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ORIGINAL ARTICLE

Impact of hormone receptor status and tumor subtypes of breast cancer in young *BRCA* carriers

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Background: Hormone receptor expression is a known positive prognostic and predictive factor in breast cancer; however, limited evidence exists on its prognostic impact on prognosis of young patients harboring a pathogenic variant (PV) in the BRCA1 and/or BRCA2 genes.

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Patients and methods: This international, multicenter, retrospective cohort study included young patients (aged ≤40 years) diagnosed with invasive breast cancer and harboring germline PVs in *BRCA* genes. We investigated the impact of hormone receptor status on clinical behavior and outcomes of breast cancer. Outcomes of interest [disease-free survival (DFS), breast cancer-specific survival (BCSS), and overall survival (OS)] were first investigated according to hormone receptor expression (positive versus negative), and then according to breast cancer subtype [luminal A-like versus luminal B-like versus triple-negative versus human epidermal growth factor receptor 2 (HER2)-positive breast cancer].

Results: From 78 centers worldwide, 4709 *BRCA* carriers were included, of whom 2143 (45.5%) had hormone receptor-positive and 2566 (54.5%) hormone receptor-negative breast cancer.

Median follow-up was 7.9 years. The rate of distant recurrences was higher in patients with hormone receptor-positive disease (13.1% versus 9.6%, $P < 0.001$), while the rate of second primary breast cancer was lower (9.1% versus 14.7%, $P < 0.001$) compared to patients with hormone receptor-negative disease. The 8-year DFS was 65.8% and 63.4% in patients with hormone receptor-positive and negative disease, respectively. The hazard ratio of hormone receptor-positive versus negative disease changed over time for DFS, BCSS, and OS ($P < 0.05$ for interaction of hormone receptor status and survival time). Patients with luminal A-like breast cancer had the worst long-term prognosis in terms of DFS compared to all the other subgroups (8-year DFS: 60.8% in luminal A-like versus 63.5% in triple-negative versus 65.5% in HER2-positive and 69.7% in luminal B-like subtype).

Conclusions: In young *BRCA* carriers, differences in recurrence pattern and second primary breast cancer among hormone receptor-positive versus negative disease warrant consideration in counseling patients on treatment, follow-up, and risk-reducing surgery.

Key words: *BRCA*, early breast cancer, young patients, hormone receptor status, tumor subtypes

INTRODUCTION

In women aged 40 years or younger, breast cancer is the most common malignancy and the leading cause of cancer-related death.[1,2] Hormone receptor-positive breast cancer remains the most frequent subtype across ages, including among young women.[3,4] Young age at diagnosis appears to retain a negative prognostic value specifically in hormone receptor-positive breast cancer.[3,5-7] However, hormone receptor positivity is recognized as a positive prognostic factor in breast cancer, irrespective of age at diagnosis.[8]

Approximately 12% of young women with newly diagnosed breast cancer are expected to carry a germline pathogenic variant (PV) in the *BRCA1* and/or *BRCA2* genes.[9,10] Breast cancer arising in *BRCA* carriers is characterized by peculiar biological features, with a higher prevalence of triple-negative breast cancer in *BRCA1* carriers and hormone receptor-positive disease in *BRCA2* carriers.[10,11] Carrying a germline *BRCA* PV does not seem to affect breast cancer prognosis.[9,12] Nevertheless, hormone receptor status appears to have a different prognostic value compared to non-hereditary breast cancer, with better outcomes in *BRCA* carriers with triple-negative disease as compared to non-carriers.[9,13,14] This may be related to the deficient DNA repair mechanisms in *BRCA* carriers that may increase sensitivity to chemotherapy.[15,16] On the contrary, hormone receptor-positive breast cancer in *BRCA* carriers appears to have greater biological aggressiveness compared to sporadic diseases.[17,18] Therefore, hormone receptor positivity in *BRCA* carriers may not have a positive prognostic value unlike in sporadic diseases.[19,20]

However, these data are derived from few retrospective studies with a limited sample size and thus no solid evidence exists to properly counsel *BRCA* carriers in this regard. Considering the increasing number of patients tested for *BRCA* and its implications in follow-up, risk-reducing strategies, and treatment,[21] clarifying the impact of hormone receptor expression in *BRCA* carriers with breast cancer is increasingly prominent.[20]

This study aimed to investigate the impact of hormone receptor status and breast cancer subtypes on clinical behavior and outcomes of breast cancer in young *BRCA* carriers.

PATIENTS AND METHODS

Study design and participants

This is an international, multicenter, hospital-based, retrospective cohort study including patients diagnosed with invasive breast cancer between January 2000 and December 2020 at the age of ≤40 years and known to harbor germline likely PVs and PVs in *BRCA1* and/or *BRCA2* genes.[22] Main exclusion criteria were history of non-invasive breast cancer, history of other malignancies without prior breast cancer, or *BRCA* variants of unknown significance. Patients with unknown hormone receptor status or with stage IV *de novo* disease were excluded from the present analysis.

Hormone receptor status was assessed locally at each participating center by immunostaining and defined by the expression of estrogen receptors (ERs) and/or progesterone receptors (PgRs) in ≥1% of invasive tumor cells. Nine centers defined hormone receptor positivity as expression of ERs and/or PgRs in ≥10% of invasive tumor cells. Human epidermal growth factor receptor 2 (HER2) status was assessed locally, and tumors were considered as HER2 positive if 3+ or 2+ with amplification detected by FISH.

The immunohistochemistry definition of breast cancer subtypes was used to classify the cases with available information on both hormone receptors, HER2 status, and tumor grade as follow: luminal A-like (ER positive and PgR positive, HER2 negative, low/intermediate grade), luminal B-like (ER positive or PgR positive, HER2 negative, high grade), triple negative (ER negative, PgR negative, HER2 negative), or HER2 positive (any ER and PgR status, HER2 positive).[5]

The Institut Jules Bordet (Brussels, Belgium) sponsored the study and acted as central ethics committee. The study also obtained ethical approval from local, regional, or national institutional review boards of the participating centers if requested by local regulations. The last authors (EB and ML) and the study statisticians (MB and MC) guaranteed for the accuracy and completeness of the data and analyses. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement was followed to report this work.[23]

The study is registered at ClinicalTrials.gov (NCT03673306).

Outcomes

The aim of the present analysis was to investigate the impact of hormone receptor status on clinical behavior and outcomes of breast cancer in young *BRCA* carriers. The type and pattern of recurrence and survival outcomes [disease-free survival (DFS), breast cancer-specific survival (BCSS), and overall survival (OS)] were first investigated according to hormone receptor expression and then according to breast cancer subtypes. DFS was the primary endpoint; BCSS, OS, type of recurrence (locoregional or distant, secondary breast and non-breast malignancies), and patterns of recurrence over time were secondary endpoints. DFS was defined as the time from diagnosis until locoregional recurrence, distant metastases, new contralateral or ipsilateral breast cancer, second primary malignancy, or death from any cause. BCSS was defined as the time from diagnosis to death from breast cancer. OS was defined as the time from diagnosis until death from any cause. To evaluate the sensitivity of results to changes in hormone receptor positivity thresholds, the analyses were repeated by excluding centers where the cut-off for hormone receptor positivity was $\geq$10% of ER and/or PgR expression.

Statistical analysis

Descriptive analyses were conducted to assess clinicopathological characteristics and type of survival events. Observation times of patients who did not experience an event were censored on the date of their last contact. Epanechnikov kernel-smoothed annual hazards of recurrence were calculated to assess the risk of developing DFS events over time. Kaplan–Meier plots were used to present results with a follow-up time up to 15 years. Cox proportional hazards model was applied to estimate the hazard ratio (HR), adjusting for the concomitant effect of selected confounders. Multivariate models for all survival analyses included age, year of diagnosis, country, histology, tumor size, grade, nodal status, HER2 expression, type of breast surgery, and chemotherapy use.

To account for the potential confounding due to the uptake of risk-reducing mastectomy, a second multivariate model that included also this variable as time-dependent covariate was carried out. In this second model, patients without information on uptake or exact date of risk-reducing mastectomy as well as those from one center that did not provide information on risk-reducing surgeries were excluded. Proportional hazards assumption was assessed by visual inspection of Kaplan–Meier plots. If visual inspection of Kaplan–Meier plots suggested HR heterogeneity during follow-up, the proportional hazards assumption was assessed by testing the time dependency of the predictors included in the Cox models. In case of violation of the proportional hazards assumption, conditional landmark analysis was carried out to explore late survival events among patients who remained without events after 5 years from diagnosis (years $>$5): in this analysis, patients who cease follow-up before the landmark time were excluded. For the early survival event analysis (years 0-5), censoring was applied at the 5-year mark for all patients still in follow-up.

All statistical analyses were two-sided with P values $<$0.05 considered as statistically significant and were carried out by MB and MC using Stata, software version 16.1 (StataCorp LLC, College Station, TX).

RESULTS

From 78 centers worldwide, 4709 young *BRCA* carriers were eligible for inclusion in the present study, of whom 2143 (45.5%) had hormone receptor-positive and 2566 (54.5%) hormone receptor-negative disease (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.06.009). Median follow-up in the overall cohort was 7.9 years [interquartile range (IQR) 4.5-12.6 years].

Analyses by hormone receptor status

Compared to patients with hormone receptor-negative breast cancer, those with hormone receptor-positive disease were more likely to harbor a germline *BRCA2* PV (65.0% versus 10.2%, $P < 0.001$) or to have HER2-positive tumors (11.0% versus 4.0%, $P < 0.001$), while they were less likely to have nodal involvement (45.4% versus 57.4%, $P < 0.001$) and grade 3 tumors (51.3% versus 82.7%, $P < 0.001$). Women with hormone receptor-positive breast cancer were less likely to receive chemotherapy (87.2% versus 96.5%, $P < 0.001$) and to undergo breast-conserving surgery (33.1% versus 44.0%, $P < 0.001$) than those with hormone receptor-negative disease. Time from breast cancer diagnosis to *BRCA* testing was 5.6 (IQR 0.9-26.1) months and 5.1 (IQR 0.9-25.6) months in patients with hormone receptor-positive and hormone receptor-negative disease, respectively (Table 1).

Table 1. Patient, tumor, and treatment characteristics between patients with hormone receptor-positive and hormone receptor-negative breast cancer

	Hormone receptor positive *n* (%) *N* = 2143	Hormone receptor negative *n* (%) *N* = 2566	*P* value[a]
Country			<0.001
North America	48 (2.2)	98 (3.8)	
South/Center America	96 (4.5)	94 (3.7)	
Asia + Israel	314 (14.6)	415 (16.2)	
Oceania	127 (5.9)	181 (7.0)	
Northern Europe	260 (12.1)	260 (10.1)	
Southern Europe	972 (45.4)	1067 (41.6)	
Eastern Europe	326 (15.2)	451 (17.6)	
Year at diagnosis			0.04
2000-2005	322 (15.0)	427 (16.6)	
2006-2010	488 (22.8)	648 (25.2)	
2011-2015	623 (29.1)	704 (27.4)	
2016-2020	710 (33.1)	787 (30.7)	
Age at diagnosis, median (IQR), years	35 (32-38)	34 (31-37)	<0.001
Age at diagnosis			<0.001
≤30 years	368 (17.2)	602 (23.5)	
31-35 years	790 (36.9)	915 (35.7)	
36-40 years	985 (46.0)	1049 (40.9)	
Histology			<0.001
Ductal carcinoma	1730 (80.7)	2223 (86.6)	
Lobular carcinoma	114 (5.3)	19 (0.7)	
Invasive (not specified)	98 (4.6)	105 (4.1)	
Others	122 (5.7)	148 (5.8)	
Missing	79 (3.7)	71 (2.8)	
Tumor grade			<0.001
G1	69 (3.2)	10 (0.4)	
G2	765 (35.7)	234 (9.1)	
G3	1100 (51.3)	2123 (82.7)	
Missing	209 (9.7)	199 (7.8)	
Tumor size			<0.001
T1	907 (42.3)	909 (35.4)	
T2	856 (39.9)	1204 (46.9)	
T3-T4	288 (13.4)	353 (13.8)	
Missing	92 (4.3)	100 (3.9)	
Nodal status			<0.001
N0	973 (45.4)	1473 (57.4)	
N1	786 (36.7)	779 (30.4)	
N2-N3	315 (14.7)	243 (9.5)	
Missing	69 (3.2)	71 (2.8)	
BRCA cohort			<0.001
BRCA1	736 (34.3)	2282 (88.9)	
BRCA2	1394 (65.0)	261 (10.2)	
BRCA1 + *BRCA2*	8 (0.4)	18 (0.7)	
*BRCA*mut (unknown if *BRCA1* or *BRCA2*)	5 (0.2)	5 (0.2)	
Time from diagnosis to *BRCA* testing, median (IQR), months	5.6 (0.9-26.1)	5.1 (0.9-25.6)	0.325
Missing date of BRCA testing	350 (16.3)	353 (13.8)	
HER2 status			<0.001
HER2 negative	1821 (85.0)	2373 (92.5)	
HER2 positive	236 (11.0)	104 (4.0)	
Missing	86 (4.0)	89 (3.5)	
Breast surgery			<0.001
Not done	4 (0.2)	11 (0.4)	
Breast-conserving surgery	709 (33.1)	1129 (44.0)	
Mastectomy	1406 (65.6)	1401 (54.6)	
Missing	24 (1.1)	25 (1.0)	
Use of chemotherapy			<0.001
No	259 (12.1)	74 (2.9)	
Yes	1868 (87.2)	2477 (96.5)	
Missing	16 (0.7)	15 (0.6)	
Type of chemotherapy[b]			0.01
Anthracycline and taxane based	1305 (69.9)	1772 (71.5)	
Anthracycline based	334 (17.9)	466 (18.8)	
Taxane based	102 (5.5)	86 (3.5)	
Others	52 (2.8)	78 (3.1)	
Missing	75 (4.0)	75 (3.0)	
Use of endocrine therapy		NA	NA
No	112 (5.2)		
Yes	2002 (93.4)		
Missing	29 (1.3)		
Type of endocrine therapy[c]		NA	NA
Tamoxifen alone	710 (35.5)		
Tamoxifen + LHRHa	554 (27.7)		
LHRHa alone	43 (2.1)		
AI ± LHRHa	356 (17.8)		
Tamoxifen and AI (± LHRHa)	293 (14.6)		
Others	26 (1.3)		
Missing	20 (1.0)		
Duration of endocrine therapy, median (IQR), months	60 (27-60)	NA	NA

AI, aromatase inhibitor; G, tumor grade; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; LHRHa, luteinizing hormone-releasing hormone agonist; N, nodal status; NA, not assessed; T, tumor size.
[a]Calculated after exclusion of missing values.
[b]Calculated among patients who received chemotherapy.
[c]Calculated among patients with hormone receptor-positive breast cancer who received endocrine therapy.

At a median follow-up of 7.9 (IQR 4.5-12.6) years, 720 (33.6%) and 966 (37.6%) DFS events were reported in patients with hormone receptor-positive and negative disease, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.06.009). *BRCA* carriers with hormone receptor-positive breast cancer had a greater proportion of distant recurrences (13.1% versus 9.6%, $P < 0.05$) and a lower proportion of second primary breast malignancies (9.1% versus 14.7%, $P < 0.001$), while no difference was found in locoregional recurrences (7.0% versus 8.2%, $P = 0.14$) or second primary non-breast cancers (3.4% versus 4.5%, $P = 0.07$) between patients with hormone receptor-positive and -negative disease, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.06.009).

BRCA carriers with hormone receptor-positive disease had a progressive increase in the hazard rate of DFS events in the first 3 years after diagnosis and then hazard rate for DFS events was stable for years 3-10. On the contrary, patients with hormone receptor-negative disease had a higher hazard rate of DFS events in the first 2 years after diagnosis, a reduction between 3 and 4 years, and a subsequent new slow increase, reaching that of patients with hormone receptor-positive disease after around 8 years from diagnosis (Figure 1). Patients with hormone receptor-positive

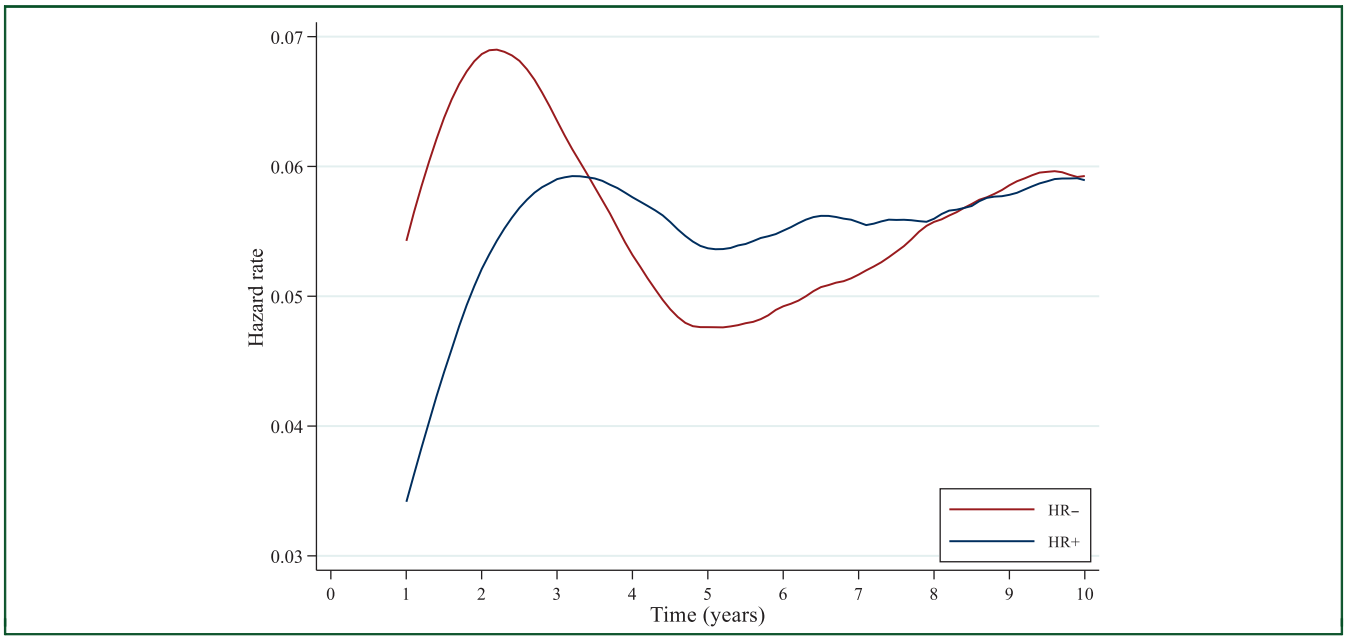

Figure 1. Epanechnikov kernel-smoothed annual hazards rate of disease-free survival events between patients with hormone receptor-positive and hormone receptor-negative disease.

HR+, hormone receptor-positive disease; HR−, hormone receptor-negative disease.

disease had a higher cumulative incidence of distant recurrences and a lower cumulative incidence of second primary breast cancer throughout the follow-up as compared to patients with hormone receptor-negative disease (Supplementary Figure S2A-D, available at https://doi.org/10.1016/j.annonc.2024.06.009).

The 8-year DFS was 65.8% [95% confidence interval (CI) 63.4% to 68.2%] in patients with hormone receptor-positive and 63.4% (95% CI 61.2% to 65.6%) in those with hormone receptor-negative disease (Figure 2A). Compared to patients with hormone receptor-negative disease, during the first 5 years from breast cancer diagnosis, patients with hormone receptor-positive tumors had a better DFS [adjusted HR (aHR) HR 0.77, 95% CI 0.65-0.91] (Figure 2B, Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.06.009) while no difference was observed after 5 years from diagnosis (aHR 0.91, 95% CI 0.75-1.12) (Figure 2C, Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.06.009).

The 8-year BCSS was 88.9% (95% CI 87.1% to 90.4%) in patients with hormone receptor-positive and 87.8% (95% CI 86.3% to 89.2%) in those with hormone receptor-negative disease (Supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2024.06.009). At the landmark analysis, during the first 5 years from breast cancer diagnosis, patients with hormone receptor-positive disease had a better BCSS (aHR 0.65, 95% CI 0.47-0.89) (Supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2024.06.009), while no difference was observed in years >5 (aHR 1.22, 95% CI 0.88-1.68) (Supplementary Figure S3C and Table S2, available at https://doi.org/10.1016/j.annonc.2024.06.009).

The 8-year OS was 88.1% (95% CI 86.3% to 89.7%) in patients with hormone receptor-positive and 87.1% (95% CI 85.5% to 88.5%) in those with hormone receptor-negative disease (Figure 3A). At the landmark analysis, during the first 5 years from breast cancer diagnosis, patients with hormone receptor-positive disease had a better OS (aHR 0.66, 95% CI 0.48-0.89) (Figure 3B) while no difference was observed for years >5 (aHR 1.12, 95% CI 0.82-1.51) (Figure 3C, Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.06.009).

The HR of hormone receptor-positive versus -negative disease changed over time for DFS, BCSS, and OS, with $P < 0.05$ for interaction of hormone receptor status and survival time, indicating nonproportionality of hazards over time.

In the subgroup analysis according to specific *BRCA* genes, differences in the prognostic impact of hormone receptor status were small in patients harboring *BRCA1* PV (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.06.009); for patients harboring *BRCA2* PV, those with hormone receptor-positive disease had a better prognosis in the first 5 years and a worse prognosis afterward, in terms of BCSS with an adjusted HR of 2.23 (95% CI 1.11-4.49) for years >5 (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.06.009). Sensitivity analyses were conducted by including only patients for whom the 1% cut-off for ER and/or PgR expression was used, and then only in patients with known HER2-negative disease: results were consistent with those reported in the main analyses (Supplementary Figures S4 and S5A-D and Tables S5-S9, available at https://doi.org/10.1016/j.annonc.2024.06.009). Among the 4497 patients with available information on risk-reducing mastectomy, results were consistent with those reported in the main (Supplementary Tables S2-S4 and S9, available at https://doi.org/10.1016/j.annonc.2024.06.009).

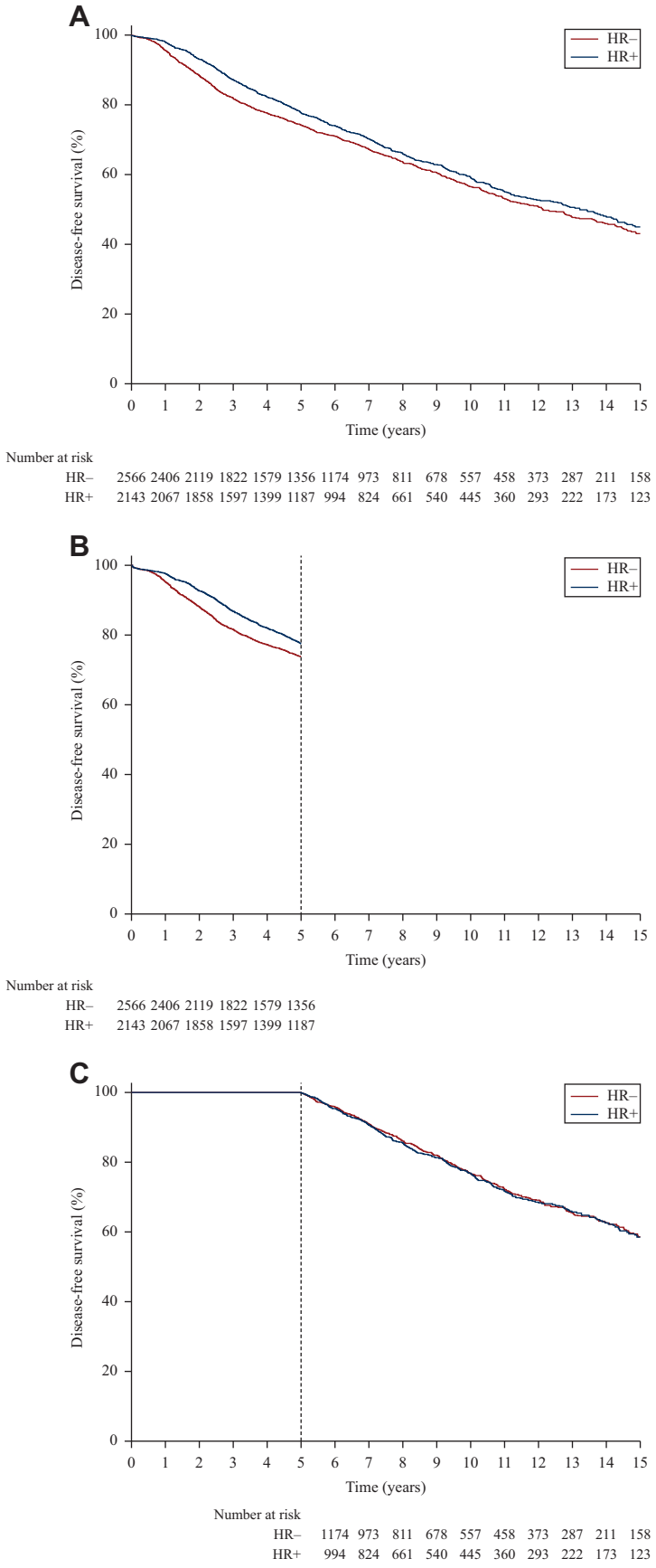

Figure 2. Disease-free survival in patients with hormone receptor-positive and negative breast cancer. (A) Disease-free survival in the whole population throughout follow-up. (B) Disease-free survival years 0-5. (C) Disease-free survival years >5.
HR+, hormone receptor-positive disease; HR−, hormone receptor-negative disease.

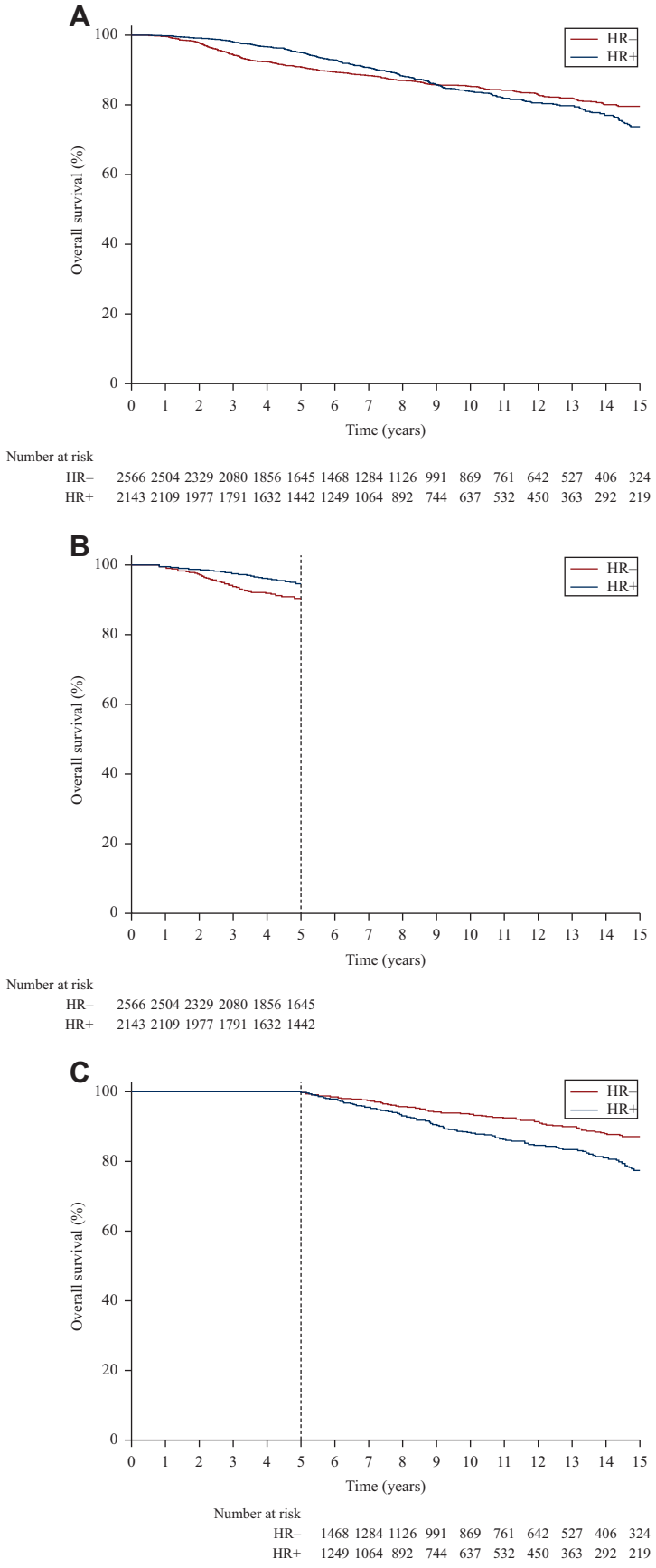

Figure 3. Overall survival in patients with hormone receptor-positive and negative breast cancer. (A) Overall survival in the whole population throughout follow-up. (B) Overall survival years 0-5. (C) Overall survival years >5.
HR+, hormone receptor-positive disease; HR−, hormone receptor-negative disease.

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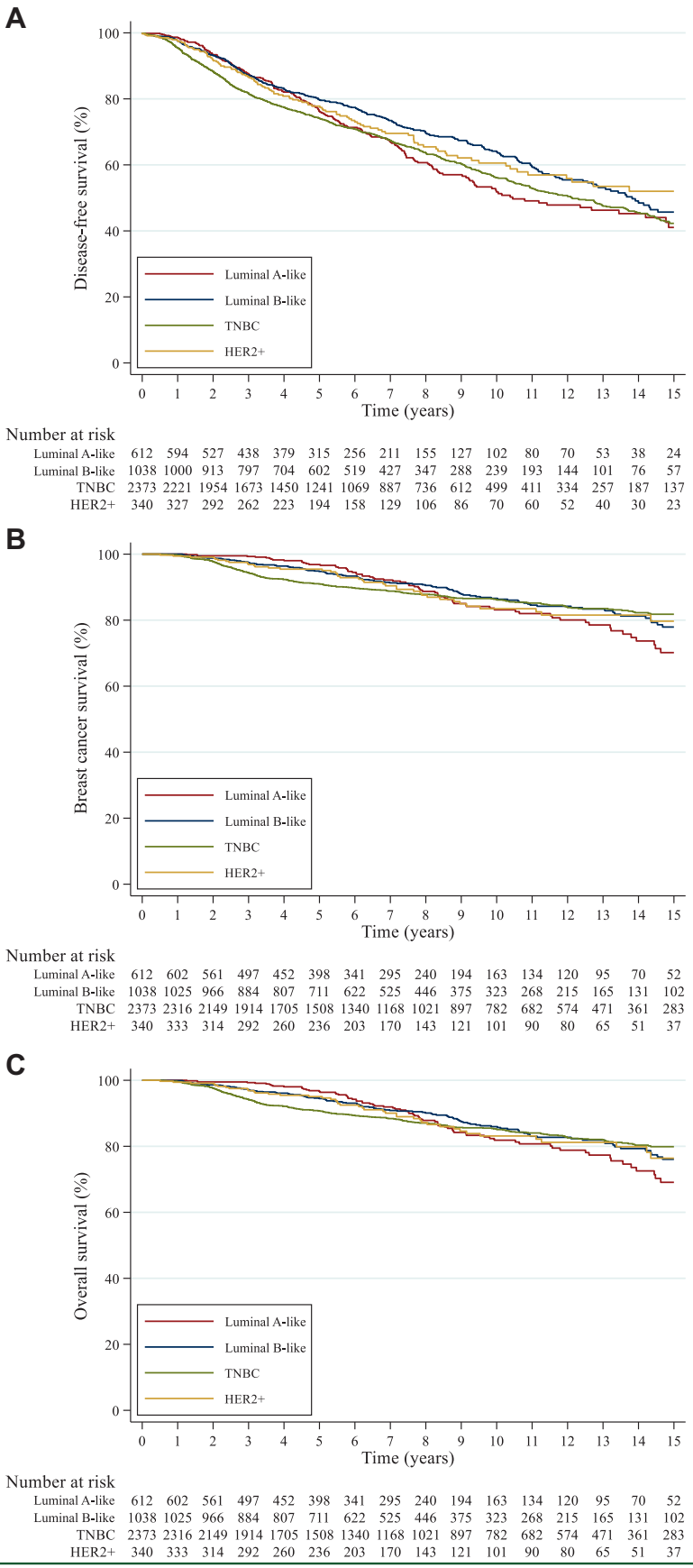

Figure 4. Prognosis of patients according to breast cancer subtypes. (A) Disease-free survival. (B) Breast cancer-specific survival. (C) Overall survival. HER2+, human epidermal growth factor receptor 2-positive breast cancer; TNBC, triple-negative breast cancer.

Analyses by tumor subtype

Among the 4363 young *BRCA* carriers eligible for this analysis, 612 (14.0%) were classified as having luminal A-like, 1038 (23.8%) luminal B-like, 2373 (54.4%) triple-negative, and 340 (7.8%) HER2-positive disease. Baseline characteristics of the patients according to tumor subtype are reported in Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2024.06.009. Patients with triple-negative disease were younger, had less T1 disease at diagnosis and less nodal involvement, were more frequently *BRCA1* carriers, and more frequently received chemotherapy when compared with those with all the other breast cancer subtypes (Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2024.06.009).

Among patients with luminal A-like disease, 90.8% had grade 2 tumors, more than half (53.3%) T1 stage, 76.8% harbored *BRCA2* PVs, and 75.0% received chemotherapy. Among patients with luminal B-like disease, 89.2% had grade 3 disease, 38.8% T1 stage 56.8% harbored *BRCA2* PVs, and 93.2% received chemotherapy (Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2024.06.009).

A total of 211 (34.5%), 332 (32.0%), 890 (37.5%), and 112 (32.9%) DFS events were reported in patients with luminal A-like, luminal B-like, triple-negative, and HER2-positive tumors, respectively. Patients with luminal A-like breast cancer had the highest rate of distant and locoregional recurrences (Supplementary Table S11, available at https://doi.org/10.1016/j.annonc.2024.06.009).

The 8-year DFS was 60.8% (95% CI 55.7% to 65.4%) in patients with luminal A-like, 69.7% (95% CI 66.2% to 72.8%) in those with luminal B-like, 63.5% (95% CI 61.1% to 65.7%) in those with triple-negative, and 65.5% (95% CI 59.1% to 71.1%) in those with HER2-positive disease (Figure 4A).

The 8-year BCSS was 88.7% (95% CI 84.9% to 91.6%) in patients with luminal A-like, 90.5% (95% CI 88.2% to 92.4%) in those with luminal B-like, 87.8% (95% CI 86.2% to 89.2%) in those with triple-negative, and 87.6% (95% CI 82.5% to 91.2%) in those with HER2-positive disease (Figure 4B).

The 8-year OS was 87.8% (95% CI 83.9% to 90.8%) in patients with luminal A-like, 90.1% (95% CI 87.7% to 92.0%) in those with luminal B-like, 87.0% (95% CI 85.4% to 88.5%) in those with triple-negative, and 87.2% (95% CI 82.1% to 90.9%) in those with HER2-positive disease (Figure 4C).

DISCUSSION

To our knowledge, this is the largest study including young women with breast cancer carrying germline *BRCA* PVs from several institutions worldwide. These data uniquely address the value of hormone receptor status and breast cancer subtypes in the setting of hereditary breast cancer. Our results suggest that hormone receptor expression did not appear to be a positive prognostic factor in young *BRCA* carriers with breast cancer; time and patterns of recurrence differed according to hormone receptor status and breast cancer subtypes.

In the general population, hormone receptor-positive disease is a well-established favorable prognostic factor, and luminal-like breast cancer is associated with better outcomes as compared to triple-negative or HER2-positive disease.[24] However, while the rates of recurrences in patients with hormone receptor-negative disease tend to have a peak in the first 2/3 years after diagnosis followed by a subsequent reduction, in those with hormone receptor-positive disease the rates of tumor recurrences (including distant metastases) remain constant up to 20 years from diagnosis.[25,26] To date, limited data are available regarding the clinical behavior and prognosis of breast cancer in *BRCA* carriers according to hormone receptor status and tumor subtype.[20] In patients harboring *BRCA* PVs, hormone receptor-positive disease appears to be biologically more aggressive than sporadic disease.[14,17,18]

In our analysis, patients with hormone receptor-positive disease harboring *BRCA* PVs had overall similar prognosis than those with hormone receptor-negative disease. In terms of DFS, a small difference of 2.4% was observed in the 8-year DFS, with a DFS of 65.8% and 63.4% in patients with hormone receptor-positive and -negative disease, respectively. In the first 5 years from diagnosis, the risk of recurrence in patients with hormone receptor-positive disease was lower than in those with hormone receptor-negative disease, but no differences were observed afterward.

We also observed that patients with hormone receptor-negative disease had a progressive increase in the HRs of DFS events at longer follow-up. However, in patients who do not carry germline *BRCA* PVs,[24,27,28] hormone receptor-negative disease is known to have a peak in the HRs of DFS events in the first 2-3 years, with a subsequent major drop over the follow-up, and events beyond year 5 after diagnosis are rare. The increase in late events observed in our study seemed to be mainly driven by the occurrence of second primary breast cancers in patients with hormone receptor-negative disease, compared to a higher rate of distant recurrences in those with hormone receptor-positive disease. These differences may be explained by the fact that >80% of patients with hormone receptor-negative disease were *BRCA1* PV carriers, who are characterized by a higher lifetime risk of secondary or contralateral breast cancers.[29]

When looking at the OS results in our cohort, similar outcomes were observed at 8 years of follow-up between patients with hormone receptor-positive and negative disease, while afterward the prognosis of patients with hormone receptor-positive disease appeared to be worse than those with hormone receptor-negative disease. This appeared to occur earlier than that described in sporadic disease, in which the worsening of prognosis in terms of OS in patients with hormone receptor-positive disease is observed after at least a follow-up of ~14-15 years.[25]

All these observations may have relevant implications from a clinical perspective: while recurrences in patients with hormone receptor-positive breast cancer may be prevented by an escalation of (neo)adjuvant treatments

(particularly with new effective endocrine-based therapies and/or targeted therapies), for patients with hormone receptor-negative disease (who are mainly *BRCA1* carriers), particular attention should be given to risk-reducing surgery that could prevent many of the second primary cancers.

Considering the different breast cancer subtypes in patients with sporadic disease, luminal A-like disease, which is characterized by less aggressive biological features, has usually a better prognosis than all the other breast cancer subtypes.[24] However, differently from prior evidence,[30] in our study, patients with luminal A-like disease did not seem to have a better prognosis in terms of DFS compared to women affected by the other breast cancer subtypes. This observation may raise further attention and concerns on the overall biological aggressiveness of hormone receptor-positive disease in this specific population of young *BRCA* carriers with breast cancer. While no substantial differences in stage at diagnosis were observed between luminal A-like disease and all the other subtypes, patients with luminal A-like disease were more often *BRCA2* carriers, who are known to be characterized by luminal-like tumors with a greater biological aggressiveness than sporadic disease.[19] In our study, we observed that patients with hormone receptor-positive disease and harboring *BRCA2* PV appeared to have the worst prognosis after the first 5 years of follow-up. It should be highlighted that patients with luminal B-like, triple-negative, and HER2-positive disease received (neo)adjuvant chemotherapy in 93.2%, 96.7%, and 96.2% of the cases, respectively, as compared to 75.0% of those with luminal A-like disease (a scenario where chemotherapy can often be spared in sporadic disease).[31] Assuming a greater biological aggressiveness of luminal-like disease in patients harboring *BRCA* PVs, implementing the use of genomic testing to improve adjuvant chemotherapy choices in patients with a traditionally less aggressive disease could be worthwhile. Moreover, other endocrine treatments such as ovarian function suppression and new agents like Cyclin-Dependent Kinase 4/6 (CDK4/6) Inhibitors and poly ADP ribose polymerase (PARP) inhibitors could further improve the outcomes of this subgroup of patients.[18]

Although our results are drawn from a large and unique dataset, some limitations should be acknowledged. This is a retrospective cohort study, which has been conducted in different centers from many countries of the world over a period of 20 years. *BRCA* status, hormone receptor expression and HER2 status, as well as tumor stage and disease characteristics were assessed locally at each participating center; accordingly, diagnostic and treatment procedures could have differed between participating centers and were carried out in accordance with local practice. Furthermore, date of germline *BRCA* testing was unknown for 703 (14.9%) patients. In patients with this information available, the time from diagnosis to genetic testing was similar in the hormone receptor-positive and -negative cohorts; however, it should be highlighted that its indication in breast cancer has radically changed during the study period. In *BRCA* carriers, some challenges should be considered in interpreting the results of DFS considering their increased risk of developing second cancers and the beneficial effect of undergoing risk-reducing surgery. Although the survival models adjusting for receipt of risk-reducing mastectomy showed consistent findings with those reported in the main analysis, updated data at longer follow-up will be critical to provide more reliable results in BCSS and OS in this special patient population, and particularly in patients with hormone receptor-positive disease.[26]

In conclusion, to our knowledge, this is the largest analysis including young *BRCA* carriers with breast cancer showing that hormone receptor positivity did not seem to have a positive prognostic value in these patients, particularly in those with luminal A-like disease and in those harboring *BRCA2* PVs. Addressing clinical behavior and outcomes of young patients with breast cancer is crucial, especially for those harboring *BRCA* PVs as they exhibit specific biological features combined with an increased susceptibility to second primary cancers. Understanding the special needs of this patient population plays a pivotal role in determining appropriate treatment options to mitigate their increased cancer risks and in defining tailored management strategies including on follow-up schedules and access to risk-reducing surgeries.

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DISCLOSURE

KPo reported receiving honoraria for consultations/lectures/training/clinical trials and payment of conference fees from AstraZeneca, Gilead, Roche, Novartis, Eli Lilly, Pfizer, MSD, Teva, Egis, and Vipharm. KPu reported receiving research grants (to his institution) from MSD and Sanofi; speaker fees and honoraria for consultancy and advisory board functions from AstraZeneca, Eli Lilly, Exact Sciences, Focus Patient, Gilead, Menarini, MSD, Novartis, Pfizer, Roche, and Seagen; speaker fees and honoraria for consultancy and advisory board functions (to his institution) from AstraZeneca, Eli Lilly, Exact Sciences, Gilead, MSD, Novartis, Pfizer, Roche, and Seagen; stock options from Need Inc; and travel grants from AstraZeneca, Novartis, Pfizer, PharmaMar, and Roche. 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DATA SHARING

Data will be available upon reasonable request to Prof. Matteo Lambertini (matteo.lambertini@unige.it), after proper revision of the data transfer agreement of each participating center and if ultimately allowed by local Ethic Committees.

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