3	2432	1.69	0.53–5.39	
5≤	0	1008	0.00	–[c]		1	1946	0.69	0.10–4.99	
Use of exogenous female hormones other than OC										
Never	109	100039	1.00			103	123387	1.00		
Ever	6	7568	0.71	0.31–1.62		8	8946	1.04	0.51–2.16	

[a] See the footnote of Table 4

[b] Additionally adjusted for type of menopause (natural, other reasons) and age at menopause (≤47, 48≤ <50, 51≤ ≤53, 54≤)

[c] Not estimated

[d] *OC* Oral contraceptive

Previously, our case–control study conducted in Miyagi Prefecture showed the different risk factors profiles of breast cancer between early and late onset: namely, a positive association for family history of breast cancer in early onset and an inverse association for parity number in late onset [17]. The present results are comparable to our previous results. Although some other studies in Japan also reported similar association for parity number among postmenopausal women [19, 26], the results among premenopausal women were inconsistent to ours, [16, 19]. On the other hand, several studies in Western countries have showed the absence of an association between parity and breast cancer risk in younger women [28], the protective effect of multiparity in older women [29, 30] and a higher risk of breast cancer associated with a family history of breast cancer among younger women [25, 31]. Our results

by menopausal status are comparable to these results in Western countries. Because some of the premenopausal women in our cohort may have become postmenopausal by the end of follow-up, the results for premenopausal women may be contaminated with those for postmenopausal women. Regardless of this phenomenon, our findings suggest that reproductive factors may have different effects on the risk of breast cancer in pre- and post menopause or in early and late onset [6, 32, 33]. Among premenopausal women, reproductive factors were not related to the risk of breast cancer. Based on the significant association for family history of breast cancer, it is likely that genetic predisposition may affect breast cancer risk among premenopausal women [33]. Meanwhile, hormonal milieu related to reproductive factors may have greater effects on the development of breast cancer among postmenopausal women [5, 34]. Women with late menopause might be exposed to ovarian hormones for a relatively longer period. After menopause, they may have higher estrogen levels than women with early menopause [35]. Further, pregnancy might change long-term hormonal levels [35–38]. There are reports describing the inverse association between parity number and estrogen levels among postmenopausal women [35, 36]. A similar association has been observed for prolactin levels among both pre- and post menopausal women [38]. Endogenous hormones are believed to play a key role in the development of breast cancer [34]. Parity and age at menopause could affect breast cancer risk among postmenopausal women through the effects of such hormones.

We evaluated the associations of exogenous female hormone use with breast cancer risk, using indicators as follows: history of OC use (ever, never), duration of OC use, and history of use of exogenous female hormones other than OC (ever, never). In Japan, one population-based cohort study demonstrated no association of the use of exogenous female hormones with breast cancer risk [19], and the cohort study of atomic bomb survivors showed a higher risk of breast cancer among women with a history of estrogen use [39]. However, few epidemiologic studies have so far focused on the association between exogenous female hormone use and breast cancer risk. A separate effect of OC use on breast cancer risk has never been investigated in Japan. The present study found that OC use was not associated with overall risk of breast cancer. There was no association between duration of OC use and the risk. In Western countries, numerous studies have evaluated the relationship between OC use and the risk of breast cancer, since OCs were first introduced in the 1960s [12]. A meta-analysis including 54 epidemiologic studies showed a slight increase in breast cancer risk associated with ever use of OC and a weak association between longer duration of use and increasing risk [13]. In the present study, such harmful effect of OC use was not observed. The prevalence of OC use (6.0%) in our study, which was similar to that in other Japanese populations [40], was lower than those in Western countries [12]. High-dose combined pills, which were allowed as treatment for menstrual disorders and sterility, have been used as OC [40]. Japanese OC users may have different background characteristics from those in other countries [40, 41]. Regarding the effect of duration of OC use, the meta-analysis demonstrated a significantly increased risk of breast cancer associated with 10 or more years of OC use [13]. In our study, few women ($n = 138$, not shown in Tables) reported 10 or more years of use. None of them developed breast cancer. A shorter duration of OC use also had no effect on the risk of breast cancer as shown in Table 4. Therefore, the short-term use of OC as well as long-term use is unlikely to be related to the risk of breast cancer. However, the number of breast cancer cases among OC users might be too small to evaluate the risk according to the duration of OC. To obtain a reliable conclusion, a longer follow-up is, therefore, required.

The menopausal status has also been reported to be an important determinant of breast cancer risk for OC use. Some previous studies have showed a higher breast cancer risk for OC use among premenopausal women [42, 43]. Our study observed an inverse association with OC use among premenopausal women and a positive association among postmenopausal women, although the associations were statistically insignificance; these were inconsistent with the previous results. The statistical power in our study was limited due to the small number of breast cancer cases among OC users; therefore, these results must be carefully interpreted. However, the difference in risk for OC use between pre- and post menopausal women may be in line with the different associations for reproductive factors according to the menopausal status as mentioned earlier. The high-dose pills contain large doses of progesterone and estrogen. There is a possibility that the use of the exogenous hormones during the premenopausal period may increase the risk of postmenopausal breast cancer.

Regarding health effects of other exogenous female hormones, the association of postmenopausal HRT with breast cancer risk has already been established in Western countries [14, 44]. No association was observed between the use of other exogenous female hormones other than OC and the risk of breast cancer in our study. Based on this finding, it is unlikely that so-called HRT may affect breast cancer risk in Japanese women. However, information on the constituents of exogenous hormones and the timing of exposure including age at first use and duration of use were not available in our study, which are limitations. The number of breast cancer cases found in hormone users was small, raising the problem of a limited statistical power. It,

therefore, seems impossible to precisely estimate the risk for postmenopausal HRT.

There are both strengths and limitations in this study. The strengths include its prospective design and the high quality of the follow-up survey. Participants were recruited from the general population, and breast cancer cases were identified by the Miyagi Prefecture Cancer Registry which is one of the most accurate population-based cancer registries in Japan. Further, the rate of loss to follow-up was low. Therefore, several types of bias, i.e., selection and information bias were avoided. The limitations of this study are as follows: First, we must consider the effects of missing data. In the present study, 2,927 subjects with missing data regarding menopausal status were excluded from the analyses by menopausal status. The exclusion of such a great amount of data might have distorted the results. Taking into account the mean age at natural menopause in this cohort (49.5 years), we attempted to perform additional analyses, by treating 2,555 subjects aged 50 and over with missing data as postmenopausal, and considering the other 372 subjects, who were under 50 years, as premenopausal. These analyses, thereafter, showed quite similar results. The effects of missing data regarding menopausal status are thus considered to be small. Second, most of OC users in this study might have used high-dose pills. The results cannot necessarily be extrapolated to the risk for low-dose pills, which were first allowed to be prescribed in Japan in 1999. In the future, it may be necessary to reevaluate the risk for the new pill which is now being used by younger women.

In summary, this prospective cohort study clarified the associations of menstrual and reproductive factors and exogenous female hormone use with breast cancer risk among Japanese women. Multiparity was significantly associated with a decreased risk of breast cancer among both overall and postmenopausal women. Among postmenopausal women, later age at menopause was associated with an increased risk of breast cancer. No association was observed between age at menarche or age at first birth and breast cancer risk. Neither oral contraceptive (OC) use nor the use of exogenous female hormones other than OC was associated with breast cancer risk. These suggest that parity number and age at menopause have great effects on breast cancer risk among Japanese women.

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