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Pregnancy After Breast Cancer in Young *BRCA* Carriers
An International Hospital-Based Cohort Study

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IMPORTANCE Young women with breast cancer who have germline pathogenic variants in *BRCA1* or *BRCA2* face unique challenges regarding fertility. Previous studies demonstrating the feasibility and safety of pregnancy in breast cancer survivors included limited data regarding *BRCA* carriers.

OBJECTIVE To investigate cumulative incidence of pregnancy and disease-free survival in young women who are *BRCA* carriers.

DESIGN, SETTING, AND PARTICIPANTS International, multicenter, hospital-based, retrospective cohort study conducted at 78 participating centers worldwide. The study included female participants diagnosed with invasive breast cancer at age 40 years or younger between January 2000 and December 2020 carrying germline pathogenic variants in *BRCA1* and/or *BRCA2*. Last delivery was October 7, 2022; last follow-up was February 20, 2023.

EXPOSURE Pregnancy after breast cancer.

MAIN OUTCOMES AND MEASURES Primary end points were cumulative incidence of pregnancy after breast cancer and disease-free survival. Secondary end points were breast cancer–specific survival, overall survival, pregnancy, and fetal and obstetric outcomes.

RESULTS Of 4732 *BRCA* carriers included, 659 had at least 1 pregnancy after breast cancer and 4073 did not. Median age at diagnosis in the overall cohort was 35 years (IQR, 31-38 years). Cumulative incidence of pregnancy at 10 years was 22% (95% CI, 21%-24%), with a median time from breast cancer diagnosis to conception of 3.5 years (IQR, 2.2-5.3 years). Among the 659 patients who had a pregnancy, 45 (6.9%) and 63 (9.7%) had an induced abortion or a miscarriage, respectively. Of the 517 patients (79.7%) with a completed pregnancy, 406 (91.0%) delivered at term (≥37 weeks) and 54 (10.4%) had twins. Among the 470 infants born with known information on pregnancy complications, 4 (0.9%) had documented congenital anomalies. Median follow-up was 7.8 years (IQR, 4.5-12.6 years). No significant difference in disease-free survival was observed between patients with or without a pregnancy after breast cancer (adjusted hazard ratio, 0.99; 95% CI, 0.81-1.20). Patients who had a pregnancy had significantly better breast cancer–specific survival and overall survival.

CONCLUSIONS AND RELEVANCE In this global study, 1 in 5 young *BRCA* carriers conceived within 10 years after breast cancer diagnosis. Pregnancy following breast cancer in *BRCA* carriers was not associated with decreased disease-free survival.

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Supplemental content

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A substantial proportion of young women with newly diagnosed breast cancer are interested in future fertility.[1,2] More than 12% of these young patients carry a germline pathogenic variant in the *BRCA1* or *BRCA2* genes.[3] Reproductive counseling of *BRCA* carriers is particularly complex considering the psychological fear of transmitting the pathogenic variant to their offspring,[4] the possible negative impact of deficient BRCA function on their ovarian reserve and fertility potential,[5] and the indication to undergo risk-reducing bilateral salpingo-oophorectomy at a young age due to increased risk of ovarian cancer.[6] Moreover, while several studies have demonstrated the safety of conceiving following treatment completion for breast cancer, the evidence for *BRCA* carriers is very limited.[7] Concerns exist about maternal and fetal safety of conceiving after breast cancer due to the hormone surge during pregnancy potentially increasing breast cancer (a hormone-driven tumor) recurrence risk and the possible negative fetal effects of prior exposure of women and their reproductive organs to anticancer therapies.[7]

We previously reported preliminary results from a study including 1252 *BRCA* carriers from 30 centers showing no apparent negative consequences in maternal or fetal outcomes in patients with a pregnancy after breast cancer.[8] However, the overall sample size was smaller than expected per study initial statistical assumptions and limited analyses could be performed.[8] Hence, concerns remain regarding feasibility and safety of pregnancy in this population.[9] Thus, additional patients have been included in this larger international study, which includes the 1252 *BRCA* carriers in the first report,[8] in order to investigate the cumulative incidence of pregnancy after breast cancer and reproductive and disease outcomes in *BRCA* carriers.

Key Points

Question Among women carrying germline *BRCA* pathogenic variants, is pregnancy after breast cancer associated with adverse maternal or fetal outcomes?

Findings This international, hospital-based, retrospective cohort study including 4732 *BRCA* carriers showed that 1 in 5 patients conceived within 10 years after breast cancer diagnosis. Pregnancy following breast cancer in *BRCA* carriers was not associated with adverse maternal prognosis or fetal outcomes.

Meaning The cumulative incidence of pregnancy after breast cancer and disease-free survival in this large international cohort of young *BRCA* carriers may inform care for affected patients.

Methods

Study Design, Setting, and Patients

This was an international, multicenter, hospital-based, retrospective cohort study including female *BRCA* carriers with a history of breast cancer.[8]

To be eligible for inclusion, female participants (sex was assigned based on medical records) had to be diagnosed at age 40 years or younger with invasive breast cancer between January 2000 and December 2020 carrying germline likely pathogenic or pathogenic variants in the *BRCA1* and/or *BRCA2* genes. Healthy *BRCA* carriers or patients with *BRCA* variants of unknown significance, noninvasive breast cancer, or history of other malignancies prior to breast cancer diagnosis were excluded. Patients with de novo stage IV breast cancer or lack of data on posttreatment pregnancies were also excluded. Data sets from countries with more than 1 participating center were cross-checked to exclude potential patient duplication.

Data Collection and Study Oversight

Data collected for all eligible patients included breast cancer history and treatment, type of germline *BRCA* pathogenic variant and risk-reducing management, recurrence data, survival, and reproductive outcomes. Diagnostic and staging workup, treatment, and follow-up were performed by each center according to clinical practice. Patients' pregnancy status was determined based on follow-up information collected from the medical records (by patient self-report during follow-up clinic visits and/or by serial patient survey depending on the center). Information on pregnancy status was based on the first pregnancy (regardless of outcome) after breast cancer diagnosis. Patients whose initial breast cancer diagnosis occurred while pregnant, without a subsequent new pregnancy, were not considered to have become pregnant after diagnosis.

The Institut Jules Bordet (Brussels, Belgium) was the coordinating center and served as the central ethics committee. The study also received ethics approval by the local, regional, or national institutional review boards of participating centers whenever required by regulations. Written informed consent was obtained from participants before inclusion for centers with this requirement. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was followed to report this work.[10]

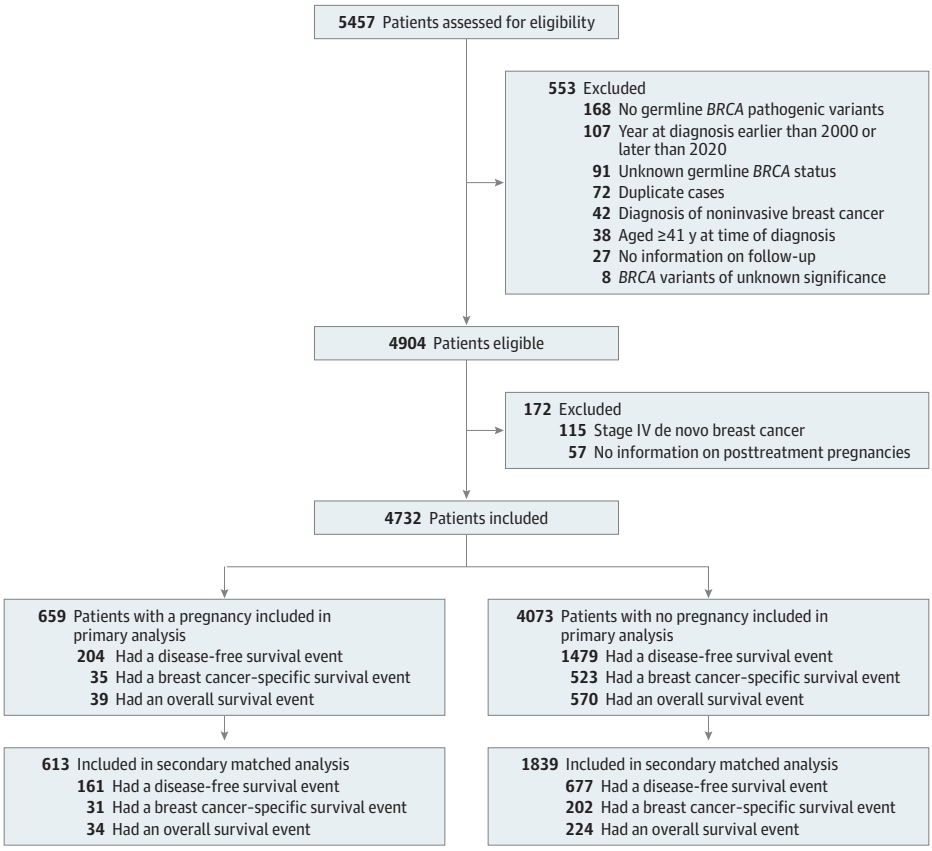
Statistical Analysis

The study protocol is available in Supplement 1. The primary objectives of this study were to determine the cumulative incidence of pregnancy after breast cancer and its prognostic impact in *BRCA* carriers. The primary end points were the cumulative incidence of pregnancy and disease-free survival. There were 12 secondary end points, including breast cancer-specific survival and overall survival, as well as pregnancy, fetal, and obstetric outcomes. The following parameters for fetal and obstetric outcomes were assessed: patient age at conception, time from breast cancer diagnosis to conception (ie, pregnancy interval), type of conception, number of preterm (<37 weeks) or full-term (≥37 weeks) pregnancies, live births, induced or spontaneous abortions, congenital malformations, pregnancy and/or obstetric complications, and incidence and duration of breastfeeding.

Predefined subgroup analyses according to specific *BRCA* gene (*BRCA1* or *BRCA2*), hormone receptor status (positive or negative), *ERBB2* status (positive or negative), exposure to chemotherapy (prior exposure or no prior exposure), and exposure to endocrine therapy (prior exposure or no prior exposure) were conducted.

Categorical variables were summarized using proportions, and the χ^2 test for heterogeneity was used for comparison; continuous variables were summarized using medians and

Figure 1. Participant Flow



IQRs and compared using the Wilcoxon-Mann-Whitney test. The Kaplan-Meier method was used to compute the cumulative incidence of pregnancy. The median follow-up was computed using the reverse Kaplan-Meier method.[11]

To assess the prognostic impact of pregnancy after breast cancer, we examined the association of pregnancy status with the rate of several outcomes. A disease-free survival event was defined as the occurrence of 1 of the following invasive events: locoregional recurrence, distant metastases, new contralateral or ipsilateral invasive breast cancer, second primary malignancy, or death due to any cause. A breast cancer–specific survival event was defined as death due to breast cancer, and patients who died for reasons other than breast cancer were censored at the date of death. An overall survival event was defined as death due to any cause. Observation time of patients without a survival event of interest was censored on the date of their last contact. Rates for disease-free survival events were computed as the ratio between the total number of events and the total of the observation times. Patients who became pregnant after breast cancer contributed to the nonpregnant observation time until estimated time of conception.

To quantify the association between pregnancy and subsequent events, we used an extended Cox model with occurrence of pregnancy as a time-varying covariate. The multivariate models included as stratification factors the variables associated with survival outcomes that were differently distributed between patients who became pregnant after breast cancer and those who did not (ie, region, age, nodal status, hormone receptor status, and type of breast surgery). To avoid the exclusion of patients with missing information, we grouped into the "unknown" category patients with missing values on each covariate included in the model. No imputation or other method for handling missing data was applied.

A secondary analysis matched each patient with a pregnancy after breast cancer with 3 patients without subsequent pregnancy according to disease-free interval (defined as time from breast cancer diagnosis to conception), specific *BRCA* gene, hormone receptor status, nodal status, and year at diagnosis (eAppendix in Supplement 2). For this analysis, all survival outcomes were calculated from the date of conception (or a similar disease-free interval in matched patients with no pregnancy) and are presented by Kaplan-Meier plots.

All statistical analyses were 2-sided with $P < .05$ considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Patients

From 78 centers worldwide, 4732 of 5457 patients were eligible for this analysis; for most of the 1252 *BRCA* carriers from

Table 1. Patient Characteristics at Diagnosis of Breast Cancer

Characteristics	No. (%)		
	Overall cohort (n = 4732)	Patients with a pregnancy (n = 659)[a]	Patients with no pregnancy (n = 4073)
Region			
Southern Europe	2080 (44.0)	303 (46.0)	1777 (43.6)
Asia	780 (16.5)	130 (19.7)	650 (16.0)
Northern Europe	709 (15.0)	110 (16.7)	599 (14.7)
North America	519 (11.0)	59 (9.0)	460 (11.3)
Eastern Europe	304 (6.4)	22 (3.3)	282 (6.9)
Australia/Oceania	193 (4.1)	26 (3.9)	167 (4.1)
Latin America/South America	147 (3.1)	9 (1.4)	138 (3.4)
Year at diagnosis of breast cancer			
2000-2004	604 (12.8)	106 (16.1)	498 (12.2)
2005-2008	788 (16.7)	141 (21.4)	647 (15.9)
2009-2012	1005 (21.2)	170 (25.8)	835 (20.5)
2013-2016	1158 (24.5)	159 (24.1)	999 (24.5)
2017-2020	1177 (24.9)	83 (12.6)	1094 (26.9)
Age at diagnosis of breast cancer, y			
≤30	977 (20.7)	331 (50.2)	646 (15.9)
31-35	1720 (36.4)	262 (39.8)	1458 (35.8)
36-40	2035 (43.0)	66 (10.0)	1969 (48.3)
Median (IQR)	35 (31-38)	30 (28-33)	35 (32-38)
Specific *BRCA* gene			
BRCA1	3033 (64.1)	483 (73.3)	2550 (62.6)
BRCA2	1663 (35.1)	170 (25.8)	1493 (36.7)
BRCA1 and *BRCA2*	26 (0.6)	3 (0.5)	23 (0.6)
BRCA, unknown if *BRCA1* or *BRCA2*	10 (0.2)	3 (0.5)	7 (0.2)
Tumor characteristics			
Histology	n = 4575	n = 634	n = 3941
Ductal carcinoma	3921 (85.7)	560 (88.3)	3361 (85.3)
Lobular carcinoma	135 (3.0)	10 (1.6)	125 (3.2)
Mixed ductal/lobular	57 (1.3)	7 (1.1)	50 (1.3)
Invasive, not specified	201 (4.4)	24 (3.8)	177 (4.5)
Other[b]	261 (5.7)	33 (5.2)	228 (5.8)
Grade[c]	n = 4266	n = 605	n = 3661
G1	79 (1.9)	8 (1.3)	71 (1.9)
G2	991 (23.2)	119 (19.7)	872 (23.8)
G3	3196 (74.9)	478 (79.0)	2718 (74.2)
Size[d]	n = 4500	n = 629	n = 3871
T1 (≤2 cm)	1811 (40.2)	282 (44.8)	1529 (39.5)
T2 (>2 to ≤5 cm)	2050 (45.6)	270 (42.9)	1780 (46.0)
T3 (>5 cm) to T4	639 (14.2)	77 (12.2)	562 (14.5)
Nodal status[d]	n = 4546	n = 638	n = 3908
N0	2434 (53.5)	399 (62.5)	2035 (52.1)
N1	1556 (34.2)	180 (28.2)	1376 (35.2)
N2 to N3	556 (12.2)	59 (9.3)	497 (12.7)
Hormone receptor status	n = 4655	n = 648	n = 4007
ER and/or PR positive	2126 (45.7)	216 (33.3)	1910 (47.7)
ER and PR negative	2529 (54.3)	432 (66.7)	2097 (52.3)
ERBB2 status	n = 4490	n = 625	n = 3865
Negative	4151 (92.5)	589 (94.2)	3562 (92.2)
Positive	339 (7.6)	36 (5.8)	303 (7.8)

(continued)

Table 1. Patient Characteristics at Diagnosis of Breast Cancer (continued)

Characteristics	No. (%)		
	Overall cohort (n = 4732)	Patients with a pregnancy (n = 659)[a]	Patients with no pregnancy (n = 4073)
Treatment			
Breast surgery	n = 4635	n = 646	n = 3989
None	15 (0.3)	2 (0.3)	13 (0.3)
Breast-conserving surgery	1826 (39.4)	315 (48.8)	1511 (37.9)
Mastectomy	2794 (60.3)	329 (50.9)	2465 (61.8)
Received chemotherapy	4319/4700 (91.9)	611/658 (92.9)	3708/4042 (91.7)
Type of chemotherapy[e]	n = 4169	n = 598	n = 3571
Anthracycline and taxane based	3051 (73.2)	414 (69.2)	2637 (73.8)
Anthracycline based	798 (19.1)	143 (23.9)	655 (18.3)
Taxane based	188 (4.5)	19 (3.2)	169 (4.7)
Other	132 (3.2)	22 (3.7)	110 (3.1)
Received endocrine therapy[f]	1987/2098 (94.7)	197/215 (91.6)	1790/1883 (95.1)
Type of endocrine therapy[g]	n = 1969	n = 196	n = 1773
Tamoxifen alone	702 (35.7)	64 (32.7)	638 (36.0)
Tamoxifen plus LHRH agonist	550 (27.9)	81 (41.3)	469 (26.5)
LHRH agonist alone	43 (2.2)	7 (3.6)	36 (2.0)
Aromatase inhibitor with or without LHRH agonist	355 (18.0)	21 (10.7)	334 (18.8)
Tamoxifen and aromatase inhibitor (with or without LHRH agonist)	293 (14.9)	19 (9.7)	274 (15.5)
Other	26 (1.3)	4 (2.0)	22 (1.2)
Duration of endocrine therapy, median (IQR), mo	60 (27-60)	48 (24-60)	60 (28-60)
Unknown, No.	507	40	467

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; LHRH, luteinizing hormone–releasing hormone.

[a] Patients with a pregnancy included women with at least 1 pregnancy (irrespective of the outcome) any time following breast cancer diagnosis. Information on pregnancy after breast cancer was collected from medical records based on patient self-report during follow-up clinic visits and/or by serial patient survey, depending on the center.

[b] Other histology findings included medullary (n = 87), metaplastic (n = 25), mucinous (n = 19), papillary (n = 9), micropapillary (n = 7), apocrine (n = 7), squamous cell (n = 4), tubular carcinoma (n = 4), salivary gland type (n = 3), secretory (n = 3), pleomorphic variant (n = 3), comedocarcinoma (n = 1), neuroendocrine (n = 1), adenosquamous (n = 1), cribriform (n = 1), colloid (n = 1), and unknown (n = 85).

[c] Histologic grade was based on the degree of tumor histologic differentiation.

[d] Tumor size and nodal status were assessed clinically for patients who received neoadjuvant systemic therapy and pathologically for those who received breast surgery as first treatment.

[e] Calculated among patients who received chemotherapy.

[f] Calculated among patients with hormone receptor–positive breast cancer.

[g] Calculated among patients with hormone receptor–positive breast cancer who received endocrine therapy.

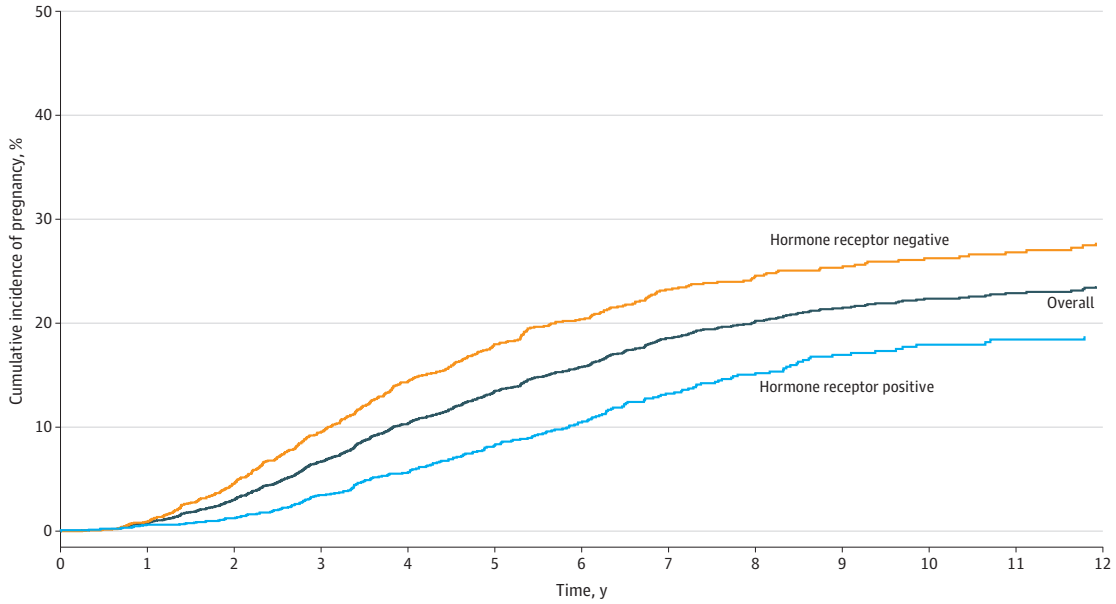
30 centers previously reported, the follow-up was updated.[8] Among the included patients, during the observation time, 659 had at least 1 pregnancy following breast cancer and 4073 did not (**Figure 1**). Overall, median follow-up was 7.8 years (IQR, 4.5-12.6 years) (eTable 1 in Supplement 2). The last delivery was October 7, 2022; the last follow-up was February 20, 2023.

Median age at diagnosis in the overall cohort was 35 years (IQR, 31-38 years). Compared with patients with no pregnancy, those with a pregnancy after breast cancer were younger at diagnosis of breast cancer. They were also more likely to carry *BRCA1* pathogenic variants, to have node-negative and hormone receptor–negative breast cancer, to undergo breast-conserving surgery, and, if diagnosed with hormone receptor–positive disease, to receive ovarian suppression treatment as part of adjuvant endocrine therapy for a shorter period (**Table 1**; eTable 2 in Supplement 2). During follow-up, 2443 patients (51.6%) underwent risk-reducing salpingo-oophorectomy, 279 (42.3%) of those with a pregnancy after breast cancer and 2164 (53.1%) of those with no pregnancy.

Overall, the cumulative incidence of pregnancy at 10 years was 22% (95% CI, 21%-24%) (**Figure 2**). In patients with hormone receptor–positive and hormone receptor–negative breast cancer, the cumulative incidence of pregnancy at 10 years was 18% (95% CI, 16%-21%) and 26% (95% CI, 24%-29%), respectively ($P < .001$) (Figure 2).

The median age at conception was 34.7 years (IQR, 31.8-37.3 years). The median time from breast cancer diagnosis to conception was 3.5 years (IQR, 2.2-5.3 years; 27.8% of pregnancies occurred after 5 years). This interval was significantly longer in patients with hormone receptor–positive breast cancer (4.3 years [IQR, 2.8-6.3 years]; 39.8% of pregnancies occurred after 5 years) than in those with hormone receptor–negative disease (3.2 years [IQR, 2.0-4.8 years]; 22.0% of pregnancies occurred after 5 years) ($P < .001$). A total of 121 patients (20.8%) had a pregnancy with use of assisted reproductive technology. Of the 659 patients who had a pregnancy (**Table 2**; eTable 3 in Supplement 2), 45 (6.9%) and 63 (9.7%) had an induced abortion or a miscarriage, respectively. Among 517 patients (79.7%) with a completed pregnancy,

Figure 2. Cumulative Incidence of Pregnancy Overall and According to Hormone Receptor Status



No. at risk (No. of pregnancies)													
Overall	4732 (0)	4475 (210)	3915 (466)	3253 (524)	2723 (410)	2262 (370)	1880 (326)	1510 (313)	1229 (253)	1006 (202)	826 (169)	669 (152)	538 (126)
Hormone receptor													
Negative	2529 (0)	2360 (143)	2017 (261)	1650 (269)	1354 (213)	1125 (175)	946 (148)	762 (153)	631 (119)	525 (98)	431 (88)	355 (73)	286 (65)
Positive	2126 (0)	2042 (65)	1830 (200)	1543 (249)	1328 (182)	1104 (188)	909 (171)	732 (151)	585 (132)	470 (102)	385 (80)	305 (78)	245 (59)

Median observation time in the overall cohort was 5.6 years (IQR, 2.9-9.4 years); in patients with hormone receptor–positive disease, 5.8 years (IQR, 3.0-9.3 years); and in patients with hormone receptor–negative disease, 5.6 years (IQR, 2.7-9.6 years).

406 (91.0%) delivered at term (≥37 weeks) and 54 (10.4%) had twins. Congenital anomalies were documented in 4 of 470 infants (0.9%) born with known information on pregnancy complications.

Disease-Free Survival

There were 1683 disease-free survival events (Figure 1). The pattern of disease-free survival events among patients with a pregnancy after breast cancer and those without a pregnancy are reported in eTable 1 in Supplement 2. The association between pregnancy and the occurrence of disease-free survival events was not statistically significant (unadjusted hazard ratio [HR], 0.97 [95% CI, 0.82-1.15], $P = .74$; adjusted HR, 0.99 [95% CI, 0.81-1.20], $P = .90$). In adjusted subgroup analyses, a statistically significant interaction between occurrence of pregnancy and the following variables was observed: specific *BRCA* gene (*BRCA1*: adjusted HR, 0.80 [95% CI, 0.63-1.01]; *BRCA2*: adjusted HR, 1.55 [95% CI, 1.12-2.16]; $P = .007$ for interaction); hormone receptor status (hormone receptor-positive: adjusted HR, 1.30 [95% CI, 0.95-1.76]; hormone receptor-negative: adjusted HR, 0.76 [95% CI, 0.60-0.95]; $P = .009$ for interaction); and use of endocrine therapy (no use of endocrine therapy: adjusted HR, 0.85; [95% CI, 0.67-1.08]; use of endocrine therapy: adjusted HR, 1.55 [95% CI, 1.08-2.21]; $P = .01$ for interaction) (**Table 3**; eTable 4 in Supplement 2).

Secondary Survival Outcomes

There were 558 breast cancer–specific survival events (Figure 1). The occurrence of pregnancy was associated with a lower rate of breast cancer–specific survival events (HR, 0.53 [95% CI, 0.37-0.74], $P < .001$; adjusted HR, 0.60 [95% CI, 0.40-0.88], $P = .009$). No significant interaction was observed between occurrence of pregnancy and any variable in adjusted subgroup analyses (eTable 5 in Supplement 2).

There were 609 overall survival events (Figure 1). The occurrence of pregnancy was associated with a lower rate of death due to any cause (unadjusted HR, 0.52, [95% CI, 0.38-0.72], $P < .001$; adjusted HR, 0.58 [95% CI, 0.40-0.85], $P = .005$). No significant interaction was observed between occurrence of pregnancy and any variable in adjusted subgroup analyses (eTable 6 in Supplement 2).

The eAppendix in Supplement 2 shows results from a secondary matched analysis that included 2452 patients, 613 with a pregnancy after breast cancer and 1839 matched patients with no pregnancy (eAppendix, eTables 2-9, and eFigures 1-3 in Supplement 2).

Discussion

This global study provides descriptive information on pregnancy after breast cancer in *BRCA* carriers from a much larger cohort than prior findings.[8] For the 22% of young *BRCA* carriers who conceived within 10 years after breast cancer diagnosis, subsequent pregnancy was not associated with adverse maternal prognosis or fetal outcomes.

The cumulative incidence of pregnancy observed in this study is higher than previously reported in young breast cancer

survivors.[7] This may be due to younger patient age at time of diagnosis, an increased priority of pregnancy for the indication to undergo risk-reducing bilateral salpingo-oophorectomy during reproductive years, and the large proportion of patients not requiring adjuvant endocrine therapy (54.3% had hormone receptor-negative breast cancer). As expected,[12] young women with a history of hormone receptor-positive breast cancer had lower cumulative incidence of pregnancy and longer time from diagnosis to conception than those with hormone receptor-negative disease, presumably due to use of endocrine therapy, during which pregnancy is contraindicated.[13] Nevertheless, 60% of pregnancies in patients with hormone receptor-positive breast cancer occurred within 5 years of diagnosis. This percentage is expected to increase based on the reassuring early results of the POSITIVE trial showing the safety of temporary interruption of endocrine therapy to attempt pregnancy 18 to 30 months into endocrine therapy.[14]

Women who are *BRCA* carriers face unique reproductive concerns. Significant knowledge gaps and misconceptions exist among physicians in their oncofertility counseling.[4] Young breast cancer survivors have reduced chances of future conception compared with the general population and young survivors of most other malignancies.[7] Current guidelines recommend close monitoring of posttreatment pregnancies in adult women with a history of cancer due to a higher risk of pregnancy complications, including preterm births, in cancer survivors compared with the general population.[15] The current recommendation is to wait at least 1 year following chemotherapy completion to attempt pregnancy due to a higher risk of pregnancy complications in women conceiving within 1 year following the end of cytotoxic therapy.[7,16] Results from our study, in which 80.1% of pregnancies occurred more than 2 years after diagnosis, provide evidence in the specific cohort of young *BRCA* carriers with a rate of pregnancy complications that are in line with the expectations in a population of women with similar age and no history of breast cancer.[17-19] The majority of information for this analysis was extracted from oncology medical records. These records are not specifically designed for recording maternal or fetal outcomes; hence, there is a potential risk of underreporting of adverse pregnancy outcomes and the data should be considered with caution.

The majority of the pregnancies occurred spontaneously (79.2%) despite receipt of prior chemotherapy in more than 90% of patients. Considering that the median age at diagnosis in patients with a pregnancy after breast cancer was 30 years, the risk of treatment-induced premature ovarian insufficiency and associated infertility can be considered relatively low in these patients.[15] Nevertheless, all young women diagnosed with cancer during reproductive years should be offered the opportunity to access fertility preservation strategies before initiating systemic anticancer therapies.[15,20,21] This is particularly relevant in young *BRCA* carriers considering their possible interest in accessing preimplantation genetic diagnosis for monogenic diseases,[15] as well as the potential increased risk of chemotherapy-induced premature ovarian insufficiency compared with age-matched noncarriers.[22] In addition, further treatments, including adjuvant olaparib for 1 year following cytotoxic therapy in *BRCA* carriers at higher risk of disease recurrence or carboplatin and pembrolizumab as neoadjuvant therapy for triple-negative breast cancer, may pose added risk to fertility, having shown possible gonadotoxicity in mouse models.[23-25] Future studies are needed to understand these risks.[26]

Only limited prior maternal safety data have specifically focused on *BRCA* carriers conceiving after breast cancer.[7] With

Table 2. Pregnancy, Fetal, and Obstetric Outcomes in Patients With a Pregnancy After Breast Cancer

Outcomes	No. (%) (n = 659)
Age at pregnancy, median (IQR), y	34.7 (31.8-37.3)
Time from diagnosis to conception, median (IQR) y	3.5 (2.2-5.3)
Pregnancy interval	
≤2 Years after diagnosis	131 (19.9)
Between >2 and ≤5 years after diagnosis	345 (52.4)
>5 Years after diagnosis	183 (27.8)
Type of conception	
Spontaneous pregnancy	461/582 (79.2)
Use of assisted reproductive technology	121/582 (20.8)
Embryo transfer after oocyte/embryo cryopreservation at diagnosis of breast cancer	48
Embryo transfer following oocyte donation	29
Ovarian stimulation for IVF/ICSI/ovulation induction after anticancer treatment	36
Unknown type of assisted reproductive technology	8
Pregnancy outcome	n = 649
Delivered	517 (79.7)
Ongoing pregnancy	24 (3.7)
Miscarriage	63 (9.7)
Induced abortion	45 (6.9)
No. of live births from first pregnancy after breast cancer[a]	n = 517
1	463 (89.6)
2	54 (10.4)
Timing of delivery[a]	n = 446
At term (≥37 wk)	406 (91.0)
Preterm (<37 wk)	40 (9.0)
Complications[a]	n = 423
None	365 (86.3)
Pregnancy complications	27 (6.4)
Delivery complications	22 (5.2)
Congenital abnormalities[b,c]	4 (0.9)
Fetal complications[b,c]	3 (0.6)
Other complications[c]	2 (0.5)
Breastfeeding[a]	133/403 (33.0)
Duration, median (IQR), mo	5 (2-6)
Unknown, No.	50

Abbreviations: IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

[a] Calculated from the total number of delivered pregnancies.

[b] Calculated from the total number of infants born to patients with known information on pregnancy complications (n = 470).

[c] Congenital abnormalities included cardiac malformation (n = 2), congenital diaphragmatic hernia (n = 1), and chromosome abnormality with karyotype 47,XXY (n = 1). Fetal complications included respiratory distress (n = 2) and neonatal icterus treated with phototherapy (n = 1). Other complications included maternal internal carotid artery aneurysm (n = 1) and kidney failure in the infant due to hypoxia (n = 1).

Table 3. Subgroup Analyses of Disease-Free Survival in Patients Who Had a Pregnancy (vs Patients With No Pregnancy)

Variables	No. of patients/No. of events	Univariate hazard ratio (95% CI)	*P* value	Multivariate hazard ratio (95% CI)	*P* value
Study group	4732/1683	0.97 (0.82-1.15)	.74	0.99 (0.81-1.20)	.90
Specific *BRCA* gene					
BRCA1	3033/1101	0.79 (0.64-0.97)	<.001[a]	0.80 (0.63-1.01)	.007[a]
BRCA2	1663/569	1.61 (1.22-2.12)		1.55 (1.12-2.16)	
BRCA1 and *BRCA2*	26/11	1.82 (0.33-10.1)		4.49 (0.28-72.17)	
BRCA, unknown if *BRCA1* or *BRCA2*	10/2	1.11 (0.05-23.2)		NE	
Hormone receptor status					
Positive	2126/715	1.29 (0.98-1.70)	.04[a]	1.30 (0.95-1.76)	.009[a]
Negative	2529/951	0.82 (0.67-1.01)		0.76 (0.60-0.95)	
Unknown	77/17	1.08 (0.25-4.74)		0.28 (0.04-2.21)	
ERBB2 status					
Positive	339/111	0.66 (0.24-1.80)	.30[a]	0.61 (0.22-1.71)	.08[a]
Negative	4151/1471	1.01 (0.85-1.21)		1.07 (0.87-1.31)	
Unknown	242/101	0.61 (0.30-1.26)		0.42 (0.17-1.02)	
Chemotherapy					
No chemotherapy	381/138	1.06 (0.61-1.87)	.31[a]	0.77 (0.39-1.52)	.47[a]
(Neo)adjuvant chemotherapy	4319/1534	0.97 (0.82-1.16)		1.00 (0.82-1.23)	
Unknown	32/11	NE		0.77 (0.39-1.52)	
Endocrine therapy					
No endocrine therapy	2640/998	0.82 (0.67-1.01)	.02[a]	0.85 (0.67-1.08)	.01[a]
Endocrine therapy	1987/659	1.35 (1.01-1.81)		1.55 (1.08-2.21)	
Unknown	105/26	0.77 (0.18-3.23)		0.13 (0.01-2.95)	

Abbreviation: NE, not evaluable.

[a] *P* value for interaction.

the exception of the disease-free survival analysis with the extended Cox model showing an adjusted HR of 0.99 (95% CI, 0.81-1.20), the other analyses of breast cancer-specific survival and overall survival showed significantly better outcomes for young *BRCA* carriers with a pregnancy after breast cancer. The consistent findings of safety in the different models and analyzed outcomes, the large sample size with global representation, and the median follow-up of nearly 8 years support the lack of detrimental prognostic effect of pregnancy after breast cancer in *BRCA* carriers.

Results for most of the analyzed subgroups were consistent with those of the overall study. However, there was a significant interaction between occurrence of pregnancy and specific *BRCA* gene. Specifically, pregnancy appeared to be associated with lower event rates among *BRCA1* carriers in all the analyses. On the contrary, among *BRCA2* carriers, the analysis identified a signal for a possible association between pregnancy and adverse disease-free survival outcomes (adjusted HR, 1.55; 95% CI, 1.12-2.16). No interaction between occurrence of pregnancy and specific *BRCA* gene was observed for the other survival outcomes. An apparent protective association was observed in *BRCA1* carriers in breast cancer-specific survival and overall survival; HRs were close to 1.00 with the 95% CI crossing unity in both directions in *BRCA2* carriers. Thus, while the results appear reassuring for *BRCA1* carriers, more caution is needed to counsel *BRCA2* carriers. Considering that there is evidence of a potentially differential impact of reproductive factors on breast cancer risk and outcomes according to the specific *BRCA* gene,[27-30] our data highlight the need to pursue further research efforts in this area. A possible impact of hormone receptor status cannot be excluded considering that *BRCA1* and *BRCA2* carriers tend to more often develop hormone receptor-negative and hormone receptor-positive breast cancers, respectively. Several prior studies suggested that pregnancy after breast cancer is associated with improved outcomes in patients with a history of hormone receptor-negative disease and may have no effect in those with hormone receptor-positive tumors.[7] Our study has also shown an interaction between occurrence of pregnancy and hormone receptor status (and, subsequently, use of endocrine therapy) for the disease-free survival end point only. Our finding that the 95% CI crossed unity suggests no detrimental impact of pregnancy in the group of patients with hormone receptor-positive breast cancer. This is in line with the evidence from other studies addressing specifically the question on the safety of pregnancy following history of hormone receptor-positive breast cancer.[31] In our study, more than half of these patients had a pregnancy within the first 5 years, and timing of pregnancy after breast cancer did not appear to affect the results. Long-term follow-up of the POSITIVE trial,[14] which included a small group of *BRCA* carriers, will provide further evidence in this regard.

Interpretation of these results should note that the treatment landscape of early breast cancer has evolved substantially over the past 20 years. This is particularly relevant for premenopausal women with hormone receptor-positive

breast cancer; currently, these patients more frequently receive a recommendation to have ovarian function suppression as part of adjuvant endocrine therapy.[21] Moreover, in some health systems, patients with high risk of disease recurrence may receive adjuvant abemaciclib for 2 years in addition to endocrine therapy or adjuvant olaparib for 1 year following standard chemotherapy to further reduce the risk of recurrence.[21] Therefore, the lack of clear detriment seen in survival outcomes in this study, including among patients with hormone receptor–positive disease (the majority of them being *BRCA2* carriers), should be considered in the context of patient risk of recurrence and the better available treatment today.

Limitations

This study has some limitations. First, the retrospective observational design of the study and the choice of exposure variable limit the ability to draw causal conclusions. Second, information on pregnancies after breast cancer as well as pregnancy, fetal, and obstetric outcomes was extracted mainly from oncology medical records that were not set up specifically for these outcomes or serial patient survey, and was based on patient self-report; this may be particularly true for peripartum and neonatal complications. Hence, a potential risk of underreporting cannot be excluded. Third, some information on pregnancy outcomes was missing or not recorded (eg, reasons for induced abortion); data on pregnancy desire, contraceptive use, or potential use of restaging imaging studies before attempting pregnancy were not collected. Fourth, the study included data from 78 centers worldwide with different health care systems; patients were treated over a period of 20 years, during which the treatment of early breast cancer has improved, particularly for hormone receptor–positive disease. Patients diagnosed toward the end of the period for study inclusion had less observation time to conceive as well as to evaluate outcomes and recurrences. Finally, despite all attempts to account for the potential confounding in this type of analyses, it cannot be excluded that patients at higher risk of disease recurrence were counseled differently and/or that healthier women without impending subclinical recurrence were more able to become pregnant.

Conclusions

This study showed that more than 1 in 5 young *BRCA* carriers became pregnant following diagnosis of early breast cancer and that disease-free survival was comparable with those who did not become pregnant. Our results can inform counseling of young *BRCA* carriers interested in conceiving following breast cancer diagnosis.

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