

ORIGINAL RESEARCH

Characteristics and clinical outcomes of breast cancer in young *BRCA* carriers according to tumor histology

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Background: Young women with breast cancer (BC) have an increased chance of carrying germline *BRCA* pathogenic variants (PVs). Limited data exist on the prognostic impact of tumor histology (i.e. ductal versus lobular) in hereditary breast cancer.

Methods: This multicenter retrospective cohort study included women aged ≤ 40 years with early-stage breast cancer diagnosed between January 2000 and December 2020 and known to carry germline PVs in *BRCA1/2*. Histology was locally assessed in each center. The Kaplan–Meier method and Cox regression analysis were used to assess disease-free survival and overall survival.

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Results: Of 4628 patients included from 78 centers worldwide, 3969 (86%) had pure ductal, 135 (3%) pure lobular, and 524 (11%) other histologies. Compared with ductal tumors, lobular tumors were more often grade 1/2 (57.7% versus 22.1%), stage III (29.6% versus 18.5%), and luminal A-like (42.2% versus 12.2%). Lobular tumors were more often associated with *BRCA2* PVs (71.1% *BRCA2*), while ductal tumors were more often associated with *BRCA1* PVs (65.7% *BRCA1*). Patients with lobular tumors more often had mastectomy (68.9% versus 58.3%), and less often received chemotherapy (83.7% versus 92.9%). With a median follow-up of 7.8 years, no significant differences were observed in disease-free survival (adjusted hazard ratio 1.01, 95% confidence interval 0.74-1.37) or overall survival (hazard ratio 0.96, 95% confidence interval 0.62-1.50) between patients with ductal versus lobular tumors. No significant survival differences were observed according to specific *BRCA* gene, breast cancer subtype, or body mass index.

Conclusions: In this large global cohort of young *BRCA* carriers with breast cancer, the incidence of pure lobular histology was low and associated with higher disease stage at diagnosis, luminal-like disease and *BRCA2* PVs. Histology did not appear to impact prognosis.

Key words: *BRCA*, breast cancer, histology, lobular

INTRODUCTION

Breast cancers can be categorized into different histological subtypes based on cell morphology, growth, and architectural patterns.¹ The most common histology accounting for ~75%-80% of all invasive breast cancers is invasive carcinoma of no special type, commonly known as invasive ductal carcinoma.² The remaining 20%-25% of breast cancers consist of special histologies, with lobular breast cancer being the most prevalent among them.² Compared with ductal tumors, lobular cancers exhibit differences in clinical presentation,² long-term outcomes,³ site of disease progression,⁴ histopathological characteristics,⁵ and biological features.⁶ Current international guidelines provide some specific indications for selected breast cancer of special histologies (e.g. adenoid cystic, secretory, medullary), but not specifically on lobular tumors, in part due to limited research focusing on histologic distinctions.⁷

In particular, the prognostic impact of different histologies in breast cancers arising in young patients with a germline *BRCA* pathogenic or likely pathogenic variant (PV) has not been previously extensively studied. Limited data exist on the prevalence of lobular tumors among young *BRCA* carriers,^{8,9} as well as on the clinicopathological characteristics and survival outcomes of this specific subset of patients.

The *BRCA* BCY Collaboration (NCT03673306) is the largest international cohort study including young women with breast cancer carrying germline *BRCA* PVs.¹⁰ With its large real-world cohort of young *BRCA* carriers with breast cancer, this study represents a unique opportunity to explore the impact of the different histologies on the distribution of clinicopathological characteristics and on patients' clinical outcomes.

METHODS

Study design and procedures

This international retrospective observational cohort study, conducted across 78 centers worldwide, included women

aged ≤ 40 years who were diagnosed with invasive breast cancer between January 2000 and December 2020 and tested positive for germline *BRCA1/2* PVs. Criteria for inclusion/exclusion in the study were previously detailed.¹⁰ Information collected included country of treatment, year and age at diagnosis, menopausal status, type of *BRCA1/2* PV, primary tumor size, lymph node involvement at diagnosis, histology, grade, human epidermal growth factor receptor 2 (HER2) and hormone receptor status as well as administered treatments [type of surgery, type of chemotherapy (if administered), type of endocrine therapy (if administered)]. Histology, grade, HER2, and hormone receptor status were locally assessed and no central review was carried out.

Breast cancer subtypes were centrally defined following immunohistochemistry and/or *in situ* hybridization-based criteria (according to the current guidelines)^{11,12} as follows¹³: (i) luminal A-like, as estrogen receptor (ER)- and progesterone receptor (PgR)-positive, HER2-negative tumors of grade 1 or 2; (ii) luminal B-like, as either ER-negative/PgR-positive or ER-positive/PgR-negative, HER2-negative tumors, or ER- and/or PgR-positive, HER2-negative tumors of grade 3; (iii) HER2-positive as tumors with positive HER2 expression (regardless of other characteristics); (iv) triple-negative breast cancer (TNBC) as ER- and PgR-negative, HER2-negative tumors (any grade).

BRCA testing was locally carried out and re-classifications over time were eventually applied by each site as per internal guidelines.

The study was approved by the ethical review committee of the Institut Jules Bordet (Brussels, Belgium) as coordinating center. Whenever required, ethics approval was obtained in compliance with local regulations from independent ethical review committees or institutional review boards of participating centers.

Study objectives

The primary objective of this analysis was to investigate the impact of the different histologies of breast cancer on the

clinical outcomes of young *BRCA* carriers (pure ductal versus pure lobular).

The impact of histologies on prognosis was investigated by comparing the following time-to-event endpoints, defined as per STEEP criteria¹⁴: disease-free survival (DFS), defined by the occurrence of one of the following invasive events: local recurrence, distant metastases, contralateral or ipsilateral breast tumor, second primary malignancy, or death from any cause; overall survival (OS), defined by the occurrence of death from any cause.

Secondary objectives included: describing baseline patient and tumor characteristics according to the different histologies; investigating the impact of the different histologies on the clinical outcomes of young *BRCA* carriers according to the type of specific *BRCA* gene (*BRCA 1* versus *BRCA 2*), breast cancer subtype (luminal A-like, luminal B-like, HER2-positive, TNBC), and body mass index (BMI) (<25 versus ≥25).

Statistical analysis

Categorical and continuous variables of ductal versus lobular tumor were compared using the chi-square test and Wilcoxon rank-sum test as appropriate.

The Kaplan–Meier method was used to compute survival probabilities. The log-rank test was used to compare survival probabilities. Cox proportional hazards model was used to calculate unadjusted and adjusted hazard ratios (HR) with 95% confidence interval (CI). Adjustment in survival models was made for age, specific *BRCA* gene, year of diagnosis, tumor grade, tumor size, nodal status, tumor subtype, breast surgery, and use of chemotherapy. Cox models were used to assess the impact of different histologies on the clinical outcomes (i.e. DFS and OS) according to the type of specific *BRCA* gene (*BRCA1* versus *BRCA2*), breast cancer subtype (luminal A-like, luminal B-like, HER2-positive, TNBC), and BMI (<25 versus ≥25). The presence of interaction between histology and type of specific *BRCA* gene (1 versus 2), breast cancer subtypes, or BMI were also assessed. For survival analysis, patients whose tumors had mixed histologies (i.e. mixed ductal and lobular) were excluded from the comparative analysis of ductal versus lobular tumors.

RESULTS

Population characteristics and treatment received

A total of 4628 patients were included, of whom 3969 (86%) had pure ductal, 135 (3%) pure lobular, and 524 (11%) other histologies, respectively (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmoop.2024.103714>). Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2024.103714> reports the baseline characteristics of patients with tumors of pure ductal, pure lobular or other histology.

Comparisons of baseline clinicopathological characteristics between patients with pure ductal and pure lobular tumors are shown in Table 1. Compared with ductal

Table 1. Baseline clinicopathological characteristics

| | Pure ductal BC n (%) n = 3969 | Pure lobular BC n (%) n = 135 | P value |
|--|-------------------------------------|-------------------------------------|---------|
| Region | | | 0.002 |
| North America | 319 (8.0) | 11 (8.1) | |
| South-Center America | 130 (3.3) | 5 (3.7) | |
| Asia + Israel | 727 (18.3) | 7 (5.2) | |
| Oceania | 140 (3.5) | 4 (3.0) | |
| North Europe | 620 (15.6) | 28 (20.7) | |
| South Europe | 1793 (45.2) | 65 (48.1) | |
| East Europe | 240 (6.0) | 15 (11.1) | |
| Year of diagnosis | | | 0.053 |
| 2000-2004 | 498 (12.5) | 25 (18.5) | |
| 2005-2008 | 636 (16.0) | 28 (20.7) | |
| 2009-2012 | 867 (21.8) | 19 (14.1) | |
| 2013-2016 | 966 (24.3) | 31 (23.0) | |
| 2017-2020 | 1002 (25.2) | 32 (23.7) | |
| Age at diagnosis, median (IQR) years | 35 (31 to 37) | 36 (33 to 39) | 0.018 |
| Menopausal status at diagnosis | | | 0.068 |
| Premenopausal | 3774 (95.1) | 124 (91.8) | |
| Peri-menopausal | 13 (0.3) | 1 (0.7) | |
| Post-menopausal | 91 (2.3) | 7 (5.2) | |
| Missing | 91 (2.3) | 3 (2.2) | |
| BRCA status | | | <0.001 |
| <i>BRCA1</i> | 2606 (65.7) | 38 (28.1) | |
| <i>BRCA2</i> | 1335 (33.6) | 96 (71.1) | |
| <i>BRCA1</i> and <i>BRCA2</i> | 23 (0.6) | 1 (0.7) | |
| <i>BRCA</i> pathogenic variant (unknown if 1 or 2) | 5 (0.1) | 0 (0.0) | |
| Time from diagnosis to <i>BRCA</i> testing, median (IQR) months | 5.3 (0.9-25.3) | 8.1 (1.5-44.6) | 0.081 |
| Missing date of <i>BRCA</i> testing | 500 | 13 | |
| Body mass index | | | 0.741 |
| <18.5 | 207 (5.2) | 9 (6.7) | |
| 18.5-24.9 | 2132 (53.7) | 72 (53.3) | |
| 25.0-29.9 | 660 (16.6) | 26 (19.3) | |
| ≥30 | 350 (8.8) | 10 (7.4) | |
| Missing | 620 (15.6) | 18 (13.3) | |
| Stage at breast cancer diagnosis | | | 0.002 |
| I | 1053 (26.5) | 25 (18.5) | |
| II | 2092 (52.7) | 67 (49.6) | |
| III | 734 (18.5) | 40 (29.6) | |
| Missing | 90 (2.3) | 3 (2.2) | |
| Tumor grade | | | <0.001 |
| G1 | 53 (1.3) | 11 (8.1) | |
| G2 | 826 (20.8) | 67 (49.6) | |
| G3 | 2774 (69.9) | 40 (29.6) | |
| Missing | 316 (8.0) | 17 (12.6) | |
| Tumor size | | | 0.001 |
| T1 | 1545 (38.9) | 42 (31.1) | |
| T2 | 1764 (44.4) | 53 (39.3) | |
| T3-T4 | 532 (13.4) | 33 (24.4) | |
| Missing | 128 (3.2) | 7 (5.2) | |
| Nodal status | | | <0.001 |
| N0 | 2063 (52.0) | 48 (35.6) | |
| N1 | 1321 (33.3) | 59 (43.7) | |
| N2-N3 | 474 (11.9) | 25 (18.5) | |
| Missing | 111 (2.8) | 3 (2.2) | |
| Laterality | | | 0.104 |
| Left | 1905 (48.0) | 73 (54.1) | |
| Right | 1900 (47.9) | 61 (45.2) | |
| Bilateral | 152 (3.8) | 1 (0.7) | |
| Missing | 12 (0.3) | 0 (0.0) | |
| Breast surgery | | | 0.011 |
| Not done | 11 (0.3) | 1 (0.7) | |
| Breast conserving surgery | 1603 (40.4) | 37 (27.4) | |
| Mastectomy | 2314 (58.3) | 93 (68.9) | |
| Missing | 41 (1.0) | 4 (3.0) | |

Continued

Table 1. Continued

| | Pure ductal BC n (%) n = 3969 | Pure lobular BC n (%) n = 135 | P value |
|---|-------------------------------------|-------------------------------------|---------|
| Tumor subtype | | | <0.001 |
| Luminal A | 484 (12.2) | 57 (42.2) | |
| Luminal B | 865 (21.8) | 33 (24.4) | |
| TNBC | 2049 (51.6) | 19 (14.1) | |
| HER2-positive | 282 (7.1) | 8 (5.9) | |
| Missing | 289 (7.3) | 18 (13.3) | |
| Use of radiotherapy | | | 0.576 |
| No | 1301 (32.8) | 42 (31.1) | |
| Yes | 2592 (65.3) | 93 (68.9) | |
| Missing | 76 (1.9) | 0 (0.0) | |
| Type of systemic treatment | | | 0.471 |
| Not done | 47 (1.2) | 1 (0.7) | |
| Neoadjuvant | 1713 (43.2) | 52 (38.5) | |
| Adjuvant | 2176 (54.8) | 81 (60.0) | |
| Missing | 33 (0.8) | 1 (0.7) | |
| Use of chemotherapy | | | <0.001 |
| No | 258 (6.5) | 21 (15.6) | |
| Yes | 3689 (92.9) | 113 (83.7) | |
| Missing | 22 (0.5) | 1 (0.7) | |
| Type of chemotherapy (for CT = yes) | | | 0.780 |
| Anthracycline- and taxane-based | 2607 (70.7) | 82 (72.6) | |
| Anthracycline-based | 697 (18.9) | 17 (15.0) | |
| Taxane-based | 155 (4.2) | 4 (3.5) | |
| Others | 113 (3.1) | 4 (3.5) | |
| Missing | 117 (3.2) | 6 (5.3) | |
| Use of endocrine therapy (for HR+) | | | 0.277 |
| No | 83 (4.8) | 3 (2.6) | |
| Yes | 1624 (93.9) | 111 (97.4) | |
| Missing | 23 (1.3) | 0 (0.0) | |
| Type of endocrine therapy (for HR+ and ET = yes) | | | 0.896 |
| Tamoxifen alone | 566 (34.8) | 37 (33.3) | |
| Tamoxifen + LHRHa | 465 (28.6) | 32 (28.8) | |
| LHRHa alone | 28 (1.7) | 1 (0.9) | |
| AI ± LHRHa | 277 (17.1) | 23 (20.7) | |
| Tamoxifen and AI (± LHRHa) | 250 (15.4) | 15 (13.5) | |
| Others | 23 (1.4) | 2 (1.8) | |
| Missing | 15 (0.9) | 1 (0.9) | |
| Use of anti-HER2 therapy (for HER2+) | | | 0.843 |
| No | 28 (9.9) | 1 (12.5) | |
| Yes | 243 (86.2) | 7 (87.5) | |
| Missing | 11 (3.9) | 0 (0.0) | |
| Bilateral risk-reducing mastectomy | | | 0.422 |
| No | 1651 (41.6) | 51 (37.8) | |
| Yes | 2257 (56.9) | 81 (60.0) | |
| Missing | 61 (1.5) | 3 (2.2) | |
| Bilateral risk-reducing salpingo- oophorectomy | | | 0.598 |
| No | 1849 (46.6) | 60 (44.4) | |
| Yes | 2045 (51.5) | 74 (54.8) | |
| Missing | 75 (1.9) | 1 (0.7) | |

AI, aromatase inhibitor; BC, breast cancer; CT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IQR, interquartile range; LHRHa, luteinizing hormone-releasing hormone analog; TNBC, triple-negative breast cancer.

carcinoma, lobular tumors were more often of grade 1/2 (57.7% versus 22.1%, $P < 0.001$), of stage III (29.6% versus 18.5%, $P = 0.002$), and of luminal A-like subtype (42.2% versus 12.2%, $P < 0.001$). Lobular tumors were more often associated with *BRCA2* PVs (71.1% had *BRCA2* PVs), while ductal tumors were more often associated with *BRCA1* PVs

(65.7% had *BRCA1* PVs). Patients with lobular tumors more often underwent mastectomy (68.9% versus 58.3%, $P = 0.011$), and less often chemotherapy (83.7% versus 92.9%, $P < 0.001$).

Survival analyses

Table 2 reports the incidence and type of disease-free and overall survival events in patients with pure ductal and pure lobular breast cancer. Lobular tumors had more locoregional recurrences than ductal tumors (12.6% versus 7.6%, $P = 0.047$). No significant differences were observed in terms of distant recurrences or secondary malignancies.

With a median follow-up of 7.8 years (interquartile range 4.5-12.6 years), no significant differences were observed in survival outcomes between patients with ductal versus lobular tumors, neither in the unadjusted nor in the adjusted models (Table 3).

The 5-year DFS was 76% (95% CI 74% to 77%) in patients with ductal tumors, and 75% (95% CI 66% to 82%) in patients with lobular tumors (univariate Cox HR = 1.14, 95% CI 0.88-1.49; adjusted HR 1.01, 95% CI 0.74-1.37; Figure 1).

The 5-year OS was 92% (95% CI 91% to 93%) in patients with ductal tumors, and 92% (95% CI 85% to 96%) in patients with lobular tumors (univariate Cox HR = 1.14, 95% CI 0.88-1.49; adjusted HR 0.96, 95% CI 0.62-1.50; Figure 2).

No statistically significant interactions were observed between histology and type of specific *BRCA* gene [*BRCA1* versus 2; P for interaction (DFS) = 0.586, P for interaction (OS) = 0.246], breast cancer subtypes [P for interaction (DFS) = 0.886, P for interaction (OS) = 0.626], and BMI [P for interaction (DFS) = 0.250, P for interaction (OS) = 0.298].

Table 2. Type of disease-free events in young *BRCA* carriers with pure ductal versus pure lobular breast cancer

| | Pure ductal BC n (%) n = 3969 | Pure lobular BC n (%) n = 135 | P value |
|---|-------------------------------------|-------------------------------------|------------|
| Follow-up (years), median (IQR) | 7.77 (4.47-12.62) | 8.25 (4.73-14.41) | |
| No events | 2529 (63.7) | 77 (57.0) | 0.122 |
| Locoregional recurrence | 301 (7.6) | 17 (12.6) | 0.047 |
| Distant recurrence | 446 (11.2) | 18 (13.3) | 0.410 |
| Second primary malignancy | 159 (4.0) | 2 (1.5) | 0.175 |
| Ovary | 91 (2.3) | 1 (0.7) | |
| Pancreas | 9 (0.2) | 0 (0.0) | |
| Cervix | 9 (0.2) | 0 (0.0) | |
| Colorectal | 11 (0.3) | 0 (0.0) | |
| Hematology | 8 (0.2) | 0 (0.0) | |
| Skin | 18 (0.5) | 1 (0.7) | |
| Thyroid | 9 (0.2) | 0 (0.0) | |
| Endometrial | 8 (0.2) | 0 (0.0) | |
| Upper gastrointestinal tract | 5 (0.1) | 0 (0.0) | |
| Other | 30 (0.8) | 0 (0.0) | |
| Second primary breast cancer | 496 (12.5) | 18 (13.3) | 0.791 |
| Death without any disease- free survival event | 38 (1.0) | 3 (2.2) | 0.151 |

BC, breast cancer; IQR, interquartile range.

| Table 3. Multivariate analysis of disease-free and overall survival in young <i>BRCA</i> carriers with pure ductal versus pure lobular breast cancers | | | | | | |
|---|-----------------------|-----------|----------------|------------------|-----------|----------------|
| | Disease-free survival | | | Overall survival | | |
| | HR | 95% CI | <i>P</i> value | HR | 95% CI | <i>P</i> value |
| Histological type | | | 0.536 | | | 0.987 |
| Ductal | Ref. | — | | Ref. | — | |
| Lobular | 1.01 | 0.74-1.37 | | 0.96 | 0.62-1.50 | |
| Year of diagnosis | | | 0.717 | | | 0.047 |
| 2000-2004 | Ref. | — | | Ref. | — | |
| 2005-2008 | 1.07 | 0.89-1.24 | | 1.33 | 1.01-1.75 | |
| 2009-2012 | 0.97 | 0.81-1.15 | | 1.32 | 0.99-1.77 | |
| 2013-2016 | 1.03 | 0.85-1.23 | | 1.61 | 1.19-2.18 | |
| 2017-2020 | 1.10 | 0.88-1.37 | | 1.63 | 1.12-2.39 | |
| Tumor grade | | | 0.066 | | | 0.115 |
| G1 | Ref. | — | | Ref. | — | |
| G2 | 1.42 | 0.85-2.36 | | 1.99 | 0.73-5.42 | |
| G3 | 1.20 | 0.71-2.04 | | 1.50 | 0.54-4.16 | |
| Tumor size | | | <0.001 | | | <0.001 |
| T1 | Ref. | — | | Ref. | — | |
| T2 | 1.14 | 1.01-1.29 | | 1.53 | 1.24-1.89 | |
| T3-T4 | 1.47 | 1.23-1.74 | | 2.21 | 1.70-2.88 | |
| Nodal status | | | <0.001 | | | <0.001 |
| N0 | Ref. | — | | Ref. | — | |
| N1 | 1.30 | 1.14-1.47 | | 1.78 | 1.44-2.18 | |
| N2-N3 | 1.70 | 1.44-2.01 | | 2.60 | 2.02-3.35 | |
| Tumor subtype | | | 0.034 | | | 0.584 |
| Luminal A | Ref. | — | | Ref. | — | |
| Luminal B | 1.02 | 0.80-1.31 | | 1.19 | 0.81-1.75 | |
| TNBC | 1.27 | 0.99-1.63 | | 1.31 | 0.89-1.93 | |
| HER2-positive | 1.04 | 0.79-1.36 | | 1.18 | 0.76-1.82 | |
| Breast surgery | | | <0.001 | | | 0.008 |
| Breast conserving surgery | Ref. | — | | Ref. | — | |
| Not done | 3.02 | 1.53-5.95 | | 4.26 | 1.92-9.46 | |
| Mastectomy | 0.78 | 0.70-0.87 | | 1.10 | 0.92-1.33 | |
| Age at diagnosis, years | | | 0.055 | | | 0.997 |
| ≤35 | Ref. | — | | Ref. | — | |
| >35 | 0.91 | 0.81-1.01 | | 1.01 | 0.85-1.20 | |
| Use of chemotherapy | | | <0.001 | | | 0.025 |
| No | Ref. | — | | Ref. | — | |
| Yes | 0.60 | 0.48-0.75 | | 0.57 | 0.39-0.84 | |
| <i>BRCA</i> status | | | 0.827 | | | 0.532 |
| <i>BRCA1</i> | Ref. | — | | Ref. | — | |
| <i>BRCA2</i> | 0.97 | 0.84-1.12 | | 0.88 | 0.71-1.10 | |
| <i>BRCA1</i> and <i>BRCA2</i> | 0.97 | 0.53-1.77 | | 1.25 | 0.51-3.04 | |

CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; TNBC, triple-negative breast cancer.

No significant differences in survival outcomes were observed between patients with pure lobular versus pure ductal tumors according to type of specific *BRCA* gene (*BRCA* 1 versus 2) (Supplementary Tables S2 and S3 and Figures S2-S4, available at <https://doi.org/10.1016/j.esmoop.2024.103714>), breast cancer subtype (luminal-like, HER2-positive, TNBC) (Supplementary Tables S2 and S3 and Figures S5-S12, available at <https://doi.org/10.1016/j.esmoop.2024.103714>), and BMI (<25 versus ≥25) (Supplementary Tables S2 and S3 and Figures S13-S16, available at <https://doi.org/10.1016/j.esmoop.2024.103714>).

DISCUSSION

In this large real-world cohort of young *BRCA* carriers with breast cancer, we assessed the impact of the different breast cancer histologies. Among the 4628 young patients included, we observed that the incidence of pure lobular histology was low, concerning only 3% of cases.¹

Invasive lobular carcinoma represents ~5%-15% of all breast cancer diagnoses, ranking as the second most common histology following invasive ductal carcinoma. Lobular tumors are recognized by their small, detached epithelial cells, with the majority being ER-positive and HER2-negative, and occurring more often in older women compared with ductal tumors.^{15,16}

Our cohort included exclusively young women up to the age of 40 years at the time of diagnosis, and the majority of patients were carriers of a *BRCA1* PV, that is most often associated with a TNBC phenotype. This might explain the low prevalence of lobular histology in our cohort, where more than one half of patients had a TNBC. Mavaddat et al.⁹ previously described a 4.5% prevalence of lobular tumors in their cohort of *BRCA* carriers, of which 2.2% were observed in *BRCA1* and 8.3% in *BRCA2* carriers; however, it should be considered that median age at diagnosis was 40 years in *BRCA1* carriers and 43 years in *BRCA2* carriers, respectively, which is older than the median age in our cohort.

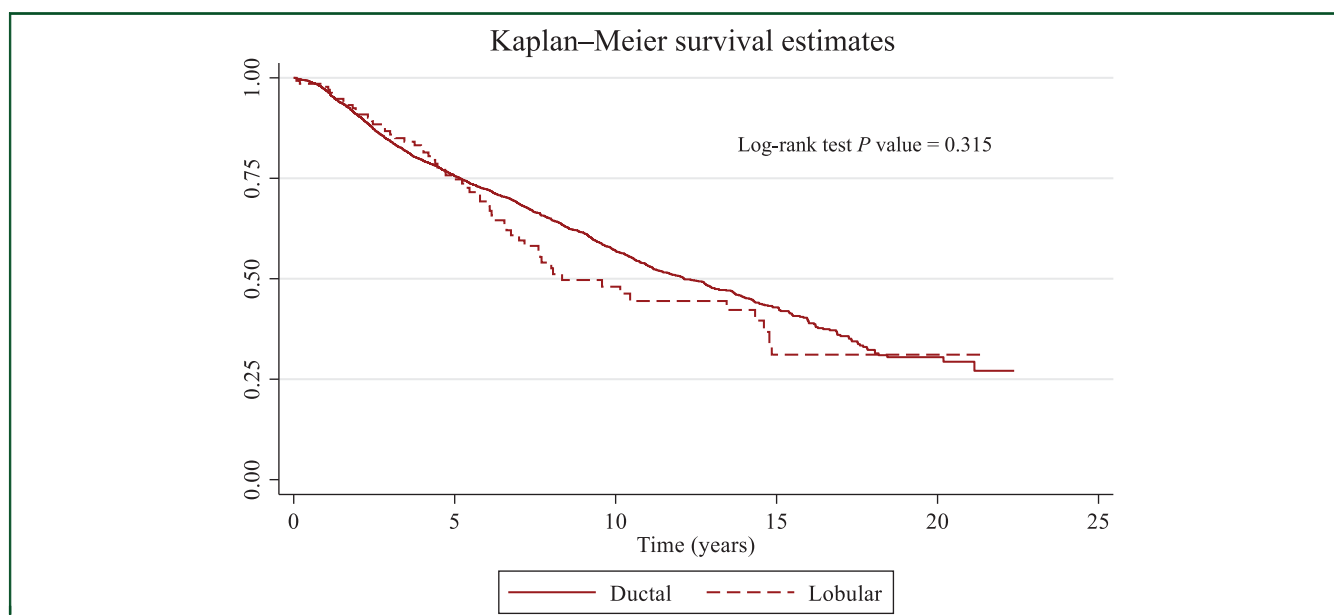


Figure 1. Kaplan–Meier survival estimates of disease-free survival in young *BRCA* carriers with pure ductal versus pure lobular breast cancer.

Clinically, lobular tumors behave differently from ductal carcinoma, often appearing as multifocal or multicentric disease.¹⁷ Although information on multifocality was not available in our study, patients with lobular tumors more often had mastectomy compared with those with ductal tumors. Multifocality may have contributed to these surgical decisions. Of note, the detached cell nature and low cell density of lobular tumors contribute to the challenge in their clinical and radiological detection.¹⁸ This may underlie the relatively higher disease stage at diagnosis observed in our lobular cohort and the higher proportion of tumors with large tumor size (T3-T4) compared with the ductal carcinomas.

Additionally, lobular tumors display a distinct metastatic pattern involving the peritoneum, ovaries, gastrointestinal tract, leptomeninges, alongside common bone lesions.¹⁹ In our cohort, patients with lobular tumors experienced more locoregional recurrences compared with those with ductal tumors, with no significant differences in the rate of distant recurrences. It should be noted, however, that only the first recurrence event was analyzed, with information not available concerning possible distant recurrences after a locoregional recurrence.

From a therapeutic perspective, early-stage lobular breast cancers exhibit lower responsiveness to (neo)adjuvant chemotherapy than ductal cancers,^{20,21} and some

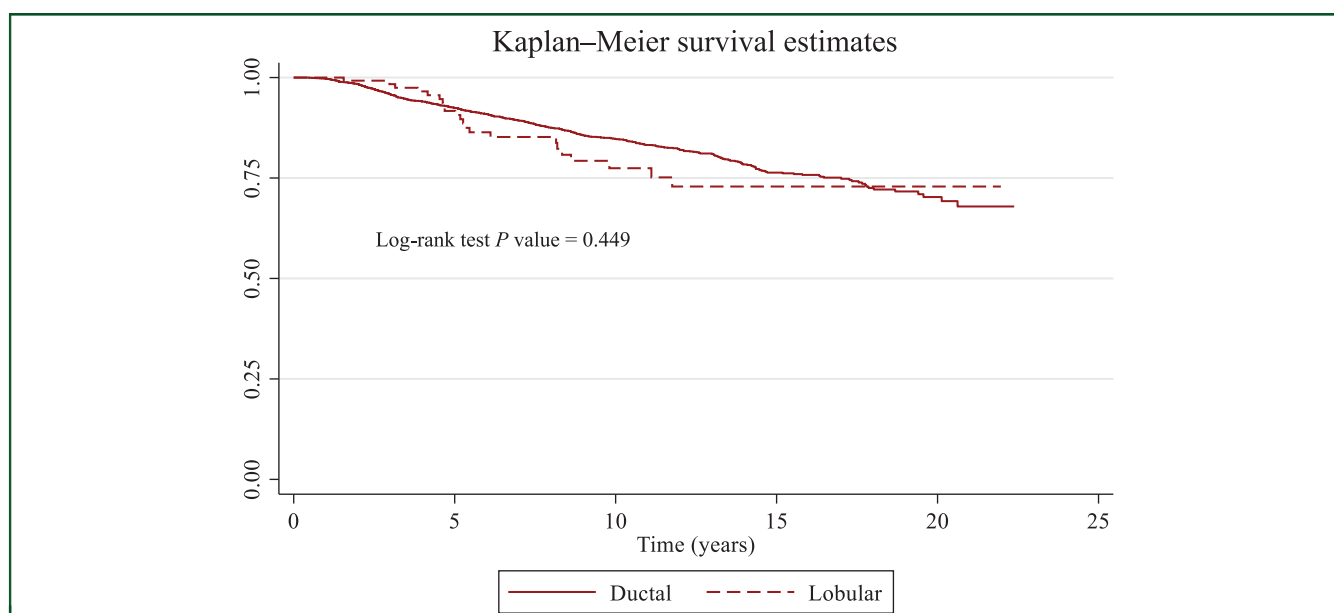


Figure 2. Kaplan–Meier survival estimates of overall survival in young *BRCA* carriers with pure ductal versus pure lobular breast cancer.

studies suggested greater benefit from aromatase inhibitors than tamoxifen as adjuvant endocrine therapy.²² The latter consideration was recently questioned by the results of a large individual patient meta-analysis showing no evidence of differential efficacy for aromatase inhibitors over tamoxifen in lobular versus ductal carcinomas, and thus suggesting histology should not be considered as a predictive marker for differential endocrine treatment benefit.²³ In our cohort, patients with lobular tumors received less chemotherapy than those with ductal tumors. We observed no significant differences on the type of endocrine therapy administered to patients with pure ductal versus pure lobular hormone receptor-positive tumors.

In our analysis, no significant differences were observed either in DFS or in OS between patients with ductal and lobular tumors, suggesting that in young *BRCA* carriers the histology does not appear to impact on prognosis. This is in contrast with some retrospective studies^{24,25} exploring prognosis of lobular tumors regardless of *BRCA* status. In a French retrospective cohort study of patients with metastatic breast cancer, lobular histology was identified as an independent adverse prognostic factor.²⁵ Of note, the different settings (early versus metastatic) hamper a direct comparison between studies. In a Korean cohort study including more than 225 000 premenopausal patients, the breast cancer-specific survival of patients with stage I-III lobular breast cancer was significantly lower than that of patients with ductal tumors within the first 10 years after diagnosis.²⁴ The presence of a *BRCA* germline mutation was not considered in this study. Overall, our data need to be carefully evaluated considering the small number of patients with lobular breast cancer (only 3%).

Besides their clinicopathological characterization, various genomic initiatives have attempted to characterize the molecular landscape of lobular breast cancer.^{26,27} PVs in *ATM*, *BRCA2*, *CDH1*, *CHEK2*, and *PALB2* are associated with an increased risk of lobular breast cancer, while *BRCA1* PVs are not.²⁶ Mutations in *CDH1*, responsible for E-cadherin, the cell adhesion molecule, are nearly pathognomonic genomic events in lobular tumors, reported in up to 90% of cases.²⁷⁻²⁹ Thus, consistent evidence supports the fact that lobular breast cancer is a distinct clinical and biological entity. Nonetheless, with few exceptions,³⁰ these patients typically undergo the same treatments and participate in the same clinical trials as those with ductal breast cancers.³¹ Moreover, many trials do not specifically report outcomes based on histology, complicating the extrapolation of data for patients with lobular tumors. Lobular breast cancers are often underrepresented in trials due to their diffuse growth pattern and lack of measurable disease.³² Consequently, addressing the numerous uncertainties and unmet needs in lobular breast cancer management requires tailored clinical studies for this specific patient subgroup.

Our study has some limitations that should be acknowledged, most of which are related to its retrospective nature. All information was extracted from medical records, and some potentially relevant variables (e.g. ethnicity, gene expression signature data) were not collected. Histology

was locally assessed, and no central pathology review was carried out. Additionally, data were collected from multiple centers worldwide, with different health care systems and different drug availabilities. Patients were diagnosed over a period of 20 years, during which the treatment of early breast cancer has improved, particularly for patients with hormone receptor-positive disease, who represent the majority of patients with lobular tumors. Patients included toward the end of the study period had less observation time to evaluate outcomes and recurrences; this limitation is particularly important for the interpretation of survival data, especially patients with hormone receptor-positive disease. Finally, this study focused on young *BRCA* carriers, so our results are not necessarily generalizable to *BRCA* carriers of all ages.

Conclusions

In this large cohort of young women with breast cancer and known germline *BRCA1/2* PVs, the incidence of pure lobular histology was low (i.e. 3%). Patients with lobular cancers had higher disease stage at diagnosis, more luminal-like disease and more *BRCA2* PVs. Histology did not appear to impact prognosis. Prospective clinical trials that are dedicated to lobular breast cancer could further elucidate best practices related to the treatment of this distinct biologic entity.

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DATA SHARING

Data are available upon reasonable request and submission of a research project proposal to the corresponding author, and after review and approval of the proposal by the BRCA BCY Collaboration.

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