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Childbirth in young Korean women with previously treated breast cancer: The SMARTSHIP study

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Abstract

Purpose Alongside the modern trend of delaying childbirth, the high incidence of breast cancer among young women is causing significant pregnancy-related problems in Korea. We estimated the incidence of childbirth for young Korean breast cancer survivors compared with women who did not have breast cancer using a nationally representative dataset.

Methods Using a database from the National Health Insurance Service in South Korea, we analyzed 109,680 women who were between 20 and 40 years old between 2007 and 2013. They were prospectively followed, and childbirth events were recorded until December 31, 2015. We compared childbirth rates and characteristics between the breast cancer survivors and the noncancer controls.

Results Compared to 10,164 childbirths among 91,400 women without breast cancer (incidence rate: 22.3/1000), 855 childbirths occurred among 18,280 breast cancer survivors (incidence rate: 9.4/1000); the adjusted hazard ratio (HR) for childbirth was 0.41 (95% CI 0.38–0.44). Chemotherapy, endocrine therapy, and target therapy were associated with the decreasing childbirths among survivors, with corresponding adjusted HRs of 0.61 (0.53–0.70), 0.44 (0.38–0.51), and 0.62 (0.45–0.86), respectively. Breast cancer survivors had a lower probability of full-term delivery and a higher frequency of preterm labor than controls, with corresponding adjusted ORs of 0.78 (0.68–0.90) and 1.33 (1.06–1.65), respectively.

Conclusions We showed that a history of breast cancer has a negative effect on childbirth among young premenopausal women in Korea. Breast cancer survivors should be aware that they have a higher risk for preterm labor and are less likely to have a full-term delivery than women without a history of breast cancer.

Keywords Childbirth · Incidence rate · Breast cancer survivor

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Introduction

Breast cancer is the second most common cancer in Korean women, and the incidence has increased sharply in recent years [1, 2]. Breast cancer presents with unique demographic characteristics among Korean women compared with western women. While most breast cancer cases among western women occur after menopause, about half of Korean women who develop breast cancer are premenopausal, and about 15% of these women are under 40 years old [2–4].

In addition to prognosis-related issues, premenopausal women who develop breast cancer will also face pregnancy- and childbirth-related problems. Standard breast cancer treatments, such as chemotherapy and endocrine therapy (ETx), are well known to have negative effects on pregnancy and childbirth. Chemotherapy (CTx) might reduce fertility and can increase the risk of ovarian failure in women under 40 years old by 22–61% [5, 6]. Tamoxifen, the most frequently used ETx in premenopausal breast cancer patients, decreases the likelihood of childbirth, although it does not directly cause infertility [7]. Previous survey research showed that more than 50% of young breast cancer patients, upon being diagnosed, expressed a wish to have children and also voiced serious concern about subsequent infertility [8]. Preliminary survey results from the study, "Helping Ourselves, Helping Others (HOHO): The Young Women's Breast Cancer Study," also confirmed that over 50% of women ≤ 40 years at diagnosis were concerned about their future fertility and a significant proportion wished to consider pregnancy after breast cancer treatment [9].

In addition, Korea has one of the oldest average ages at first birth in the world, and the mean age of Korean women at childbirth was 32.4 years in 2015 [10]. With the trend toward delaying childbirth, pregnancy-related problems in young breast cancer survivors may be a major social challenge in Korea. Unfortunately, there have been no nationally representative studies about pregnancy and childbirth among Korean breast cancer survivors. Herein, we investigated the effect of breast cancer on childbirth and pregnancy-related risk in young breast cancer survivors using a nationally representative dataset.

Methods

Data source and study population

This is a nationwide population-based study using the National Health Information Database (NHID) from the Korean National Health Insurance Service (NHIS) in South Korea. The NHIS is a single-payer organization that is mandatory for all South Korean residents. The NHIS maintains national records including patient demographics, medical use/transaction information, insurers' payment coverage, and patients' deductions, and claims (diagnosis/prescriptions/consultation statements). Consequently, the NHIS database that includes the entire population and contains all this information represents the entire Korean population [11, 12].

From the NHIS database, we selected women of ages 20–40 years newly diagnosed with breast cancer between 2007 and 2013. We excluded women who were diagnosed with breast cancer before 2007 or who had received any medical examinations or treatments for a breast cancer diagnosis during this observational period. We also excluded women with metastatic or recurrent breast cancer, those who died or emigrated. The non-breast cancer control group was selected by age matching in a 1:5 fashion, and it was composed of five times the number of cancer subjects with the same age from the same time period. Both subject groups were prospectively followed, and their childbirth events were monitored until either their delivery or until December 31, 2015. This study was approved by the Institutional Review Board of Catholic Kwandong University International St. Mary's Hospital (IS16RCMI0053).

Determinants of childbirth and definition of disease

Breast cancer survivors were defined as those newly diagnosed with breast cancer between 2007 and 2013. Development of breast cancer was defined as being registered with either the C50 or D50 code from the International Classification of Disease, 10th Revision (ICD-10), and with the V193 code from the Korean-specific cancer code system, within 30 days of undergoing breast biopsy. We identified women to be excluded by selecting those with the C50 or D05 codes and with the V193 code in their records before 2007. Those who visited hospitals for any medical examination, prescription, or treatment under the C50 or D05 codes between 2002 and 2006 were also excluded. We assumed treatments, including surgery, CTx, ETx, radiation therapy (RTx), and targeted therapy (trastuzumab, TTx), were only carried out in patients who followed given treatments guidelines within 1 year of receiving their breast cancer diagnosis.

Childbirth was defined according to the ICD-10 codes or the behavior codes associated with delivery, including natural vaginal delivery, induced delivery, breech delivery, vacuum extraction, or Cesarean section. The ICD-10 also included codes for full-term delivery, premature delivery, and miscarriage. Complications before and after childbirth were defined by the ICD-10 codes for preeclampsia, preterm

labor, premature rupture of membranes, obstetric hemorrhage, plural birth, and hydramnios/oligoamnios.

Data analyses and statistical methods

Data were expressed as means (standard deviations), geometric means (95% CI), or percentages. The baseline characteristics of the subjects were compared using Student's *t* test for continuous variables and the χ^2 tests for categorical variables. We calculated the incidence rate (IR) per 1000 childbirths during the follow-up period.

$$\text{Incidence rate (per 1000)} = \frac{\text{N.of childbirth}}{\text{FU duration}} * 1000$$

Study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for the probability of childbirth were calculated. Cox proportional hazard regression models were used to estimate the association between breast cancer and childbirth. HRs were adjusted for age, income status (upper 80% and lower 20%), residential location (urban and rural), diabetes mellitus (DM), hypertension (HTN), and dyslipidemia. The influence of breast cancer treatment modalities on childbirth was also estimated using the Cox model. Multivariable-adjusted logistic regression models were fit to evaluate the effect of breast cancer on childbirth outcome and pregnancy-related complications. Statistical analyses were performed with the SAS survey procedure using sampling weights to provide nationally representative estimates. We used SAS software version 9.2 (SAS Institute, Cary, NC, USA) for all analyses. A P value < 0.05 was considered statistically significant.

Results

We analyzed 18,280 women with a breast cancer history, and we matched those subjects with 91,400 control subjects. There was no age difference between two groups and the mean age at breast cancer diagnosis was 34.9 ± 3.8 years old (Table 1). There were 6705 breast cancer cases (36.7%) among women in their twenties and 11,575 (63.3%) cases among women in their thirties. The breast cancer survivors were more likely to be urban living and have a higher income status than women in the control group. DM, HTN, and dyslipidemia were significantly higher in breast cancer survivors. During approximately 5 years of follow-up, 855 (4.7%) breast cancer survivors and 10,164 (11.1%) women in the control group gave birth ($P < 0.0001$).

The association between breast cancer and childbirth is shown in Table 2 and Fig. 1. Breast cancer survivors had fewer children than women without breast cancer history. The IR for childbirth among breast cancer survivors was 9.4, compared with 22.3 among the matched controls.

Table 1 Characteristics of breast cancer survivors and matched women without breast cancer

Characteristics	Breast cancer survivors ($n = 18,280$)	Control group ($n = 91,400$)	P value
Age (years)			> 0.9999
20–29	6705 (36.7)	33,525 (36.7)	
30–39	11,575 (63.3)	57,875 (63.3)	
Mean age ± SD	34.94 ± 3.81	34.94 ± 3.81	
Residential location			0.0012
Urban	8912 (48.8)	43,359 (47.4)	
Rural	9368 (51.2)	48,041 (52.6)	
Income			< 0.0001
Upper 80%	14,546 (79.6)	70,435 (77.1)	
Lower 20%	3734 (20.4)	20,965 (22.9)	
Diabetes mellitus			< 0.0001
No	18,108 (99.1)	90,800 (99.3)	
Yes	172 (0.9)	600 (0.7)	
Hypertension			< 0.0001
No	17,844 (97.6)	90,048 (98.5)	
Yes	436 (2.4)	1352 (1.5)	
Dyslipidemia			< 0.0001
No	17,960 (98.3)	90,490 (99.0)	
Yes	320 (1.7)	910 (1.0)	
Childbirth			< 0.0001
No	17,425 (95.3)	81,236 (88.9)	
Yes	855 (4.7)	10,164 (11.1)	
Year			> 0.9999
2007	2416 (13.2)	12,080 (13.2)	
2008	2494 (13.6)	12,470 (13.6)	
2009	2565 (14.0)	12,825 (14.0)	
2010	2670 (14.6)	13,350 (14.6)	
2011	2786 (15.2)	13,930 (15.2)	
2012	2628 (14.4)	13,140 (14.4)	
2013	2721 (14.9)	13,605 (14.9)	
Mean duration ± SD, years	4.99 ± 2.14	5 ± 2.24	0.8536

Multivariate analysis indicate that breast cancer had a negative effect on childbirth: compared with the control women, the adjusted HR for childbirth among breast cancer survivors was 0.41 (95% CI 0.38–0.44).

The influence of breast cancer treatment modalities on childbirth is shown in Table 3 and Fig. 2. We found that RTx had no significant effect on childbirth, with an adjusted HR of 0.89 (95% CI 0.78–1.03). CTx, ETx, and TTx all had significantly negative effects on childbirth, with corresponding IRs of 13.2, 16.2, and 9.6, compared with women who did not undergo CTx (HR 7.5), ETx (HR 5.6), or TTx (5.9). In multivariate analyses for childbirth outcomes where we compared women for each treatment modality to referent women who did not receive that treatment, the adjusted

Table 2 Incidence rates and adjusted hazard ratios for childbirth in breast cancer survivors compared with controls

	No.	No. childbirths	Duration (year)	IR[a]	Model 1[b]	Model 2[c]
Control group	91,400	10,164	456,765.65	22.25	Reference	Reference
Breast cancer survivors	18,280	855	91,292.44	9.37	0.41 (0.38–0.44)	0.41 (0.38–0.44)

[a]IR, incidence rate (per 1000) during follow-up period

[b]Cox proportional hazards model adjusted for age, income

[c]Cox proportional hazards model adjusted for age, income, location, DM, hypertension, and dyslipidemia

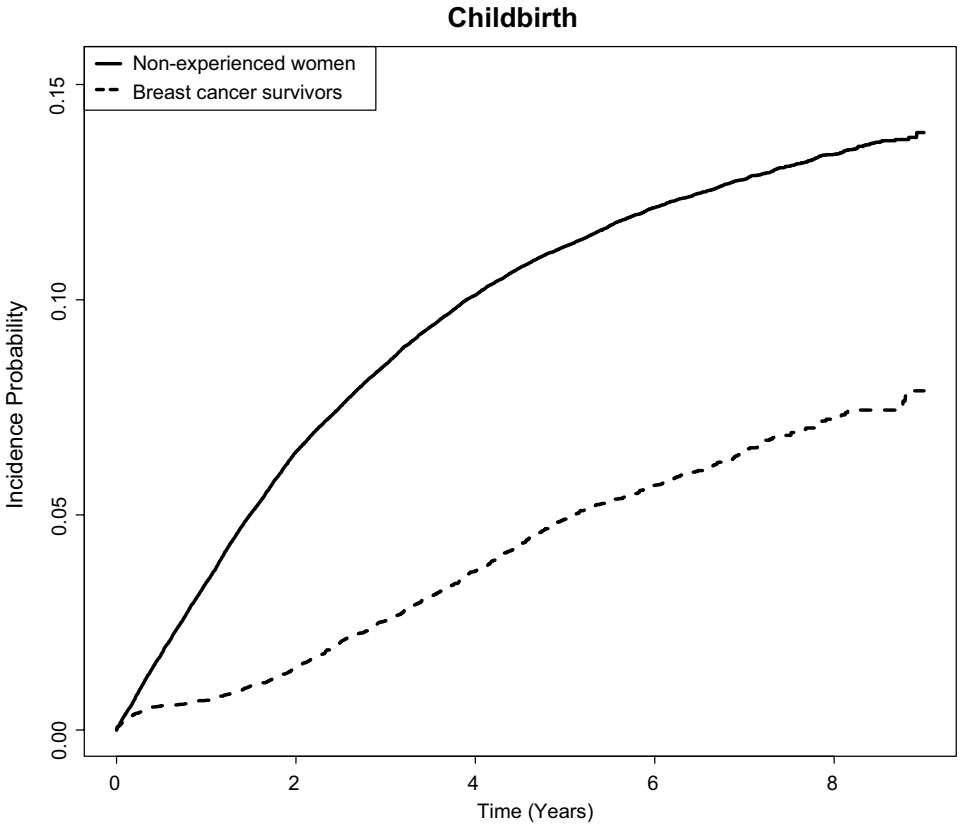

Fig. 1 Childbirth incidence among breast cancer survivors and women without a history of breast cancer

Time (years)	0	1	3	5	7	9
Control	91,400	88,216	71,145	45,222	21,538	51
Case	18,280	17,939	14,371	8839	4070	10

HRs for CTx, ETx, and TTx, were 0.61 (95% CI 0.53–0.70), 0.44 (95% CI 0.38–0.51), and 0.62 (95% CI 0.45–0.86), respectively.

The clinical characteristics of 11,019 women who experienced childbirth during the follow-up period are presented in Table 4. There were significant differences in age at first birth between the breast cancer survivors and the control women. The breast cancer survivors experienced childbirth at a younger age than control women, with mean ages at first birth of 30.3 ± 3.7 and 31.2 ± 3.7 years old, respectively ($P < 0.0001$). There was a significant difference with regard to length of time between baseline (breast cancer diagnosis) and delivery date, which corresponded to a mean time to delivery of 3.09 ± 1.93 years for breast cancer survivors and 2.1 ± 1.68 years for the control group ($P < 0.0001$). Other clinical characteristics, such as residential location, income status, DM, HTN, and dyslipidemia, were not significantly different between the two groups.

We also analyzed whether breast cancer influences delivery outcomes and pregnancy-related complications. As

Table 3 Incidence rates and adjusted hazard ratios for childbirth in breast cancer survivors compared with controls

	No.	No. childbirths	Duration (year)	IR[a]	Model 1[b]	Model 2[c]
Radiation therapy						
No	6030	306	30,235.07	10.12	Reference	Reference
Yes	12,250	549	61,057.38	8.99	0.90 (0.78–1.03)	0.89 (0.78–1.03)
Chemotherapy						
No	6102	400	30,396.48	13.16	Reference	Reference
Yes	12,178	455	60,895.96	7.47	0.61 (0.53–0.70)	0.61 (0.53–0.70)
Endocrine therapy						
No	6817	527	32,535.86	16.20	Reference	Reference
Yes	11,463	328	58,756.58	5.58	0.44 (0.38–0.51)	0.44 (0.38–0.51)
Targeted therapy						
No	16,568	815	84,482.63	9.65	Reference	Reference
Yes	1712	40	6809.81	5.87	0.62 (0.45–0.85)	0.62 (0.45–0.86)

[a]IR, incidence rate (per 1000) during follow-up period

[b]Cox proportional hazards model adjusted for age, income

[c]Cox proportional hazards model adjusted for age, income, location, DM, hypertension, and dyslipidemia

shown in Table 5, breast cancer survivors were less likely to have a full-term delivery. In multivariate analysis, when we compared breast cancer survivors with referent control women, we estimated an adjusted OR for full-term delivery of 0.78 (95% CI 0.68–0.90) for the cancer survivor group. However, there were no differences in the risk for preterm delivery between the two groups (OR 1.02, 95% CI 0.79–1.31). Among the factors associated with complications before and after delivery, preterm labor occurred more frequently in breast cancer survivors, corresponding to an adjusted OR of 1.33 (95% CI 1.06–1.65). There were no differences between the subject groups regarding risk for preeclampsia, obstetric hemorrhage, plural birth, miscarriage, or hydramnios/oligoamnios.

Discussion

In this nationally representative population-based study, we found that breast cancer has a negative effect on childbirth in Korea. The incidence of childbirth in young breast cancer survivors is about 60% lower than that in women with no breast cancer history. To the best of our knowledge, this is the first quantitative comparison of the birth-rate differences between breast cancer survivors and the general population. Although many studies of Western populations have explored the adverse effects of breast cancer on reproductive health, most focused on reproductive ability and fertility [5, 6, 13, 14]. This is because most breast cancer cases among Western women occur in postmenopausal women, and reproductive-aged breast cancer patients are rare. The Korean National Dataset (NHID) from the NHIS includes many young premenopausal women, and it is easy to follow up with patients in the dataset because the NHIS is mandatory for all South Korean residents, and the NHIS maintains a national record database [11, 12].

There have been a few population-based studies that explore an actual effect on childbirth [15–18]. A Swedish study based on the Swedish Medical Birth Registry with data linking to the cancer registry examined the prevalence of preterm birth, low birth weight, and small size for gestational age by breast cancer history [15]. The authors found that breast cancer history had no adverse effect on birth rates overall but that women with a history of breast cancer had an increased risk of delivery complications, requiring a C-section, having a very preterm birth, and delivering a baby with a low birth weight. An American study using linked data from a North Carolina birth registry and the Central Cancer Registry found similar patterns that indicated that a breast cancer history may correspond to 30–67% increases in risk of delivering a preterm birth and having a baby with low birth weight and being small for gestational age compared with the general population [16]. A Danish study of the Danish Cancer Registry found discordant results from the Swedish and American studies, wherein they found no increased risk of adverse birth outcomes among breast cancer patients [17]. Although the above studies all concluded that breast cancer does not have an adverse effect on birth overall, they could not compare childbirth incidence rates because their study populations were based on a retrospective birth cohort or breast cancer cohort linked to a birth registry. Herein, we prospectively confirmed that Korean breast cancer survivors had lower childbirth rates than the general population, regardless of the effects of income, place, DM, HTN, and dyslipidemia.

We also showed that breast cancer survivors were less likely to have a full-term delivery, which is consistent with findings from the Swedish and American studies. However,

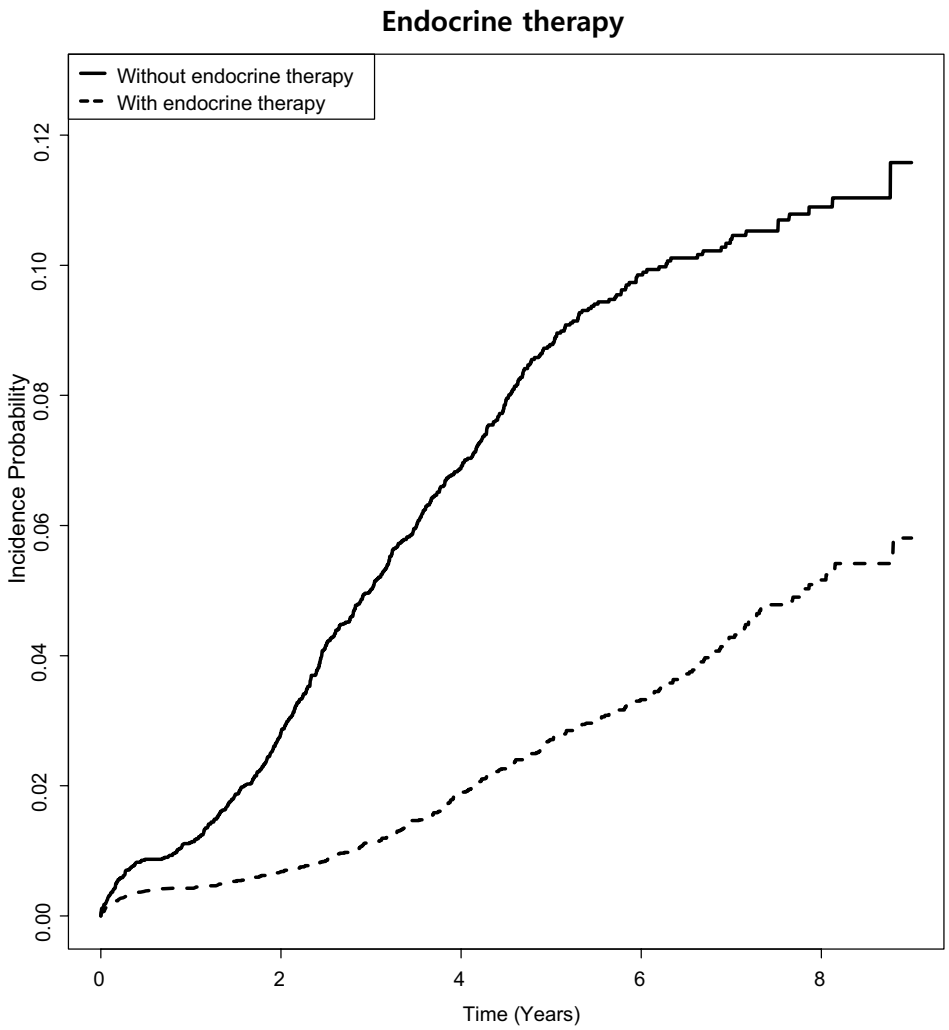

Fig. 2 The effects of endocrine therapy on childbirth incidence among breast cancer survivors

Time (years)	0	1	3	5	7	9
Control	6817	6549	4979	3107	1469	3
Case	11,463	11,390	9392	5732	2601	7

we did not find significant differences in risk for preterm delivery between the two groups. This discrepancy between the studies may be because our data are completely based on the mother's diagnosis, while all of the other studies were based or linked on birth-registry data. A major limitation of this study is that diagnoses based on ICD-10 codes could be misdiagnoses or even could be missed, especially when associated with a newborn baby (e.g. preterm or full-term delivery). The definition of delivery could be more accurate by revision using behavior codes. The disease status such as miscarriage, preterm labor, plural birth, preeclamsia, hydramnios/oligo-, and obstetric hemorrhages seemed to be accurate because doctors should give correct diagnosis for admission or treatment in order to get coverage of national insurance in Korea. On the other hands, the diagnosis including full-term and preterm delivery might seem to be missed and large of them were reported as delivery only. This might influence on our results. Another limitation of the present study was that we could not identify the status of marriage, previous pregnancy, or delivery which could influence on delivery. The precise data about the timing of diagnosis and recent pregnancy even might show the effect of pregnancy on breast cancer risk, as a recent pooled analysis of 15 prospective studies which suggested that women who are recently pregnant have an increased risk of breast cancer [19]. Nevertheless, we speculate that breast cancer survivors might have a higher risk for preterm delivery than women with no breast cancer history because women who

Table 4 Characteristics of childbearing women with and without breast cancer histories

Characteristics	Breast cancer survivors ($n=855$)	Control group ($n=10,164$)	P value
Age (years)			< 0.0001
20–29	745 (87.1)	8157 (80.2)	
30–39	110 (12.9)	2007 (19.8)	
Mean age ± SD	30.27 ± 3.65	31.2 ± 3.66	
Residential location			0.1175
Urban	462 (54.0)	5209 (51.2)	
Rural	393 (46.0)	4955 (48.8)	
Income			0.8876
Upper 80%	679 (79.4)	8051 (79.2)	
Lower 20%	176 (20.6)	2113 (20.8)	
Diabetes mellitus			0.4515
No	851 (99.5)	10,132 (99.7)	
Yes	4 (0.5)	32 (0.3)	
Hypertension			0.2839
No	849 (99.3)	10,119 (99. 6)	
Yes	6 (0.7)	45 (0. 4)	
Dyslipidemia			0.0501
No	848 (99.2)	10,126 (99.6)	
Yes	7 (0.8)	38 (0.6)	
Mean time to delivery ± SD, years	3.09 ± 1.93	2.1 ± 1.68	< 0.0001

experience preterm labor usually have a high risk of preterm birth, and preterm labor occurred at a significantly higher rate among breast cancer survivors than among the control women.

A previous population-based study found that the mean maternal age at delivery among breast cancer patients was 34.6 years, while that of the general population was 27.1 years [15]. This pattern seems to be the result of treatments, because patients usually spend several years undergoing breast cancer treatments and are generally advised to delay pregnancy for at least 1 or 2 years after treatment on the basis of previous data [20, 21]. A previous study showed that over 60% of breast cancer survivors gave birth 2 years after their diagnosis [16], which was similar to our data that the mean time from breast cancer diagnosis to delivery was more than 3 years. However, we found that breast cancer survivors had an earlier age at birth than control women. We carefully interpreted this to indicate that CTx might reduce reproductive ability and induce premature ovarian failure [5, 6], and patients in their mid- to late-thirties could miss pregnancy opportunities while undergoing breast cancer treatments, especially women who receive ETx. This is in accordance with our other findings that CTx, TTx, and ETx were associated with a decreased childbirth rate.

One of the most important contributions of our work is that we analyzed the relationship between breast cancer history

Table 5 Childbirth complications among breast cancer survivors versus women with no breast cancer history

	Group	Event		P value	OR[a]	
		No	Yes		Model 1[a]	Model 2[b]
Full-term delivery	Control	5381 (52.9)	4783 (47.1)	0.0007	Reference	Reference
	Breast cancer	504 (59.0)	351 (41.0)		0.77 (0.67–0.89)	0.78 (0.68–0.90)
Preterm delivery	Control	9325 (91.8)	839 (8.2)	0.7727	Reference	Reference
	Breast cancer	782 (91.5)	73 (8.5)		1.02 (0.80–1.32)	1.02 (0.80–1.31)
Miscarriage	Control	8675 (85.4)	1489 (14.6)	0.7989	Reference	Reference
	Breast cancer	727 (85.0)	128 (15.0)		1.04 (0.86–1.27)	1.05 (0.86–1.27)
Preterm labor	Control	9259 (91.1)	905 (8.9)	0.0065	Reference	Reference
	Breast cancer	755 (88.3)	100 (11.7)		1.34 (1.07–1.67)	1.33 (1.06–1.65)
PROM[c]	Control	8393 (82.6)	1771 (17.4)	0.099	Reference	Reference
	Breast cancer	725 (84.8)	130 (15.2)		0.83 (0.69–1.01)	0.83 (0.68–1.01)
Plural birth	Control	9884 (97.3)	280 (2.7)	0.3573	Reference	Reference
	Breast cancer	836 (97.8)	19 (2.2)		0.83 (0.52–1.33)	0.83 (0.52–1.33)
Preeclampsia	Control	10,053 (98.9)	111 (1.1)	0.2848	Reference	Reference
	Breast cancer	849 (99.3)	6 (0.7)		0.63 (0.28–1.45)	0.61 (0.27–1.40)
Hydramnios/Oligo-	Control	9702 (95.5)	462 (4.5)	0.5159	Reference	Reference
	Breast cancer	812 (95.0)	43 (5.0)		1.15 (0.83–1.59)	1.15 (0.83–1.58)
Obstetric hemorrhage	Control	9530 (93.8)	634 (6.2)	0.9640	Reference	Reference
	Breast cancer	802 (93.8)	53 (6.2)		1.00 (0.75–1.34)	1.00 (0.75–1.34)

[a]Odds ratios estimated with logistic regression adjusted for age, income

[b]Odds ratios estimated with logistic regression adjusted for age, income, location, DM, hypertension, and dyslipidemia

[c]PROM, premature rupture of membranes

and risk of complications before and after childbirth, and ours is one of only a few studies that explored those relationships. While previous studies have estimated associations between preeclampsia and breast cancer risk [22, 23], there are no data about the influence of breast cancer on preeclampsia risk. We hypothesized that there might be significant differences between breast cancer survivors and the general population regarding childbirth risks and outcomes. However, we found no differences between breast cancer survivors and the control group with regard to preeclampsia, obstetric hemorrhage, plural birth, miscarriage, or hydramnios/oligoamnios risk. Consistent with a Swedish study, we also found that a history of breast cancer did not increase women's risk for obstetric hemorrhage.

Conclusion

Herein, we present evidence from a nationally representative Korean database that breast cancer in premenopausal women has a negative effect on childbirth. CTx and ETx particularly decreased birth rates among breast cancer survivors. Young breast cancer patients should be warned and counseled in an individualized manner about the impacts of cancer treatment on subsequent delivery. In addition, because breast cancer survivors are at higher risk for preterm labor and have lower odds of full-term delivery, they should be cautioned to be more careful than mothers who do not have a cancer history.

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Data availability The data that support the findings of this study are available from the NHIS but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the NHIS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The authors declare that the present study complies with the current laws of Korea, and this study was approved by the Institutional Review Board of Catholic Kwandong University International St. Mary's Hospital (IS16RCMI0053).

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