



Original Investigation | Surgery

Surgical Management of Early-Onset Breast Cancer Among Young *BRCA1* and *BRCA2* Carriers

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Abstract

IMPORTANCE Young *BRCA* carriers may undergo breast-conserving surgery (BCS) or mastectomy with or without contralateral risk-reducing mastectomy at the time of an index breast cancer diagnosis. A variety of factors may influence surgical decision-making.

OBJECTIVE To explore surgical patterns of care and factors associated with uptake of bilateral mastectomy among affected *BRCA1* or *BRCA2* (*BRCA1/2*) carriers diagnosed with early-onset breast cancer.

DESIGN, SETTING, AND PARTICIPANTS The *BRCA* BCY Collaboration is an international, hospital-based retrospective cohort study conducted at 109 centers across 5 continents. Women aged 40 years or younger with germline pathogenic or likely pathogenic variants in *BRCA1/2* who were diagnosed between January 1, 2000, and December 31, 2020, with invasive stage I to III breast cancer were included. Data were collected between January 2022 and June 2024, and analyses were performed between May 21 and 28, 2025.

MAIN OUTCOME AND MEASURES The main outcome was the evaluation of surgical management as primary treatment for a first diagnosis of invasive breast cancer, defined as BCS, unilateral mastectomy, or bilateral mastectomy.

RESULTS Of 5660 eligible *BRCA1/2* carriers, 4715 women (median [IQR] age, 35 [31-38] years) had unilateral stage I to III breast cancer with surgical treatment details available. In the cohort, 1805 patients (38.3%) underwent BCS, 1752 (37.2%) underwent unilateral mastectomy, and 1158 (24.6%) underwent bilateral mastectomy. The proportion of *BRCA1/2* carriers undergoing BCS decreased over the study period (55.7% [49 of 88] in 2000 vs 27.0% [82 of 304] in 2020), whereas the use of bilateral mastectomy significantly increased (8.0% [7 of 88] in 2000 vs 44.4% [135 of 304] in 2020). Bilateral mastectomy was more common in women who had genetic testing performed before (248 of 435 [57.0%]) or within 6 months (729 of 1892 [38.5%]) of a breast cancer diagnosis compared with those tested after diagnosis (111 of 2167 [5.1%]). On multivariable analysis, compared with those tested after diagnosis, earlier genetic testing was the factor most strongly associated with bilateral mastectomy receipt (testing prior to diagnosis: adjusted odds ratio, 20.72 [95% CI, 15.27-28.13]; testing at diagnosis: adjusted odds ratio, 6.83 [95% CI, 5.39-8.66]). In subgroup analyses, including 2327 patients who had genetic testing performed before or within 6 months of

(continued)

Key Points

Question Among women carrying germline *BRCA* pathogenic variants who are diagnosed with early-onset breast cancer, what factors are associated with surgical decisions and uptake of bilateral mastectomy?

Findings This cohort study that included 4715 young *BRCA* carriers across 5 continents found that 1 in 4 patients underwent bilateral mastectomy as their primary breast surgery, with increasing uptake over time. In adjusted analyses, geographic region and genetic testing performed at or before diagnosis were associated with bilateral mastectomy receipt.

Meaning The findings of this study support early genetic testing for young women with breast cancer to help optimize local therapy decisions.

+ Supplemental content

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Abstract (continued)

diagnosis, 977 (42.0%) underwent bilateral mastectomy, with the lowest rates reported in Asia and Africa (130 of 499 [26.1%]) and the highest rates reported in North America (233 of 351 [66.4%]).

CONCLUSIONS AND RELEVANCE The findings of this cohort study of young *BRCA1/2* carriers suggest that geographic region and timing of genetic testing were the factors most strongly associated with surgical management.

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Introduction

Women diagnosed with breast cancer under the age of 40 years have a 12% to 18% likelihood of testing positive for a germline pathogenic or likely pathogenic variant (PV) in the *BRCA1* or *BRCA2* (*BRCA1/2*) breast cancer susceptibility genes.^{1,2} *BRCA* carriers with a history of early-onset breast cancer must be counseled around their elevated risk of developing new primary cancers in the contralateral breast, with cumulative lifetime estimates ranging from 60% to 68% by age 80 years.^{3,4} Although breast-conserving surgery (BCS) remains a reasonable option for young *BRCA* carriers,^{5,6} many will consider unilateral therapeutic and contralateral risk-reducing mastectomy at the time of an index breast cancer diagnosis to prevent additional breast cancers. While bilateral mastectomy does not appear to confer significant survival benefit in older *BRCA* carriers,^{7,8} it has been associated with improvements in overall survival in this unique group of young carriers diagnosed with breast cancer under the age of 40 years.⁹

In the setting of unilateral breast cancer, the choice to undergo breast conservation, unilateral mastectomy, or bilateral mastectomy depends largely on clinical and patient-level factors, as well as the availability of genetic counseling and testing.¹⁰ Timely testing that occurs early in cancer care delivery is important for surgical decision-making; single institution studies suggest that delays in genetic testing results can create missed opportunities to optimize surgical prevention.¹¹⁻¹³ In prior cohort studies of *BRCA1/2* carriers who were aware of their positive genetics results, a variety of demographic and sociocultural determinants—age, parity, family history of breast cancer, and prior oophorectomy—were shown to influence surgical choices.^{14,15} There also appears to be significant geographic variation in surgical decision-making, with prior studies reporting bilateral mastectomy rates among carriers as low as 5% in some countries and as high as 57% in others such as the US.¹⁶

The *BRCA* BCY Collaboration is an international, hospital-based retrospective cohort study that was designed to evaluate outcomes in young *BRCA1/2* carriers with breast cancer. In this planned secondary analysis, we sought to explore surgical patterns of care and factors associated with uptake of bilateral mastectomy among *BRCA1/2* carriers with early-onset breast cancer.

Methods

Study Design, Setting, and Patients

This cohort study included eligible women diagnosed between January 1, 2000, and December 31, 2020, with invasive breast cancer prior to or at age 40 years who were found to carry a germline PV or likely PV in the *BRCA1* and/or *BRCA2* genes. Women without a confirmed pathogenic or likely PV or variant of unknown significance, those diagnosed outside of the study period, those with noninvasive breast cancer, or those diagnosed after 40 years of age were excluded (**Figure 1**). For this preplanned surgical analysis, women with stage IV breast cancer, those with bilateral breast cancer or unknown laterality, those who did not undergo surgery or who had unknown surgical details, and those with reported follow-up of less than 1 year were also excluded. Data collection began in January 2022 and ended in June 2024, and all analyses were performed between May 21 and 28, 2025. The

study received ethics approval by all local, regional, or national institutional review boards of participating centers, and the Institut Jules Bordet (Brussels, Belgium) served as the coordinating center and central ethics committee. Written informed consent was obtained from participants before inclusion unless institutional-determined waivers were granted due to the use of deidentified, retrospective data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

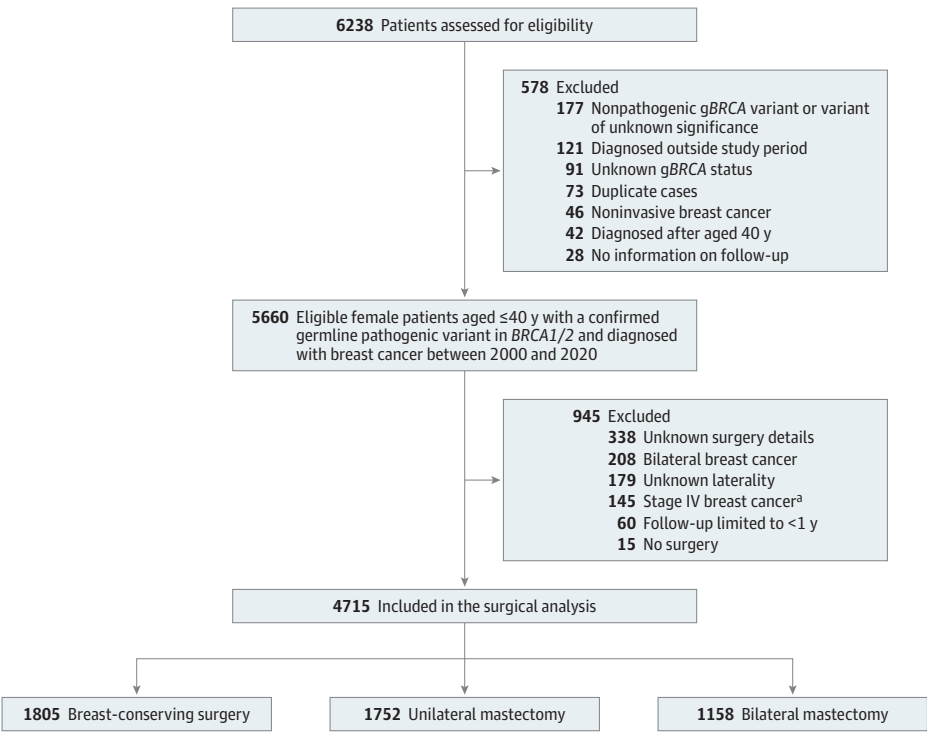
Data Collection and Study Procedures

Data collected from medical records and case report forms on all eligible patients included breast cancer characteristics, laterality, staging, type of germline *BRCA* (*gBRCA*) PV, *BRCA* testing, primary breast and axillary surgery, use of reconstruction, adjuvant therapies, subsequent risk-reducing surgeries, and survival. Genetic testing, surgery, treatment, and follow-up were performed according to routine clinical care at individual institutions.

Statistical Analysis

The primary objectives of the present analysis were to evaluate surgical patterns of care and factors associated with uptake of bilateral mastectomy as primary breast surgery. Primary breast surgery was defined as surgery administered as part of primary treatment for a first diagnosis of invasive breast cancer. Patients were grouped as having undergone BCS (lumpectomy, quadrantectomy, or partial or segmental mastectomy), unilateral mastectomy (simple or total mastectomy, including skin or nipple-sparing mastectomy, or modified radical mastectomy), or bilateral mastectomy (unilateral mastectomy with contralateral risk-reducing mastectomy). Patients who underwent BCS or unilateral mastectomy for a primary tumor followed by bilateral mastectomy within 6 months from diagnosis for patients undergoing upfront surgery or within 12 months from diagnosis for patients undergoing neoadjuvant systemic therapy were categorized into the bilateral mastectomy group. Descriptive statistics were used to summarize continuous and categorical variables. Continuous

Figure 1. Patient Selection Flowchart



BRCA1/2 indicates *BRCA1* or *BRCA2*; *gBRCA*, germline *BRCA*.
^a Per the American Joint Committee on Cancer anatomic staging.

variables were reported as median (IQR), with categorical variables reported as frequencies and percentages. The χ^2 test or the Kruskal-Wallis test was used, as appropriate, to compare clinicopathologic characteristics according to primary breast surgery. Multivariable logistic regression was performed to assess factors associated with bilateral mastectomy receipt, with all preoperative demographic and clinical variables, treatment approach, geographic region, and year of diagnosis included in the model. Subgroup analysis was performed to assess surgical management in patients who had knowledge of their *BRCA* status through genetic testing performed before or within 6 months of their breast cancer diagnosis, with sensitivity analysis performed in the subgroup of women who had genetic testing performed before or within 3 months of their breast cancer diagnosis. All statistical analyses were performed between May 21 and May 28, 2025, using SAS, version 9.4 (SAS Institute Inc) and R, version 4.3.3 (R Project for Statistical Computing). All statistical analyses were 2-sided, and $P < .05$ was considered statistically significant.

Results

Cohort Characteristics

Between January 1, 2000, and December 31, 2020, 5660 eligible patients (*BRCA1/2* carriers who had unilateral stage I to III breast cancer) from 109 centers across 5 continents were identified, of whom 4715 underwent surgery and were eligible for the current analysis (Figure 1). Cohort characteristics are detailed in **Table 1**. The median (IQR) age of the cohort was 35 (31-38) years, 2983 (63.3%) were *BRCA1* carriers, and 2327 (49.4%) had genetic testing before or at the time of diagnosis. Overall, 2762 carriers (58.6%) underwent upfront surgery, while 1928 (40.9%) received neoadjuvant systemic therapy followed by surgery. In addition to surgery, the majority of *BRCA* carriers received both chemotherapy (4371 [92.7%]) and adjuvant radiation (3134 [66.5%]).

Patterns of Care in Surgical Management

Primary breast surgery was BCS in 1805 carriers (38.3%), unilateral mastectomy in 1752 carriers (37.2%), and bilateral mastectomy in 1158 carriers (24.6%). Table 1 details clinicopathologic and treatment-related differences by surgery. The proportion of carriers undergoing BCS decreased over the study period (55.7% [49 of 88] in 2000 vs 27.0% [82 of 304] in 2020), whereas the use of bilateral mastectomy significantly increased (8.0% [7 of 88] in 2000 vs 44.4% [135 of 304] in 2020) ($P < .001$) (**Figure 2A**).

In 2910 patients undergoing unilateral or bilateral mastectomy, the use of reconstruction also increased significantly over time (Figure 2B). By 2020, 174 of 222 (78.4%) patients undergoing mastectomy underwent some type of breast reconstruction compared with only 21 of 39 (53.8%) in 2000 ($P < .001$). Immediate breast reconstruction became the most common reconstructive approach in later years of treatment, occurring in 146 of 222 patients undergoing mastectomy (65.8%) who were diagnosed in 2020 compared with only 11 of 39 patients (28.2%) in 2000, when delayed reconstruction was also prevalent (10 of 39 [25.6%]).

Factors Associated With Receipt of Bilateral Mastectomy

In addition to temporal trends, there were significant differences in surgical treatment by geographic region (**Table 2**). Bilateral mastectomy as primary surgery was the most common surgical management strategy in North America (273 of 491 [55.6%]) and least common in Asia and Africa (151 of 871 [17.3%]) ($P < .001$). Higher rates of bilateral mastectomy were seen in women with genetic testing performed before (248 of 435 [57.0%]) or within 6 months of (729 of 1892 [38.5%]) a breast cancer diagnosis compared with those tested after diagnosis (111 of 2167 [5.1%]) ($P < .001$). Neoadjuvant systemic therapy was also associated with higher rates of bilateral mastectomy as compared with those undergoing upfront surgery (718 of 1928 [37.2%] vs 436 of 2762 [15.8%]; $P < .001$).

Table 1. Cohort Characteristics and Comparison of Clinicopathologic Characteristics by Surgery

Characteristic	Carriers, No. (%)				P value
	Total (N = 4715)	BCS (n = 1805)	Unilateral mastectomy (n = 1752)	Bilateral mastectomy (n = 1158)	
Age at breast cancer diagnosis, y					
≤30	973 (20.6)	375 (20.8)	349 (19.9)	249 (21.5)	.74
31-35	1750 (37.1)	676 (37.5)	661 (37.7)	413 (35.7)	
36-40	1992 (42.3)	754 (41.8)	742 (42.4)	496 (42.8)	
Year of diagnosis					
2000-2004	608 (12.9)	347 (19.2)	219 (12.5)	42 (3.6)	<.001
2005-2008	748 (15.9)	372 (20.6)	300 (17.1)	76 (6.6)	
2009-2012	999 (21.2)	416 (23.1)	404 (23.1)	179 (15.5)	
2013-2016	1143 (24.2)	373 (20.7)	419 (23.9)	351 (30.3)	
2017-2020	1217 (25.8)	297 (16.5)	410 (23.4)	510 (44.0)	
Region					
Central and South America	245 (5.2)	90 (5.0)	110 (6.3)	45 (3.9)	<.001
Australia and Oceania	175 (3.7)	73 (4.0)	64 (3.7)	38 (3.3)	
Northern Europe	712 (15.1)	230 (12.7)	283 (16.2)	199 (17.2)	
Eastern Europe	307 (6.5)	91 (5.1)	149 (8.5)	67 (5.8)	
Southern Europe	1914 (40.6)	793 (43.9)	736 (42.0)	385 (33.3)	
North America	491 (10.4)	79 (4.4)	139 (7.9)	273 (23.6)	
Asia and Africa	871 (18.5)	449 (24.9)	271 (15.4)	151 (13.0)	
Germline <i>BRCA</i> pathogenic variant					
<i>BRCA1</i>	2983 (63.3)	1252 (69.4)	938 (53.5)	793 (68.5)	<.001
<i>BRCA2</i>	1700 (36.1)	537 (29.8)	807 (46.1)	356 (30.7)	
<i>BRCA1</i> and <i>BRCA2</i>	24 (0.5)	12 (0.7)	7 (0.4)	5 (0.4)	
<i>BRCA</i> not otherwise specified	8 (0.2)	4 (0.2)	0	4 (0.4)	
Timing of germline <i>BRCA</i> testing					
Testing before diagnosis	435 (9.2)	83 (4.6)	104 (5.9)	248 (21.4)	<.001
Testing at diagnosis	1892 (40.1)	509 (28.2)	654 (37.3)	729 (63.0)	
Testing after diagnosis	2167 (46.0)	1134 (62.8)	922 (52.6)	111 (9.6)	
Unknown date of <i>BRCA</i> testing	221 (4.7)	79 (4.4)	72 (4.1)	70 (6.0)	
Histology					
Invasive ductal carcinoma	4035 (85.6)	1555 (86.2)	1483 (84.7)	997 (86.1)	.06
Invasive lobular carcinoma or other histology	645 (13.7)	232 (12.9)	254 (14.5)	159 (13.7)	
Unknown histology	35 (0.74)	18 (1.0)	15 (0.9)	2 (0.2)	
Tumor subtype					
Luminal A-like	669 (14.2)	204 (11.3)	303 (17.3)	162 (14.0)	<.001
Luminal B-like	1058 (22.4)	357 (19.8)	447 (25.5)	254 (21.9)	
<i>ERBB2</i> + (formerly <i>HER2</i> or <i>HER2/neu</i>)	324 (6.9)	104 (5.8)	144 (8.2)	76 (6.6)	
TNBC	2328 (49.4)	999 (55.4)	714 (40.8)	615 (53.1)	
Unknown	336 (7.1)	141 (7.8)	144 (8.2)	51 (4.4)	
Histologic grade					
I	84 (1.8)	29 (1.6)	27 (1.5)	28 (2.4)	<.001
II	1109 (23.5)	356 (19.7)	490 (28.0)	263 (22.7)	
III	3150 (66.8)	1250 (69.3)	1099 (62.7)	801 (69.2)	
Unknown	372 (7.9)	170 (9.4)	136 (7.8)	66 (5.7)	
Tumor size ^{a,b}					
T1	1765 (37.4)	860 (47.7)	477 (27.2)	428 (37.0)	<.001
T2	2183 (46.3)	791 (43.8)	842 (48.1)	550 (47.5)	
T3-T4	619 (13.1)	105 (5.8)	367 (21.0)	147 (12.7)	
Unknown	148 (3.1)	49 (2.7)	66 (3.8)	33 (2.9)	

(continued)

Table 1. Cohort Characteristics and Comparison of Clinicopathologic Characteristics by Surgery (continued)

	Carriers, No. (%)				
Characteristic	Total (N = 4715)	BCS (n = 1805)	Unilateral mastectomy (n = 1752)	Bilateral mastectomy (n = 1158)	P value
Nodal status ^{a,b}					
N0	2481 (52.6)	1154 (63.9)	702 (40.1)	625 (54.0)	<.001
N1	1563 (33.2)	504 (27.9)	664 (37.9)	395 (34.1)	
N2-N3	571 (12.1)	112 (6.2)	346 (19.8)	113 (9.8)	
Unknown	100 (2.1)	35 (1.9)	40 (2.3)	25 (2.2)	
Anatomic stage ^b					
I	1197 (25.4)	639 (35.4)	267 (15.2)	291 (25.1)	<.001
II	2576 (54.6)	966 (53.5)	941 (53.7)	669 (57.8)	
III	862 (18.3)	167 (9.3)	510 (29.1)	185 (16.0)	
Unknown	80 (1.7)	33 (1.8)	34 (1.9)	13 (1.1)	
Treatment approach					
Upfront surgery	2762 (58.6)	446 (25.8)	744 (42.5)	718 (62.0)	<.001
Neoadjuvant systemic therapy	1928 (40.9)	1324 (73.4)	1002 (57.2)	436 (37.7)	
Unknown	25 (0.5)	15 (0.8)	6 (0.3)	4 (0.4)	
Axillary surgery					
None	88 (1.9)	37 (2.1)	30 (1.7)	21 (1.8)	<.001
Sentinel node biopsy ^c	2077 (44.1)	936 (51.8)	499 (28.5)	635 (54.8)	
Axillary dissection	2550 (54.1)	832 (46.1)	1223 (69.8)	495 (42.8)	
Chemotherapy use					
Yes	4371 (92.7)	1666 (92.3)	1654 (94.4)	1051 (90.8)	.001
No	324 (6.9)	128 (7.1)	92 (5.3)	104 (9.0)	
Unknown	20 (0.4)	11 (0.6)	6 (0.3)	3 (0.3)	
Adjuvant radiation					
Yes	3134 (66.5)	1560 (86.4)	1071 (61.1)	503 (43.4)	<.001
No	1521 (32.3)	232 (12.9)	658 (37.6)	631 (54.5)	
Unknown	60 (1.3)	13 (0.7)	23 (1.3)	24 (2.1)	

Abbreviations: BCS, breast-conserving surgery; TNBC, triple-negative breast cancer.

^a Assessed clinically for patients who received neoadjuvant systemic therapy and pathologically for those who received upfront surgery.

^b Per the American Joint Committee on Cancer anatomic staging.

^c Includes targeted axillary dissection and marking axillary node with radioactive iodine seed procedure.

In adjusted analyses, factors that remained independently associated with bilateral mastectomy included year of diagnosis, geographic region, timing of *gBRCA* testing, tumor size, nodal status, and treatment approach (Table 2). Relative to those who underwent genetic testing after diagnosis, earlier genetic testing at the time of breast cancer diagnosis was associated with an increase in bilateral mastectomy (adjusted odds ratio [AOR], 6.83 [95% CI, 5.39-8.66]), and genetic testing prior to diagnosis was associated with higher odds of bilateral mastectomy receipt (AOR, 20.72 [95% CI, 15.27-28.13]). The extent of disease was inversely associated with bilateral mastectomy, such that those with larger tumors (T3 to T4: AOR, 0.55 [95% CI, 0.41-0.73]) and increased nodal burden (N2 to N3: AOR, 0.68 [95% CI, 0.51-0.91]) (per the American Joint Committee on Cancer anatomic staging) had decreased odds of bilateral mastectomy relative to those with smaller tumors and node-negative disease. Relative to those receiving neoadjuvant systemic therapy, upfront surgery was associated with a 73% reduction in the odds of bilateral mastectomy (AOR, 0.27 [95% CI, 0.22-0.33]).

Surgical Decision-Making in Women With Knowledge of *gBRCA* Status

In subgroup analyses of 2327 patients who had genetic testing performed before or within 6 months of diagnosis, 977 (42.0%) underwent bilateral mastectomy (Table 3). In women with knowledge of their *gBRCA* status, the lowest bilateral mastectomy rates were reported in Asia and Africa (130 of 499 [26.1%]), and the highest rates were reported in North America (233 of 351 [66.4%]) ($P < .001$). The proportion of carriers undergoing bilateral mastectomy as primary surgery increased from 25.0% (2 of 8) in 2000 to 50.4% (124 of 246) in 2020 ($P < .001$) (Figure 2C).

In adjusted subgroup analyses, *gBRCA1* carriers, later year of diagnosis, luminal A-like disease, smaller tumor size, node-negative disease, neoadjuvant treatment, and geographic region remained independently associated with bilateral mastectomy (Table 3). Women with a *gBRCA2* PV were less likely to undergo bilateral mastectomy relative to *gBRCA1* carriers (AOR, 0.74 [95% CI, 0.59-0.94]), and women who received upfront surgery were less likely to receive bilateral mastectomy (AOR, 0.31 [95% CI, 0.25-0.39]) as compared with those who underwent neoadjuvant treatment. Sensitivity analysis restricting the cohort to 1826 women who had testing performed before or within 3 months of breast cancer diagnosis supported these findings (eTable in Supplement 1).

Knowledge of *BRCA* status through genetic testing performed before or within 6 months of a breast cancer diagnosis increased over time (Figure 2D). Knowledge of *gBRCA* status before a breast cancer diagnosis (referred to as prediagnostic awareness) occurred in 435 patients (9.2%), increasing from 0 carriers diagnosed in 2000 to 45 of 304 carriers (14.8%) diagnosed with breast cancer in 2020 ($P < .001$). The proportion of patients who received genetic testing at diagnosis also increased over the study period, from 9.1% (8 of 888) of young carriers in 2000 to 66.1% (201 of 304) in 2020 ($P < .001$).

Figure 2. Bar Graphs of Patterns of Care Among Young *BRCA1/2* Carriers Diagnosed With Breast Cancer at Age 40 Years or Younger



Panels A and D include data for 4715 carriers, panel B includes data for 2910 carriers who underwent unilateral or bilateral mastectomy, and panel C includes 2327 carriers. BCS indicates breast-conserving surgery; *BRCA1/2*, *BRCA1* or *BRCA2*.

Table 2. Factors Associated With Bilateral Mastectomy in *gBRCA1/2* Carriers With Unilateral Breast Cancer

Characteristic	Carriers, No. (%)		Receipt of bilateral mastectomy, AOR (95% CI)
	Total (N = 4715)	Bilateral mastectomy (n = 1158)	
Age at breast cancer diagnosis, y			
≤30	973 (20.6)	249 (21.5)	1 [Reference]
31-35	1750 (37.1)	413 (35.7)	0.89 (0.71-1.11)
36-40	1992 (42.3)	496 (42.8)	0.97 (0.78-1.20)
Year of diagnosis			
2000-2004	608 (12.9)	42 (3.6)	1 [Reference]
2005-2008	748 (15.9)	76 (6.6)	1.11 (0.71-1.72)
2009-2012	999 (21.2)	179 (15.5)	1.45 (0.97-2.18)
2013-2016	1143 (24.2)	351 (30.3)	2.24 (1.51-3.33)
2017-2020	1217 (25.8)	510 (44.0)	3.07 (2.06-4.56)
Geographic region			
Southern Europe	1914 (40.6)	385 (33.3)	1 [Reference]
Central and South America	245 (5.2)	45 (3.9)	1.19 (0.79-1.78)
Australia and Oceania	175 (3.7)	38 (3.3)	1.79 (1.12-2.87)
Northern Europe	712 (15.1)	199 (17.2)	1.05 (0.83-1.34)
Eastern Europe	307 (6.5)	67 (5.8)	0.70 (0.49-0.98)
North America	491 (10.4)	273 (23.6)	4.79 (3.69-6.21)
Asia and Africa	871 (18.5)	151 (17.3)	0.65 (0.51-0.84)
gBRCA pathogenic variant			
BRCA1	3015 (63.9)	802 (69.3)	1 [Reference]
BRCA2	1700 (36.1)	356 (30.7)	0.83 (0.67-1.02)
Timing of gBRCA testing			
Testing after diagnosis	2167 (46.0)	111 (9.6)	1 [Reference]
Testing at diagnosis	1892 (40.1)	729 (63.0)	6.83 (5.39-8.66)
Testing before diagnosis	435 (9.2)	248 (21.4)	20.72 (15.27-28.13)
Unknown date of BRCA testing	221 (4.7)	70 (6.0)	6.9 (4.73-10.01)
Histology			
Invasive ductal carcinoma	4035 (85.6)	997 (86.1)	1 [Reference]
Invasive lobular carcinoma or other histology	645 (13.7)	159 (13.7)	0.96 (0.75-1.22)
Unknown histology	35 (0.74)	2 (0.2)	0.42 (0.08-2.15)
Biologic subtype			
TNBC	2328 (49.4)	615 (53.1)	1 [Reference]
Luminal A-like	669 (14.2)	162 (14.0)	1.40 (0.97-2.01)
Luminal B-like	1058 (22.4)	254 (21.9)	1.07 (0.85-1.34)
ERBB2+ (formerly HER2 or HER2/neu)	324 (6.9)	76 (6.6)	0.99 (0.70-1.41)
Unknown	336 (7.1)	51 (4.4)	1.05 (0.68-1.61)
Histologic grade			
I	84 (1.8)	28 (2.4)	1 [Reference]
II	1109 (23.5)	263 (22.7)	0.64 (0.35-1.17)
III	3150 (66.8)	801 (69.2)	0.67 (0.36-1.25)
Unknown	372 (7.9)	66 (5.7)	0.50 (0.25-1.02)
Tumor size ^a			
T1	1765 (37.4)	428 (37.0)	1 [Reference]
T2	2183 (46.3)	550 (47.5)	0.79 (0.65-0.96)
T3-T4	619 (13.1)	147 (12.7)	0.55 (0.41-0.73)
Unknown	148 (3.1)	33 (2.9)	0.34 (0.19-0.63)

(continued)

Table 2. Factors Associated With Bilateral Mastectomy in *gBRCA1/2* Carriers With Unilateral Breast Cancer (continued)

Characteristic	Carriers, No. (%)		Receipt of bilateral mastectomy, AOR (95% CI)
	Total (N = 4715)	Bilateral mastectomy (n = 1158)	
Nodal status ^a			
N0	2481 (52.6)	625 (54.0)	1 [Reference]
N1	1563 (33.2)	395 (34.1)	0.91 (0.76-1.09)
N2-N3	571 (12.1)	113 (9.8)	0.68 (0.51-0.91)
Unknown	100 (2.1)	25 (2.2)	1.80 (0.93-3.51)
Treatment approach			
Neoadjuvant systemic therapy	1928 (40.9)	718 (62.0)	1 [Reference]
Upfront surgery	2762 (58.6)	436 (37.7)	0.27 (0.22-0.33)
Unknown	25 (0.5)	4 (0.3)	0.29 (0.08-1.06)

Abbreviations: AOR, adjusted odds ratio; *gBRCA1/2*, germline *BRCA1* or *BRCA2*; TNBC, triple-negative breast cancer.

^a Assessed clinically for patients who received neoadjuvant systemic therapy and pathologically for those who received upfront surgery; per the American Joint Committee on Cancer anatomic staging.

Discussion

In this large international cohort study of 4715 young *BRCA1/2* carriers undergoing primary breast surgery for early-onset breast cancer, increasing use of bilateral mastectomy occurred over time, from 8% in 2000 to 44% in 2020. Temporal trends in breast reconstruction showed a similar increase, with nearly 80% (78.4%) of patients undergoing mastectomy receiving some form of reconstruction. Importantly, the findings suggest that geographic region and timing of genetic testing were associated with surgical management decisions, with women significantly more likely to elect bilateral surgery if they had knowledge of their *gBRCA* status before or at the time of a breast cancer diagnosis.

These findings strongly support early genetic testing for young women with breast cancer to help optimize local therapy decisions. Women diagnosed in this age group have a 12% to 18% likelihood of testing positive for a germline pathogenic or likely PV in a high-penetrance breast cancer susceptibility gene, with higher estimates in the setting of triple-negative disease.^{1,2,17,18} Timely testing that identifies carriers at or immediately following diagnosis renders patients eligible for novel therapeutics such as poly(adenosine diphosphate-ribose) polymerase inhibitors¹⁹ and expands surgical options to include consideration of bilateral mastectomy, a procedure that is rarely recommended to women at average risk.²⁰ Incorporating both therapeutic and contralateral risk-reducing mastectomy into primary breast surgery minimizes the need for multiple procedures and allows for the avoidance of whole breast radiation in many patients with early-stage disease.¹¹ Several single-institution series have demonstrated that patients who are aware of their *gBRCA* status preoperatively elect bilateral mastectomy in 57% to 88% of cases.^{13,21,22} Our study extends these findings within an international context, showing that 42% of young carriers who underwent genetic testing before or within 6 months of their breast cancer diagnosis opted for bilateral mastectomy as their primary breast surgery, including 50% of confirmed carriers diagnosed in 2020. Furthermore, we found that women who underwent neoadjuvant chemotherapy, a treatment approach that prolongs the interval between diagnosis and surgery to allow for genetic testing and preoperative result disclosure, were more likely to elect bilateral mastectomy.

Our study highlights temporal and geographic trends in risk-management strategies for young women with hereditary breast cancer. In a 2019 study of 6223 unaffected and affected *BRCA* carriers from 10 countries, Metcalfe et al¹⁶ reported the highest bilateral mastectomy rates in the US (50%) and the lowest rates in Poland (4.5%), with a general trend toward increased uptake of bilateral mastectomy in those who received testing after 2008. In another study of 1238 *BRCA* carriers diagnosed with breast cancer in South Korea, only 10% of carriers underwent risk-reducing mastectomy, although rates increased 5.8-fold between 2013 and 2017.²³ The increased adoption of bilateral mastectomy over the last decade mirrors guideline recommendations to offer contralateral risk-reducing mastectomy in this patient population, although BCS or unilateral mastectomy also

Table 3. Factors Associated With Bilateral Mastectomy in *gBRCA1/2* Carriers With Unilateral Breast Cancer Who Underwent Genetic Testing Before or Within 6 Months of Breast Cancer Diagnosis

Characteristic	Carriers, No. (%)		Receipt of bilateral mastectomy, AOR (95% CI)
	Total (N = 2327)	Bilateral mastectomy (n = 977)	
Age at breast cancer diagnosis, y			
≤30	499 (21.4)	208 (21.3)	1 [Reference]
31-35	861 (37.0)	346 (35.4)	0.90 (0.71-1.16)
36-40	967 (41.6)	423 (43.3)	1.07 (0.84-1.36)
Year of diagnosis			
2000-2004	85 (3.7)	21 (2.2)	1 [Reference]
2005-2008	210 (9.0)	54 (5.5)	1.02 (0.55-1.89)
2009-2012	424 (18.2)	145 (14.8)	1.21 (0.69-2.13)
2013-2016	709 (30.5)	312 (31.9)	1.88 (1.08-3.27)
2017-2020	899 (38.6)	445 (45.6)	2.22 (1.28-3.86)
Geographic region			
Southern Europe	790 (34.0)	330 (33.8)	1 [Reference]
Central and South America	53 (2.3)	21 (2.2)	0.85 (0.46-1.56)
Australia and Oceania	80 (3.4)	26 (2.7)	1.23 (0.72-2.09)
Northern Europe	391 (16.8)	176 (18.0)	0.95 (0.73-1.23)
Eastern Europe	163 (7.0)	61 (6.2)	0.68 (0.46-0.98)
North America	351 (15.1)	233 (23.9)	3.65 (2.74-4.87)
Asia and Africa	499 (21.4)	130 (13.3)	0.61 (0.46-0.98)
gBRCA pathogenic variant			
BRCA1	1567 (67.3)	683 (69.9)	1 [Reference]
BRCA2	760 (32.7)	294 (30.1)	0.74 (0.59-0.94)
Histology			
Invasive ductal carcinoma	2017 (86.7)	848 (86.8)	1 [Reference]
Invasive lobular carcinoma or other histology	303 (13.0)	127 (13.0)	0.95 (0.71-1.25)
Unknown histology	7 (0.30)	2 (0.20)	0.95 (0.17-5.44)
Biologic subtype			
TNBC	1222 (52.5)	517 (52.9)	1 [Reference]
Luminal A-like	306 (13.2)	143 (14.6)	2.00 (1.32-3.04)
Luminal B-like	533 (22.9)	215 (22.0)	1.13 (0.88-1.45)
ERBB2+ (formerly HER2 or HER2/neu)	142 (6.1)	66 (6.8)	1.24 (0.83-1.85)
Unknown	124 (5.3)	36 (3.7)	0.90 (0.54-1.50)
Histologic grade			
I	39 (1.7)	25 (2.6)	1 [Reference]
II	512 (22.0)	217 (22.2)	0.41 (0.20-0.85)
III	1578 (67.8)	680 (69.6)	0.51 (0.24-1.08)
Unknown	198 (8.5)	55 (5.6)	0.38 (0.16-0.87)
Tumor size ^a			
T1	899 (38.6)	360 (36.9)	1 [Reference]
T2	1076 (46.2)	473 (48.4)	0.77 (0.61-0.95)
T3-T4	302 (13.0)	123 (12.6)	0.52 (0.38-0.72)
Unknown	50 (2.2)	21 (2.2)	0.22 (0.10-0.43)
Nodal status ^a			
N0	1273 (54.7)	538 (55.1)	1 [Reference]
N1	765 (32.9)	329 (33.7)	0.88 (0.72-1.08)
N2-N3	259 (11.1)	94 (9.6)	0.67 (0.49-0.93)
Unknown	30 (1.3)	16 (1.6)	1.93 (0.78-4.80)
Treatment approach			
Neoadjuvant systemic therapy	1140 (49.0)	609 (62.3)	1 [Reference]
Upfront surgery	1178 (60.6)	365 (37.4)	0.31 (0.25-0.39)
Unknown	9 (0.4)	3 (0.3)	0.33 (0.07-1.51)

Abbreviations: AOR, adjusted odds ratio; *gBRCA1/2*, germline *BRCA1/2*; TNBC, triple-negative breast cancer.

^a Assessed clinically for patients who received neoadjuvant systemic therapy and pathologically for those who received upfront surgery; per the American Joint Committee on Cancer anatomic staging.

remain options for affected carriers.^{5,24,25} However, sociocultural and system-level factors may strongly influence uptake of mastectomy globally, with our study demonstrating a wide spectrum of bilateral mastectomy rates in known carriers: as low as 26.1% in Asia and Africa and as high as 66.4% in North America.

The trend toward increased adoption of bilateral mastectomy is commensurate with rising rates of breast reconstruction, particularly for young *BRCA* carriers.²⁶ In our study, we found that the proportion of patients undergoing mastectomy with immediate breast reconstruction increased from 28.2% in 2000 to 65.8% in 2020. During the same period, delayed breast reconstruction became less common. These trends parallel clinical practice guidelines that have endorsed the use of postmastectomy reconstruction in *BRCA* carriers,²⁵ with studies demonstrating better preservation of body image and psychological well-being with immediate vs delayed approaches.^{27,28} Future studies evaluating how access to different mastectomy approaches and reconstructive options influences surgical decision-making in carriers would be informative.

Although declining costs and improved efficiency have made genetic testing more accessible to young women with breast cancer, a significant minority of patients do not receive genetic testing at the time of diagnosis.^{29,30} In our cohort 46% of carriers overall and 22% of those diagnosed with breast cancer after 2017 did not undergo genetic testing within 6 months of diagnosis. As in other studies, we saw an encouraging trend over time with increasing delivery of genetic testing early in the cancer care trajectory.^{31,32} Not only is genetic testing cost-effective for women with breast cancer,³³ but measures that support prompt genetic testing are likely to expand treatment options for younger *BRCA* carriers. In a recent cohort study from members of our group, we showed no significant difference in overall survival between unilateral breast-conserving therapy and unilateral mastectomy performed at breast cancer diagnosis, although we did find 33% higher odds of second primary breast cancer events in adjusted analyses, which was more pronounced for *BRCA1* carriers and those with stage III disease.³⁴ Our group has also previously shown that bilateral mastectomy (performed as primary breast surgery or during follow-up) is associated with significant improvements in overall survival and that this survival advantage remains irrespective of patient and tumor characteristics.⁹ This finding differed from prior cohort studies, which did not show an overall survival advantage with bilateral mastectomy for *BRCA* carriers with breast cancer.^{35,36} Since 2021, targeted systemic therapies with measurable survival benefit are available for *BRCA* carriers with high-risk breast cancer, with 1 year of adjuvant olaparib treatment, resulting in a meaningful 4.4% absolute overall survival benefit at 6 years' follow-up.^{19,37}

In our analyses of patients who had knowledge of their *BRCA* status at diagnosis, we saw, in addition to temporal and geographic trends, specific clinical factors associated with bilateral mastectomy receipt. Relative to *BRCA2* carriers, *BRCA1* carriers were more likely to undergo bilateral mastectomy, a finding likely explained by earlier age at diagnosis and higher reported 10-year contralateral breast cancer risks for these variants (26%-27% for women under aged 40 years with *BRCA1*-associated breast cancer vs 16%-17% for *BRCA2*-associated breast cancer).^{3,38,39} Increased tumor size and nodal positivity were also inversely associated with bilateral mastectomy, suggesting that patients and practitioners may be balancing the increased risk of relapse of the primary breast cancer with risk of a second, contralateral malignant tumor.

Limitations

Our study has limitations, owing to its retrospective design with limited information on surgical recommendations and decision-making between patients and practitioners. Although treatment sequence and type of treatment administered are well documented in the cohort, we lacked precise information on dates of index breast surgery, which precluded our ability to verify whether genetic testing was performed before or after surgery, as well as more granular details on surgical approach (ie, total, skin-sparing, or nipple-sparing mastectomy for those undergoing mastectomy) and access to breast reconstruction. Access to genetics services were also not documented but likely varied considerably across sites, geographic regions, and over the study period and warrant future study.

Furthermore, several factors that are known to influence surgical decisions in *gBRCA* carriers, including but not limited to insurance coverage, family history of breast cancer, family planning and the desire to breastfeed, concerns about quality of life, cosmesis, and sexual functioning, were not evaluated in this study. In addition, the current analysis did not incorporate patients who underwent bilateral mastectomy during follow-up after more than 6 months or 12 months from the primary breast cancer diagnosis, such that reported data may underestimate the true number of carriers who have undergone bilateral mastectomy. However, despite the stated limitations, to our knowledge, this study represents the largest global cohort of *BRCA* carriers with early-onset breast cancer and provides data about trends in genetic testing and surgical treatment for this unique patient population.

Conclusions

This cohort study of young *BRCA1/2* carriers with early-onset breast cancer found increasing use of bilateral mastectomy and reconstruction over time. While substantial geographic variation in surgical management exists, the factor most strongly associated with bilateral mastectomy receipt remained timing of genetic testing, with women tested prior to or at breast cancer diagnosis having the highest uptake of the procedure. These data support efforts to improve access to early genetic testing for young women with breast cancer, as results may help to optimize local therapy decisions.

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SUPPLEMENT 1.

eTable. Factors Associated With Bilateral Mastectomy in gBRCA1/2 Carriers With Unilateral Breast Cancer Who Underwent Genetic Testing Before or Within 3 Months of Breast Cancer Diagnosis

SUPPLEMENT 2.

Data Sharing Statement