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

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

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

E. Agostinetto[1*], M. Bruzzone[2], A.-S. Hamy[3], H. J. Kim[4], C. Chiodi[5], R. Bernstein-Molho[6], S. Linn[7], K. Pogoda[8], E. Carrasco[9], F. Derouane[10], J. Bajpai[11], G. Nader-Marta[1], N. Lopetegui-Lia[12], A. H. Partridge[13], L. Cortesi[14], C. Rousset-Jablonski[15,16,17], F. Giugliano[18,19], T. Renaud[20], A. Ferrari[21,22], S. Paluch-Shimon[23,24], R. Fruscio[25,26], W. Cui[27,28], S. M. Wong[29,30], C. Vernieri[31,32], K. J. Ruddy[33], M. V. Dieci[34,35], A. Matikas[36,37], M. Rozenblit[38], D. Aguilar y Mendez[39], L. De Marchis[40,41], R. Borea[42,43], F. Puglisi[44,45], M. Pistelli[46], J. Kufel-Grabowska[47], R. Di Rocco[48], E. Mariamidze[42,49], F. Atzori[50], H. R. Kourie[51], L. Popovic[52], E. de Azambuja[1], E. Blondeaux[2†] & M. Lambertini[42,43†]

[1]Academic Trials Promoting Team, Institut Jules Bordet, Université Libre de Bruxelles (U.L.B.), Hôpital Universitaire de Bruxelles (HUB), Brussels, Belgium; [2]U.O. Epidemiologia Clinica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [3]Department of Medical Oncology, Universite Paris Cité, Institut Curie, Paris, France; [4]Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [5]Cancer Survivorship Program — Molecular Predictors and New Targets in Oncology, INSERM Unit 981, Gustave Roussy, Villejuif, France; [6]Susanne Levy Gertner Oncogenetics Unit, The Danek Gertner Institute of Human Genetics, Chaim Sheba Medical Center Affiliated to Tel Aviv University, Tel Hashomer, Israel; [7]Department of Molecular Pathology, Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands; [8]Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]Hereditary Cancer Genetics Unit, Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Department of General Medical Oncology and Multidisciplinary Breast Center, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; [11]Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India; [12]Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland; [13]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; [14]Department of Oncology and Haematology, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy; [15]Department of Surgery, Leon Berard Cancer Center, Lyon; [16]Hôpital Femme-Mère-Enfant, Hospices Civils de Lyon, Bron; [17]Unité INSERM U1290 RESHAPE, Lyon; [18]Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan; [19]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [20]Cancer Genetics Unit, Bergonie Institute, Bordeaux, France; [21]Hereditary Breast and Ovarian Cancer (HBOC) Unit and General Surgery 3 — Senology, Surgical Department, Fondazione IRCCS Policlinico San Matteo, Pavia; [22]University of Pavia, Pavia, Italy; [23]Breast Oncology Unit, Sharett Institute of Oncology, Hadassah University Hospital, Jerusalem; [24]Faculty of Medicine, Hebrew University, Jerusalem, Israel; [25]UO Gynecology, Fondazione IRCCS San Gerardo, Monza; [26]Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; [27]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Victoria; [28]Department of Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia; [29]Stroll Cancer Prevention Centre, Jewish General Hospital, Montreal; [30]McGill University Medical School, Montreal, Canada; [31]Medical Oncology Department, Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [32]Oncology and Hematology-Oncology Department, University of Milan, Milan, Italy; [33]Department of Oncology, Mayo Clinic College of Medicine, Rochester, USA; [34]Department of Surgical, Oncological and Gastroenterological Sciences, Università di Padova, Padua; [35]Oncologia 2, Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; [36]Department of Oncology/Pathology, Karolinska Institute, Stockholm; [37]Breast Center, Karolinska University Hospital, Stockholm, Sweden; [38]Yale University, Medical Oncology, New Haven, USA; [39]Tecnologico de Monterrey, Breast Cancer Center, Hospital Zambrano Hellion - TecSalud, Monterrey, Mexico; [40]Division of Medical Oncology, Department of Radiological, Oncological and Pathological Sciences, 'La Sapienza' University of Rome, Rome; [41]Oncology Unit, Umberto 1 University Hospital, Rome; [42]Medical Oncology Department, U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa; [43]Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genova, Genoa; [44]Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano; [45]Department of Medicine, University of Udine, Udine; [46]Azienda Ospedaliero-Universitaria delle Marche, Ancona, Italy; [47]Medical University of Gdańsk, Gdańsk, Poland; [48]Department of Medical Oncology, Azienda USL Toscana Sud Est - Misericordia Hospital, Grosseto, Italy; [49]Department of Oncology and Hematology, Todua Clinic, Tbilisi, Georgia; [50]Azienda Ospedaliero Universitaria di Cagliari, Cagliari, Italy; [51]Saint Joseph University of Beirut, Beirut, Lebanon; [52]Oncology Institute of Vojvodina — Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

Available online xxx

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.

*Correspondence to: Dr Elisa Agostinetto, Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B.), Rue Meylemeersch, 90 (Rez Haut Nord), B-1070 Anderlecht, Belgium. Tel: + 32-(0)-2-541-3099

E-mail: elisa.agostinetto@hubruxelles.be (E. Agostinetto).

†These authors contributed equally to this work.

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 *BRCA*2 PVs (71.1% *BRCA*2), while ductal tumors were more often associated with *BRCA1* PVs (65.7% *BRCA*1). 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 *BRCA*2 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 follows[13]: (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 criteria[14]: 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 (*BRCA*1 versus *BRCA*2), 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
BRCA1	2606 (65.7)	38 (28.1)	
BRCA2	1335 (33.6)	96 (71.1)	
BRCA1 and *BRCA2*	23 (0.6)	1 (0.7)	
BRCA pathogenic variant (unknown if 1 or 2)	5 (0.1)	0 (0.0)	
Time from diagnosis to *BRCA* testing, median (IQR) months	5.3 (0.9-25.3)	8.1 (1.5-44.6)	0.081
Missing date of *BRCA* 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 [*BRCA* 1 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 *BRCA* carriers with pure ductal versus pure lobular breast cancers

	Disease-free survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* 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	
BRCA status			0.827			0.532
BRCA1	Ref.	—		Ref.	—	
BRCA2	0.97	0.84-1.12		0.88	0.71-1.10	
BRCA1 and *BRCA2*	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.

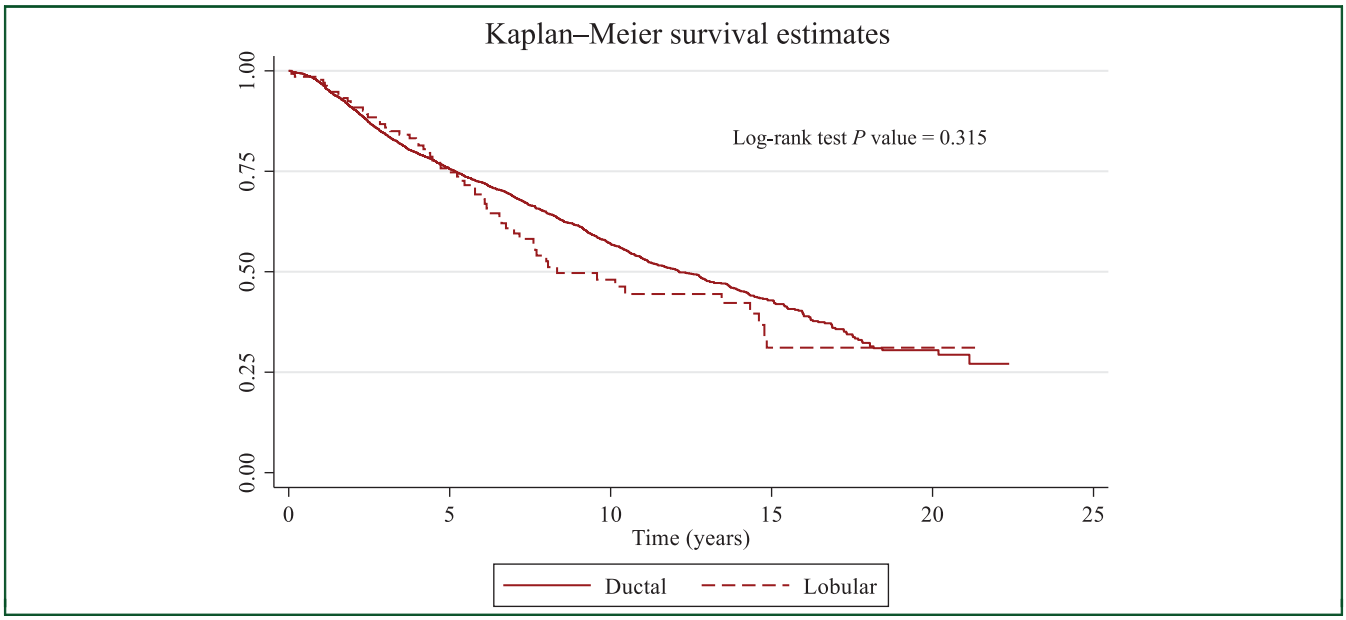

Figure 1. **Kaplan–Meier survival estimates of disease-free survival in young *BRCA* carriers with pure ductal versus pure lobular breast cancer.**

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

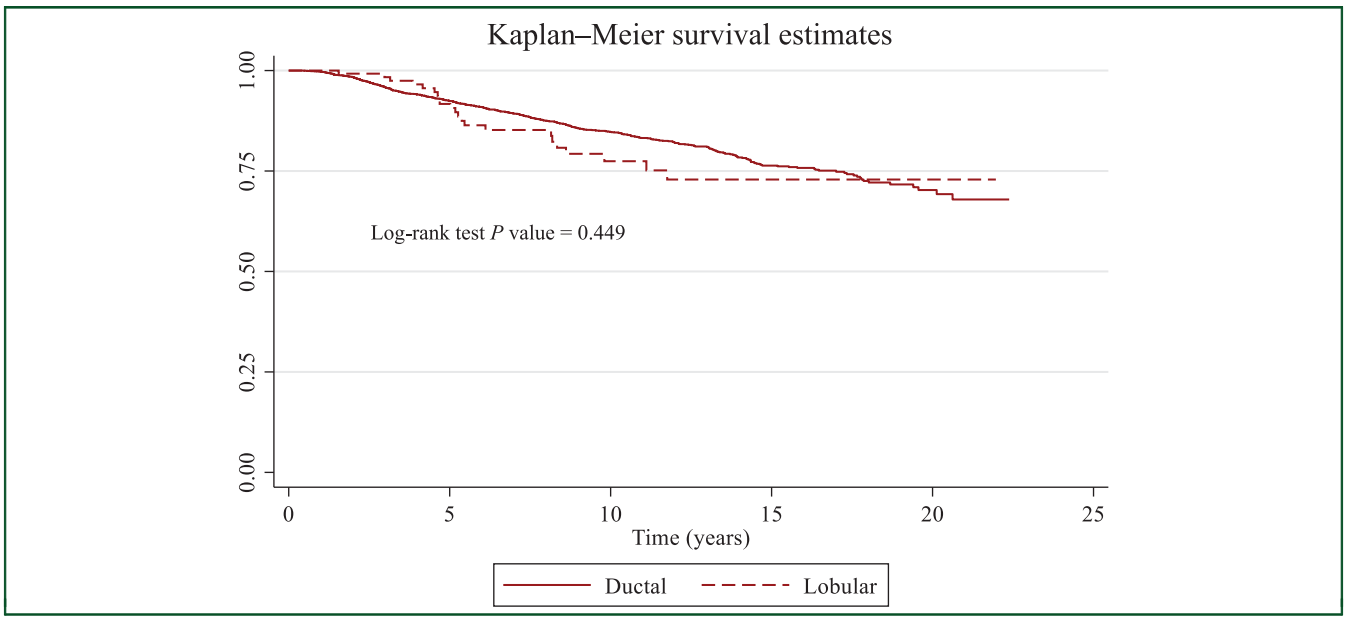

Figure 2. **Kaplan–Meier survival estimates of overall survival in young *BRCA* carriers with pure ductal versus pure lobular breast cancer.**

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 *BRCA*1/2 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 *BRCA*2 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.

ACKNOWLEDGEMENTS

The abstract of the present work was accepted for presentation at the ESMO Breast Cancer Annual Meeting 2024 and was awarded with an ESMO Merit Travel Grant Award.

EA acknowledges Dr Daphné t'Kint de Roodenbeke and Dr Masa Auprih, Institut Jules Bordet, Brussels (Belgium) for their contributions. JB acknowledges Prof. Rajeev Sarin and Cancer Genetic Clinic, Tata Memorial Centre, Mumbai for their contributions. RF acknowledges the Breast Unit and Medical Oncology Unit, Fondazione IRCCS San Gerardo, Monza (Italy) for their contribution.

FUNDING

This work was supported by the Italian Association for Cancer Research [AIRC grant number MFAG 2020 ID 24698 to the BRCA BCY Collaboration (NCT03673306)]. The European Society for Medical Oncology (ESMO) for a translational research fellowship at the Institut Jules Bordet in Brussels, Belgium, at the time this study was initiated [to ML] (no grant number). The Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea [grant number HC20C0135 to HJK]. Data collection for most Australian participants was through the kConFab Follow-Up Study with support from Cancer Australia and the National Breast Cancer Foundation [grant number PdCCRS 1100868], Cancer Australia [grant number 809195], the Australian National Breast Cancer Foundation (IF 17), the Australian National Health and Medical Research Council [grant numbers 454508, 288704, and 145684], the United

States National Institutes of Health [grant number 1RO1CA159868], the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania, and South Australia, and the Cancer Foundation of Western Australia. The Breast Cancer Research Foundation and Susan G. Komen [to AHP] (no grant number).

The study supporters had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

DISCLOSURE

EA: honoraria and/or advisory boards from: Eli Lilly, Sandoz, AstraZeneca. Research grant to my Institution from Gilead. travel grants from: Novartis, Roche, Eli Lilly, Genetic, Istituto Gentili, Daiichi Sankyo, AstraZeneca (all outside the submitted work). RBM: support for attending medical conferences from: Pfizer; speakers fee from Novartis, AstraZeneca (all outside the submitted work). SL: reports grants paid to the institute from AstraZeneca, Eurocept Plaza, Roche, Genentech, Gilead Sciences, GlaxoSmithKline (GSK), Novartis, and Agendia outside the submitted work; consulting fees from AstraZeneca paid to the institute; educational fees from Daiichi Sankyo paid to the institute; other financial support for attending meetings from Daiichi Sankyo; non-financial support from Genentech (drug), Roche (drug), Gilead Sciences (drug), Novartis (drug), Agendia (gene expression tests), and AstraZeneca (drug). SCL has a patent (PCT/EP2022/73958) pending on a method for assessing homologous recombination deficiency in ovarian cancer cells. KP: honoraria for consultations/lectures/training/clinical trials and payment of conferences fees from AstraZeneca, Gilead, Roche, Novartis, Eli Lilly, Pfizer, Merck Sharp & Dohme (MSD), Teva, Egis, and Vipharm (all outside the submitted work). FD: support for attending medical conferences from: Novartis, Gilead; speakers fee from Novartis. GNM: support to attend medical conference from AstraZeneca. LC: speaker honoraria from AstraZeneca, Pfizer, Novartis, Gilead, MSD; advisory role for AstraZeneca, Pfizer, MSD, Amgen, Roche. RDR: AstraZeneca, MSD, GSK, Janssen, Bayer, Orion Pharma. CRJ: honoraria (paid to my institution) from Theramex, advisory board (paid to my institution) from Theramex, Roche, Gedeon Richter, speakers bureau (paid to my institution) from Bristol Myers Squibb, Organon, Novartis, research funding (paid to my institution) from Gedeon Richter and Bayer Healthcare. WC: honoraria from Merck, Pfizer, and Eisai. CV: consultancy or role in advisory board: Eli Lilly, Novartis, Pfizer, Daiichi Sankyo, Menarini. Honoraria as a speaker: Novartis, Eli Lilly, Istituto Gentili, MSD, Accademia di Medicina. Research grants (to the institution): Roche. LP: speaker/advisor/investigator: MSD, BMS, Pfizer, AstraZeneca, Roche, Merck, Novartis, Lilly, Takeda, Helsinn, Astellas, Janssen, Sanofi, Sandoz, Actavis, Amgen, Archigen, Amicus, Taiho, Infinity, Bioclin, G1 Therapeutics, MEI Pharma, Immunocore/Medison, NAPO Pharmaceuticals, Oktal, PharmaSwiss, AbbVie, Medica Linea, MAK Pharma, Agendia, Recordati, Incyte. FP: honoraria for advisory boards, activities as a speaker, travel grants, research grants: Amgen, AstraZeneca, Daichii Sankyo, Celgene, Eisai, Eli Lilly, Exact Sciences, Gilead, Ipsen, Menarini, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seagen, Takeda, Viatris. Research funding: AstraZeneca, Eisai, Roche. EdA: Financial: Honoraria and/or advisory board from Roche/GNE, Novartis, SeaGen, Zodiac, Libbs, Pierre Fabre, Lilly, AstraZeneca, MSD, Gilead Sciences; travel grants from Roche/GNE and AstraZeneca; Research grant to my institution from Roche/GNE, AstraZeneca, and GSK/Novartis, Gilead Sciences; non-financial: ESMO director of Membership 2023-2025; BSMO President 2023-2026. EB: research funding (to the institution) from Gilead, speakers fee from Eli Lilly. ML: advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Menarini, Daiichi Sankyo, and Exact Sciences; receiving speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Knight, Ipsen, Gilead, and AstraZeneca; receiving travel grants from Gilead, Roche and Daiichi Sankyo; receiving research *funding (to his institution) from Gilead; and having non-financial interests as the chair of the European Society for Medical Oncology (ESMO) Young Oncologists Committee (YOC) and as* a member of the national council of the Italian Association of Medical Oncology. All other authors have declared no conflicts of interest.

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.

REFERENCES

1. Tan PH, Ellis I, Allison K, et al. The 2019 World Health Organization classification of tumours of the breast. *Histopathology*. 2020;77:181-185.
2. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. *Br J Cancer*. 2005;93:1046-1052.
3. Adachi Y, Ishiguro J, Kotani H, et al. Comparison of clinical outcomes between luminal invasive ductal carcinoma and luminal invasive lobular carcinoma. *BMC Cancer*. 2016;16:248.
4. Mathew A, Rajagopal PS, Villgran V, et al. Distinct pattern of metastases in patients with invasive lobular carcinoma of the breast. *Geburtshilfe Frauenheilkd*. 2017;77:660-666.
5. De Schepper M. Results of a worldwide survey on the currently used histopathological diagnostic criteria for invasive lobular breast cancer (ILC). In: *Proceedings of the San Antonio Breast Cancer Symposium, December 7-10, 2021, Gonzalez Convention Center, San Antonio, Texas*. Philadelphia, PA: American Association for Cancer Research; 2021.
6. Ciriello G, Gatza ML, Beck AH, et al. Comprehensive molecular portraits of invasive lobular breast cancer. *Cell*. 2015;163:506-519.
7. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35:159-182.
8. Ditchi Y, Broudin C, El Dakdouki Y, et al. Low risk of invasive lobular carcinoma of the breast in carriers of BRCA1 (hereditary breast and ovarian cancer) and TP53 (Li-Fraumeni syndrome) germline mutations. *Breast J*. 2019;25:16-19.
9. Mavaddat N, Barrowdale D, Andrulis IL, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results

from the consortium of investigators of modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev*. 2012;21:134-147.
10. Lambertini M, Blondeaux E, Agostinetto E, et al. Pregnancy after breast cancer in young BRCA carriers: an international hospital-based cohort study. *JAMA*. 2024;331:49-59.
11. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline focused update. *Arch Pathol Lab Med*. 2018;142:1364-1382.
12. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP Guideline update. *J Clin Oncol*. 2020;38:1346-1366.
13. Partridge AH, Hughes ME, Warner ET, et al. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. *J Clin Oncol*. 2016;34:3308-3314.
14. Tolaney SM, Garrett-Mayer E, White J, et al. Updated Standardized Definitions for Efficacy End Points (STEEP) in adjuvant breast cancer clinical trials: STEEP Version 2.0. *J Clin Oncol*. 2021;39:2720-2731.
15. Christgen M, Steinemann D, Kühnle E, et al. Lobular breast cancer: clinical, molecular and morphological characteristics. *Pathol Res Pract*. 2016;212:583-597.
16. Pestalozzi BC, Zahrieh D, Mallon E, et al. Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. *J Clin Oncol*. 2008;26:3006-3014.
17. Iorfida M, Maiorano E, Orvieto E, et al. Invasive lobular breast cancer: subtypes and outcome. *Breast Cancer Res Treat*. 2012;133:713-723.
18. Johnson K, Sarma D, Hwang ES. Lobular breast cancer series: imaging. *Breast Cancer Res*. 2015;17:94.
19. Guiu S, Wolfer A, Jacot W, et al. Invasive lobular breast cancer and its variants: how special are they for systemic therapy decisions? *Crit Rev Oncol Hematol*. 2014;92:235-257.
20. Cocquyt VF, Blondeel PN, Depypere HT, et al. Different responses to preoperative chemotherapy for invasive lobular and invasive ductal breast carcinoma. *Eur J Surg Oncol*. 2003;29:361-367.
21. Van Baelen K, Geukens T, Maetens M, et al. Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer. *Ann Oncol*. 2022;33:769-785.
22. Metzger Filho O, Giobbie-Hurder A, Mallon E, et al. Relative effectiveness of letrozole compared with tamoxifen for patients with lobular carcinoma in the BIG 1-98 trial. *J Clin Oncol*. 2015;33:2772-2779.
23. Hills RK, Oesterreich S, Metzger O, et al. Abstract PD14-08: Effectiveness of aromatase inhibitors versus tamoxifen in lobular compared to ductal carcinoma: individual patient data meta-analysis of 9328 women with central histopathology, and 7654 women with e-Cadherin status. *Cancer Res*. 2002;82:PD14-08.
24. Yoon TI, Jeong J, Lee S, et al. Survival outcomes in premenopausal patients with invasive lobular carcinoma. *JAMA Netw Open*. 2023;6:e2342270.
25. Dalenc F, Lusque A, De La Motte Rouge T, et al. Impact of lobular versus ductal histology on overall survival in metastatic breast cancer: a French retrospective multicentre cohort study. *Eur J Cancer*. 2022;164:70-79.
26. Yadav S, Hu C, Nathanson KL, et al. Germline pathogenic variants in cancer predisposition genes among women with invasive lobular carcinoma of the breast. *J Clin Oncol*. 2021;39:3918-3926.
27. Desmedt C, Zoppoli G, Gundem G, et al. Genomic characterization of primary invasive lobular breast cancer. *J Clin Oncol*. 2016;34:1872-1881.
28. Morrogh M, Andrade VP, Giri D, et al. Cadherin-catenin complex dissociation in lobular neoplasia of the breast. *Breast Cancer Res Treat*. 2012;132:641-652.
29. Dossus L, Benusiglio PR. Lobular breast cancer: incidence and genetic and non-genetic risk factors. *Breast Cancer Res*. 2015;17:37.
30. Agostinetto E, Nader-Marta G, Paesmans M, et al. ROSALINE: a phase II, neoadjuvant study targeting ROS1 in combination with endocrine therapy in invasive lobular carcinoma of the breast. *Future Oncol*. 2022;18:2383-2392.
31. Trapani D, Curigliano G. How to treat lobular cancer in the adjuvant setting? *Curr Opin Oncol*. 2020;32:561-567.
32. Abel MK, Melisko ME, Rugo HS, et al. Decreased enrollment of patients with advanced lobular breast cancer compared to ductal breast cancer in interventional clinical trials. *J Clin Oncol*. 2021;39:1092.