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ORIGINAL ARTICLE

Reproductive history and breast cancer survival: a prospective patient cohort study in Japan

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Abstract

Background Reproductive factors may influence breast cancer progression and patient survival; however, evidence has been limited.

Methods The associations of reproductive factors with tumor characteristics and patient survival were analyzed among 1468 breast cancer patients diagnosed during 1997–2013 at a single institute in Japan. The patients were followed until 2016. During a median follow-up period of 8.6 years, 272 all-cause and 199 breast cancer deaths were documented.

Results In case–case comparisons, later age at menarche was inversely associated with advanced tumors. Nulliparous patients tended to have receptor-positive [estrogen receptor (ER)+ or progesterone receptor (PR)+] tumors. Conversely, the Cox proportional-hazards model including adjustment for tumor characteristics revealed U-shaped relationship between parity number and the risk of all-cause death among the patients overall [hazard ratio (HR) = 2.10 for nulliparous, 1.28 for 2, and 1.50 for ≥ 3 vs. one child]. According to hormone receptor, later age at menarche and later age at last birth were positively associated with the risk of all-cause death among patients with ER– and PR– cancer (menarche, HR = 2.18 for ≥ 15 vs. ≤ 12 years, $p_{trend} = 0.03$; last birth, HR = 3.10 for ≥ 35 vs. ≤ 29 years, $p_{trend} = 0.01$). A shorter time since last birth was associated with the risk of death among receptor-positive patients (HR = 5.72 for ≤ 4 vs. ≥ 10 years, $p_{trend} = 0.004$).

Conclusion The results indicate that the timing of menarche and parity have significant effects on patient survival, providing clues for understanding the association between women's life course and breast cancer outcome.

Keywords Breast cancer · Survival · Age at menarche · Parity · Reproductive factors · Hormone receptor

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Introduction

It is well known that reproductive factors are associated with breast cancer risk [1, 2]. Earlier menarche has a positive association with breast cancer risk, and nulliparous women tend to have a higher risk of breast cancer than parous women. On the other hand, these reproductive factors may also have an impact on survival after breast cancer diagnosis; however, previous studies have yielded conflicting results. Furthermore, most of those studies have been conducted in Western countries, and Asian data have been limited [3–5]. To our knowledge, only two studies have evaluated the associations of reproductive factors with breast cancer survival in Japanese population [3, 4].

With regard to age at menarche, some studies have reported an association between an early age at menarche and reduced survival of breast cancer patients [6, 7], whereas other studies have found no association [3, 8–11] or an adverse effect of later age at menarche [5, 12]. The associations of parity histories including parity number, age at first birth, and age at last birth with breast cancer survival have also been inconsistent in the previous studies [3, 5, 6, 8–15], although some more recent studies have indicated that a shorter time since last birth was significantly associated with reduced survival [4–6, 13, 16, 17]. These inconsistent results may have been due to differences in the distributions of characteristics such as tumor subtype among the studies, because prognostic factors may differ among subjects with these different characteristics. However, data based on tumor subtype, including hormone receptor status, have been insufficient [4, 5, 13, 17].

A number of issues may make it difficult to directly compare the results of different studies and to clarify the impact of reproductive factors on survival. First, as patients with breast cancer have been exposed to various reproductive factors in the recent or distant past, such factors may impact not only survival after diagnosis, but also tumor characteristics such as stage and hormone receptor status at the time of diagnosis. This would make it difficult to clarify the independent effect of each reproductive factor on patient survival [6, 7, 11]. Second, the endpoint of the studies has varied (e.g., all-cause death or breast cancer death), which may partly explain the inconsistent results.

Taking the above issues into account, we conducted a hospital-based patient cohort study to investigate the relationships between reproductive factors and the risk of all-cause and breast cancer-specific death in breast cancer patients. Data on reproductive history and clinical information in breast cancer patients were obtained from a questionnaire survey and a hospital-based cancer registry at a single institute in Japan, and a long-term follow-up survey was conducted.

Patients and methods

Study subjects

Between January 1997 and December 2013, 1570 first-admitted female patients aged 20 years or over without a history of cancer were diagnosed as having breast cancer at the Miyagi Cancer Center Hospital (MCCH). At the time of admission, these patients were requested to complete a self-administered questionnaire. After diagnosis, their details including clinical and pathological findings and information on initial treatments were entered into the hospital-based cancer registry and the patients were followed up. Among the patients, 1488 (94.8%) completed the questionnaire. After excluding 20 patients who had cancers other than breast cancer at the time of breast cancer diagnosis, the remaining 1468 patients were included in the present study.

Data collection and follow-up

Data for reproductive factors were collected in the above questionnaire survey. Clinical information including tumor stage based on the UICC TNM classification, and initial adjuvant treatment was obtained from the MCCH cancer registry. Information on estrogen/progesterone receptor (ER/PR) expression was extracted from medical records. Details of the questionnaire survey have already been described elsewhere [18–21]. The purpose of the survey was stated on the cover page of the questionnaire. We considered the return of self-administered questionnaires signed by the patients to imply their consent to participate.

Follow-up of patients was performed by reference to the MCCH cancer registry up to December 2016. The registry conducted active follow-up by accessing hospital visit records, resident registration cards, and permanent domicile data. For deceased patients, information on the date and cause of death was obtained with permission from the Ministry of Justice. As a general rule of this registry, each individual follow-up ends in the 11th year after diagnosis [21]. Therefore, information on vital status at 11 years was available for the patients diagnosed during 1997–2005. For the patients diagnosed after 2006, vital status as of December 2016 was obtained. During the follow-up period, 3 patients (0.2%) were lost to follow-up, and these were treated as censored cases.

This study was approved by the ethical review board of the Miyagi Cancer Center (Protocol Identification Number 23–7, May 20, 2011) and conducted in accordance with the principles specified in the Declaration of Helsinki.

Statistical analysis

In the present study, two types of analysis were performed as follows. To clarify the associations of reproductive factors with tumor characteristics at the time of diagnosis, unconditional logistic regression was performed (case–case comparisons). To evaluate the risk of mortality in relation to reproductive factors, Kaplan–Meier analysis and Cox proportional-hazards regression were conducted (patient cohort study).

In the case–case comparisons, the associations of major reproductive factors, i.e., age at menarche and parity number, with tumor characteristics such as stage and hormone receptor status were analyzed. The odds ratios (ORs) for regionally invasive (stage II and III) and advanced (stage IV) tumors compared with localized tumors (stage 0 and I) were computed, respectively, using polytomous unconditional logistic regression. Hormone receptor (HR) subtype was classified as ER+ or PR+ (luminal type, HR-positive) and ER– and PR– (HR-negative). The OR for HR-positive was computed with reference to HR-negative status.

In the patient cohort study, the end point was all-cause and breast cancer-specific death. Survival time was calculated for each patient from the date of diagnosis to the date of death or the end of follow-up. The crude associations of major exposure variables with survival were evaluated by Kaplan–Meier analysis. The Cox proportional-hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals controlled by confounders. The exposure variables were age at menarche, parity number, age at first birth, age at last birth, time since last birth, and history of breast-feeding. Time since last birth was calculated by subtracting age at last birth from age at diagnosis. We considered the following variables to be potential confounders: age at diagnosis, year of diagnosis, referral status (from screening, other), family history of breast cancer in parents or siblings, menopausal status, tumor stage (0–I, II, III, and IV), hormone receptor status (ER+ or PR+, ER– and PR–), adjuvant treatment (radiation therapy, chemotherapy, and endocrine therapy), comorbidities, occupation, and body mass index (BMI). Referral status may be related to the timing of breast cancer diagnosis; for example, women with a recent birth might have a delay in diagnosis because of some difficulties in visiting cancer-screening centers. Comorbidities, which included hypertension, ischemic heart disease, stroke, and diabetes mellitus, may have some adverse effects on prognosis. Cut-off points for exposures and confounders were determined arbitrarily, with reference to our previous study [18]. Time since last birth was classified into three categories (≤ 4 years, 5–9 years, and ≥ 10 years) based on the cut-off points used in some previous studies [5, 8, 9, 17]. Missing values for confounders were treated as an additional variable category and included in the statistical model. In the analysis, we first evaluated the risk of all-cause and breast cancer-specific death among the patients overall, and then performed stratification according to hormone receptor and menopausal status.

Results

During a median follow-up period of 8.6 years (11,560.7 person-years of follow-up), 272 all-cause and 199 breast cancer deaths were documented. Table 1 shows the characteristics of the study subjects according to age at menarche and parity number. The subjects with later age at menarche tended to be heavy and to have comorbidities. Nulliparous subjects tended to have a family history of breast cancer.

Reproductive factors and tumor characteristics

Table 2 shows the associations of age at menarche and parity number with tumor characteristics among the patients overall. Later age at menarche was inversely associated with advanced tumors (stage IV), although a trend test showed non-significance ($p_{trend} = 0.14$). There was a positive association between parity number including nulliparity and regionally invasive tumors ($p_{trend} = 0.05$). Nulliparous patients tended to have receptor-positive tumors (OR = 2.08 in comparison with patients with one child).

Reproductive factors and the risk of all-cause and breast cancer-specific death

Figure 1 shows the Kaplan–Meier overall and breast cancer-specific survival curves in relation to age at menarche and parity number among the patients overall. In general, patients with later age at menarche tended to have shorter survival. Regarding to parity number, shorter survival was observed for both nulliparous and multiparous (3 ≤) patients.

Table 3 shows the associations of menstrual and reproductive factors with mortality among the patients overall. In the table, HRs estimated from three different models are presented. First, in the model including adjustment for some reproductive factors (Model 1), a U-shaped relationship was found between parity number and the risk of all-cause and breast cancer-specific death. Nulliparous patients had a high risk of death. Analysis among parous patients revealed positive associations between higher parity, later age at last birth, and a risk of death. A shorter time since last birth was associated with an increased risk of all-cause death. Age at first birth and history of breast-feeding were not associated with the risk of all-cause and breast cancer-specific death. Second, additional adjustment for tumor characteristics was performed (Model 2), since case–case comparisons had indicated that some reproductive factors were associated with tumor characteristics, as mentioned above. In Model 2, the effects of later age at last birth became clear. The U shape for parity number also became clear. Patients with a later age at menarche showed a non-significant higher risk of breast cancer-specific death (HR = 1.35 for ≥ 15 years). The survival curves in Fig. 1 may support these mortality risks for age at menarche and parity number. Third, further adjustment for patient characteristics at the time of diagnosis and adjuvant treatment was performed. This multivariate analysis (Model 3) yielded results similar to those obtained from Model 2.

Table 4 shows the risk of death according to hormone receptor status (HR-positive, HR-negative). The HRs in the table were estimated using Models 1 and 3, respectively. The U-shaped relationship in relation to parity number was observed for both receptor subtypes. Among parous patients with HR-positive cancer, shorter time since last birth was significantly associated with an increased risk of all-cause death (HR = 5.72 for ≤ 4 vs. ≥ 10 years; $p_{trend} = 0.004$ in Model 3). Among patients with HR-negative cancer, the association of age at menarche with the risk of death was unclear in Model 1, whereas Model 3 including adjustment

Table 1 Characteristics of study subjects at baseline according to exposure variable

Factor	All subjects	Age at menarche					Parity history					
		≤ 12	13	14	≥ 15	Missing	Nulliparous	Parous (parity number)				Missing
								1	2	≥ 3	Missing	
Number of subjects	1468	469	320	299	315	65	156	168	643	384	62	55
Person-years	11,560.7	3609.9	2598.4	2366.9	2530.7	454.8	1122.3	1368.6	5125.0	3047.9	489.0	407.9
Number of deaths (*n*)	272	68	51	53	78	22	32	25	102	85	14	14
Cause of death (*n*)												
Vascular diseases	18	3	1	4	7	3	1	1	4	10	1	1
Pneumonia	6	1	0	1	1	3	0	0	1	3	0	2
Other cancers	23	5	2	4	10	2	4	4	9	5	0	1
Other	26	1	7	6	11	1	2	3	8	9	3	1
Breast cancer	199	58	41	38	49	13	25	17	80	58	10	9
Age (years)												
Mean	57.5	50.1	56.6	58.5	66.6	65.7	52.5	56.5	56.1	60.5	62.2	63.6
SD	12.5	10.6	10.9	10.8	10.9	13.7	13.6	12.5	11.3	12.6	13.5	13.5
Year of diagnosis (%)												
1997–2005	44.7	36.2	45.0	47.2	55.2	43.1	34.0	44.1	44.2	49.5	51.6	43.6
2006–2013	55.3	63.8	55.0	52.8	44.8	56.9	66.0	55.9	55.8	50.5	48.4	56.4
Stage (%)												
0–I	50.5	50.3	49.7	51.5	52.7	40.0	55.1	48.8	51.9	47.1	51.6	47.3
II	30.8	30.3	33.4	29.4	30.2	30.8	25.6	29.8	30.2	34.1	33.9	29.1
III	11.0	10.7	10.3	11.7	10.5	16.9	8.3	14.9	9.9	12.0	8.1	16.4
IV	6.5	8.1	5.9	5.7	5.4	6.1	9.0	5.9	6.7	6.0	6.4	1.8
Missing	1.2	0.6	0.6	1.7	1.3	6.1	1.9	0.6	1.2	0.8	0.0	5.5
Hormone receptor status (%)												
Positive (ER + or PR +)	68.9	70.4	68.1	70.2	67.3	63.1	77.6	67.9	68.3	66.4	69.4	70.9
Negative (ER– and PR–)	24.0	23.2	25.0	24.1	24.4	21.5	14.7	26.8	24.7	26.0	24.2	18.2
Missing	7.1	6.4	6.9	5.7	8.3	15.4	7.7	5.4	7.0	7.6	6.4	10.9
Referral status (%)												
From screening	18.5	20.5	19.4	16.4	18.1	10.8	18.0	18.4	20.1	18.2	12.9	9.1
Other	81.5	79.5	80.6	83.6	81.9	89.2	82.0	81.6	79.9	81.8	87.1	90.9
Menopausal status (%)												
Pre	37.4	62.3	38.1	29.1	13.0	10.8	50.6	43.4	40.6	28.9	30.6	10.9
Post	57.8	33.7	58.4	64.6	82.9	75.4	43.6	51.8	55.4	66.9	61.3	76.4
Missing	4.8	4.0	3.4	6.3	4.1	13.8	5.8	4.8	4.0	4.2	8.1	12.7

Table 1 (continued)

Factor	All subjects	Age at menarche					Parity history					
		≤ 12	13	14	≥ 15	Missing	Nulliparous	Parous (parity number)				Missing
								1	2	≥ 3	Missing	
Radiation therapy (%)												
No	59.9	54.6	55.6	60.2	70.8	64.6	59.0	60.1	56.9	65.1	61.3	58.2
Yes	40.1	45.4	44.4	39.8	29.2	35.4	41.0	39.9	43.1	34.9	38.7	41.8
Chemotherapy (%)												
No	69.1	64.0	65.0	71.6	77.1	75.4	78.9	65.5	65.6	70.1	79.0	74.5
Yes	30.9	36.0	35.0	28.4	22.9	24.6	21.1	34.5	34.4	29.9	21.0	25.5
Endocrine therapy (%)												
No	56.1	56.1	55.0	55.5	59.4	49.2	49.4	57.1	56.4	58.8	51.6	54.5
Yes	43.9	43.9	45.0	44.5	40.6	50.8	50.6	42.9	43.6	41.2	48.4	45.5
Occupation (%)												
Housewife	19.8	15.1	17.8	20.7	27.6	21.5	8.3	22.0	21.6	21.9	12.9	18.2
Other	67.5	76.8	73.1	67.2	51.1	53.9	80.1	66.7	68.6	62.5	71.0	52.7
Missing	12.7	8.1	9.1	12.0	21.3	24.6	11.5	11.3	9.8	15.6	16.1	29.1
Family history of breast cancer in parents or siblings (%)												
No	90.1	88.3	90.0	91.3	90.8	95.4	84.6	89.9	90.7	90.9	88.7	96.4
Yes	9.9	11.7	10.0	8.7	9.2	4.6	15.4	10.1	9.3	9.1	11.3	3.6
BMI (kg/m^2) (%)												
< 21.1	24.7	26.4	27.8	23.1	22.2	15.4	44.2	31.5	22.9	17.5	22.6	21.8
21.1– < 23.3	24.0	25.0	27.8	25.7	17.1	23.1	17.3	22.6	26.0	26.3	17.7	14.6
23.3– < 26.0	25.2	24.3	22.8	24.1	29.8	26.1	17.3	25.0	25.5	25.8	38.7	25.4
26.0–	24.8	23.9	20.6	26.1	29.2	24.6	20.5	20.2	24.6	29.4	19.4	27.3
Missing	1.4	0.4	0.9	1.0	1.6	10.8	0.6	0.6	1.1	1.0	1.6	10.9
Comorbidities (%)[a]												
No	75.9	83.6	80.6	71.6	63.2	78.5	89.7	75.0	76.8	71.1	62.9	76.4
Yes	24.1	16.4	19.4	28.4	36.8	21.5	10.3	25.0	23.2	28.9	37.1	23.6

ER estrogen receptor, *PR* progesterone receptor, *BMI* body mass index

[a]Comorbidities include hypertension/ischemic heart disease/stroke/diabetes mellitus

Table 2 Associations of age at menarche and parity history with breast tumor characteristics

	Stage							Hormone receptor status			
	Stage 0–I, n	Stage II–III			Stage IV			ER− and PR−, *n*	ER+ or PR+		
		n	OR	95% CI	*n*	OR	95% CI		*n*	OR	95% CI
Age at menarche (years)[a]											
≤ 12	236	192	1	Reference	38	1	Reference	109	330	1	Reference
13	159	140	1.05	0.77–1.44	19	0.68	0.36–1.27	80	218	1.02	0.72–1.45
14	154	123	0.93	0.67–1.29	17	0.55	0.29–1.07	72	210	1.14	0.79–1.65
≥ 15	166	128	0.94	0.66–1.35	17	0.66	0.32–1.35	77	212	1.12	0.75–1.68
p for trend				0.60			0.14				0.47
Parity number[b]											
Nulliparous	86	53	0.64	0.40–1.03	14	1.07	0.43–2.64	23	121	2.08	1.17–3.69
1	82	75	1	Reference	10	1	Reference	45	114	1	Reference
2	334	258	0.82	0.57–1.19	43	0.93	0.44–1.99	159	439	1.11	0.75–1.65
3 ≤	181	177	1.06	0.72–1.56	23	1.01	0.44–2.27	100	255	1.06	0.69–1.62
p for trend				0.05			0.85				0.05
p for trend among parous women only				0.41			0.86				

OR odds ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor

[a]Adjusted by age, year of diagnosis, referral status (from screening and other), family history of breast cancer in parents or siblings (no and yes), parity history (parous, nulliparous, and missing), and menopausal status (pre, post, and missing)

[b]Adjusted by age, year of diagnosis, referral status (from screening and other), family history of breast cancer in parents or siblings (no and yes), age at menarche (≤ 12, 13, 14, ≥ 15, and missing), and menopausal status (pre, post, and missing)

for tumor stage showed that later age at menarche was significantly associated with an increased risk of all-cause (HR = 2.18 for ≥ 15 vs. ≤ 12 years; $p_{trend} = 0.03$ in Model 3) and breast cancer-specific death (HR = 2.06; $p_{trend} = 0.04$). In the analysis limited to parous patients with HR-negative cancer, Model 3 showed that higher parity and later age at last birth were associated with an increased risk of all-cause and breast cancer-specific death.

Table 5 shows the HRs according to both hormone receptor and menopausal status based on Model 3. Among premenopausal patients with HR-negative cancer, later age at menarche and later age at last birth were significantly associated with the risk of all-cause and breast cancer-specific death. Analysis of premenopausal parous patients with HR-positive cancer showed a non-significant higher risk of breast cancer-specific death associated with a history of recent birth (HR = 6.01 for ≤ 4 vs. ≥ 10 years). Among postmenopausal patients, the U-shaped relationship with parity number was observed for both hormone receptor subtypes.

Discussion

The present study has clarified the roles of reproductive factors in tumor progression and survival among patients with breast cancer. Our case–case comparisons revealed associations between reproductive factors and both stage and hormone receptor status at the time of diagnosis. The patient prospective study showed that some reproductive factors were associated with the risk of all-cause and breast cancer-specific death after diagnosis.

With regard to the associations between reproductive factors and tumor characteristics, the present analysis found that patients with earlier menarche tended to have advanced tumors and that parous patients tended to have regionally invasive tumors. Nulliparous patients tended to have receptor-positive tumors. These findings suggest that reproductive history may have some effects on tumor progression and the expression of hormone receptors. Some previous studies have investigated the associations between reproductive factors including age at menarche and parity number, and tumor characteristics [7, 13, 22, 23]. For example, a study from Sweden showed that nulliparity was associated with the risk of relatively more aggressive breast cancer [22]. Another study from Sweden revealed that earlier menarche was significantly associated with a higher tumor grade and lymph node involvement [7].

In our analysis of associations between reproductive factors and patient survival, some significant results emerged. First, although the effect of age at menarche was non-significant in the model without adjustment for tumor characteristics (Model 1), the models including adjustment for this

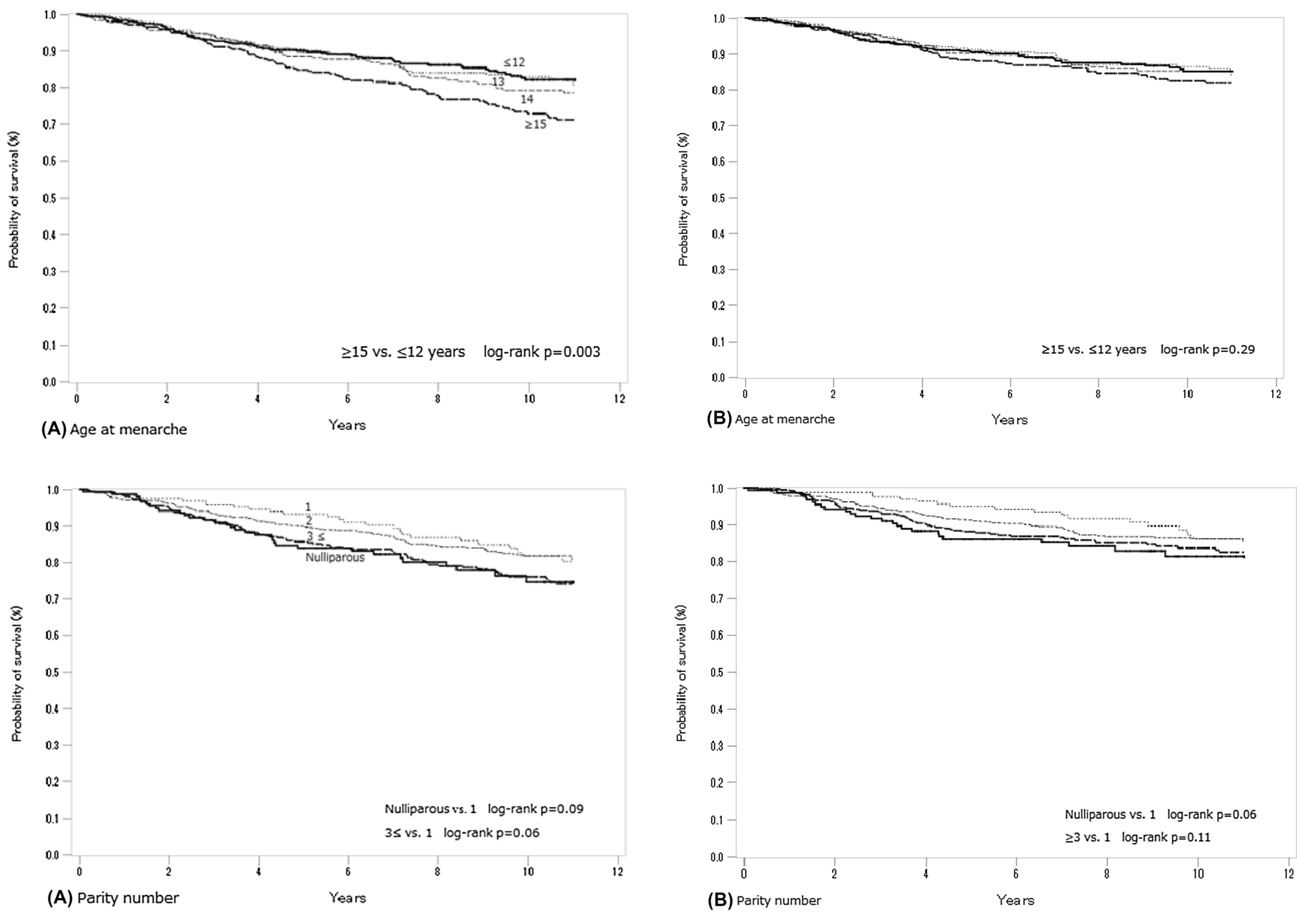

Fig. 1 Probability of survival according to age at menarche and parity number. **a** Overall survival; **b** breast cancer-specific survival

factor (Models 2 and 3) showed that later menarche might be associated with an increased risk of breast cancer-specific death. This was mainly evident among patients with HR-negative cancer. In this context, the previous studies have addressed whether or not adjustment for tumor characteristics is appropriate [6, 7, 9, 11, 16, 17, 24]. Some researchers have considered that tumor characteristics might be an intermediate step in the causal path from timing of menarche to prognosis and that adjustment for these characteristics might be incorrect [6, 7, 11]. However, the present study found that adjustment for tumor characteristics strengthened the adverse effect of later menarche, despite the fact that later menarche was unlikely to shift tumors toward advanced characteristics, as shown in Table 2. Furthermore, sensitivity analysis including patients with stage 0–III cancer also demonstrated an adverse effect of later menarche (data not shown). Therefore, it is likely that the risk associated with age at menarche can be appropriately predicted by analysis that includes adjustment for tumor characteristics. After diagnosis, age at menarche may act by not only altering tumor characteristics in the intermediate step, but also through host factors. We considered that the following host factors might explain the adverse effect of later menarche, especially among patients with HR-negative cancer. First, from a biological viewpoint, age at menarche has been regarded as a surrogate of growth pattern at puberty [25, 26]. Although hypothetical, specific growth patterns may influence mortality risk in later life. For example, detailed analysis of our data revealed that mean height, an indicator of child growth, among deceased HR-negative subjects who were older at menarche was greater than that among living subjects, although the mechanism explaining the association between height and prognosis must be clarified in subsequent studies. Second, the timing of menarche is related to individual's socioeconomic status (SES), which may be responsible for the risk of death. Although the roles of SES in puberty onset have been controversial [26–29], some studies reported that girls born in low-income families had a late menarche [26, 27]. Socioeconomic factors determining the timing of menarche, which may affect lifestyles and general health status in later life, may have some effects on prognosis. Thus, we have listed some hypothetical mechanisms; however, the relationships between age at menarche, tumor characteristics, and survival are possibly complicated.

Table 3 Hazard ratio of all-cause and breast cancer-specific death among patients overall

	Number of subjects	Person-years	All-cause death							Breast cancer-specific death						
			Number of deaths	Model 1		Model 2[e]		Model 3[f]		Number of deaths	Model 1		Model 2[e]		Model 3[f]	
				HR	95 CI	HR	95 CI	HR	95 CI		HR	95 CI	HR	95 CI	HR	95 CI
Age at menarche (years)																
≤12	469	3609.9	68	1	Reference[a]	1	Reference	1	Reference	58	1	Reference[a]	1	Reference	1	Reference
13	320	2598.4	51	0.88	0.61–1.28	0.98	0.68–1.43	0.96	0.66–1.39	41	0.94	0.62–1.42	1.05	0.70–1.58	1.03	0.68 –1.56
14	299	2366.9	53	0.89	0.61–1.30	1.07	0.73–1.56	1.03	0.70–1.51	38	0.85	0.55–1.31	1.08	0.70–1.66	1.04	0.67 –1.61
≥ 15	315	2530.7	78	1.01	0.69–1.47	1.17	0.79–1.71	1.11	0.76–1.64	49	1.08	0.69–1.68	1.35	0.86–2.12	1.25	0.79 –1.96
p for trend					0.94		0.39		0.55			0.91		0.23		0.39
Parity number																
Nulliparous	156	1122.3	32	1.76	1.04 –2.98	2.15	1.25 –3.69	2.10	1.21 –3.65	25	1.88	1.01 –3.49	2.43	1.28 –4.59	2.33	1.22 –4.47
1	168	1368.6	25	1	Reference[b]	1	Reference	1	Reference	17	1	Reference[b]	1	Reference	1	Reference
2	643	5125.0	102	1.12	0.72 –1.74	1.22	0.78 –1.91	1.28	0.81 –2.01	80	1.23	0.73 –2.08	1.31	0.77 –2.23	1.35	0.79 –2.32
3 ≤	384	3047.9	85	1.34	0.85 –2.10	1.37	0.86 –2.16	1.50	0.94 –2.40	58	1.50	0.87 –2.58	1.57	0.90 –2.75	1.72	0.97 –3.04
p for trend					0.64		0.30		0.69			0.86		0.47		0.85
p for trend among parous women only					0.14		0.17		0.08			0.09		0.09		0.04
Age at first birth (only parous women)																
≤ 24	494	4000.4	102	1	Reference[c]	1	Reference	1	Reference	75	1	Reference[c]	1	Reference	1	Reference
25–29	555	4504.1	82	0.79	0.58–1.06	0.77	0.57–1.03	0.74	0.54 –1.00	61	0.78	0.55–1.10	0.76	0.53–1.07	0.72	0.50 –1.02
≥ 30	157	1191.8	28	1.13	0.72–1.78	1.26	0.78–2.03	1.24	0.77 –1.99	19	1.04	0.61–1.78	1.21	0.68–2.15	1.20	0.68 –2.13
p for trend					0.70		0.78		0.68			0.55		0.67		0.58
Age at last birth (only parous women)																
≤ 29	536	4451.6	83	1	Reference[c]	1	Reference	1	Reference	68	1	Reference[c]	1	Reference	1	Reference
30–34	439	3435.1	78	1.22	0.89–1.68	1.48	1.07–2.04	1.53	1.10 –2.12	54	1.09	0.75–1.58	1.34	0.92–1.95	1.39	0.95 –2.05
≥ 35	127	975.2	30	1.67	1.08–2.57	2.34	1.50–3.65	2.28	1.44 –3.60	23	1.67	1.02–2.72	2.51	1.52–4.14	2.35	1.39 –3.96
p for trend					0.02		0.0001		0.0002			0.07		0.001		0.002
Time since last birth (years) (only parous women)																
≥ 10	1020	8256.9	172	1	Reference[d]	1	Reference	1	Reference	128	1	Reference[d]	1	Reference	1	Reference
5–9	56	418.4	13	2.87	1.46–5.64	2.68	1.34–5.36	2.64	1.29 –5.40	11	2.01	0.96–4.19	1.86	0.87–3.96	1.71	0.77 –3.80
≤ 4	26	186.6	6	3.57	1.41–9.04	2.81	1.09–7.26	3.40	1.29 –8.94	6	2.35	0.90–6.13	1.65	0.62–4.40	1.90	0.69 –5.20
p for trend					0.0005		0.004		0.002			0.03		0.17		0.13
Breast-feeding (only parous women)																
No	238	1903.6	37	1	Reference[c]	1	Reference	1	Reference	32	1	Reference[c]	1	Reference	1	Reference
Yes	995	7946.7	183	1.04	0.73–1.50	0.99	0.68–1.43	0.98	0.68 –1.42	129	0.89	0.60–1.32	0.78	0.52–1.17	0.77	0.51 –1.16

Table 3 (continued)

HR hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor

[a]Adjusted by age, year of diagnosis, family history of breast cancer in parents or siblings (no and yes), parity history (parous, nulliparous, and missing), and menopausal status (pre, post, and missing)

[b]Adjusted by age, year of diagnosis, family history of breast cancer in parents or siblings (no and yes), age at menarche (≤12, 13, 14, ≥15, and missing), and menopausal status (pre, post, and missing)

[c]Adjusted by age, year of diagnosis, family history of breast cancer in parents or siblings (no and yes), age at menarche (≤12, 13, 14, ≥15, and missing), parity number (1, 2, ≥3, and missing), and menopausal status (pre, post, and missing)

[d]Adjusted by age, year of diagnosis, family history of breast cancer in parents or siblings (no and yes), age at menarche (≤12, 13, 14, ≥15, and missing), age at first birth (≤24, 25–29, ≥30, and missing), parity number (1, 2, ≥3, and missing), and menopausal status (pre, post, and missing)

[e]Additionally adjusted by stage (0–I, II, III, IV, and missing), hormone receptor (ER+or PR+, ER− and PR−, and missing), and referral status (from screening and other)

[f]Further adjusted by comorbidities (no and yes), radiation therapy (no and yes), chemotherapy (no and yes), endocrine therapy (no and yes), occupation (housewife, other, and missing), and BMI (<21.1, 21.1–<23.3, 23.3-<26.0, ≥26.0, and missing)

Furthermore, the association of age at menarche with breast cancer survival has been inconsistent among previous studies [3, 5–11]. To elucidate the role of age at menarche in tumor progression and survival, further studies focusing on the long-term biologic effects of reproductive factor will be needed.

Regarding the associations of parity number with breast cancer survival, the previous studies yielded inconsistent results [3, 5, 6, 8–15, 17, 30, 31]. Several studies demonstrated the poorer survival in patients with high parity [3, 5, 6, 12–14, 17], whereas the mortality risk among nulliparous patients has been unclear [30, 31]. In the present study, a higher risk of death was found for nulliparous patients. The relationship between parity number and all-cause and breast cancer-specific death was U-shaped. Furthermore, the U-shaped relationship, which was strengthened by analysis that included adjustment for tumor characteristics (Models 2 and 3), was clearer among postmenopausal patients. Previously, Butt et al. demonstrated such a U-shaped relationship, although the U shape in their report was evident among younger patients [14]. We considered the mechanisms explaining the effect of parity number as follows. First, some previous reports have indicated an inverse association between parity number and estrogen level among postmenopausal women [32, 33]. Therefore, some hormonal factors may affect mortality risk in relation to parity number, although the associations between sex hormone levels and breast cancer prognosis have been poorly understood [34]. Second, psychological stress, lifestyle, and compliance with cancer treatment in relation to high parity and nulliparity may have unfavorable effects on health and survival among postmenopausal patients [5, 35, 36].

Our analysis of parous patients found that a shorter time since last birth and a later age at last birth were associated with an increased risk of all-cause and breast cancer-specific death. Stratification by both hormone receptor and menopausal status revealed that a shorter time since last birth tended to be associated with an increased risk of all-cause and breast cancer-specific death among premenopausal HR-positive patients and that age at last birth appeared to have a significant effect among premenopausal HR-negative patients. With regard to the effect of recent birth, the previous studies have reported an association between a shorter time since last birth and an increased risk of mortality [4, 5, 9, 10, 13, 15–17, 37]. Furthermore, some studies including one conducted in Japan have demonstrated a positive effect of a shorter time since last birth among patients with receptor-positive tumors [4, 5, 17]. From the viewpoint of breast cancer risk, it is possible that exposure to sex hormones in pregnancy may be responsible for an increased risk in the few years after childbirth [38, 39]. If breast cancer clones have already been generated before pregnancy, then gestational sex hormones might stimulate any hormone

Table 4 Hazard ratio of all-cause and breast cancer-specific death by hormone receptor status

	Number of subjects	Person-years	All-cause death					Breast cancer-specific death				
			Number of deaths	Model 1		Model 3[e]		Number of deaths	Model 1		Model 3[e]	
				HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Positive (ER+ or PR+)												
Age at menarche (years)												
≤ 12	330	2571.4	35	1	Reference[a]	1	Reference	27	1	Reference[a]	1	Reference
13	218	1843.9	24	0.76	0.45–1.30	0.89	0.52–1.54	18	0.88	0.47–1.62	1.08	0.57 –2.06
14	210	1675.8	27	0.85	0.50–1.43	0.94	0.54–1.64	15	0.68	0.35–1.31	0.67	0.33 –1.36
≥ 15	212	1786.0	41	0.86	0.51–1.45	0.95	0.55–1.66	23	1.01	0.53–1.95	1.11	0.54 –2.26
p for trend					0.68		0.92			0.79		0.84
Parity number												
Nulliparous	121	905.5	19	2.03	0.96–4.31	2.07	0.94 –4.55	14	1.88	0.78–4.51	1.73	0.66 –4.56
1	114	942.5	11	1	Reference[b]	1	Reference	8	1	Reference[b]	1	Reference
2	439	3588.8	47	1.13	0.59–2.19	1.20	0.60 –2.38	31	1.00	0.46–2.18	1.02	0.44 –2.41
3 ≤	255	2082.4	45	1.50	0.77–2.94	1.64	0.83 –3.26	26	1.45	0.65–3.26	1.44	0.61 –3.38
p for trend					0.63		0.94			0.62		0.86
p for trend among parous women only					0.13		0.10			0.15		0.26
Age at first birth (only parous women)												
≤ 24	319	2682.8	52	1	Reference[c]	1	Reference	30	1	Reference[c]	1	Reference
25–29	390	3205.8	40	0.76	0.50–1.16	0.72	0.47 –1.10	29	0.90	0.53–1.51	0.79	0.45 –1.38
≥ 30	112	863.3	14	1.15	0.61–2.18	1.22	0.63 –2.36	9	1.20	0.54–2.68	1.38	0.59 –3.23
p for trend					0.76		0.71			0.90		0.91
Age at last birth (only parous women)												
≤ 29	355	3010.6	44	1	Reference[c]	1	Reference	31	1	Reference[c]	1	Reference
30–34	302	2419.1	36	0.92	0.58–1.47	1.17	0.71 –1.93	21	0.84	0.47–1.51	1.23	0.63 –2.38
≥ 35	95	764.4	15	1.19	0.65–2.18	1.28	0.67 –2.45	10	1.23	0.59–2.57	1.33	0.59 –3.02
p for trend					0.74		0.41			0.82		0.45
Time since last birth (years) (only parous women)												
≥ 10	699	5790.0	86	1	Reference[d]	1	Reference	55	1	Reference[d]	1	Reference
5–9	34	271.5	5	2.94	1.04–8.29	2.44	0.83 –7.20	3	1.44	0.39–5.25	1.37	0.35–5.31
≤ 4	19	132.7	4	5.98	1.82–19.60	5.72	1.64 –19.90	4	3.70	1.06–12.95	3.23	0.80–13.05
p for trend					0.0012		0.004			0.05		0.12
Breast-feeding (only parous women)												
No	167	1368.2	18	1	Reference[c]	1	Reference	14	1	Reference[c]	1	Reference
Yes	672	5500.0	91	1.04	0.62–1.77	1.08	0.63 –1.86	55	0.87	0.47–1.59	0.91	0.47 –1.74
Negative (ER– and PR–)												
Age at menarche (years)												
≤ 12	109	828.1	21	1	Reference[a]	1	Reference	20	1	Reference[a]	1	Reference
13	80	606.0	18	1.15	0.60–2.22	1.40	0.71–2.73	15	1.09	0.54–2.18	1.33	0.65 –2.75
14	72	550.5	21	1.43	0.74–2.78	1.64	0.83–3.23	20	1.63	0.82–3.23	1.85	0.91 –3.77
≥ 15	77	562.9	24	1.34	0.68–2.62	2.18	1.08–4.41	17	1.30	0.61–2.76	2.06	0.93 –4.55
p for trend					0.34		0.03			0.31		0.04
Parity number												
Nulliparous	23	139.9	8	2.45	0.94–6.38	2.76	1.01 –7.59	7	2.96	1.04–8.46	3.76	1.24 –11.36
1	45	352.0	11	1	Reference[b]	1	Reference	8	1	Reference[b]	1	Reference
2	159	1233.0	37	1.04	0.53–2.06	1.42	0.69 –2.92	35	1.29	0.59–2.80	1.68	0.74 –3.81
3 ≤	100	738.4	28	1.17	0.58–2.36	2.02	0.95 –4.33	22	1.28	0.57–2.89	2.20	0.92 –5.28
p for trend					0.41		0.50			0.42		0.69

Table 4 (continued)

	Number of subjects	Person-years	All-cause death					Breast cancer-specific death				
			Number of deaths	Model 1		Model 3[e]		Number of deaths	Model 1		Model 3[e]	
				HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
p for trend among parous women only					0.60		0.05			0.56		0.05
Age at first birth (only parous women)												
≤ 24	138	1048.5	38	1	Reference[c]	1	Reference	35	1	Reference[c]	1	Reference
25–29	128	1007.7	27	0.78	0.46 –1.30	0.71	0.40 –1.26	22	0.67	0.38 –1.16	0.51	0.27 –0.95
≥ 30	39	292.5	10	1.14	0.52 –2.48	1.23	0.52 –2.91	7	0.86	0.35 –2.09	0.80	0.29 –2.19
p for trend					0.83		0.86			0.33		0.17
Age at last birth (only parous women)												
≤ 29	146	1164.1	31	1	Reference[c]	1	Reference	30	1	Reference[c]	1	Reference
30–34	105	796.3	25	1.20	0.69 –2.09	1.45	0.79 –2.66	21	1.03	0.57 –1.83	1.18	0.63 –2.21
≥ 35	25	163.0	11	2.74	1.28 –5.87	3.10	1.31 –7.31	9	2.50	1.10 –5.68	2.77	1.11 –6.90
p for trend					0.03		0.01			0.11		0.06
Time since last birth (years) (only parous women)												
≥ 10	250	1934.6	59	1	Reference[d]	1	Reference	52	1	Reference[d]	1	Reference
5–9	20	137.4	7	2.73	0.98–7.62	3.99	1.25–12.70	7	2.53	0.87–7.30	3.69	1.13–12.08
≤ 4	6	51.3	1	1.26	0.15–10.56	1.66	0.18–15.68	1	0.86	0.10–7.35	0.96	0.10–9.24
p for trend					0.21		0.12			0.45		0.34
Breast-feeding (only parous women)												
No	57	433.9	13	1	Reference[c]	1	Reference	12	1	Reference[c]	1	Reference
Yes	252	1942.1	63	1.05	0.56–1.94	1.08	0.55 –2.12	53	1.01	0.53–1.92	0.99	0.48 –2.03

HR hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor

[a]Adjusted by age, year of diagnosis, family history of breast cancer in parents or siblings (no and yes), parity history (parous, nulliparous, and missing), and menopausal status (pre, post, and missing)

[b]Adjusted by age, year of diagnosis, family history of breast cancer in parents or siblings (no and yes), age at menarche (≤ 12, 13, 14, ≥ 15, and missing), and menopausal status (pre, post, and missing)

[c]Adjusted by age, year of diagnosis, family history of breast cancer in parents or siblings (no and yes), age at menarche (≤ 12, 13, 14, ≥ 15, and missing), parity number (1, 2, ≥ 3, and missing), and menopausal status (pre, post, and missing)

[d]Adjusted by age, year of diagnosis, family history of breast cancer in parents or siblings (no and yes), age at menarche (≤ 12, 13, 14, ≥ 15, missing), age at first birth (≤ 24, 25–29, ≥ 30, and missing), parity number (1, 2, ≥ 3, and missing), and menopausal status (pre, post, and missing)

[e]Additionally adjusted by stage (0–I, II, III, and IV), referral status (from screening and other), comorbidities (no and yes), radiation therapy (no and yes), chemotherapy (no and yes), endocrine therapy (no and yes), occupation (housewife, other, and missing), and BMI (< 21.1, 21.1– < 23.3, 23.3– < 26.0, ≥ 26.0, and missing)

receptor-positive clones [16]. Thus, receptor-positive breast cancers diagnosed shortly after child birth may have malignant potential, resulting in a higher risk of breast cancer-specific death.

Age at last birth may be related to time since last birth among premenopausal women. However, in the present study, a significant effect of age at last birth was observed among HR-negative patients. Daling et al. reported an association of later age at last birth with poorer survival [13]; however, the risk in relation to hormone receptor status was unknown. Women whose final parity occurred at an older age may have been exposed to greater physical and psychological stress when caring for their children, and such stress may have a worse effect on prognosis, especially the risk of all-cause death among premenopausal patients with HR-negative cancer. Otherwise, the hormonal environment in women who give birth at an older age may impact survival. There are experimental studies suggesting that estrogen may promote the growth of receptor-negative cancer [40]. Although hypothetically, exposure to gestational sex hormones at an older age may have adverse effects on prognosis of HR-negative cancer.

Based on the present results, we have discussed the roles of reproductive factors in tumor progression and survival. Although reproductive factors affect tumor characteristics such as stage and hormone receptor status, they may have independent effects on survival after breast cancer diagnosis. Our findings may provide clues for better understanding the association between women's life course and the outcome of breast cancer.

Table 5 Hazard ratio of all-cause and breast cancer-specific death by hormone receptor and menopausal status

	Premenopause							Postmenopause						
	Number of subjects	All-cause death			Breast cancer -specific death			Number of subjects	All-cause death			Breast cancer -specific death		
		Number of death	HR	95% CI	Number of death	HR	95% CI		Number of deaths	HR	95% CI	Number of deaths	HR	95% CI
Positive (ER + or PR +)														
Age at menarche (years)[a]														
≤ 12	211	19	1	Reference	14	1	Reference	110	13	1	Reference	10	1	Reference
13	90	5	0.63	0.22–1.83	5	1.05	0.34–3.28	125	18	1.29	0.59–2.78	12	1.23	0.47–3.21
14	66	5	0.79	0.28–2.27	5	1.13	0.38–3.42	129	19	1.34	0.61–2.97	8	0.65	0.21–1.97
≥ 15	26	4	1.58	0.48–5.26	4	2.13	0.59–7.76	179	35	1.01	0.48–2.12	17	1.03	0.38–2.79
p for trend				0.83			0.36				0.80			0.81
Parity number[b]														
Nulliparous	60	2	0.21	0.04–1.16	2	0.18	0.03–1.06	55	14	4.30	1.31–14.08	10	12.11	1.26–116.28
1	57	7	1	Reference	7	1	Reference	51	4	1	Reference	1	1	Reference
2	184	13	0.47	0.16–1.38	9	0.28	0.08–0.97	240	30	2.33	0.77–7.02	18	6.24	0.67–57.76
3 ≤	79	8	0.58	0.18–1.93	7	0.42	0.11–1.64	172	36	3.00	1.02–8.82	18	9.64	1.07–86.97
p for trend				0.55			0.76				0.95			0.83
p for trend among parous women only				0.58			0.39				0.05			0.04
Age at first birth (only parous women)[c]														
≤ 24	113	13	1	Reference	12	1	Reference	194	39	1	Reference	18	1	Reference
25–29	154	13	0.76	0.33–1.78	11	0.70	0.26–1.87	227	25	0.65	0.38–1.10	16	1.03	0.47–2.26
≥ 30	61	5	1.16	0.35–3.83	3	0.88	0.19–3.99	46	6	0.95	0.35–2.59	3	3.21	0.75–13.67
p for trend				0.96			0.65				0.28			0.37
Age at last birth (only parous women)[c]														
≤29	141	13	1	Reference	12	1	Reference	200	29	1	Reference	17	1	Reference
30–34	121	11	1.61	0.61–4.26	7	1.02	0.33–3.15	178	24	1.00	0.53–1.90	13	1.27	0.50–3.22
≥ 35	40	2	0.93	0.18–4.89	2	0.91	0.14–5.91	51	11	1.19	0.51–2.77	6	1.45	0.35–6.02
p for trend				0.68			0.96				0.73			0.55
Time since last birth (years) (only parous women)[d]														
≥ 10	249	17	1	Reference	14	1	Reference	429	64	1	Reference	36	1	Reference
5–9	34	5	1.03	0.22–4.90	3	1.12	0.17–7.41	0	0	–	–	0	–	–
≤ 4	19	4	2.28	0.28–18.49	4	6.01	0.58–62.54	0	0	–	–	0	–	–
p for trend				0.48			0.18				–			–
Breast-feeding (only parous women)[c]														
No	69	6	1	Reference	6	1	Reference	93	10	1	Reference	6	1	Reference
Yes	260	25	1.41	0.49–4.07	20	0.96	0.30–3.08	390	63	1.19	0.57–2.47	32	1.38	0.51–3.70

Table 5 (continued)

	Premenopause							Postmenopause						
	Number of subjects	All-cause death			Breast cancer -specific death			Number of subjects	All-cause death			Breast cancer -specific death		
		Number of death	HR	95% CI	Number of death	HR	95% CI		Number of deaths	HR	95% CI	Number of deaths	HR	95% CI
Negative (ER– and PR–)														
Age at menarche (years)[a]														
≤12	66	12	1	Reference	11	1	Reference	35	8	1	Reference	8	1	Reference
13	25	5	1.41	0.39–5.14	5	2.13	0.55–8.24	50	11	1.05	0.39–2.85	8	0.71	0.24–2.11
14	16	5	4.02	0.97–16.66	5	5.23	1.11–24.69	53	15	1.25	0.48–3.27	14	1.18	0.44–3.17
≥ 15	14	6	4.73	1.14–19.59	4	4.85	0.96–24.46	57	16	1.66	0.61–4.46	11	1.45	0.49–4.26
p for trend				0.01			0.02				0.27			0.32
Parity number[b]														
Nulliparous	13	5	2.20	0.40–12.27	4	2.39	0.31–18.19	7	2	1.28	0.15–10.68	2	2.98	0.31–28.47
1	14	5	1	Reference	4	1	Reference	29	5	1	Reference	3	1	Reference
2	64	12	0.55	0.14–2.17	11	1.05	0.22–5.08	87	23	5.16	1.68–15.87	22	8.02	1.98–32.43
3 ≤	25	6	1.48	0.30–7.24	6	3.01	0.50–18.28	66	20	5.21	1.68–16.17	14	7.23	1.73–30.24
p for trend				0.53			0.65				0.01			0.03
p for trend among parous women only				0.56			0.24				0.01			0.01
Age at first birth (only parous women)[c]														
≤ 24	40	10	1	Reference	10	1	Reference	85	25	1	Reference	22	1	Reference
25–29	47	9	0.34	0.10–1.13	7	0.29	0.08–1.10	75	16	0.69	0.32–1.52	13	0.45	0.18–1.09
≥ 30	17	4	0.72	0.14–3.63	4	1.18	0.22–6.25	21	6	2.21	0.66–7.45	3	0.75	0.13–4.37
p for trend				0.39			0.64				0.69			0.19
Age at last birth (only parous women)[c]														
≤ 29	46	7	1	Reference	7	1	Reference	89	22	1	Reference	21	1	Reference
30–34	37	7	1.97	0.33–11.75	6	1.65	0.26–10.31	62	16	1.09	0.46–2.58	13	0.85	0.35–2.09
≥ 35	11	6	16.23	2.34–112.46	6	15.41	2.21–107.63	14	5	1.36	0.34–5.49	3	0.90	0.19–4.34
p for trend				0.01			0.01				0.68			0.77
Time since last birth (years) (only parous women)[d]														
≥ 10	68	12	1	Reference	11	1	Reference	165	43	1	Reference	37	1	Reference
5–9	20	7	1.60	0.24–10.82	7	1.28	0.18–9.00	0	0	–	–	0	–	–
≤ 4	6	1	0.67	0.02–20.80	1	0.39	0.01–14.68	0	0	–	–	0	–	–
p for trend				0.97			0.80				–			–
Breast-feeding (only parous women)[c]														
No	15	3	1	Reference	3	1	Reference	38	8	1	Reference	7	1	Reference

Table 5 (continued)

	Premenopause							Postmenopause						
	Number of subjects	All-cause death			Breast cancer -specific death			Number of subjects	All-cause death			Breast cancer -specific death		
		Number of death	HR	95% CI	Number of death	HR	95% CI		Number of deaths	HR	95% CI	Number of deaths	HR	95% CI
Yes	89	20	1.15	0.22–6.02	18	0.75	0.14–3.99	148	40	1.31	0.53–3.25	32	1.48	0.54–4.06

HR hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor

[a] Adjusted by age, year of diagnosis, stage (0–I, II, III, IV, and missing), referral status (from screening and other), family history of breast cancer in parents or siblings (no and yes), parity history (parous, nulliparous, and missing), comorbidities (no and yes), radiation therapy (no and yes), chemotherapy (no and yes), endocrine therapy (no and yes), occupation (housewife, other, and missing), and BMI (< 21.1, 21.1– < 23.3, 23.3– < 26.0, ≥ 26.0, and missing)

[b] Adjusted by age, year of diagnosis, stage (0–I, II, III, IV, and missing), referral status (from screening and other), family history of breast cancer in parents or siblings (no and yes), age at menarche (≤ 12, 13,14, ≥ 15, and missing), comorbidities (no and yes), radiation therapy (no and yes), chemotherapy (no and yes), endocrine therapy (no and yes), occupation (housewife, other, and missing), and BMI (< 21.1, 21.1– < 23.3, 23.3– < 26.0, ≥ 26.0, and missing)

[c] Adjusted by age, year of diagnosis, stage (0–I, II, III, IV, and missing), referral status (from screening and other), family history of breast cancer in parents or siblings (no and yes), age at menarche (≤ 12, 13, 14, ≥ 15, and missing), parity number (1, 2, ≥ 3, and missing), comorbidities (no and yes), radiation therapy (no and yes), chemotherapy (no and yes), endocrine therapy (no and yes), occupation (housewife, other, and missing), and BMI (< 21.1, 21.1– < 23.3, 23.3– < 26.0, ≥ 26.0, and missing)

[d] Adjusted by age, year of diagnosis, stage (0–I, II, III, IV, and missing), referral status (from screening and other), family history of breast cancer in parents or siblings (no and yes), age at menarche (≤ 12, 13,14, ≥ 15, and missing), age at first birth (≤ 24, 25–29, ≥ 30, and missing), parity number (1, 2, ≥ 3, and missing), comorbidities (no and yes), radiation therapy (no and yes), chemotherapy (no and yes), endocrine therapy (no and yes), occupation (housewife, other, and missing), and BMI (< 21.1, 21.1– < 23.3, 23.3– < 26.0, ≥ 26.0, and missing)

The present study had both strengths and limitations. One of its strengths was the high quality of patient recruitment and follow-up. Only three of the study subjects were lost to follow-up. Furthermore, confounding factors were appropriately controlled for, including related reproductive factors and family history. Our study also considered referral status, comorbidities, and adjuvant treatments. Another strength was that our study could clarify the risk in relation to age at last birth and birth recency. In Japan, these factors have been rarely investigated in breast cancer epidemiological studies [4].

The limitations of the study were as follows. First, although this is one of the largest patient cohort studies yet reported in Japan, stratification by hormone receptor and menopausal status may have produced false positive or false-negative results because of the small number of patients and events. To obtain a more reliable assessment, subsequent recruitment of patients and follow-up will be required. Second, the generalizability of our results may be limited. To verify our results and to assess their generalizability, further studies in other regions will be required.

In conclusion, the present study has clarified the roles of reproductive factors in tumor progression and survival among patients with breast cancer. Later age at menarche was inversely associated with advanced tumors. Nulliparous patients tended to have receptor-positive tumors. On the other hand, a U-shaped relationship between parity number and the risk of all-cause and breast cancer-specific death was found among the patients overall. Stratification by hormone receptor status showed that later age at menarche and later age at last birth were associated with an increased risk of death among HR-negative patients. A shorter time since last birth was associated with the risk of death among HR-positive patients. These findings indicate that the timing of menarche and parity history have significant effects on patient survival, providing clues for better understanding the association between women's life course and the outcome of breast cancer.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev. 1993;15:36–47.
2. Kawai M, Minami Y, Kuriyama S, Kakizaki M, Kakugawa Y, Nishino Y, Ishida T, Fukao A, Tsuji I, Ohuchi N. Reproductive factors, exogenous female hormone use and breast cancer risk in Japanese: the Miyagi Cohort Study. Cancer Causes Control. 2010;21:135–45.
3. Kyogoku S, Hirohata T, Takeshita S, Nomura Y, Shigematsu T, Horie A. Survival of breast-cancer patients and body size indicators. Int J Cancer. 1990;46:824–31.
4. Nagatsuma AK, Shimizu C, Takahashi F, Tsuda H, Saji S, Hojo T, Sugano K, Takeuchi M, Fujii H, Fujiwara Y. Impact of recent parity on histopathological tumor features and breast cancer outcome in premenopausal Japanese women. Breast Cancer Res Treat. 2013;138:941–50.
5. Song N, Choi JY, Sung H, Jeon S, Chung S, Song M, Park SK, Han W, Lee JW, Kim MK, Yoo KY, Ahn SH, Noh DY, Kang D. Tumor subtype-specific associations of hormone-related reproductive factors on breast cancer survival. PLoS One. 2015;10:e0123994.
6. Trivers KF, Gammon MD, Abrahamson PE, Lund MJ, Flagg EW, Kaufman JS, Moorman PG, Cai J, Olshan AF, Porter PL, Brinton LA, Eley JW, Coates RJ. Association between reproductive factors and breast cancer survival in younger women. Breast Cancer Res Treat. 2007;103:93–102.
7. Orgéas CC, Hall P, Rosenberg LU, Czene K. The influence of menstrual risk factors on tumor characteristics and survival in postmenopausal breast cancer. Breast Cancer Res. 2008;10:R107.
8. Ewertz M, Gillanders S, Meyer L, Zedeler K. Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. Int J Cancer. 1991;49:526–30.
9. Reeves GK, Patterson J, Vessey MP, Yeates D, Jones L. Hormonal and other factors in relation to survival among breast cancer patients. Int J Cancer. 2000;89:293–9.
10. Barnett GC, Shah M, Redman K, Easton DF, Ponder BA, Pharoah PD. Risk factors for the incidence of breast cancer: do they affect survival from the disease? J Clin Oncol. 2008;26:3310–6.
11. Alsaker MD, Opdahl S, Asvold BO, Romundstad PR, Vatten LJ. The association of reproductive factors and breastfeeding with long term survival from breast cancer. Breast Cancer Res Treat. 2011;130:175–82.
12. Korzeniowski S. Dyba T (1994) Reproductive history and prognosis in patients with operable breast cancer. Cancer. 1994;74:1591–4.
13. Daling JR, Malone KE, Doody DR, Anderson BO, Porter PL. The relation of reproductive factors to mortality from breast cancer. Cancer Epidemiol Biomark Prev. 2002;11:235–41.
14. Butt S, Borgquist S, Garne JP, Landberg G, Tengrup I, Olsson A, Manjer J. Parity in relation to survival following breast cancer. Eur J Surg Oncol. 2009;35:702–8.
15. Alsaker MD, Opdahl S, Romundstad PR, Vatten LJ. Association of time since last birth, age at first birth and parity with breast cancer survival among parous women: a register-based study from Norway. Int J Cancer. 2013;132:174–81.
16. Phillips KA, Milne RL, Friedlander ML, Jenkins MA, McCredie MR, Giles GG, Hopper JL. Prognosis of premenopausal breast cancer and childbirth prior to diagnosis. J Clin Oncol. 2004;22:699–705.
17. Sun X, Nichols HB, Tse CK, Bell MB, Robinson WR, Sherman ME, Olshan AF, Troester MA. Association of parity and time since last birth with breast cancer prognosis by intrinsic subtype. Cancer Epidemiol Biomark Prev. 2016;25:60–7.
18. Kawai M, Kakugawa Y, Nishino Y, Hamanaka Y, Ohuchi N, Minami Y. Reproductive factors and breast cancer risk in relation to hormone receptor and menopausal status in Japanese women. Cancer Sci. 2012;103:1861–70.
19. Kawai M, Minami Y, Nishino Y, Fukamachi K, Ohuchi N, Kakugawa Y. Body mass index and survival after breast cancer diagnosis in Japanese women. BMC Cancer. 2012;12:149.
20. Kakugawa Y, Kawai M, Nishino Y, Fukamachi K, Ishida T, Ohuchi N, Minami Y. Smoking and survival after breast cancer diagnosis in Japanese women: a prospective cohort study. Cancer Sci. 2015;106:1066–74.
21. Minami Y, Kanemura S, Oikawa T, Suzuki S, Hasegawa Y, Miura K, Nishino Y, Kakugawa Y, Fujiya T. Associations of cigarette smoking and alcohol drinking with stomach cancer survival: a prospective patient cohort study in Japan. Int J Cancer. 2018;143:1072–85.
22. Butt S, Borgquist S, Anagnostaki L, Landberg G, Manjer J. Parity and age at first childbirth in relation to the risk of different breast cancer subgroups. Int J Cancer. 2009;125:1926–34.
23. Somasegar S, Li L, Thompson CL. No association of reproductive risk factors with breast cancer tumor grade. Eur J Cancer Prev. 2018;27:140–3.
24. Johansson AL, Andersson TM, Hsieh CC, Jirström K, Dickman P, Cnattingius S, Lambe M. Stage at diagnosis and mortality in women with pregnancy-associated breast cancer (PABC). Breast Cancer Res Treat. 2013;139:183–92.
25. Wang Z, Dang S, Xing Y, Li Q, Yan H. Correlation of body mass index levels with menarche in adolescent girls in Shaanxi, China: a cross sectional study. BMC Womens Health. 2016;16:61.
26. Dossus L, Kvaskoff M, Bijon A, Fervers B, Boutron-Ruault MC, Mesrine S, Clavel-Chapelon F. Determinants of age at menarche and time to menstrual cycle regularity in the French E3N cohort. Ann Epidemiol. 2012;22:723–30.
27. Braithwaite D, Moore DH, Lustig RH, Epel ES, Ong KK, Rehkopf DH, Wang MC, Miller SM, Hiatt RA. Socioeconomic status in relation to early menarche among black and white girls. Cancer Causes Control. 2009;20:713–20.
28. Al-Sahab B, Ardern CI, Hamadeh MJ, Tamim H. Age at menarche in Canada: results from the National Longitudinal Survey of Children & Youth. BMC Public Health. 2010;10:736.
29. Lee MH, Kim SH, Oh M, Lee KW, Park MJ. Age at menarche in Korean adolescents: trends and influencing factors. Reprod Health. 2016;13:121.
30. Kroman N, Wohlfahrt J, Andersen KW, Mouridsen HT, Westergaard T, Melbye M. Parity, age at first childbirth and the prognosis of primary breast cancer. Br J Cancer. 1998;78:1529–33.
31. Warren Andersen S, Newcomb PA, Hampton JM, Titus-Ernstoff L, Egan KM, Trentham-Dietz A. Reproductive factors and histologic subtype in relation to mortality after a breast cancer diagnosis. Breast Cancer Res Treat. 2011;130:975–80.
32. Chubak J, Tworoger SS, Yasui Y, Ulrich CM, Stanczyk FZ, McTiernan A. Associations between reproductive and menstrual factors and postmenopausal sex hormone concentrations. Cancer Epidemiol Biomark Prev. 2004;13:1296–301.
33. Hankinson SE, Colditz GA, Hunter DJ, Manson JE, Willett WC, Stampfer MJ, Longcope C, Speizer FE. Reproductive factors and family history of breast cancer in relation to plasma estrogen and prolactin levels in postmenopausal women in the Nurses' Health Study (United States). Cancer Causes Control. 1995;6:217–24.
34. Duggan C, Stanczyk F, Campbell K, Neuhouser ML, Baumgartner RN, Baumgartner KB, Bernstein L, Ballard R, McTiernan A. Associations of sex steroid hormones with mortality in women with breast cancer. Breast Cancer Res Treat. 2016;155:559–67.
35. Grundy E. Women's fertility and mortality in late mid life: a comparison of three contemporary populations. Am J Hum Biol. 2009;21:541–7.

36. Choi JI, Han KD, Kim SJ, Kim MJ, Shin JE, Lee HN. Relationship between delivery history and health-related quality of life in menopausal South Korean women: the Korea National Health and Nutrition Examination Surveys. Maturitas. 2016;92:24–9.
37. Rosenberg L, Thalib L, Adami HO, Hall P. Childbirth and breast cancer prognosis. Int J Cancer. 2004;111:772–6.
38. Albrektsen G, Heuch I, Kvåle G. The short-term and long-term effect of a pregnancy on breast cancer risk: a prospective study of 802,457 parous Norwegian women. Br J Cancer. 1995;72:480–4.
39. Adami HO, Persson I, Ekbom A, Wolk A, Pontén J, Trichopoulos D. The aetiology and pathogenesis of human breast cancer. Mutat Res. 1995;333:29–35.
40. Gupta PB, Kuperwasser C. Contributions of estrogen to ER–negative breast tumor growth. J Steroid Biochem Mol Biol. 2006;102:71–8.