Impact of reproductive factors on breast cancer incidence: Pooled analysis of nine cohort studies in Japan

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Abstract
Prior studies reported the association of reproductive factors with breast cancer (BC), but the evidence is inconsistent. We conducted a pooled analysis of nine cohort studies in Japan to evaluate the impact of six reproductive factors (age at menarche/age at first birth/number of births/age at menopause/use of female hormones/breastfeeding) on BC incidence. We conducted analyses according to menopausal status at the baseline or at the diagnosis. Hazard ratio (HR) and 95% confidence interval (CI) were estimated by applying Cox proportional-hazards model in each study. These hazard ratios were integrated using a random-effects model. Among 187,999 women
INTRODUCTION

Among women, breast cancer is one of the most prevalent cancer types.\textsuperscript{1,2,3} Although its incidence is lower in Asian countries than in Western countries,\textsuperscript{4,5} it has been increasing in Asian countries.\textsuperscript{4} Reproductive factors are one of the possible risk factors.\textsuperscript{3,6-8}

Although previous epidemiological studies have reported the impact of reproductive factors on breast cancer,\textsuperscript{9-15} results were inconsistent between studies, especially in Asian countries. Particularly, the impact of age at menarche/breastfeeding history on breast cancer were inconsistent between studies,\textsuperscript{9-15} mainly because some studies could not conduct stratified analyses according to the menopausal status. The impact of age at menarche/breastfeeding history on breast cancer were inconsistent between studies,\textsuperscript{9-15} but results were inconsistent. Nagata C and colleagues\textsuperscript{9} and Liu R and colleagues\textsuperscript{15} reported that breast cancer occurrence was significantly lower among women with age at menarche ≥16 years than those with ≤13 years. Iwasaki M and colleagues\textsuperscript{11} reported that breast cancer incidence was significantly lower among women with ≥16 years than those with <14 years. However, other studies in Asia\textsuperscript{10,12,14} reported that the incidence did not change according to age at menarche. The association between the history of breastfeeding and breast cancer was also inconclusive. Pooled analysis of epidemiological studies\textsuperscript{7} revealed that breastfeeding decreased the risk of breast cancer. The systematic review conducted in Japan\textsuperscript{13} showed that breastfeeding possibly decreased that risk, but they did not report such an association in cohort studies.\textsuperscript{13}

We aimed to elucidate the impact of reproductive factors on breast cancer incidence by conducting a pooled analysis of nine population-based cohort studies in Japan.

METHODS

2.1 Study participants

The methods of the study were previously published in detail.\textsuperscript{16-19} In this study, the study participants were females collected from nine population-based cohort studies conducted in Japan: the Japan Public Health Center-based Prospective Study, Cohort I (JPHC-I),\textsuperscript{11} Cohort II (JPHC-II),\textsuperscript{11} the Japan Collaborative Cohort Study (JACC),\textsuperscript{10} the Miyagi Cohort Study (MIYAGI-I),\textsuperscript{12} the Three-Prefecture Cohort Study in Miyagi (MIYAGI-II),\textsuperscript{15,20} the Three-Prefecture Cohort Study in Aichi (AICHI),\textsuperscript{15,20} the Takayama Study (TAKAYAMA),\textsuperscript{21} the Ohsaki National Health Insurance Cohort Study (OHSAKI),\textsuperscript{22} and the Life Span Study (LSS).\textsuperscript{23} The relevant ethics review committee approved each study. Details on informed consent were previously published.\textsuperscript{10,12,20,22-25} Since JPHC, JACC, MIYAGI-I, MIYAGI-II, and AICHI published...
the results of analyses on the same topic, we used the latest version of the dataset and re-analyzed the study results.

2.2 Exposures

We categorized six reproductive factors as follows: age at menarche (≤12, 13–14, 15–16, 17 years), age at first birth (≤20, 21–25, 26–30, 31–35, ≥36 years), number of births [nulliparous, 1, 2, ≥3], age at menopause [44, 45–49, 50–54, ≥55 years], use of female hormones [never, ever] (for cohort studies excluding MIYAGI-II, AICHI, LSS), and breastfeeding history [never, ever] (for cohort studies excluding JACC, MIYAGI-II, AICHI, Takayama).

2.3 Statistical analyses

In each population-based cohort study, patients were excluded if (i) they had breast cancer history at baseline, (ii) their menopausal status at baseline was missing, or (iii) they were exposed to estimated radiation doses due to the atomic bomb of 100 mGy or more (for LSS only). Person years were calculated from the baseline date till the date of breast cancer diagnosis, date of death, and lost to follow-up or the end of the study follow-up, whichever occurred earliest.

We conducted analyses according to the menopausal status at baseline and according to the menopausal status at breast cancer diagnosis. Because none of the studies collected information on menopausal status after baseline, we hypothesized that women who were in premenopausal status at baseline became postmenopausal when they passed their 51st birthday. We set a cut point at age 51 based on prior studies. For women younger than 51 years old at the date of censoring who were reported to not be postmenopausal at baseline, we considered years of observation as the premenopausal period. For women who were 51 years old or older and/or were reported to be postmenopausal at baseline, we considered years of observation as the postmenopausal period. If women who were reported to not be postmenopausal at baseline became 51 years old during their observation period, we divided their years of observation into premenopausal period and postmenopausal period according to the 51st birthday.

For all population-based cohort studies, we calculated hazard ratio (HR) and 95% confidence interval (CI) by applying the Cox proportional-hazards model. The reference category of each reproductive factor was defined as follows: ≤12 years (age at menarche), 21–25 years (age at first birth), nulliparous (number of births), ≤44 years (age at menopause), never (use of female hormones), and never (breastfeeding history). We applied two different models: model 1 in which we adjusted age and area (for multicentric studies including JPHC-I, JPHC-II, JACC, and LSS), model 2 in which we adjusted age, area (for multicentric studies including JPHC-I, JPHC-II, JACC, and LSS), history of smoking [never, former, current], body mass index (BMI) [<18.5, 18.5–<23, 23–<25, ≥25], history of drinking [nondrinker, occasional drinker (one to three times a month or less than once a week), one to four times a week, current drinker (more than five times a week)], environmental tobacco smoke (ETS) exposure during childhood [yes, no] (for studies excluding TAKAYAMA and LSS), environmental tobacco smoke (ETS) exposure at home and/or at work [yes, no] (for studies excluding TAKAYAMA and LSS), and mutually adjusted by each reproductive factor. Model 2 was the primary analytic model for the present study. Analyses on age at first birth were conducted among parous women. Age at menopause was not adjusted in the analyses on premenopausal at baseline or premenopausal at diagnosis. We created indicator terms for missing data of categorical variables. We also estimated the increase of breast cancer incidence per category of each reproductive factor by calculating P value for trend.

In each population-based cohort study, the cohort-specific hazard ratio and 95% CI were calculated. Then, they were combined by applying the random-effects model. Heterogeneity between studies was evaluated by calculating I²-statistic.

We conducted analyses by using SAS statistical software package version 9.3 (JPHC-I, JPHC-II) or version 9.4 (MIYAGI-I, MIYAGI-II, TAKAYAMA, and OHSAKI), SPSS Statistics version 25.0 (JACC), Stata/MP 14.2 (AICHI), Stata/SE 15.1 (LSS), and Stata/MP 16.0 (random-effects model). p values were two-sided, and we considered p value <0.05 as statistically significant.

3 RESULTS

The baseline information of nine studies included in our analyses was summarized (Table 1). 187,999 women from nine population-based cohorts were included: 61,113 women (32.5%) who were premenopausal at baseline and 126,886 women (67.5%) who were postmenopausal at baseline. The total breast cancer cases were 873 and 1456 for premenopausal and postmenopausal cancer, respectively.

Table 2 describes the results of analyses according to menopausal status at the baseline. Among premenopausal women at baseline, model 1 showed that age at menarche, age at first birth, number of births, and use of female hormones were not associated with breast cancer incidence (P for trend: 1.00, 0.12, 0.05, and 0.10, for age at menarche, age at first birth, number of births, and use of female hormones, respectively). Model 1 also showed that breastfeeding history significantly decreased breast cancer incidence (HR: 0.78, 95% CI: 0.61–1.00). Model 2 showed that age at menarche,
| Study          | Population                                                                 | Age range at baseline, y | Follow-up (start-end) | Age mean, y | Latest follow-up time | Mean follow-up period, y | Menopausal status at baseline (mean age, y) | Number of cases |          |          |
|---------------|-----------------------------------------------------------------------------|--------------------------|-----------------------|------------|-----------------------|-------------------------|---------------------------------------------|----------------|----------|----------|
| JPHC-I†       | Japanese residents of five public health center areas in Japan               | 40–59                    | 1990–2010             | 49.60      | 2013/12/31            | 21.30                   | 9822 (44.72)                                | 11629 (53.72)  | 203     | 207     |
| JPHC-II       | Japanese residents of six public health center areas in Japan                | 40–69                    | 1993–2010             | 53.42      | 2013/12/31            | 17.92                   | 11986 (44.51)                               | 19875 (58.79)  | 159     | 195     |
| JACC§         | Residents from 45 areas throughout Japan                                     | 40–79                    | 1988–2001             | 58.20      | 2009/12/31            | 13.02                   | 7821 (44.30)                               | 30082 (61.90)  | 79      | 223     |
| MIYAGI-I      | Residents of 14 municipalities in Miyagi Prefecture, Japan                   | 40–64                    | 1990–2007             | 51.69      | 2014/12/31            | 22.03                   | 9127 (45.10)                               | 11985 (56.72)  | 246     | 253     |
| MIYAGI-II     | Residents of three municipalities in Miyagi Prefecture, Japan                | 40–79                    | 1984–1992             | 56.76      | 1992/12/31            | 7.72                    | 5065 (47.82)                               | 9583 (61.53)   | 35      | 69      |
| AICHI         | Residents of two municipalities in Aichi Prefecture, Japan                   | 40–103                   | 1985–2000             | 56.57      | 2000/12/31            | 11.81                   | 5846 (45.78)                               | 11081 (62.27)  | 62      | 106     |
| TAKAYAMA      | Residents of Takayama city, Gifu Prefecture, Japan                          | 35–101                   | 1992–2008             | 56.07      | 2008/3/31             | 13.91                   | 6373 (43.04)                               | 9801 (63.69)   | 38      | 143     |
| OHSAKI        | Residents of 14 municipalities in Miyagi Prefecture, Japan                   | 40–79                    | 1994–2005             | 59.79      | 2008/3/31             | 10.94                   | 4217 (45.97)                               | 16088 (63.41)  | 50      | 161     |
| LSS¶          | Atomic bomb survivors in Hiroshima and Nagasaki, Japan                      | 46–104                   | 1991–2003             | 65.00      | 2003/12/31            | 10.80                   | 856 (48.57)                                | 6762 (67.08)   | 1       | 99      |
| **Total**     |                                                                          |                          |                       |            |                      |                         |                                             | 61113          | 126886  | 873     | 1456    |

Abbreviations: AICHI, The Three-Prefecture Cohort Study in Aichi; JACC, The Japan Collaborative Cohort Study; JPHC, The Japan Public Health Center-based prospective Study; LSS, Life Span Study; MIYAGI-I, The Miyagi Cohort Study; MIYAGI-II, The Three-Prefecture Cohort Study in Miyagi; OHSAKI, The Ohsaki National Health Insurance Cohort Study; TAKAYAMA, The Takayama Study

†In JPHC-I, subjects of one public health center area were excluded due to lack of incidence data.

§In JACC, selected 22 areas with cancer incidence follow-up data were used in this analysis.

¶LSS originally started in 1950. This analysis included subjects who responded to both the 1978 and the 1991 surveys.
use of female hormones, and breastfeeding history were not associated with breast cancer incidence (P for trend: 0.76, 0.14, and 0.65, for age at menarche, use of female hormones, and breastfeeding history, respectively). Although P value for trend was not significant for age at first birth and number of births (P for trend: 0.15 and 0.30, respectively), women giving birth for the first time at ages ≥36 experienced significantly higher breast cancer incidence than at ages 21–25 years (Adjusted HR: 2.30, 95% CI: 1.39–3.79), and women who had 2 or ≥3 births experienced significantly lower breast cancer incidence than nulliparous women (Adjusted HR: 0.39, 95% CI: 0.19–0.81 and 0.28, 95% CI: 0.15–0.53, for 2 and ≥3 births, respectively).

Among postmenopausal women at baseline, model 1 showed that higher age at first birth significantly increased breast cancer incidence (p for trend: <0.01), and breastfeeding history significantly decreased breast cancer incidence (HR: 0.66, 95% CI: 0.51–0.86). Model 1 also showed that age at menarche, number of births, age at menopause, and use of female hormones were not associated with breast cancer incidence (P for trend: 0.47, 0.17, 0.45, and 0.80, for age at menarche, number of births, age at menopause, and use of female hormones, respectively). Model 2 showed that more births significantly decreased breast cancer incidence (p for trend: 0.03). Model 2 also showed that age at menarche, use of female hormones, and breastfeeding history were not associated with breast cancer incidence (P for trend: 0.17, 0.60, and 0.39, for age at menarche, use of female hormones, and breastfeeding history, respectively). Although P value for trend was not significant on age at first birth and age at menopause (p for trend: 0.30 and 0.37, respectively), women giving first birth at ages 26–30 or 31–35 years experienced significantly higher breast cancer incidence than women giving first birth at ages 21–25 years (Adjusted HR: 1.38, 95% CI: 1.21–1.58 and 1.52, 95% CI: 1.16–2.00, for ages 26–30 and 31–35 years, respectively), and women whose age at menopause: 50–54 or ≥55 years experienced significantly higher breast cancer incidence than age at menopause: ≤44 years (Adjusted HR: 1.27, 95% CI: 1.02–1.57 and 1.48, 95% CI: 1.01–2.17, for 50–54 and ≥55 years, respectively).

Supplementary Table S1 describes the results of our analyses according to the menopausal status at the diagnosis of breast cancer. Results were mostly consistent with those presented in Table 2, excluding use of female hormones among premenopausal women and age at first birth among postmenopausal women. Female hormones significantly increased breast cancer incidence among premenopausal women (Adjusted HR: 1.53, 95% CI: 1.04–2.25) in model 2. Higher age at first birth significantly increased the incidence of breast cancer among postmenopausal women at cancer diagnosis (p < 0.001) in model 2.

4 | DISCUSSION

The present study targeted more than 180,000 Japanese women, and elucidated the association of reproductive factors with the incidence of breast cancer. Among premenopausal women, use of female hormones significantly increased premenopausal breast cancer. Although P value for trend was not significant for age at first birth and number of births, women giving first birth at ages ≥36 experienced significantly higher incidence and women who had ≥2 births experienced significantly lower incidence. Among postmenopausal women, more births significantly decreased breast cancer incidence. Although P value for trend was not significant for age at first birth and age at menopause, women giving first birth at ages 26–35 years and women with age at menopause ≥50 years experienced significantly higher breast cancer incidence. Breast cancer incidence was similar regardless of age at menarche or breastfeeding history among both premenopausal and postmenopausal women.

Lower age at menarche has been regarded as one of the risk factors of breast cancer.6,9,11,15 Kelsey et al6 indicated that younger age of menarche increased breast cancer because of earlier onset of ovulatory cycles, longer period of exposure to estrogen or higher estrogen level for some years after menarche. However, we did not observe such an association in our study, which might be due to the small breast cancer cases (=34) in our study of women whose age at menarche: ≥17 years. Improved nutrition has resulted in lower age at menarche in Asian countries as well as in Western countries.30-32 In our study, the percentage of women whose age at menarche: ≥17 years old was 4.8% (premenopausal women at baseline) and 22.3% (postmenopausal women at baseline), which may have resulted in the failure to find a significant result. It is also speculated that breast cancer incidence is higher among women whose age at menarche: ≥17 years due to factors except for reproductive factors.

Significantly higher breast cancer incidence was observed in women with age at menopause: 50–54 and ≥55 years than those with age at menopause: ≤44 years. Although a previous meta-analysis in Japan9 compared women whose age at menopause: ≥50 years with women whose age at menopause ≤49 years, the present pooled analysis created another category of age at menopause (≥55 years). Previous studies have showed that longer exposure to female hormones may have resulted in higher breast cancer risk among women with higher age of menopause.6,33

The association of parity with breast cancer incidence was also reported in previous studies.11,34-36 Previous reports have showed that parity decreased breast cancer risk because differentiation of mammary gland epithelium was promoted by pregnancy, and these differentiated cells would be protected from neoplastic transformation.5,37 The impact of parity on breast cancer was greater among postmenopausal women.
| TABLE 2 | Reproductive factors and breast cancer risk according to menopausal status at baseline. |
|-----------------|---------------------------|---------------------------|-------------------|-------------------|
|                | Number of subjects (n=) | Person Years              | Number of Cases (n=) | HR*               | 95% CI*           |
|                |                          |                           |                    |                   |                   |
| **Model 1†**   |                          |                           |                    |                   |                   |
| **Heterogeneity** |                          |                           |                    |                   |                   |
| **p for trend** |                          |                           |                    |                   |                   |
| **I2 (%)**     |                          |                           |                    |                   |                   |
| **p**          |                          |                           |                    |                   |                   |
| **I2 (%)**     |                          |                           |                    |                   |                   |

**Premenopausal women**

- **Age at menarche**
  - \( \leq 12 \): 8943 person-years, 132652.6 cases, HR 1.06, 95% CI 0.87–1.30
  - 13–14: 29733 person-years, 437791.1 cases, HR 0.95, 95% CI 0.75–1.20
  - 15–16: 14081 person-years, 208713.7 cases, HR 0.93, 95% CI 0.54–1.60
  - \( \geq 17 \): 2641 person-years, 40047.3 cases, HR 1.27, 95% CI 0.76–2.17

- **Age at first birth‡**
  - \( \leq 20 \): 2958 person-years, 47971.8 cases, HR 0.81, 95% CI 0.58–1.15
  - 21–25: 32991 person-years, 494463.9 cases, HR 1.07, 95% CI 0.88–1.30
  - 26–30: 15972 person-years, 226166.9 cases, HR 1.09, 95% CI 0.89–1.31
  - 31–35: 2314 person-years, 32745.2 cases, HR 1.39, 95% CI 1.01–1.92
  - \( \geq 36 \): 645 person-years, 9549.1 cases, HR 2.69, 95% CI 1.57–4.59

- **Number of births**
  - Nulliparous: 2821 person-years, 38720.0 cases, HR 0.73, 95% CI 0.52–1.03
  - One: 3640 person-years, 53675.8 cases, HR 0.53, 95% CI 0.39–0.81
  - Two: 20663 person-years, 319145.7 cases, HR 1.39, 95% CI 0.89–1.73
  - More than three: 22205 person-years, 319953.3 cases, HR 0.45, 95% CI 0.34–0.59

- **Use of female hormones**
  - Never: 41982 person-years, 653631.3 cases, HR 1.22, 95% CI 0.96–1.55
  - Ever: 4531 person-years, 78728.2 cases, HR 1.14, 95% CI 0.68–1.89

- **Breastfeeding history**
  - Never: 3735 person-years, 70074.8 cases, HR 0.78, 95% CI 0.61–1.00
  - Ever: 29375 person-years, 562441.3 cases, HR 0.78, 95% CI 0.61–1.00

**Postmenopausal women**

- **Age at menarche**
  - \( \leq 12 \): 5681 person-years, 68191.8 cases, HR 0.98, 95% CI 0.76–1.28
  - 13–14: 36535 person-years, 426582.0 cases, HR 0.97, 95% CI 0.76–1.26
  - 15–16: 47051 person-years, 536820.1 cases, HR 0.85, 95% CI 0.66–1.08
  - \( \geq 17 \): 25672 person-years, 296025.7 cases, HR 0.78, 95% CI 0.59–1.03

- **Age at first birth‡**
  - \( \leq 20 \): 8748 person-years, 105549.8 cases, HR 0.86, 95% CI 0.67–1.12
  - 21–25: 63813 person-years, 761635.6 cases, HR 1.47, 95% CI 1.29–1.67
  - 26–30: 29440 person-years, 332021.8 cases, HR 1.80, 95% CI 1.37–2.37
  - 31–35: 4355 person-years, 48847.8 cases, HR 1.92, 95% CI 1.18–3.12
  - \( \geq 36 \): 1167 person-years, 13557.9 cases, HR 1.92, 95% CI 1.18–3.12

- **Number of births**
  - Nulliparous: 6802 person-years, 71902.9 cases, HR 0.94, 95% CI 0.72–1.25
  - One: 7548 person-years, 90537.4 cases, HR 0.88, 95% CI 0.71–1.17
  - Two: 28574 person-years, 377216.9 cases, HR 0.63, 95% CI 0.48–0.84

- **More than three**
  - 60005 person-years, 626936.5 cases, HR 0.47, 95% CI 0.33–0.65

- **Age at menopause**
  - \( \leq 44 \): 15645 person-years, 192259.3 cases, HR 1.06, 95% CI 0.87–1.30

(Continues)
| Heterogeneity | Model 2§ | Heterogeneity |
|---------------|----------|---------------|
| \( I^2 (%) \) | \( p \) | \( p \) for trend | \( I^2 \) | \( p \) | \( p \) for trend |
| 0.0 | 0.45 | Reference | 1.10 | 0.90–1.35 | 0.0 | 0.53 |
| 0.0 | 0.61 | Reference | 1.00 | 0.79–1.27 | 0.0 | 0.59 |
| 41.0 | 0.12 | 1.00 | 0.96 | 0.57–1.60 | 32.3 | 0.18 | 0.76 |
| 0.0 | 0.81 | Reference | 0.81 | 0.57–1.15 | 0.0 | 0.90 |
| 14.9 | 0.31 | Reference | 1.07 | 0.88–1.30 | 21.2 | 0.25 |
| 0.0 | 0.66 | Reference | 1.24 | 0.89–1.73 | 0.0 | 0.67 |
| 19.4 | 0.29 | 0.12 | 2.30 | 1.39–3.79 | 0.0 | 0.46 | 0.15 |
| 0.0 | 0.79 | Reference | 0.50 | 0.22–1.13 | 26.1 | 0.23 |
| 0.0 | 0.74 | Reference | 0.39 | 0.19–0.81 | 21.4 | 0.27 |
| 0.0 | 0.83 | Reference | 0.28 | 0.15–0.53 | 0.0 | 0.65 | 0.30 |
| 8.3 | 0.36 | 0.10 | 1.20 | 0.94–1.52 | 5.6 | 0.38 | 0.14 |
| 0.0 | 0.47 | Reference | 0.94 | 0.71–1.24 | 0.0 | 0.75 | 0.65 |
| 0.0 | 0.79 | Reference | 0.99 | 0.77–1.28 | 0.0 | 0.79 |
| 0.0 | 0.51 | Reference | 0.88 | 0.68–1.14 | 2.0 | 0.42 |
| 0.0 | 0.90 | Reference | 0.82 | 0.62–1.08 | 0.0 | 0.92 | 0.17 |
| 0.0 | 0.76 | 0.47 | 0.88 | 0.68–1.14 | 0.0 | 0.76 |
| 0.0 | 0.56 | Reference | 1.38 | 1.21–1.58 | 0.0 | 0.76 |
| 6.6 | 0.38 | Reference | 1.52 | 1.16–2.00 | 0.0 | 0.45 |
| 0.0 | 0.66 | Reference | 1.48 | 0.89–2.44 | 0.0 | 0.55 | 0.30 |
| 0.0 | 0.79 | Reference | 1.14 | 0.68–1.89 | 0.0 | 0.90 |
| 23.3 | 0.25 | Reference | 0.81 | 0.49–1.33 | 0.0 | 0.77 |
| 47.4 | 0.08 | 0.17 | 0.63 | 0.39–1.04 | 0.0 | 0.56 | 0.03 |

(Continues)
A previous pooled analysis 38 reported significantly higher male hormones ≥10 years ago. Another study 41 reported that association was not reported among women who had used female hormones or used them in the past 10 years, while such an effect declined among postmenopausal women. These findings are consistent with those from studies in Western countries. 38- 41 Possible mechanisms for such an association have been proposed, including hormonal changes (reduced estrogen and progesterone levels and increased prolactin level), 6,44 delaying re-establishment of ovulation, 6,44 and excreting estrogens and carcinogens out of breast ducts. 44 A pooled analysis of epidemiological studies 7 revealed that breastfeeding significantly decreased breast cancer incidence. In contrast, other epidemiological studies including our study did not find such an association. 11-14 The lack of statistical significance in our study could be explained by sample size; among nine cohort studies which were included in our pooled analysis, the information on breastfeeding was not available for four studies. Therefore, we could not include these four cohort studies in the analysis of breastfeeding, which could have resulted in the small breast cancer cases. Furthermore, we observed a significant reduction in breast cancer risk among breastfed postmenopausal women in the analysis adjusted by age and area (model 1). Because the cohort of premenopausal women may have included women who lived in the relatively recent era compared with the cohort of postmenopausal women, we speculate that duration of breastfeeding has become shorter in the recent era in Japan. The study has four limitations: (1) we could not conduct pooled analyses according to hormone receptor or histology because this information was missing in some of the included cohort studies; (2) we could not evaluate the association between breast cancer risk and duration of female hormones’ use, type of female hormones including hormone replacement therapy (HRT), oral contraceptive (OC), or...
breastfeeding because most of included studies did not collect this information; (3) we could not calculate hazard ratio per 1-year increase in age at menarche/menopause/first birth because several studies which were included in this pooled analysis collected this information as categorical variables, not as continuous variables; (4) there might be other unmeasured confounding factors that affected our study results.

In conclusion, in Japan, use of female hormones significantly increased premenopausal breast cancer, and greater number of births significantly decreased breast cancer risk in postmenopausal women. However, breast cancer risk was similar according to age at menarche/breastfeeding history in both premenopausal and postmenopausal women. Although some of reproductive factors studies in the present study are not modifiable factors, understanding high-risk population would be important for preventing breast cancer including chemoprevention and early detection. Further studies would be needed to elucidate the impact of reproductive factors according to hormone receptors or histology.

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**CONFLICT OF INTEREST**

None declared.

**AUTHOR CONTRIBUTIONS**

All the authors 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) were involved in drafting the manuscript or revising it critically for important intellectual content; 3) gave final approval of the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content; and 4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**DATA AVAILABILITY STATEMENT**

The datasets used in the manuscript are not publicly available. A collaboration with each cohort study groups would be required to access the datasets.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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