original reports

Pregnancy After Breast Cancer in Patients With Germline *BRCA* Mutations

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abstract

PURPOSE Young women with germline *BRCA* mutations have unique reproductive challenges. Pregnancy after breast cancer does not increase the risk of recurrence; however, very limited data are available in patients with *BRCA* mutations. This study investigated the impact of pregnancy on breast cancer outcomes in patients with germline *BRCA* mutations.

PATIENTS AND METHODS This is an international, multicenter, hospital-based, retrospective cohort study. Eligible patients were diagnosed between January 2000 and December 2012 with invasive early breast cancer at age ≤ 40 years and harbored deleterious germline *BRCA* mutations. Primary end points were pregnancy rate, and disease-free survival (DFS) between patients with and without a pregnancy after breast cancer. Pregnancy outcomes and overall survival (OS) were secondary end points. Survival analyses were adjusted for guarantee-time bias controlling for known prognostic factors.

RESULTS Of 1,252 patients with germline *BRCA* mutations (*BRCA1*, 811 patients; *BRCA2*, 430 patients; *BRCA1/2*, 11 patients) included, 195 had at least 1 pregnancy after breast cancer (pregnancy rate at 10 years, 19%; 95% CI, 17% to 22%). Induced abortions and miscarriages occurred in 16 (8.2%) and 20 (10.3%) patients, respectively. Among the 150 patients who gave birth (76.9%; 170 babies), pregnancy complications and congenital anomalies occurred in 13 (11.6%) and 2 (1.8%) cases, respectively. Median follow-up from breast cancer diagnosis was 8.3 years. No differences in DFS (adjusted hazard ratio [HR], 0.87; 95% CI, 0.61 to 1.23; $P = .41$) or OS (adjusted HR, 0.88; 95% CI, 0.50 to 1.56; $P = .66$) were observed between the pregnancy and nonpregnancy cohorts.

CONCLUSION Pregnancy after breast cancer in patients with germline *BRCA* mutations is safe without apparent worsening of maternal prognosis and is associated with favorable fetal outcomes. These results provide reassurance to patients with *BRCA*-mutated breast cancer interested in future fertility.

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INTRODUCTION

Future family planning represents a priority area of concern for a significant proportion of young women with newly diagnosed breast cancer.[1,2] As a consequence of the current trend toward delaying childbearing, increasing numbers of young patients are diagnosed before the completion of their reproductive plans.[1,2] Previously, we have demonstrated 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 disease.[3-6] On the basis of the results of these studies, no international guidelines advise against pregnancy in young patients with breast cancer who completed anticancer treatments.[7,8]

Approximately 12% of breast malignancies that arise in women age < 40 years are related to germline deleterious mutations in the breast cancer susceptibility genes *BRCA1* and/or *BRCA2*.[9,10] These patients may have a reduced ovarian reserve and fertility potential[11,12] and are often subjected to risk-reducing bilateral salpingo-oophorectomy by their 40s because of increased ovarian cancer risk.[13] Hence, reproductive considerations and family planning may be particularly overwhelming among patients with *BRCA*-mutated breast cancer.[14] In addition, although growing evidence supports the safety of pregnancy in women with a history of breast cancer,[3-6,15] very limited data are available with regard to patients with *BRCA* mutations.[14] Therefore, to date, uncertainties remain about reproductive outcomes

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

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 disease. However, very limited data are available to counsel women who harbor germline *BRCA* mutations on this regard. To our knowledge, this is the largest study to date specifically designed to address several unmet questions related to the safety of pregnancy after breast cancer in patients with germline *BRCA* mutations and their reproductive outcomes.

Knowledge Generated

This study provides reassuring evidence that pregnancy after breast cancer in patients with *BRCA* mutations is safe without apparent worsening of maternal prognosis in terms of disease-free survival and overall survival. Favorable fetal outcomes were observed.

Relevance

These results provide reassurance to patients with *BRCA*-mutated breast cancer who are interested in future fertility. They are also of paramount importance for health care providers involved in counseling young patients with *BRCA*-mutated breast cancer who inquire about the feasibility and safety of future conception.

in these women and whether a subsequent pregnancy may have a detrimental prognostic impact. A recent survey that involved > 250 breast cancer specialists showed that approximately 50% were concerned about the safety of pregnancy after breast cancer in women harboring germline *BRCA* mutations.[16]

Here, we report the results of what is, to our knowledge, the largest study to date that investigated the impact of pregnancy on breast cancer outcomes in women harboring germline *BRCA* mutations. We also report on the proportion of women having a pregnancy after breast cancer and their reproductive outcomes.

PATIENTS AND METHODS

Study Design and Patients

This international, multicenter, hospital-based, retrospective cohort study included patients with *BRCA*-mutated breast cancer from 30 referral centers worldwide. Eligible patients were women age ≤ 40 years newly diagnosed with stage I-III invasive breast cancer between January 2000 and December 2012 and who harbored deleterious germline *BRCA1* and/or *BRCA2* mutations. Patients with *BRCA* variants of unknown significance, history of ovarian cancer or other malignancies without prior diagnosis of invasive breast cancer, noninvasive or stage IV de novo breast cancer, or no follow-up or information on post-treatment pregnancies and healthy *BRCA* carriers were excluded. In countries with more than one participating center, data sets were cross checked to exclude potential duplicated patients. Whenever requested according to local regulations, the study received ethics approval by the local independent ethical review committee/institutional review board, and participants provided written informed consent before inclusion.

Procedures

For all eligible patients, data on breast cancer history, treatment, type of *BRCA* mutation, reproductive outcomes, recurrence, and survival status after breast cancer were collected. The achievement of pregnancy after breast cancer diagnosis was the criteria used to assign 2 cohorts of patients: women with ≥ 1 pregnancies independent of their outcome at any time after breast cancer diagnosis (pregnancy cohort) and women with no subsequent pregnancies (nonpregnancy cohort). The study was coordinated and sponsored by the Institut Jules Bordet, which acted as the central ethics committee and was responsible for study design, collection and management of data, medical review, data analysis, and reporting. This work is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[17]

Statistical Analysis

Pregnancy rate and disease-free survival (DFS) were primary end points. Overall survival (OS) as well as pregnancy, fetal, and obstetric outcomes were secondary end points. Pregnancy rate was computed according to the Kaplan-Meier method. To assess the prognostic impact of pregnancy after breast cancer in patients with germline *BRCA* mutations, DFS and OS were compared between the pregnancy and nonpregnancy cohorts. A DFS event was defined as the occurrence of one of the following invasive events: locoregional recurrence, distant metastases, new contralateral or ipsilateral breast cancer, second primary malignancy, or death as a result of any cause. An OS event was defined as death as a result of any cause. For DFS and OS, observation times of patients without the event were censored on the date of their last contact.

To account for guarantee-time bias[18] (ie, possible selection bias because women with a pregnancy already had

a disease-free interval until the date of conception), 2 analyses were performed. In the extended Cox model analysis with occurrence of pregnancy as a time-varying covariate,[6] all patients included in the study were considered. DFS and OS were calculated from date of breast cancer diagnosis. The factors with known prognostic implication that were differently distributed between the pregnancy and nonpregnancy cohorts were included in the multivariable models for all survival analyses.

In the case-control analysis,[4,5] for each patient in the pregnancy cohort (case), 3 patients from the nonpregnancy cohort (controls) were selected. Each nonpregnant control had a disease-free interval equal to or longer than the time that elapsed between breast cancer diagnosis and date of pregnancy of the matched pregnant case. Patients who became pregnant after the date of the DFS event were dropped from the analysis. The other matching factors were year at diagnosis (± 2.5 years), nodal status (negative *v* positive), hormone receptor status (positive *v* negative), and type of *BRCA* mutation (*BRCA1 v BRCA2*). Because all included patients were age ≤ 40 years at the time of diagnosis, matching according to age was not performed. The matching was done centrally at the coordinating center. Cases were sorted randomly, and matching was done with an automated program blinded to patients' outcomes starting from the first case until the last. DFS and OS were calculated from the date of pregnancy (or a similar disease-free interval in the nonpregnant controls), and Kaplan-Meier plots were used to present results with a follow-up time up to 10 years.

Power calculation was based on our previous study that investigated the safety of pregnancy in patients with breast cancer with estrogen receptor–positive disease.[4,5] Assuming a DFS rate of 65% at 5 years in the nonpregnancy cohort and a 10% pregnancy rate, with 200 and 2,000 patients in the pregnancy and nonpregnancy cohorts, respectively, the study would have a power of 0.83 to detect a hazard ratio (HR) of 0.75 or a power of 0.62 to detect an HR of 0.80 in favor of the pregnancy cohort at a 2-sided significance level of .05.

Predefined subgroup analyses of DFS according to type of *BRCA* mutation (*BRCA1 v BRCA2*) and hormone receptor status (positive *v* negative) were performed. Homogeneity tests on the HRs obtained in the planned subgroups were performed using the χ^2 test to assess whether there was evidence of an interaction between pregnancy and type of *BRCA* mutation or hormone receptor status. An exploratory subgroup analysis aimed to evaluate differences in DFS according to pregnancy outcome (abortion *v* completed pregnancy).

Descriptive analyses were used to evaluate pregnancy, fetal, and obstetric outcomes. Specifically, parameters to assess reproductive history after breast cancer were age of the patients at the time of pregnancy, pregnancy interval (ie, time from breast cancer diagnosis to pregnancy), type of conception, incidence of preterm (< 37 weeks) and full-term (≥ 37 weeks) pregnancies, number of pregnancies resulting in live birth, incidence of induced abortions and miscarriages, incidence and nature (if any) of pregnancy complications, congenital malformations and/or obstetric complications, and incidence and duration of breastfeeding. CIs for proportions were produced using the Wilson score method.

All statistical analyses were 2-sided, with $P < .05$ considered statistically significant. Analyses were performed by L.A. and M.P. using SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Patients

Of 1,424 patients registered in the study, 1,252 young patients with breast cancer with germline deleterious *BRCA* mutations were eligible to be included in the current analysis, of whom 195 had at least 1 pregnancy after breast cancer (Data Supplement, online only). Baseline patient, tumor, and treatment characteristics are listed in Table 1. Most of the included patients were treated in Europe (78.5%) and diagnosed after 2005 (78.4%). Patients in the pregnancy cohort were younger at diagnosis ($P < .001$) and had a higher rate of *BRCA1* mutations ($P = .01$), tumors ≤ 2 cm ($P = .04$), node-negative ($P = .003$) and hormone receptor–negative ($P = .002$) disease compared with those in the nonpregnancy cohort. A higher number of patients in the pregnancy cohort underwent breast-conserving surgery ($P < .001$). Chemotherapy was administered to 95.3% of the patients, with no difference between the 2 cohorts. Among women with hormone receptor–positive disease, those in the pregnancy cohort were more likely to have received ovarian function suppression as part of adjuvant endocrine therapy ($P = .002$) and had a shorter median duration of adjuvant endocrine therapy ($P < .001$). Among patients in the pregnancy and nonpregnancy cohorts with available information on risk-reducing surgeries, contralateral risk-reducing mastectomy was performed in 51.1% and 51.0% ($P = .99$), while risk-reducing salpingo-oophorectomy was performed in 42.9% and 56.6% ($P < .001$), respectively (Data Supplement).

Median age at the time of pregnancy was 35.7 years (interquartile range [IQR], 32.9-38.6 years). Pregnancies occurred after a median of 4.5 years (IQR, 3.1-6.7 years) after breast cancer diagnosis, with 44.6% of them occurring after 5 years. Median time from breast cancer diagnosis to pregnancy was 6.3 years (IQR, 4.3-7.7 years) and 4.0 years (IQR, 2.7-5.6 years) in patients with hormone receptor–positive and –negative disease, respectively ($P < .001$).

Reproductive Outcomes

The pregnancy rate at 10 years was 19% (95% CI, 17% to 22%) in the overall study population (Fig 1A). The pregnancy rate at 10 years was 16% (95% CI, 13% to 21%) and 21% (95% CI, 18% to 25%) in patients with hormone receptor–positive and –negative disease, respectively (Fig 1B).

TABLE 1. Patient and Tumor Baseline Characteristics

	All Included Patients, No. (%)			Case-Control Analysis, No. (%)		
Characteristic	**Pregnant**	**Not Pregnant**	***P***	**Pregnant**	**Not Pregnant**	***P***
No. of patients	195	1,057		176	528	
Country			.040			.003
Europe	149 (76.4)	834 (78.9)		131 (74.4)	417 (79.0)	
North America	11 (5.6)	69 (6.5)		11 (6.3)	41 (7.8)	
Latin America	3 (1.5)	44 (4.2)		3 (1.7)	26 (4.9)	
Israel	32 (16.4)	110 (10.4)		31 (17.6)	44 (8.3)	
Year at diagnosis			.150			.730
2000-2004	49 (25.1)	222 (21.0)		42 (23.9)	112 (21.2)	
2005-2008	74 (38.0)	377 (35.7)		66 (37.5)	210 (39.8)	
2009-2012	72 (36.9)	458 (43.3)		68 (38.6)	206 (39.0)	
Median age at diagnosis, years (IQR)	30 (28-33)	35 (32-38)	< .001	31 (29-33)	36 (33-38)	< .001
Age at diagnosis, years			< .001			< .001
≤ 30	102 (52.3)	170 (16.1)		91 (51.7)	87 (16.5)	
31-35	67 (34.4)	365 (34.5)		60 (34.1)	175 (33.1)	
36-40	26 (13.3)	522 (49.4)		25 (14.2)	266 (50.4)	
BRCA mutation			.010			.270
BRCA1	144 (73.9)	667 (63.1)		130 (73.9)	393 (74.4)	
BRCA2	49 (25.1)	381 (36.1)		44 (25.0)	134 (25.4)	
BRCA1/2	2 (1.0)	9 (0.9)		2 (1.1)	1 (0.2)	
Histology			.620			.990
Ductal carcinoma	158 (86.8)	845 (87.2)		145 (89.0)	420 (87.7)	
Lobular carcinoma	4 (2.2)	36 (3.7)		3 (1.8)	10 (2.1)	
Mixed ductal/lobular	3 (1.7)	12 (1.2)		2 (1.2)	8 (1.7)	
Other	17 (9.3)	76 (7.8)		13 (7.8)	41 (8.6)	
Missing	13	88		13	49	
Tumor grade			.310			.860
1	5 (2.7)	18 (1.8)		5 (3.0)	6 (1.2)	
2	31 (16.9)	223 (22.5)		30 (17.9)	104 (20.7)	
3	148 (80.4)	749 (75.7)		133 (79.2)	393 (78.1)	
Missing	11	67		8	25	
Tumor size			.040			.650
T1 (≤ 2 cm)	91 (47.2)	423 (40.9)		83 (47.4)	228 (44.2)	
T2 (> 2 to ≤ 5 cm)	84 (43.5)	459 (44.4)		75 (42.9)	232 (45.0)	
T3 (> 5 cm) to T4	18 (9.3)	152 (14.7)		17 (9.7)	56 (10.9)	
Missing	2	23		1	12	
Nodal status			.003			1.000[d]
N0	124 (64.6)	550 (52.8)		114 (65.5)	339 (65.3)	
N1	54 (28.1)	351 (33.7)		49 (28.2)	130 (25.1)	
N2-N3	14 (7.3)	140 (13.5)		11 (6.3)	50 (9.5)	
Missing	3	16		0	0	
Hormone receptor status			.002			1.000
ER and/or PR positive	67 (34.4)	485 (46.1)		60 (34.1)	180 (34.1)	

(continued on following page)

TABLE 1. Patient and Tumor Baseline Characteristics (continued)

Characteristic	All Included Patients, No. (%)			Case-Control Analysis, No. (%)		
	Pregnant	Not Pregnant	*P*	Pregnant	Not Pregnant	*P*
ER and PR negative	128 (65.6)	567 (53.9)		116 (65.9)	348 (65.9)	
Missing	0	5		0	0	
HER2 status			.750			.590
HER2 negative	173 (93.0)	941 (92.4)		158 (94.6)	474 (92.9)	
HER2 positive	13 (7.0)	78 (7.7)		9 (5.4)	36 (7.1)	
Missing	9	38		9	18	
Breast surgery			< .001			.100
Conserving	112 (59.0)	480 (45.9)		101 (58.4)	270 (51.2)	
Radical	78 (41.0)	566 (54.1)		72 (41.6)	257 (48.8)	
Missing	5	11		3	1	
Chemotherapy			.520			.350
No	11 (5.6)	48 (4.6)		10 (5.7)	21 (4.0)	
Yes	184 (94.4)	1,007 (95.5)		166 (94.3)	507 (96.0)	
Missing	0	2		0	0	
Type of chemotherapy[a]			.330			.810
Anthracycline and taxane based	113 (63.5)	683 (69.3)		105 (65.2)	334 (67.3)	
Anthracycline based	55 (30.9)	257 (26.1)		48 (29.8)	138 (27.8)	
Taxane based	4 (2.3)	27 (2.7)		3 (1.9)	13 (2.6)	
Other	6 (3.4)	19 (1.9)		5 (3.1)	11 (2.2)	
Missing	6	21		5	11	
Endocrine therapy[b]			.730			.800
No	6 (9.0)	37 (7.7)		6 (10.0)	16 (8.9)	
Yes	61 (91.0)	443 (92.3)		54 (90.0)	163 (91.1)	
Missing	0	5		0	1	
Type of endocrine therapy[c]			.002			< .001
Tamoxifen alone	17 (28.8)	200 (45.4)		15 (28.9)	80 (49.4)	
Tamoxifen and LHRHa	33 (55.9)	133 (30.2)		30 (57.7)	40 (24.7)	
LHRHa alone	0	8 (1.8)		0	5 (3.1)	
AI with or without LHRHa	4 (6.8)	17 (3.8)		4 (7.7)	5 (3.1)	
Tamoxifen and AI (with or without LHRHa)	5 (8.5)	83 (18.8)		3 (5.8)	32 (19.8)	
Missing	2	2		2	1	
Median duration of endocrine therapy, months (IQR)	50 (24-60)	60 (48-60)	< .001	50 (24-60)	60 (60-60)	< .001
Missing	15	129		15	47	

Abbreviations: AI, aromatase inhibitor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; LHRHa, luteinizing hormone-releasing hormone agonist; PR, progesterone receptor.

[a]Calculated among patients who received chemotherapy.

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

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

[d]Node negative compared with node positive.

Pregnancy resulted in induced abortions and miscarriages in 16 (8.2%) and 20 (10.3%) patients, respectively. Among the 150 patients (76.9%) who gave birth, 170 babies were born. Pregnancy complications and congenital anomalies occurred in 13 (11.6%) and 2 (1.8%) cases, respectively (Table 2).

Survival Analysis

Median follow-up from breast cancer diagnosis was 8.3 years (IQR, 6.2-11.2 years), with no difference between the pregnancy and nonpregnancy cohorts (Data Supplement). In the extended Cox model analysis with occurrence

TABLE 2. Pregnancy, Fetal and Obstetric Outcomes in the Pregnancy Cohort

Outcome	Pregnancy Cohort, No. (%)	
	All Included Patients (n = 195)	Case-Control Analysis (n = 176)
Median age at the time of pregnancy, years (IQR)	35.7 (32.9-38.6)	35.5 (32.8-38.5)
Median time from diagnosis to pregnancy, years (IQR)	4.5 (3.1-6.7)	4.3 (3.0-6.1)
Pregnancy interval		
≤ 2 years from diagnosis	19 (9.7)	18 (10.2)
2-5 years from diagnosis	89 (45.6)	86 (48.9)
5 years from diagnosis	87 (44.6)	72 (40.9)
Type of conception		
Spontaneous pregnancy	133 (82.1)	124 (84.9)
Use of assisted reproductive technology	29 (17.9)	22 (15.1)
No. missing	33	30
Pregnancy outcome		
Completed	150 (76.9)	137 (77.9)
Ongoing	7 (3.6)	5 (2.8)
Induced abortion	16 (8.2)	14 (8.0)
Miscarriage	20 (10.3)	18 (10.2)
Unknown	2 (1.0)	2 (1.1)
No. of live births at the first pregnancy after breast cancer[a]		
1	130 (86.7)	118 (86.1)
2	20 (13.3)	19 (13.9)
Timing of delivery[a]		
At term (≥ 37 weeks)	108 (90.8)	98 (90.7)
Preterm (< 37 weeks)	11 (9.2)	10 (9.3)
No. missing	31	29
Pregnancy complications[a]		
None	97 (86.6)	88 (87.1)
Delivery complications	13 (11.6)	11 (10.9)
Congenital abnormalities	2 (1.8)	2 (2.0)
No. missing	38	36
Breastfeeding[a]		
No	58 (65.2)	51 (63.0)
Yes	31 (34.8)	30 (37.0)
No. missing	61	56
Median duration of breastfeeding, months (IQR)[b]	6 (2-10)	6 (3-10)
No. missing	5	5

Abbreviation: IQR, interquartile range.

[a]Calculated on the total number of patients with completed pregnancy.

[b]Calculated on the total number of patients with completed pregnancy who breastfed.

of pregnancy as a time-varying covariate, all 195 and 1,057 patients of the pregnancy and nonpregnancy cohorts were included. A total of 487 DFS events (38.9%) were observed (Data Supplement). Among them, distant (with or without locoregional) recurrences were 17.7% in the pregnancy cohort and 32.7% in the nonpregnancy cohort (Data Supplement). No significant difference in DFS was observed between the pregnancy and nonpregnancy cohorts (unadjusted HR, 0.96; 95% CI, 0.70 to 1.33; P = .83). Similar results were obtained in the multivariable analysis adjusted for age at diagnosis, tumor size, nodal status, hormone receptor status, type of endocrine therapy, breast surgery, and *BRCA* mutation (adjusted HR, 0.87; 95% CI, 0.61 to 1.23; P = .41; Data Supplement).

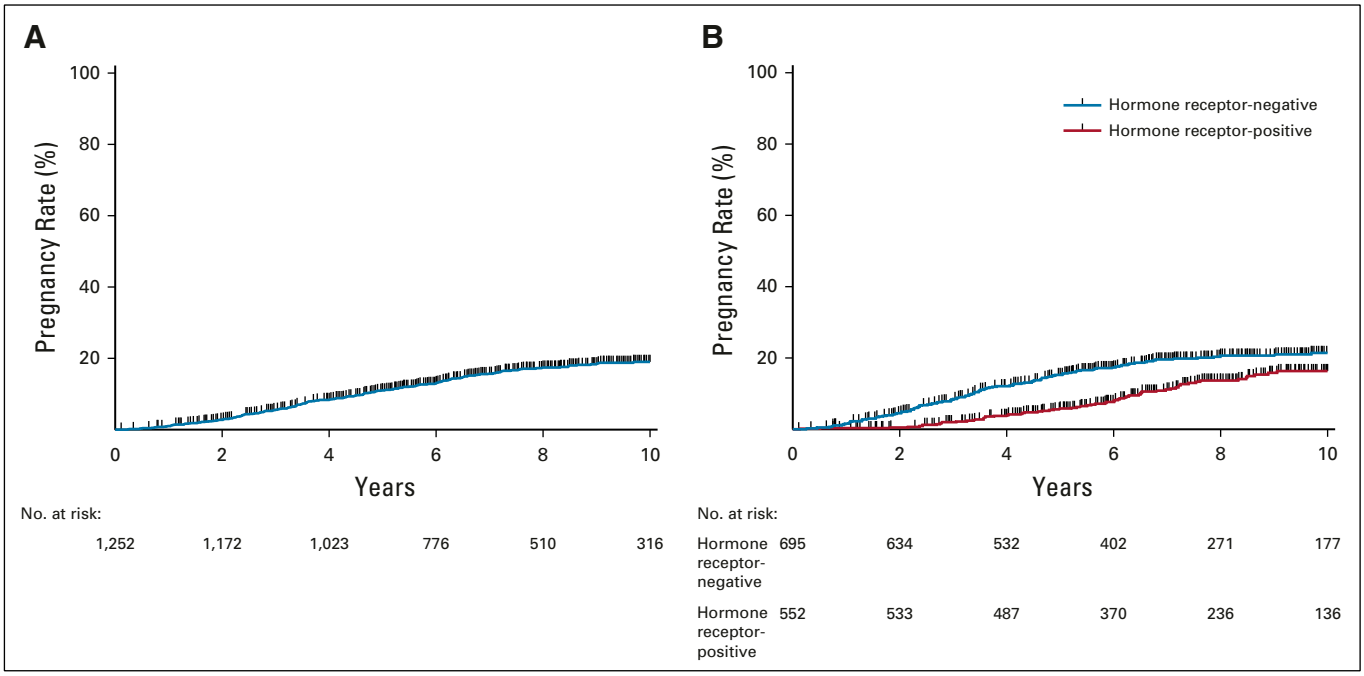

FIG 1. Pregnancy rate (A) in the overall study population and (B) according to hormone receptor status.

Subgroup analyses showed a significant interaction between pregnancy and type of *BRCA* mutation ($P < .01$) or pregnancy and hormone receptor status ($P = .03$; Table 3).

A total of 164 OS events (13.1%) were observed (Data Supplement). No significant difference in OS was observed between the pregnancy and nonpregnancy cohorts in both univariable (unadjusted HR, 0.77; 95% CI, 0.44 to 1.34; $P = .36$) and multivariable (adjusted HR, 0.88; 95% CI, 0.50 to 1.56; $P = .66$) analyses (Data Supplement).

In the case-control analysis, after excluding 19 patients in the pregnancy cohort because of the development of a DFS event before the occurrence of pregnancy, 704 patients

TABLE 3. Subgroup Analyses of Disease-Free Survival by Gene (*BRCA1 v BRCA2*) and Hormone Receptor Status (positive *v* negative)

Variable	Patients, No.	Events, No.	Univariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Extended Cox model analysis						
Study group	1,252	487	0.96 (0.70 to 1.33)	.830	0.87 (0.61 to 1.23)	.41
BRCA mutation				< .010*		< .01*
BRCA1	811	318	0.71 (0.46 to 1.07)		0.64 (0.41 to 0.99)	
BRCA2	430	167	1.88 (1.10 to 3.21)		1.94 (1.10 to 3.45)	
Hormone receptor status				.120*		.03*
Positive	552	218	1.38 (0.82 to 2.31)		1.46 (0.84 to 2.55)	
Negative	695	266	0.81 (0.53 to 1.23)		0.67 (0.42 to 1.04)	
Case-control analysis						
Study group	704	204	0.71 (0.51 to 0.99)	.045		
BRCA mutation				< .010*		
BRCA1	523	154	0.53 (0.35 to 0.81)			
BRCA2	178	49	1.60 (0.86 to 2.89)			
Hormone receptor status				.280*		
Positive	240	67	0.91 (0.52 to 1.60)			
Negative	464	137	0.62 (0.40 to 0.95)			

Abbreviation: HR, hazard ratio.
**P* value for interaction.

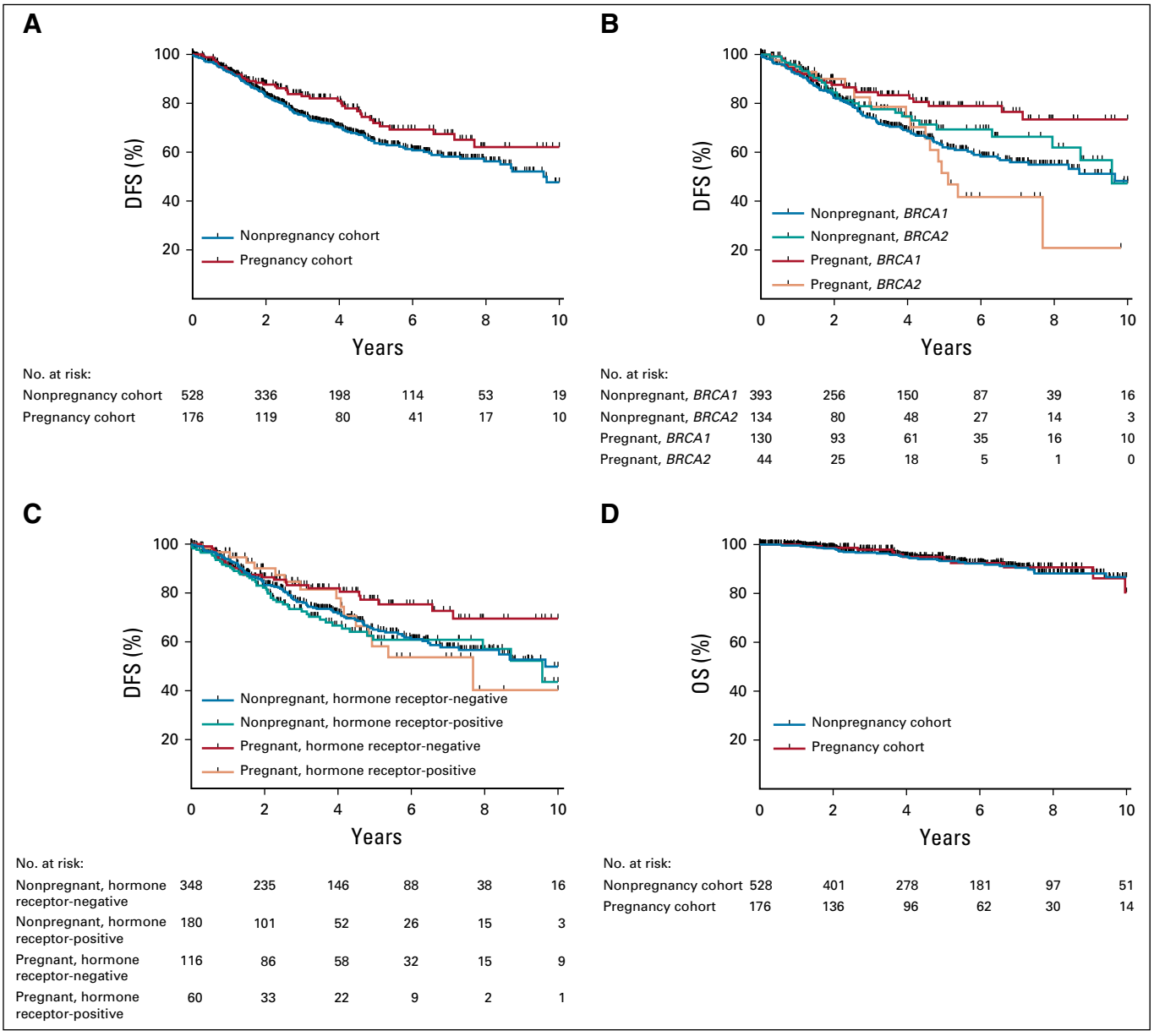

FIG 2. Prognostic impact of pregnancy after breast cancer in patients with *BRCA*-mutated breast cancer in the case-control analysis. (A) Disease-free survival (DFS); (B) DFS according to type of *BRCA* mutation; (C) DFS according to hormone receptor status; (D) Overall survival (OS).

were included (176 pregnant cases matched to 528 nonpregnant controls). More details are reported in the Data Supplement. A significantly improved DFS was observed in the pregnancy cohort (HR, 0.71; 95% CI, 0.51 to 0.99; $P = .045$; Fig 2A). Subgroup analyses (Table 3) showed a significant interaction between pregnancy and type of *BRCA* mutation ($P < .01$; Fig 2B), with no difference according to hormone receptor status ($P = .28$; Fig 2C). When comparing DFS between patients with an abortion (n = 32) and those with a live birth (n = 137), no difference was observed (HR, 1.09; 95% CI, 0.51 to 2.33; $P = .82$; Data Supplement). No significant difference in OS was observed between the pregnancy and nonpregnancy cohorts (HR, 0.86; 95% CI, 0.44 to 1.67; $P = .65$; Fig 2D).

DISCUSSION

To our knowledge, this is the largest study to date specifically designed to address several unmet questions related to the safety of pregnancy after breast cancer in patients with germline *BRCA* mutations and their reproductive outcomes. We observed that pregnancy after breast cancer is safe without apparent worsening of maternal prognosis and is associated with favorable fetal outcomes. These results provide reassurance to patients with *BRCA*-mutated breast cancer interested in future fertility.

Prior studies have shown that < 10% of patients become pregnant after breast cancer diagnosis.[19] We observed

a slightly higher-than-expected pregnancy rate (19% at 10 years) among patients with *BRCA*-mutated breast cancer. This may be due to their very young ages at onset of breast cancer as well as the lower proportion of patients with hormone receptor–positive tumors requiring long-term adjuvant endocrine therapy and more often counseled against subsequent pregnancy for fear that high hormonal levels during pregnancy and/or temporary interruption of endocrine therapy could be detrimental to patients' outcomes.[20]

Potential adverse pregnancy outcomes, including risk of congenital anomalies as a result of prior exposure to anticancer therapies, represent an important area of concern. Previous studies on the risk of congenital anomalies are reassuring; however, some have shown higher chances of preterm birth and perinatal complications in breast cancer survivors.[21] Our findings provide important evidence concerning the progeny of patients with *BRCA*-mutated breast cancer. The observed rate of preterm delivery (9.2%; 95% CI, 5.2% to 15.8%) is rather similar to the one expected in the general population (approximately 11%).[22] Similarly, reassuring results were observed in terms of miscarriages (10.3%; 95% CI, 6.7% to 15.3%) and congenital anomalies (1.8%; 95% CI, 0.5% to 6.3%), considering that the expected rates in the general population are approximately 17%[23] and 3%,[24] respectively. The low rate of miscarriages compared with historical data is intriguing. Although this may possibly represent an underreporting, it is important to note that pregnancy outcome was known in all but 2 patients (1.0%). Thus, we believe that such data further support the statement that prior cancer diagnosis and exposure to anticancer treatments do not seem to increase the risk of miscarriages. A total of 8.2% (95% CI, 5.1% to 12.9%) of patients in our study opted for an induced abortion. The reasons for an induced abortion were not collected, yet this is a lower rate compared with older series. This may possibly reflect the fact that having a pregnancy in women with a history of breast cancer has become more accepted over time, with increasing evidence, including from the current study, showing lack of any therapeutic role of induced abortion in these patients.[4,5] Another possibility is that these pregnancies were accidental and that patients were not adequately counseled on the possibility of becoming pregnant after prior anticancer treatments. Thus, it is important to ensure that safe and reliable methods of contraception are discussed and offered to young patients with cancer who do not want conception.[25]

Many physicians remain concerned about a potential detrimental prognostic effect of pregnancy in patients with germline *BRCA* mutations with a history of breast cancer.[16] While previous studies have provided reassuring data on the safety of conception in breast cancer survivors,[3-6,15] the evidence in patients with *BRCA* mutations is restricted to one small retrospective study limited to 53 pregnant cases.[26] In our study, both the extended Cox model and the case-control analyses showed that pregnancy is safe without apparent worsening of maternal prognosis. In subgroup analyses, an interaction suggestive for a potential protective effect of pregnancy in patients with *BRCA1* mutation and a possible negative impact in *BRCA2* carriers was observed. As suggested by previous preclinical and clinical studies,[27-29] it is plausible that reproductive behaviors may have different effects on the pathogenesis and outcomes of cancers associated with germline mutations in either the *BRCA1* or the *BRCA2* gene. Nevertheless, caution is required before deriving solid conclusions, considering that only 44 *BRCA2*-mutated pregnant cases were included in this analysis. Of note, in the extended Cox model analysis, a significant interaction according to hormone receptor status was also observed. However, the wide CIs that cross the unit in both subgroups make it hard to interpret whether pregnancy could be protective or detrimental in any of the subgroups. Of note, we have previously demonstrated the safety of subsequent pregnancy in patients with hormone receptor–positive breast cancer in a large statistically powered study that was specifically designed to address this question.[4,5] Additional evidence in this regard is awaited from the ongoing international IBCSG-BIG-NABCG POSITIVE trial (ClinicalTrials.gov identifier: NCT02308085) that has recently completed its accrual and aims to investigate the safety of a temporary interruption of endocrine therapy to allow pregnancy.

This study should be considered in the context of its limitations that include the retrospective nature, some missing information on the course and outcomes of pregnancy for some patients, and the relatively smaller number of patients included in the nonpregnancy cohort than expected as per the initial statistical assumptions. In addition, it cannot be excluded that some patients who desire a pregnancy were subjected to restaging before considering conception. However, our study has several unique features. This is the largest data set in our knowledge to date to include young patients with *BRCA*-mutated breast cancer, and it is not restricted to a single continent. We managed to include the target number of patients in the pregnancy cohort, and importantly, two different survival analyses that corrected for potential guarantee-time bias showed consistent findings.

In conclusion, this study provides reassuring evidence that pregnancy after breast cancer in patients with germline *BRCA* mutations is safe without apparent worsening of maternal prognosis and is associated with favorable fetal outcomes. These findings are of paramount importance for health care providers involved in counseling young patients with *BRCA*-mutated breast cancer who inquire about the feasibility and safety of future conception.

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Pregnancy After Breast Cancer in Patients With Germline *BRCA* Mutations

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