

## Prognosis of pregnancy after breast cancer diagnosis according to the type of treatment: A population-based study in Korea by the SMARTSHIP group

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### ABSTRACT

**Backgrounds:** In this study, we evaluated the incidence and outcomes of pregnancy after breast cancer was diagnosed in women of childbearing age. Additionally, we evaluated the prognosis of patients who became pregnant after breast cancer, according to the treatment.

**Methods:** This was a retrospective cohort study of women aged 20–45 years who were surgically treated for breast cancer between 2004 and 2014 using the Korean National Health Insurance database. The patients were classified into six groups according to the treatment. Propensity score matching was applied to the cohort to analyze the risk of breast cancer-associated mortality after pregnancy and childbirth.

**Results:** Of the 45,765 patients who had been newly diagnosed with breast cancer, 1826 (4%) became pregnant after breast cancer diagnosis. Among the pregnant group, the HR of the risk of death was 0.15 (95% CI, 0.06 to 0.36) for patients who became pregnant  $\geq 49$  months after the diagnosis. In patients who received endocrine therapy and chemotherapy, the pregnant group had better prognosis than the non-pregnant group. There was no significant difference between the pregnant group and the non-pregnant group in patients who received chemotherapy and trastuzumab with or without endocrine therapy.

**Conclusion:** The risk of death was low in women who became pregnant  $\geq 49$  months after the diagnosis of breast cancer. The prognosis of pregnant women was non-inferior to that of non-pregnant women, even in women who received trastuzumab. These findings provide reassurance to patients with HER2-positive cancer who are considering future pregnancy.

### 1. Introduction

Survival in breast cancer has improved significantly in recent decades and a population of women who have undergone breast cancer treatment are still of childbearing age and may wish to conceive [1]. On

average, across the Organization for Economic Co-operation and Development countries, the mean age at which women first get married and the average age at which women have their first child are increasing [2]. Because of the increasing trend of older maternal age at first birth, many young women who are diagnosed with breast cancer before the

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completion of their family plan may desire to have children in the future [3].

Several studies have evidenced that pregnancy in women with a history of breast cancer is safe and does not increase the risk of recurrence, even in patients with hormone receptor-positive breast cancer [4–7]. However, many women diagnosed with breast cancer still face several barriers to safely and successfully conceiving a child. Moreover, the fertility rate among young breast cancer survivors is lower than in the general population [8,9]. The proportions of patients with at least one full-term pregnancy after a breast cancer diagnosis are only 3% and 8% for women younger than 45 years and younger than 35 years, respectively [10]. Fertility and pregnancy after breast cancer are challenging issues faced by young women with newly diagnosed breast cancer. Chemotherapy can cause premature menopause in young patients with breast cancer [11–13], and adjuvant 5-year to 10-year endocrine therapy can result in delaying the timing of pregnancy after breast cancer because of the teratogenicity of tamoxifen [14]. As a result, young patients must have counseling regarding the impact of treatment on their fertility, and physicians should offer the fertility preservation [15].

In this study, we evaluated the incidence and outcomes of pregnancy after breast cancer was diagnosed in women of childbearing age. Additionally, we evaluated the prognosis of patients who became pregnant after breast cancer, according to the treatment they received.

## 2. Methods

### 2.1. Data source and study population

This was a nationwide retrospective cohort study using the Korean National Health Insurance (KNHI) database. Since the implementation of the National Health Insurance Act in 1989, almost 97% of the Korean population has compulsory health insurance provided by the KNHI. The KNHI maintains national records, including patient demographics, medical use/transaction information, insurers' payment coverage, and patients' deductions and the entire health claims database (diagnosis/prescriptions/consultation statements) [16]. The variables for pregnancy status, pregnancy outcomes, treatment of breast cancer, and dates of recurrence were extracted from the KNHI database.

This was a retrospective study of women aged 20–45 years who were surgically treated for primary breast cancer between 2004 and 2014 in South Korea. A nationwide questionnaire survey was used to determine the total number of patients newly diagnosed with invasive breast cancer and the age of these patients. We excluded patients who did not undergo breast cancer surgery within 1 year after diagnosis and patients who died within 1 year after diagnosis. Patients with an unknown state of pregnancy or patients who had been diagnosed with breast cancer during pregnancy or within 1 year after delivery were also excluded.

Patient survival data, including dates of death, were obtained from the Korean Central Cancer Registry, Ministry of Health and Welfare, Korea. The Korean Central Cancer Registry is linked to the Korea National Statistical Office, which has complete death statistics recorded by a unique identification number assigned to each Korean resident. The last follow-up date for surviving patients was December 31, 2017.

### 2.2. Definition of disease, pregnancy, and live birth

Medical treatment data consist of electronic bills for the medical treatment provided, prescription of drugs, and diagnosis codes established by the International Classification of Diseases 10th revision (ICD-10). The National Health Insurance Service (NHIS) has introduced a policy that reimburses the payment of cancer patients, who are identified with the specialized claim code of V193 since 2005. Patients newly diagnosed with invasive breast cancer were defined as those assigned the C50 and the V193 code in their records. Patients who were identified with D05 and V193 not earlier than 3 months before the start of using

C50 and V193 were included in the cohort because they were considered upstaged cases after breast cancer surgery. However, patients who were identified with D05 and V193 earlier than 3 months before using C50 and V193 were excluded.

We identified patients with an ICD-10 code beginning with “O” or the behavior codes associated with delivery as pregnant individuals and those without such an ICD-10 code during the follow-up period as non-pregnant individuals. The ICD-10 included codes for full-term delivery, premature delivery, and miscarriage. We additionally applied the behavior code for abortion as an outcome of pregnancy. We divided the pregnant individuals into two groups depending on the pregnancy outcome: live birth and failed to deliver.

### 2.3. Subgroup analysis according to the treatment

Patients were classified into the following six groups according to the treatment received: (1) no treatment, (2) endocrine therapy-only, (3) chemotherapy-only, (4) endocrine therapy and chemotherapy, (5) chemotherapy and trastuzumab, and (6) endocrine therapy, chemotherapy, and trastuzumab.

### 2.4. Statistical analyses

The baseline characteristics of the subjects were compared using Student's t-test for continuous variables and the  $\chi^2$  test for categorical variables. We performed a time-dependent analysis on patients who were pregnant after diagnosis of breast cancer. We considered pregnancy as a time-dependent covariate and defined exposure status from non-exposure to exposure at the time of pregnancy. In non-pregnant women, immortal time was combined with person-years [17]. We also used 1:1 propensity score matching analysis in our cohort of pregnant and non-pregnant women to reduce the effects of bias on treatment outcomes [18]. For propensity score matching, we adjusted the data for age at breast cancer diagnosis, adjuvant endocrine therapy, chemotherapy, and radiotherapy. We compared the overall survival rates between the pregnant and non-pregnant groups using the Kaplan-Meier method. Finally, we used Cox proportional hazards regressions to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between pregnancy and survival. *P*-values < 0.05 were considered statistically significant. We performed all analyses using the Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC).

### Ethical statement

This study was approved by the Institutional Review Board of Chungbuk National University Hospital (approval number: 2020-10-016-001). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

## 3. Results

### 3.1. Clinical characteristics of the study cohort

Of the 45,765 patients aged 20–45 years and who had been newly diagnosed with breast cancer between 2004 and 2014, 1826 (4%) became pregnant after receiving treatment for breast cancer and 43,939 (96%) did not. The median duration of follow-up was 97.9 (interquartile range, 69.2–132.5) months. The median time from breast cancer diagnosis to pregnancy was 3.3 (range, 2.0 to 5.0) years. The characteristics of the study population are summarized in Table 1.

The mean age of the pregnant group at breast cancer diagnosis was

**Table 1**  
Patients' characteristics.

	Total (N = 45,765)	Pregnant (N = 1,826, 4.0%)	Non-pregnant (N = 43,939, 96.0%)	P-value
Age				
mean (std)	39.7 (4.5)	32.3 (4.2)	40.0 (4.3)	<0.001
median (q1-q3)	41 (37–43)	32 (29–35)	41 (38–43)	<0.001
Age, n (%)				<0.001
<30	1498 (3.3)	460 (25.2)	1038 (2.4)	
30–34	4878 (10.7)	858 (47.0)	4020 (9.1)	
35–39	11,736 (25.6)	400 (21.9)	11,336 (25.8)	
40–45	27,653 (60.4)	108 (5.9)	27,545 (62.7)	
Chemotherapy, n (%)				0.016
No	10,155 (22.2)	447 (24.5)	9708 (22.1)	
Yes	35,610 (77.8)	1379 (75.5)	34,231 (77.9)	
Endocrine therapy, n (%)				<0.001
No	12,855 (28.1)	879 (48.1)	11,976 (27.3)	
Yes	32,910 (71.9)	947 (51.9)	31,963 (72.7)	
Trastuzumab, n (%)				<0.001
No	41,729 (91.2)	1709 (93.6)	40,020 (91.1)	
Yes	4036 (8.8)	117 (6.4)	3919 (8.9)	
Radiation therapy, n (%)				0.009
No	13,217 (28.9)	478 (26.2)	12,739 (29.0)	
Yes	32,548 (71.1)	1348 (73.8)	31,200 (71.0)	
Ovarian Function Suppression n (%)				0.101
No	38,290 (83.7)	1553 (85.1)	36,737 (83.6)	
Yes	7475 (16.3)	273 (14.9)	7202 (16.4)	
Ovarian preservation, n (%)				<0.001
Yes	109 (3.0)	14 (1.0)	95 (0.3)	
No	35,251 (97.0)	1351 (99.0)	33,900 (99.7)	
Surgery (Breast), n (%)				<0.001
Breast-conserving surgery	6371 (14.9)	328 (19.0)	6043 (14.7)	
Mastectomy	36,416 (85.1)	1392 (81.0)	35,024 (75.3)	
Subgroup according to the treatment				<0.001
No treatment	1608 (3.5)	156 (8.5)	1452 (3.30)	
Endocrine therapy-only	8494 (18.6)	291 (15.9)	8203 (18.6)	
Chemotherapy-only	9686 (21.2)	661 (36.2)	9025 (20.5)	
Endocrine therapy + chemotherapy	21,941 (47.9)	601 (32.9)	21,340 (48.6)	
Chemotherapy + Trastuzumab	1532 (3.4)	62 (3.4)	1470 (3.6)	
Endocrine therapy + chemotherapy + Trastuzumab	2451 (5.7)	55 (3.0)	2396 (5.5)	
Time between surgery and pregnancy (year)				
mean (std)		3.7 (2.2)		
median (q1-q3)		3.3 (2.0, 5.0)		

lower than that of the non-pregnant group (mean age, 32.3 years vs. 40.0 years;  $p < 0.001$ ). The proportion of women younger than 35 years was 1318 (72.1%) in the pregnant group. Patients aged 30–34 years were the most common among the pregnant group (858, 47.0%). The proportion of patients who received chemotherapy, endocrine therapy, and trastuzumab was lower in the pregnant group than in the non-pregnant group (75.5% vs. 77.9%,  $p < 0.016$ ; 51.9% vs. 72.7%,  $p < 0.001$ ; 6.4% vs. 8.9%,  $p < 0.001$ , respectively). A larger number of patients in the pregnant group underwent breast-conserving surgery (19.0% vs. 14.7%,  $p < 0.001$ ). There was no difference in receiving ovarian function suppression treatment between the pregnant and non-pregnant groups (15.0% vs. 16.4%,  $p = 0.103$ ). However, the pregnant group tried ovarian preservation, using goserelin or leuprolide before chemotherapy, more than the non-pregnant group (1.0% vs 0.3%,  $p < 0.001$ ). The characteristics of the study population after propensity score matching are presented in [Table 2](#). After matching, our results indicated that there were no significant differences between women who had live births and those who did not become pregnant after treatment for breast cancer regarding age at diagnosis, endocrine therapy, chemotherapy, radiotherapy, or trastuzumab.

### 3.2. Reproductive outcomes

Of the 1826 patients who became pregnant, 1139 (62.4%), 558 (30.6%), and 86 (7.0%) had live births, miscarriage, and abortion, respectively ([Table 3](#)). Among the live birth group, 871 (76.5%) had one child; however, there were 268 women who had more than two children, and even 14 women had more than three children successfully. Pregnancy interval from diagnosis is also shown in [Table 3](#). Patients who became pregnant between the 25- and 48-month diagnosis for breast cancer after were the most common among the pregnant group (709, 38.7%).

### 3.3. Pregnancy and prognosis of young breast cancer survivors

In survival analysis, the pregnant group had a better prognosis and reduced risk of death than the non-pregnant group (hazard ratio [HR], 0.43; 95% CI, 0.35 to 0.53,  $p < 0.001$ , [Table 4](#), [Fig. 1\(a\)](#)). Women who had live births had significantly lower risks of death than those in the non-pregnant group (HR, 0.27; 95% CI, 0.20 to 0.38,  $p < 0.001$ , [Table 4](#), [Fig. 1\(b\)](#)). After propensity score matching, the risk of death was significantly lower in women who had live births than in those who did not become pregnant (HR, 0.15; 95% CI, 0.10 to 0.21, Suppl. [Figure 1](#)).

### 3.4. Prognosis after breast cancer by the timing of pregnancy and prognosis after breast cancer according to the treatment

Among the pregnant group, the HR of the risk of death was 0.15 (95% CI, 0.06 to 0.36,  $p < 0.001$ ) for patients who became pregnant  $\geq 49$  months after the diagnosis for breast cancer, whereas there was no reduced risk of death in patients who became pregnant 49 months before the diagnosis of breast cancer ([Table 5](#), [Fig. 2](#)).

In a subgroup analysis according to the treatment received, the live birth group had a better prognosis regardless of endocrine therapy than the group who had a failure to birth and the non-pregnant group ([Table 6](#), [Fig. 3](#)). Among patients who did not receive any treatment, there was no significant difference between the group who had a live birth and the non-pregnant group. (HR, 0.43; 95% CI, 0.15 to 1.27,  $p = 0.127$  [Table 7](#), [Fig. 4\[a\]](#)). In the chemotherapy-only groups, women who had a live birth had a significantly lower risk of death than those in the non-pregnant group (HR, 0.23; 95% CI, 0.15 to 0.36,  $p < 0.001$ , [Table 7](#), [Fig. 4\(c\)](#)). In patients who received endocrine therapy and chemotherapy, the group who had a live birth had better prognosis than the non-pregnant group (HR, 0.31; 95% CI, 0.18 to 0.56,  $p < 0.001$ , [Table 7](#), [Fig. 4\(d\)](#)). There was no significant difference between the group who had a live birth and the non-pregnant group in patients who received

**Table 2**  
Patients' characteristics according to pregnancy status, after propensity score matching.

	Before PSM		P-value <sup>†</sup>	After PSM		P-value <sup>‡</sup>
	Live birth	Non-pregnant		Live birth	Non-pregnant	
Number of patients	1139	43,939		1139	1139	
Age, mean ± SD	31.0 ± 3.6	40.0 ± 4.3	<0.001	31.0 ± 3.6	31.0 ± 3.7	0.035
Age, n (%)			<0.001			0.999
<30	385 (33.8%)	1038 (2.4%)		385 (33.8%)	388 (34.1%)	
30–34	566 (49.7%)	4020 (9.1%)		566 (49.7%)	563 (49.4%)	
35–39	168 (14.7%)	11,336 (25.8%)		168 (14.7%)	168 (14.7%)	
40–45	20 (1.8%)	27,545 (62.7%)		20 (1.8%)	20 (1.8%)	
Endocrine therapy, n (%)			<0.001			0.038
No	590 (51.8%)	11,976 (27.3%)		590 (51.8%)	582 (51.1%)	
Yes	549 (48.2%)	31,963 (72.7%)		549 (48.2%)	557 (48.9%)	
Chemotherapy, n (%)			0.004			0.971
No	293 (25.7%)	9708 (22.1%)		293 (25.7%)	283 (24.8%)	
Yes	846 (74.3%)	34,231 (77.9%)		846 (74.3%)	856 (75.2%)	
Radiation therapy, n (%)			0.002			0.571
No	282 (24.8%)	12,739 (29.0%)		282 (24.8%)	283 (24.8%)	
Yes	857 (75.2%)	31,200 (71.0%)		857 (75.2%)	856 (75.2%)	
Trastuzumab, n (%)			<0.001			0.969
No	1080 (94.8%)	40,020 (91.1%)		1080 (94.8%)	1078 (94.6%)	
Yes	59 (5.2%)	3919 (8.9%)		59 (5.2%)	61 (5.4%)	

PSM, propensity score matching.

<sup>†</sup>P-value by Chi-square test and Student's t-test.<sup>‡</sup>P-value by conditional logistic regression.**Table 3**  
Pregnancy outcomes.

	Total, N = 45,765 (%)
Pregnancy, n (%)	
No	43,939 (96.0)
Yes	1826 (4.0)
No. of pregnancies	
1	1282 (70.2)
2	390 (21.4)
≥3	154 (8.4)
	Pregnant group, N = 1826 (%)
No. of live birth	
1	871 (76.5)
2	254 (22.3)
≥3	14 (1.2)
Live birth, n (%)	1139 (62.4)
Miscarriage, n (%)	558 (30.6)
Abortion, n (%)	86 (7.0)
Pregnancy interval from diagnosis (months), n (%)	
≤12 months	109 (6.0)
13–24 months	315 (17.3)
25–48 months	709 (38.7)
≥49 months	693 (38.0)

**Table 4**  
Hazard ratio regarding the association between pregnancy and live birth after breast cancer diagnosis and survival.

	HR (95% CI)	P-value	P by log rank test
Pregnancy			
No	ref		
Yes	0.43 (0.35, 0.53)	<0.001	<0.001
Birth			
Non-pregnancy	ref		
Live birth	0.27 (0.20, 0.38)	<0.001	<0.001

chemotherapy and trastuzumab with or without endocrine therapy (Table 7, Fig. 4(e) and (f)).

#### 4. Discussion

The compulsory nature of the Korean National Health Insurance

(KNHI) system means that the system provides universal coverage [19], it made the KNHI database the best national statistical indicator of fertility and pregnancy issues among young patients with breast cancer. To the best of our knowledge, this is one of the largest studies that investigated the outcome of patients who became pregnant after they were diagnosed with breast cancer in Korea. Furthermore, this is the first study that evaluated the prognosis of pregnancy after breast cancer according to the treatment received including trastuzumab. The incidence of breast cancer in young women is higher in Asian countries than in Western countries, the proportion of Asian patients with breast cancer in that age group ranges from 7.6% to 12% [20,21]. Approximately 11.4% of Korean women with breast cancer are younger than 40 years [22]. Although several studies have assessed the pregnancy outcomes and prognostic impacts of pregnancy among patients with breast cancer, there have been very few studies assessing these outcomes and impacts in Asian countries. This study showed that pregnancy after breast cancer is safe, and the prognosis of pregnancy after breast cancer was non-inferior to that in the non-pregnant group regardless of the type of treatment received.

The pregnancy rate of breast cancer survivors in this study was 4.0%, which was significantly lower than that of the general population, and this is consistent with the result of a previous study [23–25]. The live birth rate in this study was 62.4%, which is slightly higher reported in the previous SMARTSHIP study, the full-term and preterm delivery rate for the SMARTSHIP study was 49.5% [26]. Almost 70% of patients in the pregnant group experienced a pregnancy once; however, interestingly, 8.4% (154) patients experienced pregnancies more than three times. Moreover, there were 268 women who had more than two children, and even 14 (1.2%) women had more three children among the group who had live births. This suggests that there is a strong need for oncofertility counseling at the time of diagnosis. A previous study showed that a large proportion of patients facing fertility and pregnancy issues do not pursue fertility preservation strategies, most likely due to the lack of adequate counseling at the time of diagnosis [27]. A recent study showed that many patients remain interested in future fertility 4 years after being diagnosed with breast cancer, indicating that continuous fertility discussions are needed [28].

We observed that pregnancy after breast cancer did not negatively affect the prognosis of patients, and this is consistent with a previous study showing the safety of pregnancy after breast cancer [4–6]. The pregnant group had a better prognosis in overall survival than the

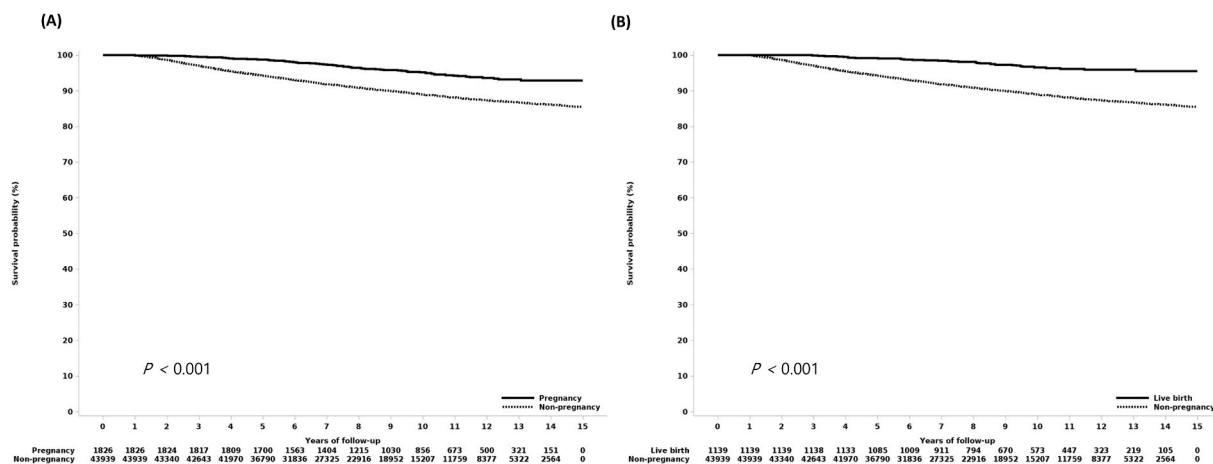


Fig. 1. Overall survival outcomes of the pregnant and the non-pregnant groups. (A) Live birth vs non-pregnant. (B) Pregnant vs non-pregnant.

Table 5

Cox’s proportional hazards model for survival in women with breast cancer stratified by time from diagnosis to pregnancy (months).

	HR (95% CI)	P-value	P by log rank test
time to subsequent pregnancy			
≤12 months	ref		<0.001
13–24 months	1.06 (0.50, 2.25)	0.873	
25–48 months	0.64 (0.31, 1.32)	0.225	
≥49 months	0.15 (0.06, 0.36)	<0.001	

non-pregnant group. Women who had live births also had better prognosis in survival than women in the non-pregnant group, and this result is consistent with that of a previous study [29].

Regarding the timing of pregnancy, a previous study has addressed the nonsignificant increased risk of recurrence and death associated with conception within 12 months of diagnosis [30]. Another study

showed that the risk of death was lowest if pregnancy occurred 6 months or more after diagnosis [31]. In this study, among the pregnant group, the risk of death was lower in patients who became pregnant ≥49 months after the diagnosis of breast cancer.

In a subgroup analysis according to the treatment received, the group who had a live birth had a better prognosis regardless of endocrine therapy than the non-pregnant group, which is also consistent with the result of a previous study [6]. In this study, the proportion of patients who received endocrine therapy was lower in the pregnant group than in the non-pregnant group. This may be attributed to the fear that high hormonal levels during pregnancy and/or temporary interruption of endocrine therapy could be detrimental to patients’ prognoses [32]. However, there was no negative impact on the prognosis of the pregnant group regardless of endocrine therapy.

Although information about the patients’ clinical and pathologic stages were not obtained in this study, the majority of patients assigned to the endocrine therapy-only group had hormone receptor-positive,

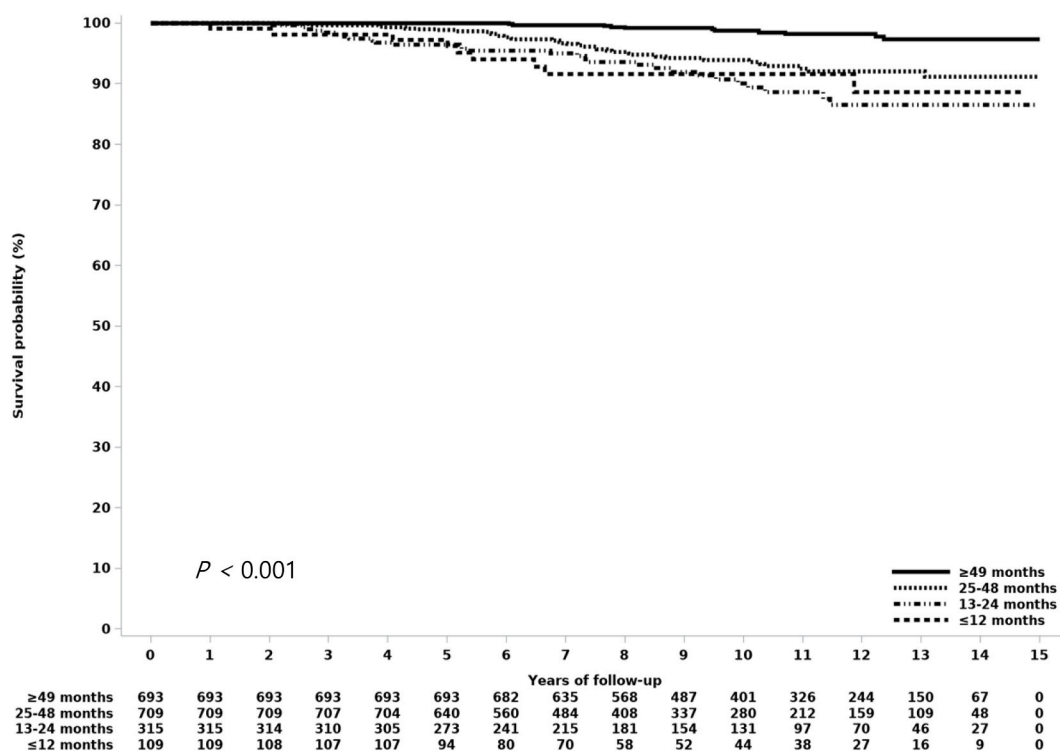


Fig. 2. Overall survival outcomes of women with breast cancer stratified by the duration from diagnosis to pregnancy (months).

**Table 6**

Hazard ratio in the live birth group, the group that failed to give birth, and the non-pregnant group after breast cancer diagnosis.

Endocrine therapy		No.	HR (95% CI)	P-value
Yes	Live birth	549	0.25 (0.14, 0.43)	<0.001
	Failure to birth	398	0.82 (0.56, 1.20)	0.299
	Non-pregnancy	31,963	ref	
No	Live birth	590	0.22 (0.14, 0.33)	<0.001
	Failure to birth	289	0.49 (0.33, 0.73)	<0.001
	Non-pregnancy	11,976	ref	

carcinoma in situ tumors or early-stage invasive tumors. Similarly, the majority of patients assigned to the chemotherapy-only group had triple-negative tumors. We observed that women who became pregnant had a significantly lower risk of death than those in the non-pregnant group. This implies that the prognosis of pregnancy after breast cancer diagnosis is not detrimental in both groups of patients, with hormone receptor-positive tumors and with hormone receptor-negative tumors.

Data assessing the prognosis of patients who conceived after the diagnosis of human epidermal growth factor receptor 2 (HER2)-positive breast cancer are limited. A recent study has proved that having a pregnancy after treatment completion is safe without compromising outcome or maternal prognosis [33]. The authors showed that there was no significant difference in disease-free survival between pregnant young patients (n = 85) and non-pregnant patients (n = 1307) diagnosed with breast cancer. In this study, in patients receiving chemotherapy and trastuzumab with or without endocrine therapy, the prognosis of the pregnant group was non-inferior to that of the non-pregnant group. Young patients with breast cancer have an increased risk of death and more aggressive clinical characteristics. Particularly, HER2-positive cancers are biologically aggressive, and patients diagnosed with these types of cancers have the fear of recurrence or death. We have evidenced that the prognosis of 117 patients in the pregnant group was non-inferior to that of patients in the non-pregnant group after receiving trastuzumab. Moreover, we believe this result would be beneficial for physicians and patients with HER2-positive cancers who are facing infertility issues.

We used data from the KNHI database, and information about the clinical and pathologic stages or immunohistochemistry status of tumors was not obtained in this study. Therefore, we could not determine the exact clinical stages and subtypes of breast cancers. To overcome this, we categorized the patients according to the treatment and analyzed the patient data by subgroups to evaluate the prognosis of pregnant patients. Additionally, information of recurrence and cause of death was not included in the KNHI database. Further evidence with a large prospective randomized trial is needed, and we expect a significant result from the ongoing international IBCSG-BIG-NACBG POSITIVE trial (ClinicalT

rials.gov identifier: NCT02308085) [34].

In conclusion, this study showed that pregnancy after breast cancer is safe, and the risk of death was low in women who became pregnant ≥49 months after the diagnosis of breast cancer. The prognosis of women who became pregnant was better than that of women who did not conceive after breast cancer diagnosis, regardless of endocrine therapy. The prognosis of pregnant women after the diagnosis of breast cancer was non-inferior to that of non-pregnant women, even in women who received chemotherapy and trastuzumab. These findings suggest the long-term safety of pregnancy after breast cancer diagnosis regardless of different types of treatment received and provide reassurance to patients with HER2-positive cancer who are considering future pregnancy.

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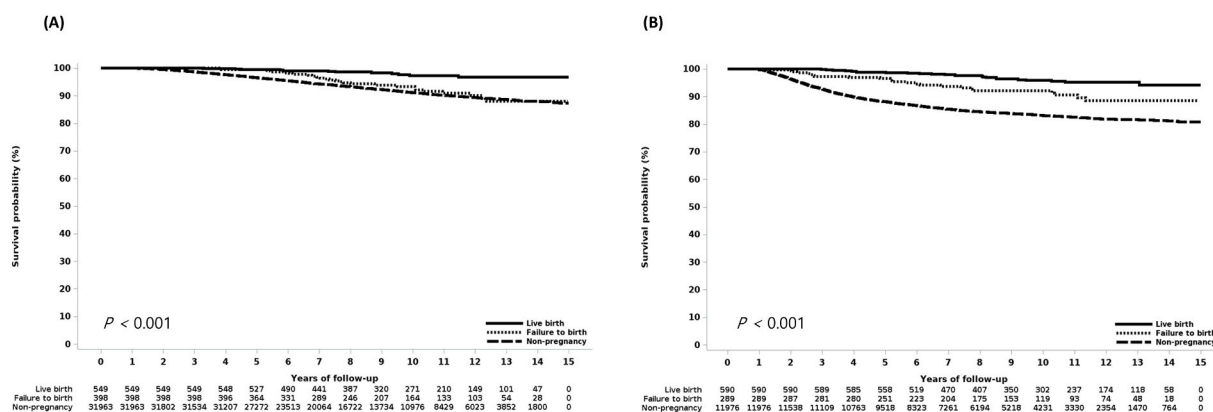
**Author contributions**

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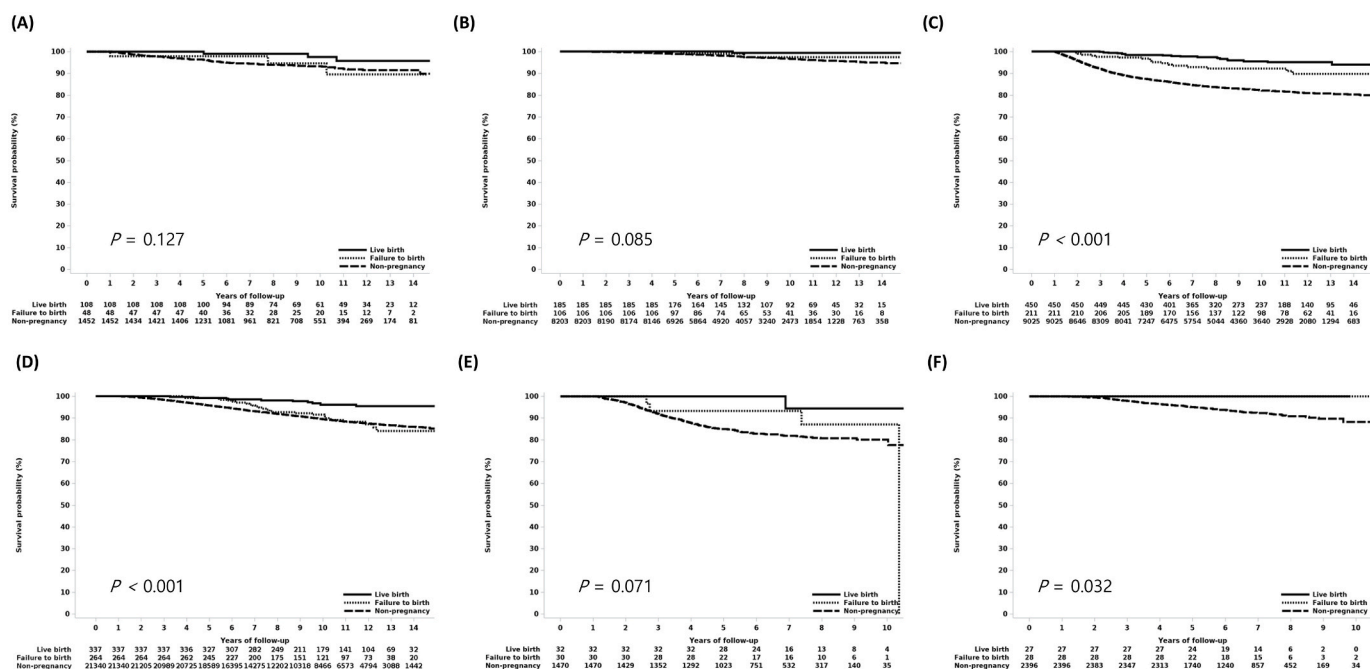
**Table 7**

Hazard ratio in the live birth group, the group that failed to give birth, and the non-pregnant group stratified by the treatment received.

	HR (95% CI)	P-value
None		
Live birth	0.43 (0.15, 1.27)	0.127
Failure to birth	1.10 (0.38, 3.22)	0.866
Non-pregnancy	ref	
Endocrine therapy only		
Live birth	0.24 (0.05, 1.22)	0.085
Failure to birth	0.76 (0.22, 2.67)	0.674
Non-pregnancy	ref	
Chemotherapy only		
Live birth	0.23 (0.15, 0.36)	<0.001
Failure to birth	0.45 (0.28, 0.72)	<0.001
Non-pregnancy	ref	
Endocrine therapy + Chemotherapy		
Live birth	0.31 (0.18, 0.56)	<0.001
Failure to birth	0.94 (0.64, 1.39)	0.762
Non-pregnancy	ref	
Chemotherapy + Trastuzumab		
Live birth	0.23 (0.05, 1.13)	0.071
Failure to birth	0.80 (0.31, 2.03)	0.630
Non-pregnancy	ref	
Endocrine therapy + Chemotherapy + Trastuzumab		
Live birth	0.24 (0.02, 3.90)	0.316
Failure to birth	0.24 (0.01, 3.82)	0.308
Non-pregnancy	ref	



**Fig. 3.** Overall survival outcomes of the live birth group, the group that failed to give birth, and the non-pregnant group. (A) The endocrine therapy group. (B) The non-endocrine therapy group.



**Fig. 4.** Overall survival outcomes of the live birth group, the group that failed to give birth, and the non-pregnant group stratified by the treatment received. (A) No treatment. (B) Endocrine therapy only. (C) Chemotherapy only. (D) Endocrine therapy + Chemotherapy. (E) Chemotherapy + Trastuzumab. (F) Endocrine therapy + Chemotherapy + Trastuzumab.

**Methodology:** Bae SY, Lee J, Park S; **Resources:** Bae SY, Park S; **Supervision:** Kim KS, Kim YS, Kim Z, Min JW, Shim EJ, Lee I, Lee MH; **Writing - original draft:** Bae SY, Lee J, Park S; **Writing - review & editing:** Bae SY, Lee J, Park S.

**Declaration of competing interest**

The authors declare that they have no competing interests.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2022.03.005>.

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