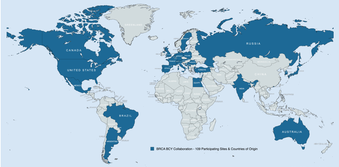
Surgical management of young *BRCA1/2* carriers with early onset breast cancer

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INTRODUCTION

- Women diagnosed with breast cancer <40 years have a 12%-18% likelihood of germline pathogenic variants in *BRCA1/2* breast cancer susceptibility genes[1,2]
- *BRCA* carriers with early onset breast cancer have an elevated lifetime risk of contralateral breast cancer, ranging from 60-68% by age 80[3]
- While bilateral mastectomy does not appear to confer survival benefit for older *BRCA* carriers, it has been shown to improve overall survival in young carriers with breast cancer diagnosed <40 years[4]
- In the setting of unilateral breast cancer, choice of breast conserving surgery (BCS), unilateral mastectomy, or bilateral mastectomy depends largely on clinical and patient-level factors, as well as the availability of genetic counselling and testing



The BRCA BCY Collaboration is an international, retrospective, hospital-based cohort study involving 109 institutions across five continents designed to evaluate outcomes in young female *BRCA* carriers with breast cancer (NCT03673306)

OBJECTIVE

The primary objective of the present analysis was to evaluate surgical patterns of care and factors associated with bilateral mastectomy as primary breast surgery in young *BRCA* carriers with breast cancer.

METHODS

Inclusion criteria: Females diagnosed with invasive breast cancer ≤40 years between January 2000-December 2020, with a known pathogenic or likely pathogenic variant (PV) in a *BRCA1* or *BRCA2;*

Exclusion criteria: Non-operable/stage IV BC, bilateral BC, unknown laterality, no surgery performed/surgical details unknown;

Outcome of interest: Primary breast surgery, defined as BCS, unilateral mastectomy, or bilateral mastectomy administered as part of index treatment;

Statistical Analysis: Chi-squared test used to compare clinicopathologic characteristics by primary breast surgery. Multivariable logistic regression was then used to assess factors associated with bilateral mastectomy receipt. Subgroup analysis was performed to assess surgical management in patients who had knowledge of *BRCA* status through genetic testing performed before or within 6 months of diagnosis.

COHORT CHARACTERISTICS

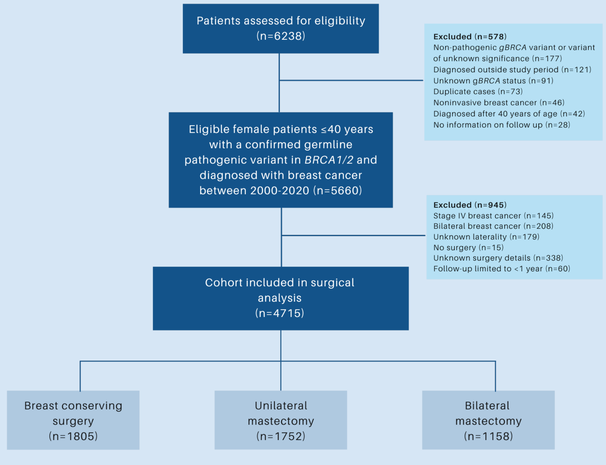


Figure 1. Between 2000-2020, 5660 eligible patients were identified, of whom **4715 underwent surgery and were eligible for the current analysis**. The median age of the cohort was 35 years (IQR, 31-38 years). Primary breast surgery was BCS in 1805 (38.3%) carriers, unilateral mastectomy in 1752 (37.2%) carriers, and bilateral mastectomy in 1158 (24.6%) carriers. Nearly all patients underwent axillary surgery; SLNB/TAD/MARI in 2077 (44.1%) and ALND in 2550 (54.1%). In addition to surgery, the majority of BRCA carriers received both chemotherapy (92.7%) and adjuvant radiation (66.5%).

RESULTS

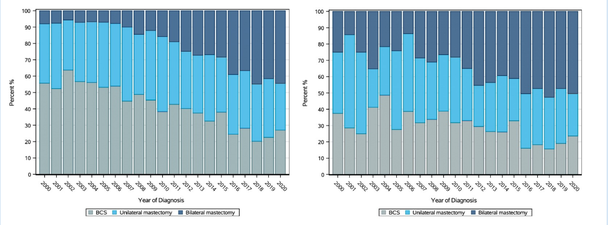


Figure 2A: Uptake of BCS, unilateral mastectomy, and bilateral mastectomy by year of diagnosis in young affected *BRCA1/2* carriers (n=4715), where the proportion undergoing BCS decreased from 55.7% in 2000 vs. 27.0% in 2020, whereas the use of bilateral mastectomy significantly increased (8.0% in 2000 vs. 44.4% in 2020, p<0.001).

Figure 2B: Subgroup analysis of surgical choices in young affected *BRCA1/2* carriers who underwent genetic testing before or at (defined as within 6 months of their) breast cancer diagnosis (n=2327). In this subgroup, higher rates of bilateral mastectomy at baseline (25% in 2000 vs. 50.4% in 2020, p<0.001).

RESULTS

Factors associated with bilateral mastectomy in *gBRCA1/2* carriers with unilateral breast cancer (n=4715)

Characteristic	Total cohort (*n*, %)	Proportion undergoing bilateral mastectomy (row %)	Adjusted odds ratio of receipt of bilateral mastectomy OR (95% CI)
Age at breast cancer diagnosis			
<30 years	973 (20.6)	25.6	*ref*
31-35 years	1750 (37.1)	23.6	0.89 (0.71-1.11)
36-40 years	1992 (42.3)	24.9	0.97 (0.78-1.20)
Year of diagnosis			
2000-2004	608 (12.9)	6.9	*ref*
2005-2008	748 (15.9)	10.2	1.11 (0.71-1.72)
2009-2012	999 (21.2)	17.9	1.45 (0.97-2.18)
2013-2016	1143 (24.2)	30.7	**2.24 (1.51-3.33)**
2017-2020	1217 (25.8)	41.9	**3.07 (2.06-4.56)**
Geographic region			
Southern Europe	1914 (40.6)	20.1	*ref*
Central/South America	245 (5.2)	18.4	1.19 (0.79-1.78)
Australia/Oceania	175 (3.7)	21.7	**1.79 (1.12-2.87)**
Northern Europe	712 (15.1)	27.9	1.05 (0.83-1.34)
Eastern Europe	307 (6.5)	21.8	**0.70 (0.49-0.98)**
North America	491 (10.4)	55.6	**4.79 (3.69-6.21)**
Asia/Africa	871 (18.5)	17.3	**0.65 (0.51-0.84)**
Germline *BRCA* pathogenic variant			
BRCA1	3015 (63.9)	26.6	*ref*
BRCA2	1700 (36.1)	20.9	0.83 (0.67-1.02)
Timing of g*BRCA* testing			
Testing after diagnosis	2167 (46.0)	5.1	*ref*
Testing at diagnosis	1892 (40.1)	38.5	**6.83 (5.39-8.66)**
Testing before diagnosis	435 (9.2)	57.0	**20.72 (15.27-28.13)**
Unknown date of *BRCA* testing	221 (4.7)	31.7	**6.88 (4.73-10.01)**
Histology			
Invasive ductal carcinoma	4035 (85.6)	24.7	*ref*
Invasive lobular carcinoma or other	645 (13.7)	24.7	0.96 (0.75-1.22)
Unknown histology	35 (0.7)	5.7	0.42 (0.08-2.15)
Biologic subtype			
TNBC	2328 (49.4)	26.4	*ref*
Luminal A	669 (14.2)	24.2	1.40 (0.97-2.01)
Luminal B	1058 (22.4)	24.0	1.07 (0.85-1.34)
HER2+	324 (6.9)	23.4	0.99 (0.70-1.41)
Unknown	336 (7.1)	15.2	1.05 (0.68-1.61)
Histologic grade			
Grade I	84 (1.8)	33.3	*ref*
Grade II	1109 (23.5)	23.7	0.64 (0.35-1.17)
Grade III	3150 (66.8)	25.4	0.67 (0.36-1.25)
Unknown	372 (7.9)	17.7	0.50 (0.25-1.02)
Tumor size			
T1	1765 (37.4)	24.2	*ref*
T2	2183 (46.3)	25.2	**0.79 (0.65-0.96)**
T3-T4	619 (13.1)	23.7	**0.55 (0.41-0.73)**
Unknown	148 (3.1)	22.3	**0.34 (0.19-0.63)**
Nodal status			
N0	2481 (52.6)	25.2	*ref*
N1	1563 (33.2)	25.3	0.91 (0.76-1.09)
N2-N3	571 (12.1)	19.8	**0.68 (0.51-0.91)**
Unknown	100 (2.1)	25.0	1.80 (0.93-3.51)
Treatment approach			
Neoadjuvant systemic therapy	1928 (40.9)	37.2	*ref*
Upfront surgery	2762 (58.6)	15.8	**0.27 (0.22-0.33)**
Unknown	25 (0.5)	16.0	**0.29 (0.08-1.06)**

RESULTS

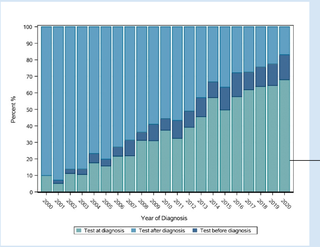
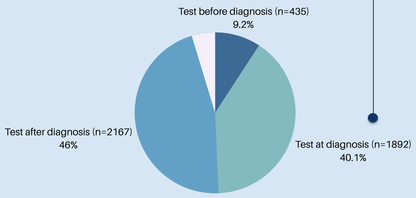


Figure 3: Knowledge of BRCA status through genetic testing performed before or at breast cancer diagnosis increased over time. Testing prior to diagnosis was present in 0% of carriers in 2000 and increased to 14.8% in 2020; genetic testing at diagnosis occurred in 9.1% in 2000 and increased to 66.1% by 2020 (p<0.001). Note: Testing at diagnosis defined as testing within 6 months.



Subgroup analysis of 2327 (49.3%) patients who had genetic testing performed before of within 6 months of diagnosis: In women with knowledge of their g*BRCA* status, 42% underwent bilateral mastectomy; the lowest bilateral mastectomy rates were reported in Asia/Africa (26.1%) and the highest rates reported in North America (66.4%, p<0.001). In adjusted subgroup analyses, g*BRCA1* carriers, later year of diagnosis, luminal A disease, smaller tumor size, node negative disease, neoadjuvant treatment, and geographic region remained independent predictors of bilateral mastectomy (p<0.05).

CONCLUSIONS

- This large, international study of 4715 young *BRCA* carriers provides evidence on increasing uptake of bilateral mastectomy as primary breast surgery for a first diagnosis of unilateral breast cancer;
- While significant geographic variation in surgical management exists, the strongest predictor of bilateral mastectomy remained timing of genetic testing;
- Genetic testing performed before or at diagnosis increased to 80% of carriers diagnosed with breast cancer in 2020;
- These data support efforts to improve access to early genetic testing for young women with breast cancer in order to help optimize local therapy decisions.

REFERENCES

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