UNIVERSITÀ DEGLI STUDI DI GENOVA

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Scuola di Specializzazione in Oncologia Medica

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Impact of Hormone Receptor Status and Tumor Subtypes of Breast Cancer in Young *BRCA* Carriers

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ABSTRACT

Background

Hormone receptor expression is a known positive prognostic and predictive factor in breast cancer; however, limited evidence exists on its impact on prognosis of young patients harboring *BRCA* pathogenic variant (PV).

Patients and Methods

This international, multicenter, retrospective cohort study included young patients (≤40 years) diagnosed with invasive breast cancer and harboring germline PV 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 receptors expression (positive vs. negative), and then according to breast cancer subtype (luminal A-like vs. luminal B-like vs. triple-negative vs. HER2-positive breast cancer).

Results

From 78 centers worldwide, 4,709 *BRCA* carriers were included, of whom 2,143 (45.5%) had hormone receptor-positive and 2,566 (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% vs. 9.6%, $p<0.001$), while the rate of second primary breast cancer was lower (9.1% vs. 14.7%, $p<0.001$) compared to patients with hormone receptor-negative disease. The 8-years DFS was 65.8% and 63.4% in patients with hormone receptor-positive and negative disease, respectively. Patients with luminal A-like breast cancer had the worst long-term prognosis in terms of DFS compared to all the other subgroups (8-years DFS: 60.8% in luminal A-like vs. 63.5% in triple-negative vs. 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 vs. negative disease warrants consideration in counseling patients on treatment, follow-up, and risk-reducing surgery.

ABSTRACT (Italiano)

Contesto

L'espressione dei recettori ormonali è un fattore prognostico e predittivo positivo nel carcinoma mammario; tuttavia esistono poche evidenze del loro ruolo sulla prognosi delle giovani pazienti con una variante patogenetica (PV) di *BRCA*.

Pazienti e Metodi

Questo studio retrospettivo, internazionale e multicentrico ha incluso giovani pazienti (≤40 anni) con diagnosi di carcinoma mammario invasivo e portatrici di PV nei geni *BRCA*. È stato esaminato l'impatto dello stato dei recettori ormonali sul decorso clinico e sulla sopravvivenza libera da malattia (DFS), sopravvivenza cancro-specifica (BCSS) e sopravvivenza globale (OS) in base all'espressione dei recettori ormonali (positivi vs. negativi) e al sottotipo di carcinoma mammario (luminale A-like, luminale B-like, triplo negativo e HER2-positivo).

Risultati

Sono state incluse 4,709 donne portatrici di PV *BRCA* da 78 centri, di cui 2,143 (45.5%) con tumore positivo ai recettori ormonali e 2,566 (54.5%) negativo ai recettori ormonali. Il follow-up mediano è stato di 7.9 anni. Il tasso di recidive a distanza era più alto nelle pazienti con malattia positiva ai recettori ormonali (13.1% vs. 9.6%, $p<0.001$), mentre il tasso di seconde neoplasie mammarie più basso (9.1% vs. 14.7%, $p<0.001$) rispetto alle pazienti con malattia negativa ai recettori ormonali. La DFS a 8 anni è stata del 65.8% nelle pazienti con malattia positiva e del 63.4% nelle pazienti con malattia negativa ai recettori ormonali. Le pazienti con malattia luminale A-like avevano la peggiore prognosi a lungo termine in termini di DFS rispetto agli altri sottogruppi (DFS a 8 anni: 60.8% in luminale A-like vs. 63.5% in triplo negativo, 65.5% in HER2-positivo e 69.7% in luminale B-like).

Conclusioni

Le differenze nei pattern di recidiva e seconde neoplasie mammarie in base all'espressione dei recettori ormonali richiedono particolare attenzione nella scelta dei trattamenti, follow-up e chirurgie profilattiche nelle giovani portatrici di PV *BRCA.*

1. INTRODUCTION

In female women 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 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 cases 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 disease.[19,20] However, these data derive 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 outcomes of breast cancer in young *BRCA* carriers.

2. METHODS

2.1 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-PV and PV 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 (ER) receptors and/or progesterone (PgR) receptors in ≥1% of invasive tumor cells. Nine centers defined hormone receptor positivity as expression of ER and/or PgR receptors in ≥10% of invasive tumor cells. HER2 status was assessed locally, and tumors were considered as HER2-positive if 3+ or 2+ with amplification detected by fluorescent in situ hybridization (FISH). The immunohistochemistry (IHC) 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 and 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 research also obtained ethical approval from any appropriate local, regional, or national institutional review boards of the participating centers as 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).

2.2. Outcomes

The aim 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 firstly 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 loco-regional 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 at ≥10% of ER and/or PgR receptor expression and also by including only the cases with known HER2 status to investigate outcomes of the different breast cancer subtypes (luminal A-like vs. luminal B-like vs. triple-negative vs. HER2-positive disease).

2.3 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 hazard 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, 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 performed. 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 hazard 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 hazard assumption was assessed by testing the time-dependency of the predictors included in the Cox models.

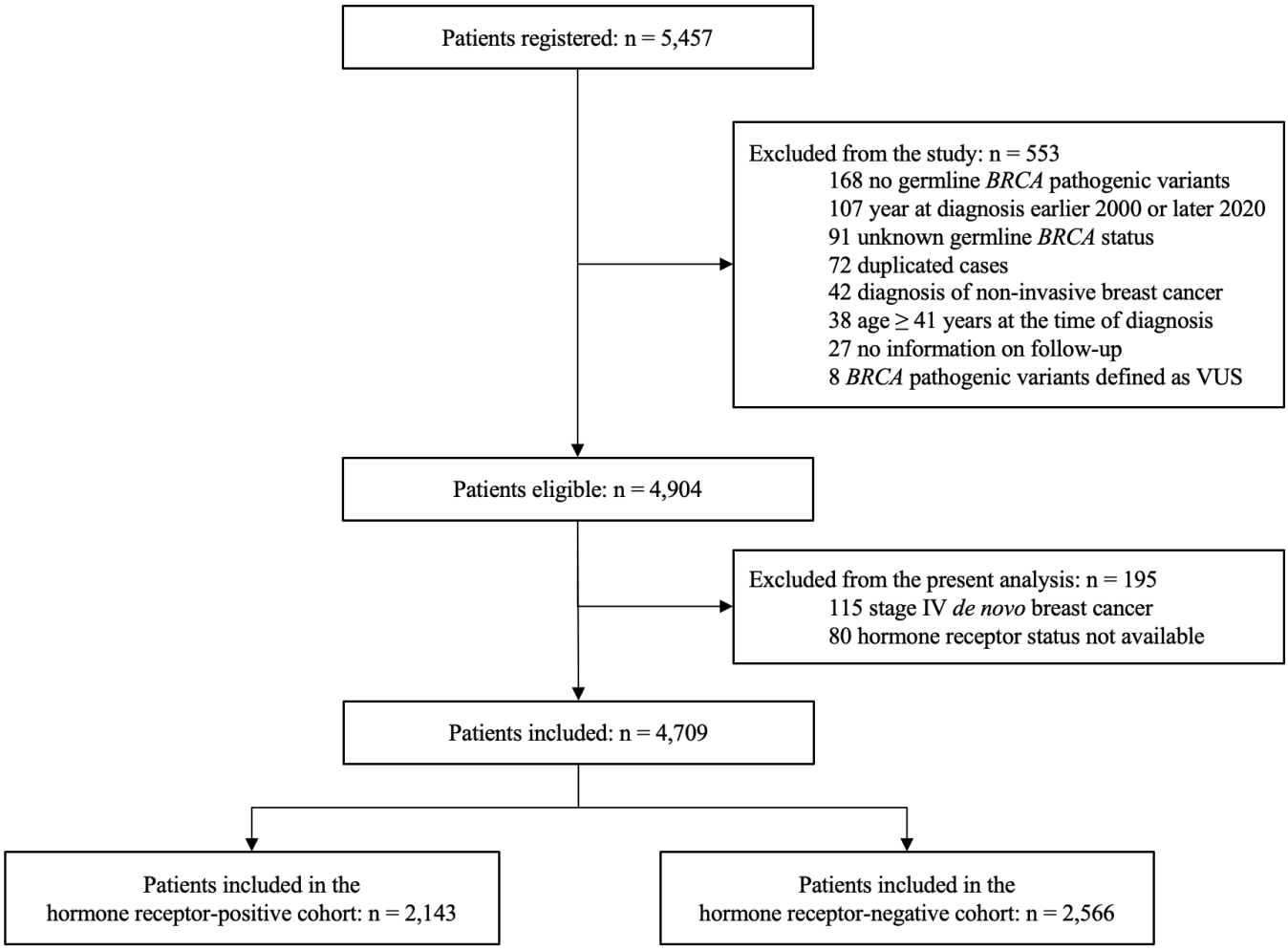
In case of violation of the proportional hazard assumption, conditional landmark analysis was performed to explore late survival events among patients who remained without events after 5 years from diagnosis (years >5): in this analysis, patients who cease follow-up before the landmark time were excluded. For the early survival events 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 performed by MB and MC using Stata, software version 16.1 (StataCorp LLC, College Station, TX, USA).

3. RESULTS

From 78 centers worldwide, 4,709 young *BRCA* carriers were eligible for inclusion in the present study, of whom 2,143 (45.5%) had hormone receptor-positive and 2,566 (54.5%) hormone receptor-negative disease (Figure 1). Median follow-up in the overall cohort was 7.9 years (interquartile range [IQR] 4.5-12.6 years).

Figure 1. Study flowchart of included patients



Abbreviations: VUS, variant of uncertain significance

3.1 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% vs 10.2%, p<0.001) or to have HER2-positive tumors (11.0% vs 4.0%, p<0.001), while they were less likely to have nodal involvement (45.4% vs 57.4%, p<0.001) and grade 3 tumors (51.3% vs 82.7%, p<0.001).

Women with hormone receptor-positive breast cancer were less likely to receive chemotherapy (87.2% vs 96.5%, p<0.001) and to undergo breast conserving surgery (33.1% vs 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=2,143	**Hormone receptor-negative N (%) N=2,566**	***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)	
North Europe	260 (12.1)	260 (10.1)	
South Europe	972 (45.4)	1,067 (41.6)	
East 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 to 38)	34 (31 to 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)	1,049 (40.9)	
Histology:			<0.001
Ductal carcinoma	1,730 (80.7)	2,223 (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	1,100 (51.3)	2,123 (82.7)	
Missing	209 (9.7)	199 (7.8)	
Tumor size:			<0.001
T1	907 (42.3)	909 (35.4)	
T2	856 (39.9)	1,204 (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)	1,473 (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
*BRCA*1	736 (34.3)	2,282 (88.9)	
*BRCA*2	1,394 (65.0)	261 (10.2)	
*BRCA*1 + *BRCA*2	8 (0.4)	18 (0.7)	
*BRCA*mut (unknow if *BRCA*1 or *BRCA*2)	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	350 (16.3)	353 (13.8)	
HER2 status:			<0.001
HER2 negative	1,821 (85.0)	2,373 (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)	1,129 (44.0)	
Mastectomy	1,406 (65.6)	1,401 (54.6)	
Missing	24 (1.1)	25 (1.0)	
Use of chemotherapy:			<0.001
No	259 (12.1)	74 (2.9)	
Yes	1,868 (87.2)	2,477 (96.5)	
Missing	16 (0.7)	15 (0.6)	
Type of chemotherapy*:			0.01
Anthracycline- and taxane-based	1,305 (69.9)	1,772 (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**:			
No	112 (5.2)	NA	NA
Yes	2,002 (93.4)		
Missing	29 (1.3)		
Type of endocrine therapy***:			
Tamoxifen alone	710 (35.5)		
Tamoxifen + LHRHa	554 (27.7)		
LHRHa alone	43 (2.1)		
AI ± LHRHa	356 (17.8)	NA	NA
Tamoxifen and AI (± LHRHa)	293 (14.6)		
Others	26 (1.3)		
Missing	20 (1.0)		
Duration of endocrine therapy, median (IQR) months	60 (27 to 60)	NA	NA

[a] Calculated after exclusion of missing values
* Calculated among patients who received chemotherapy
** Calculated among patients with hormone receptor-positive breast cancer
*** Calculated among patients with hormone receptor-positive breast cancer who received endocrine therapy

Abbreviations: IQR, interquartile range; G, tumor grade; T, tumor size; N, nodal status; ER, estrogen receptor; PR, progesterone receptor; LHRHa, luteinizing hormone-releasing hormone agonists; AI, aromatase inhibitors; NA, not assessed.

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 (Table 2). *BRCA* carriers with hormone receptor-positive breast cancer had a greater proportion of distant recurrences (13.1% vs. 9.6%, p<0.05) and a lower proportion of second primary breast malignancies (9.1% vs. 14.7%, p<0.001), while no difference was found in loco-regional recurrences (7.0% in vs. 8.2%, p=0.14) or second primary non-breast cancer (3.4% vs. 4.5%, p=0.07) between patients with hormone receptor-positive and negative disease, respectively (Table 2).

Table 2. Pattern of first disease-free survival event according to hormone receptor status

	Hormone receptor-positive N (%) N=2,143	**Hormone receptor-negative N (%) N=2,566**	***P* value[a]**
Follow-up, median (IQR)	7.6 (4.5-12.1)	8.1 (4.5-13.0)	0.83
No events	1,423 (66.4)	1,600 (62.4)	0.01
Loco-regional recurrence	150 (7.0)	211 (8.2)	0.14
Distant recurrence	280 (13.1)	245 (9.6)	0.01
Second primary malignancy	72 (3.4)	115 (4.5)	0.07
Ovaries	25 (1.2)	60 (2.3)	
Pancreas	6 (0.3)	4 (0.2)	
Cervix	3 (0.1)	6 (0.2)	
Colon-rectal-anal	3 (0.1)	6 (0.2)	
Haematological	3 (0.1)	4 (0.2)	
Skin	8 (0.4)	10 (0.4)	
Thyroid	2 (0.1)	5 (0.2)	
Endometrial	5 (0.2)	3 (0.1)	
Upper-gastrointestinal	2 (0.1)	3 (0.1)	
Others	15 (0.7)	14 (0.6)	
Second primary breast cancer	195 (9.1)	378 (14.7)	<0.0001
Death without any disease-free survival event	23 (1.1)	17 (0.7)	0.13

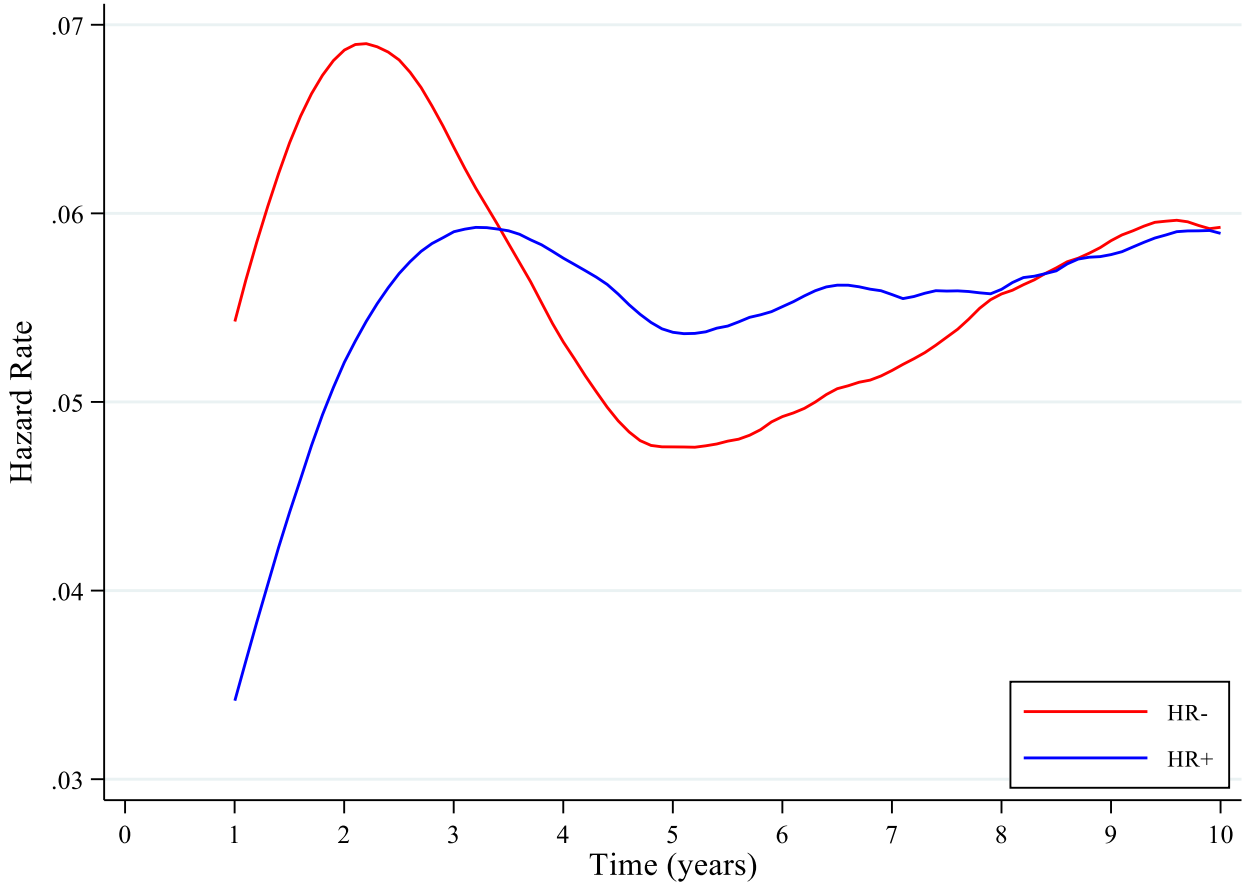
[a] P-values for time-dependent events estimated by means of the Log-rank test.

Abbreviations: IQR, interquartile range.

BRCA carriers with hormone receptor-positive disease had a progressive increase in the hazard rate of DFS in the first three years after diagnosis and then year-over-year hazard rate for DFS were stable for years 3-10. On the contrary, patients with hormone receptor-negative disease had a higher rate of

DFS events in the first two years after diagnosis, a reduction between three and four years and a subsequent new slow increase, reaching those of patients with hormone receptor-positive disease after around 8 years from diagnosis (Figure 2).

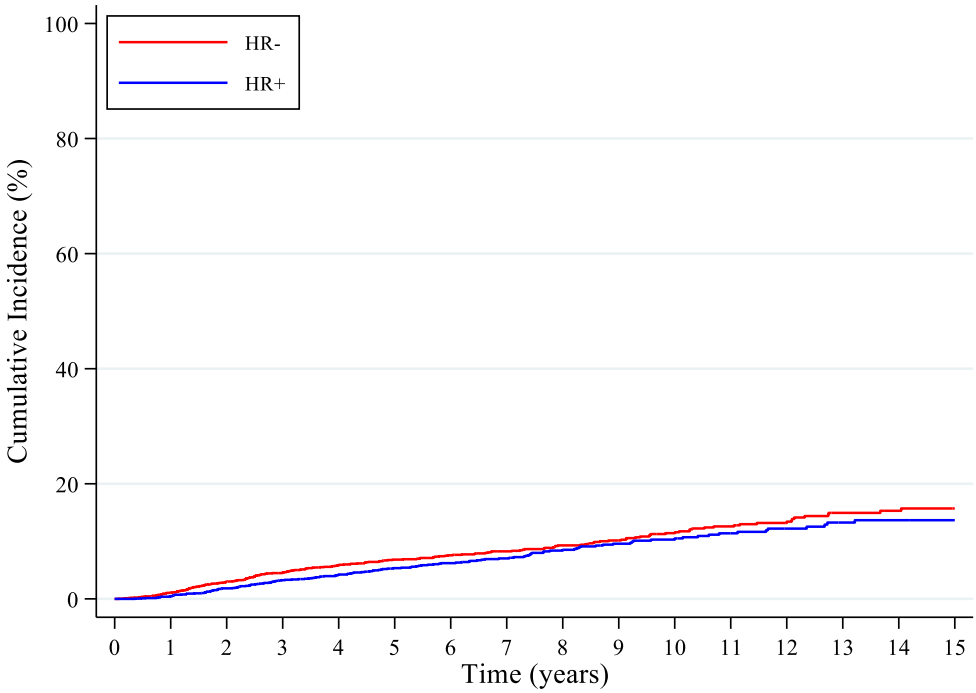
Figure 2. Epanechnikov Kernel-Smoothed annual hazards of disease-free survival between patients with hormone receptor-positive and hormone receptor-negative disease



Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

Patients with hormone receptor-positive disease had 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 (Figure 3 A-D).

Figure 3. Cumulative incidence of disease-free survival events
A) Local recurrence

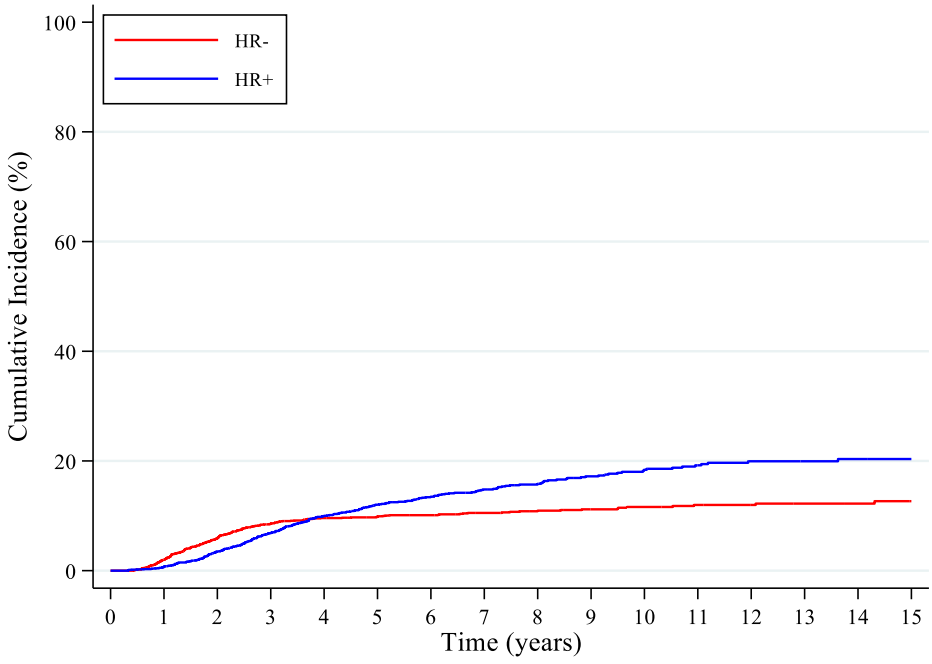


Number at risk

HR-	2562	2406	2119	1822	1579	1356	1174	973	811	678	557	458	373	287	211	158
HR+	2136	2067	1858	1597	1399	1187	994	824	661	540	445	360	293	222	173	123

Abbreviations: DFS, disease-free survival; HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

B) Distant recurrence



Number at risk

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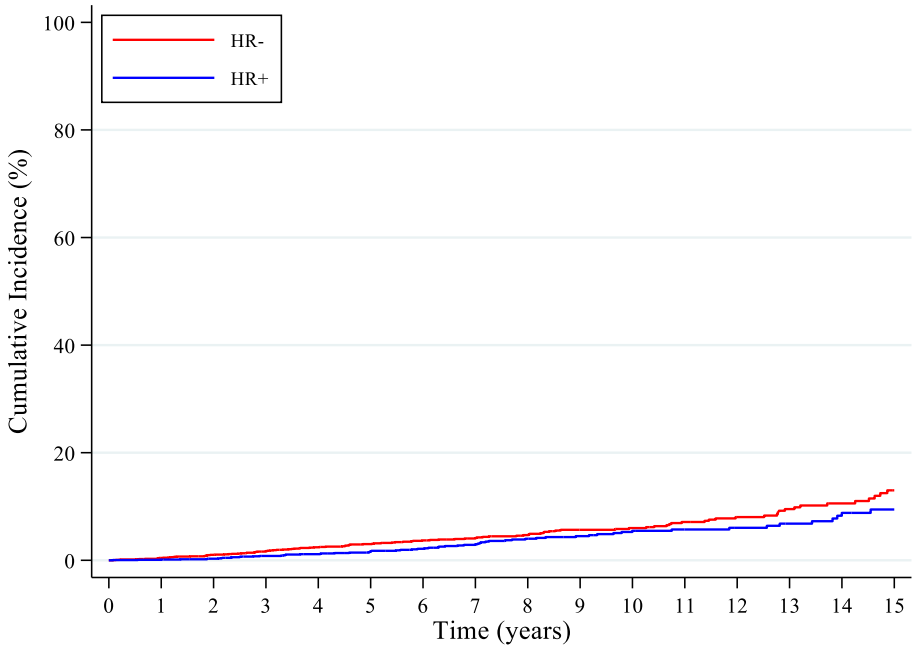
Abbreviations: DFS, disease-free survival; HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

C) 2nd malignancy other than breast cancer



Number at risk

HR-	2562	2406	2119	1822	1579	1356	1174	973	811	678	557	458	373	287	211	158
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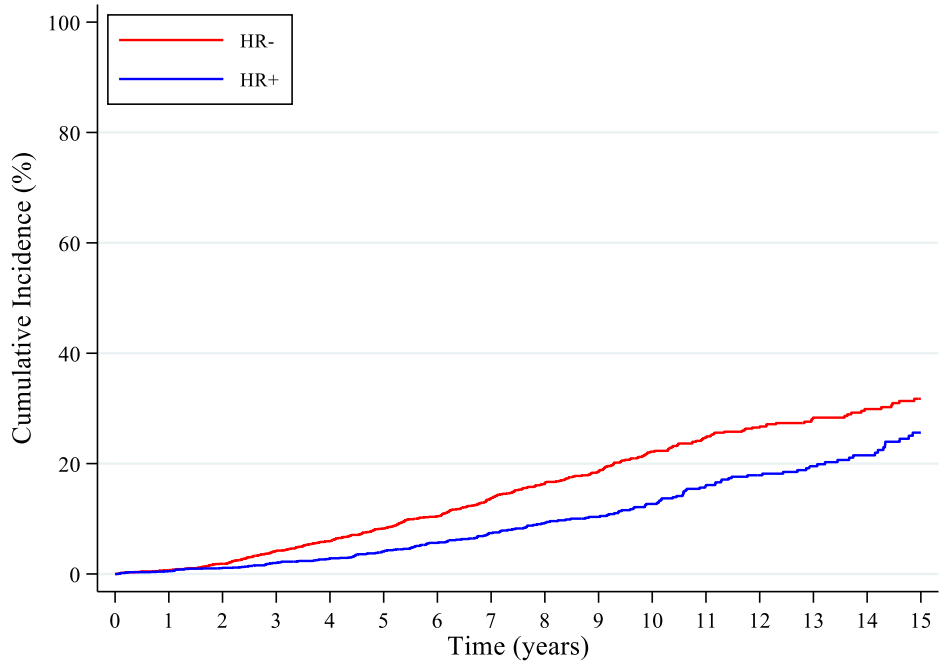
Abbreviations: DFS, disease-free survival; HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

D) 2nd breast cancer malignancy



Number at risk

HR-	2562	2406	2119	1822	1579	1356	1174	973	811	678	557	458	373	287	211	158
HR+	2136	2067	1858	1597	1399	1187	994	824	661	540	445	360	293	222	173	123

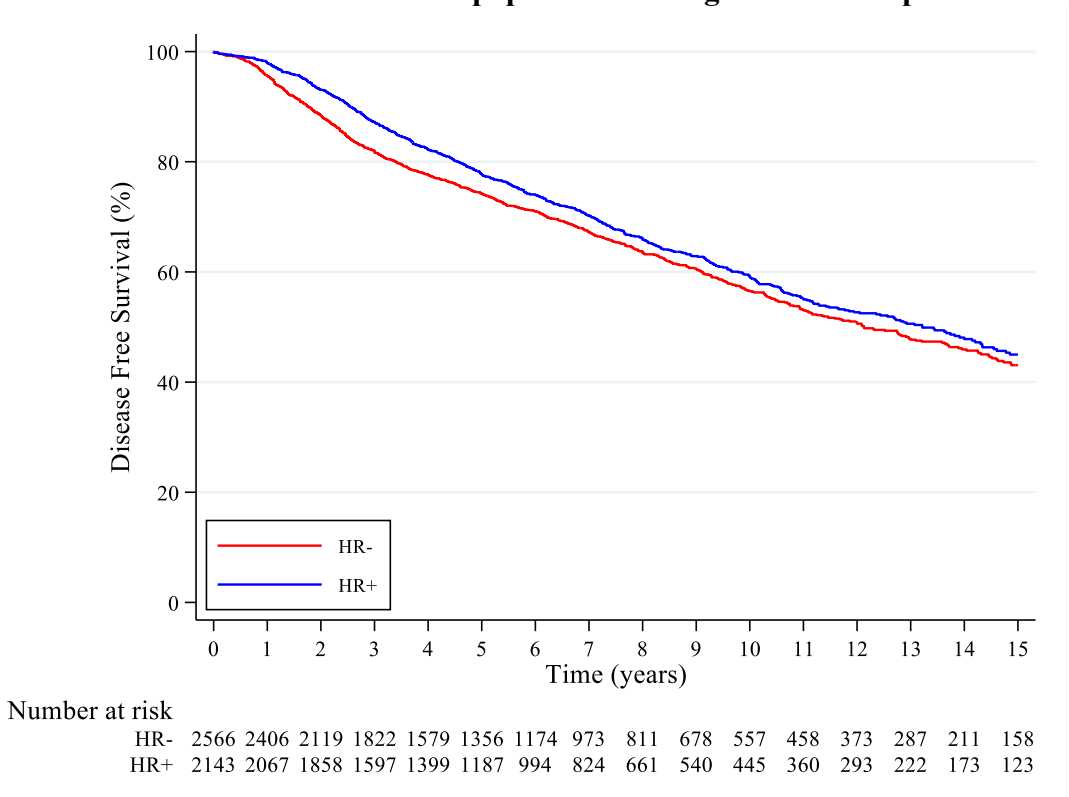
Abbreviations: DFS, disease-free survival; HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

The 8-years DFS was 65.8% (95%CI, 63.4%-68.2%) in patients with hormone receptor-positive and 63.4% (95%CI, 61.2%-65.6%) in those with hormone receptor-negative disease (Figure 4A).

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 (HR 0.77, 95%CI 0.65-0.91) (Figure 4B, Supplementary Table S1) while no difference was observed after 5 years from diagnosis (HR 0.91, 95%CI 0.75-1.12) (Figure 4C, Supplementary Table S1).

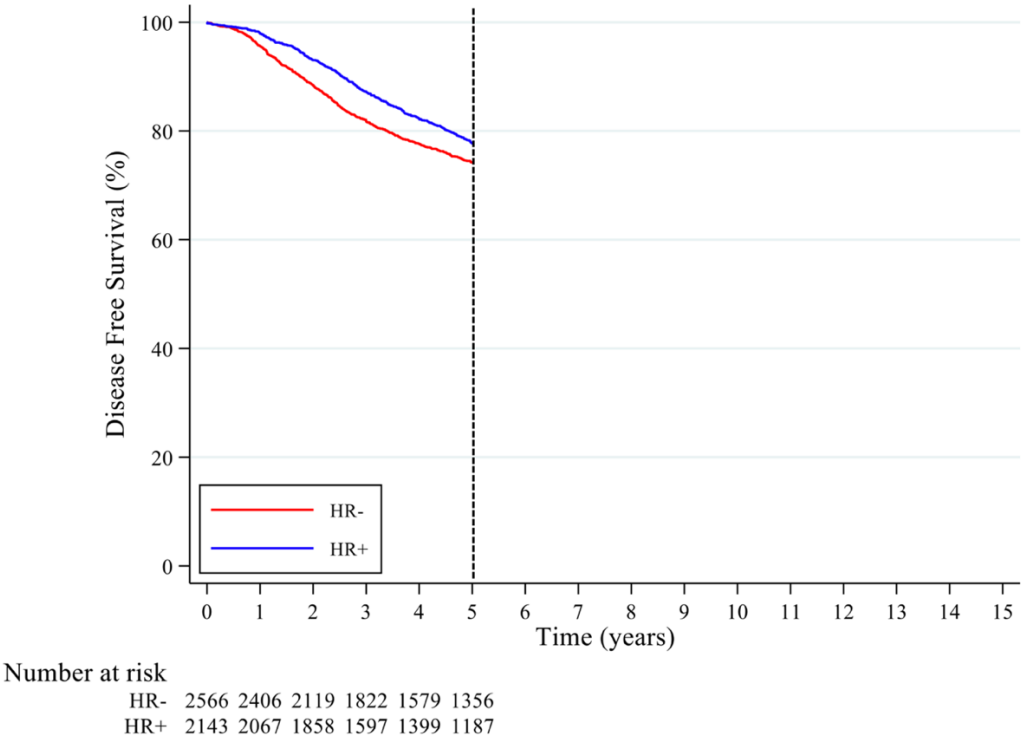
Figure 4. Disease-free survival in patients with hormone receptor-positive and negative breast cancer

A) Disease-free survival in the whole population throughout follow-up.



Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

B) Disease-free survival (years 0-5)

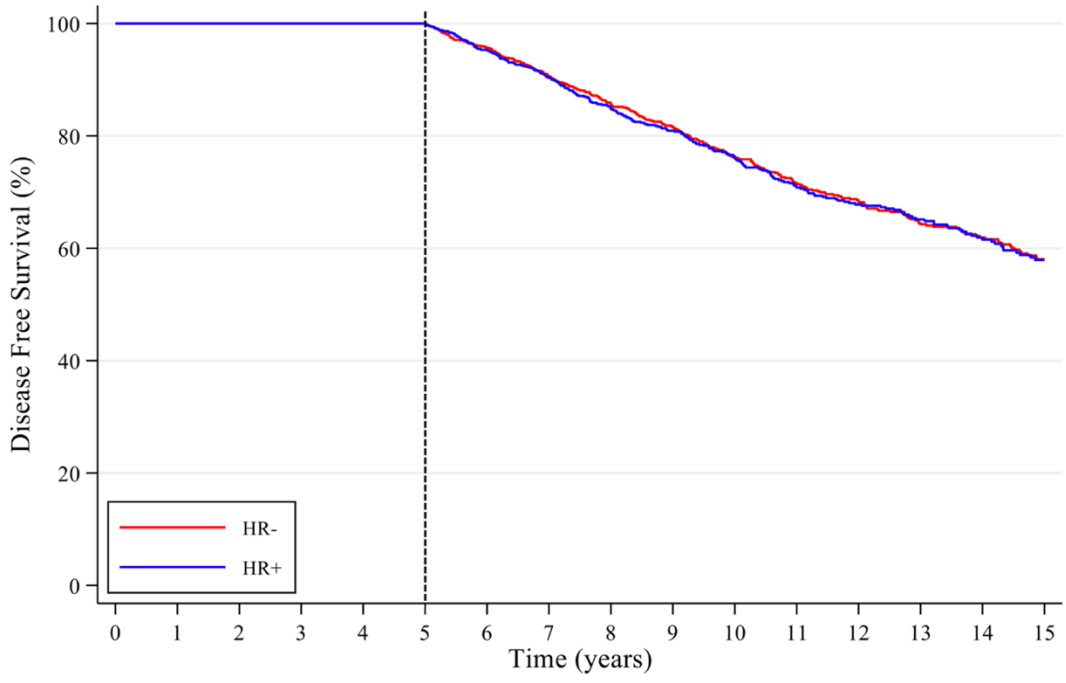


Number at risk

HR-	2566	2406	2119	1822	1579	1356
HR+	2143	2067	1858	1597	1399	1187

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

C) Disease-free survival (years >5)



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HR+	994	824	661	540	445	360	293	222	173	123

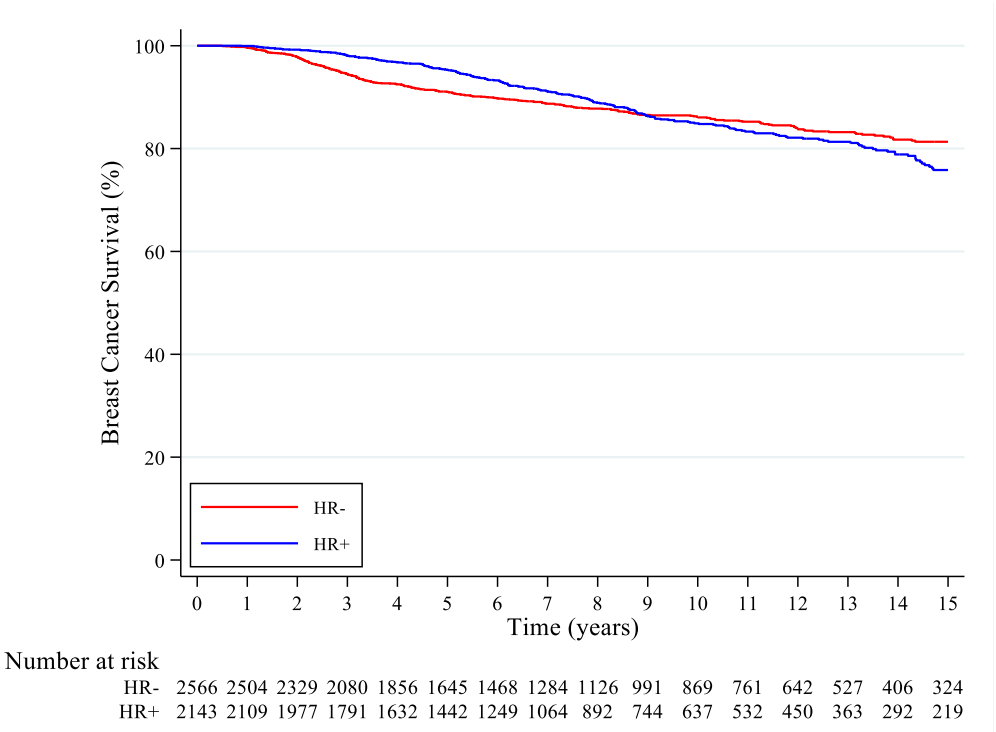
Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

The 8-years BCSS was 88.9% (95%CI, 87.1%-90.4%) in patients with hormone receptor-positive and 87.8% (95%CI, 86.3%-89.2%) in those with hormone receptor-negative disease (Figure 5A).

In the landmark analysis, during the first 5 years from breast cancer diagnosis, patients with hormone receptor-positive disease had a better BCSS (HR 0.65, 95%CI 0.47-0.89) (Figure 5B), while no difference was observed in years >5 (HR 1.22, 95%CI 0.88-1.68) (Figure 5C, Supplementary Table S1).

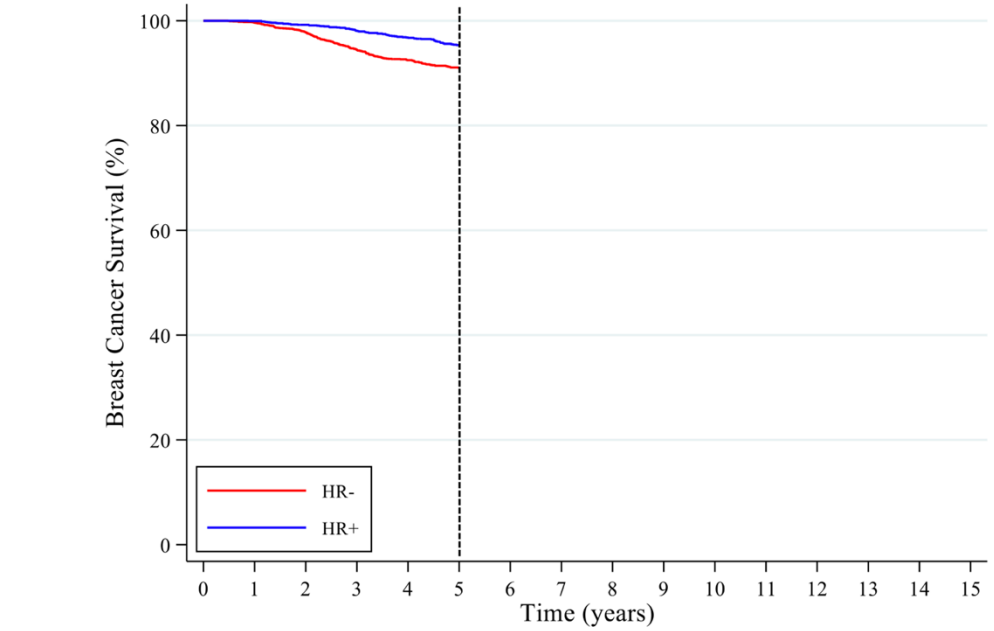
Figure 5. Breast cancer specific survival in patients with hormone receptor-positive and negative breast cancer

A) Breast cancer specific survival in whole population throughout follow-up



Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

B) Breast cancer specific survival (years 0-5)

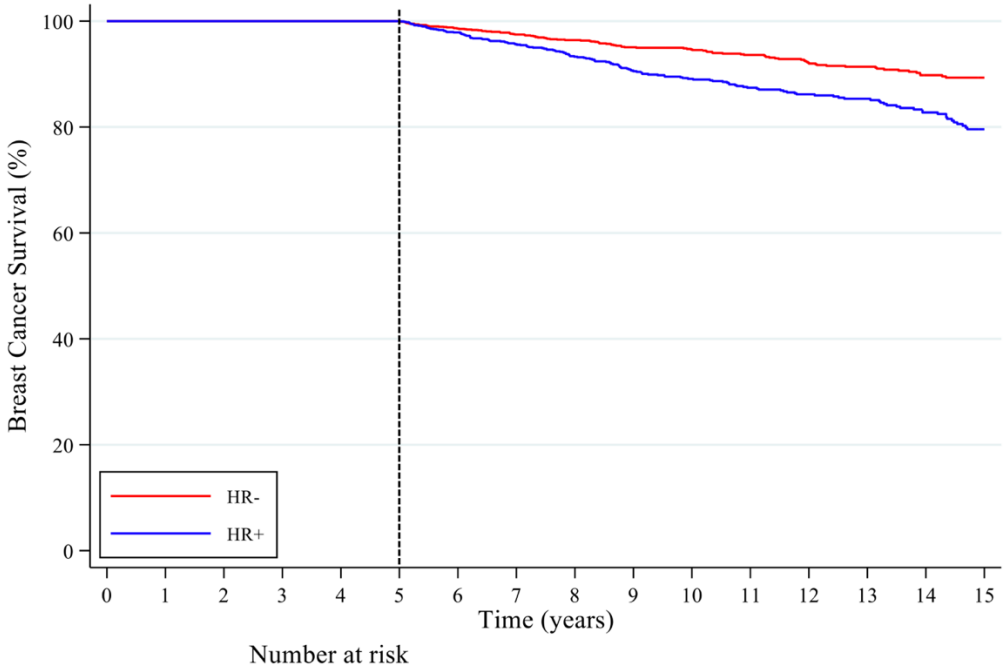


Number at risk

HR-	2566	2504	2329	2080	1856	1645
HR+	2143	2109	1977	1791	1632	1442

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

C) Breast cancer specific survival (years >5)



Number at risk

HR-	1468	1284	1126	991	869	761	642	527	406	324
HR+	1249	1064	892	744	637	532	450	363	292	219

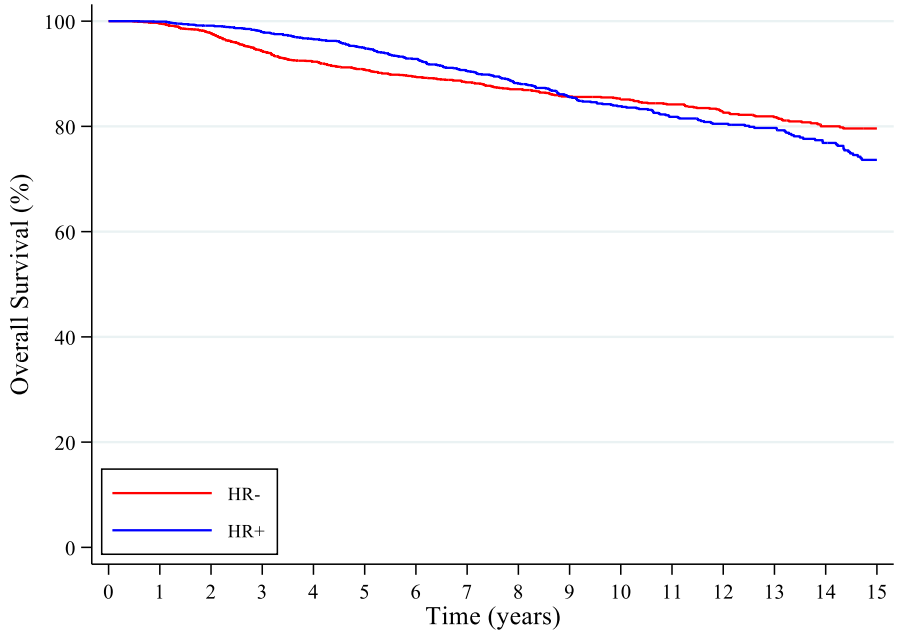
Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

The 8-years OS was 88.1% (95%CI, 86.3%-89.7%) in patients with hormone receptor-positive and 87.1% (95%CI, 85.5%-88.5%) in those with hormone receptor-negative disease (Figure 6A). Adjusted HR for landmark analysis of OS was 0.66 (95%CI 0.48-0.89) for years ≤5 (Figure 6B) and adjusted HR of 1.12 (95%CI 0.82-1.51) for years >5 (Figure 6C, Supplementary Table S1).

The hazards ratio of hormone receptor-positive vs. negative disease changed over time for DFS, BCSS, and OS, with $p<0.05$ for interactions of hormone receptor status and survival time, indicating nonproportionality of hazards over time.

Figure 6. Overall survival in patients with hormone receptor-positive and negative breast cancer.

A) Overall survival in whole population throughout follow-up.

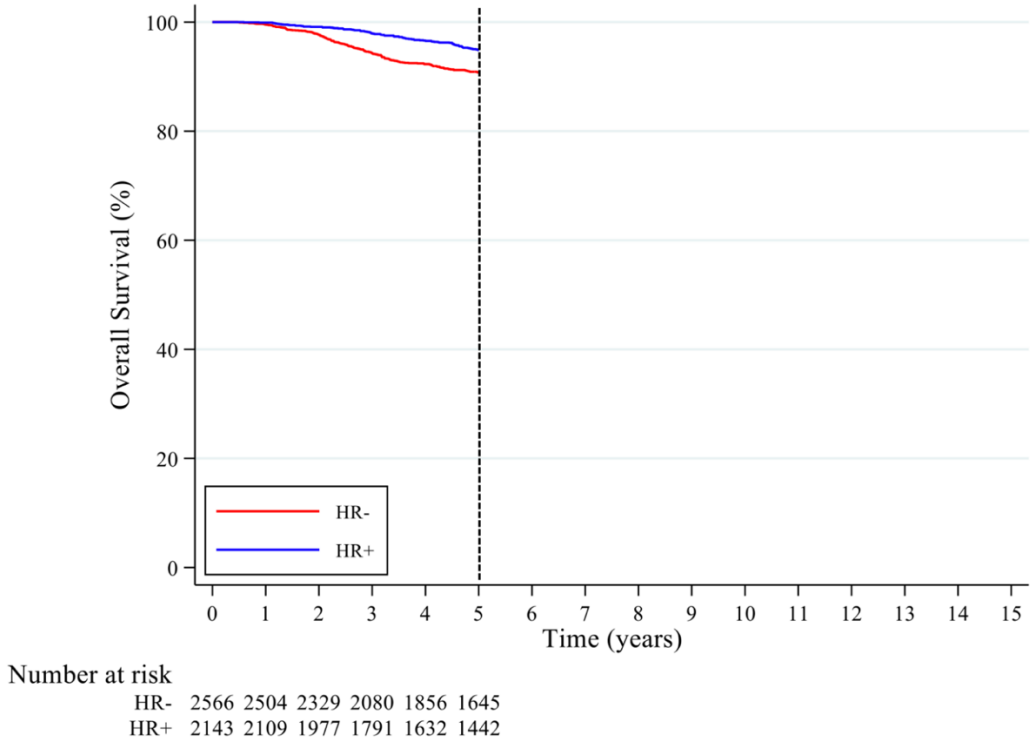


Number at risk

HR-	2566	2504	2329	2080	1856	1645	1468	1284	1126	991	869	761	642	527	406	324
HR+	2143	2109	1977	1791	1632	1442	1249	1064	892	744	637	532	450	363	292	219

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

B) Overall survival (years 0-5)

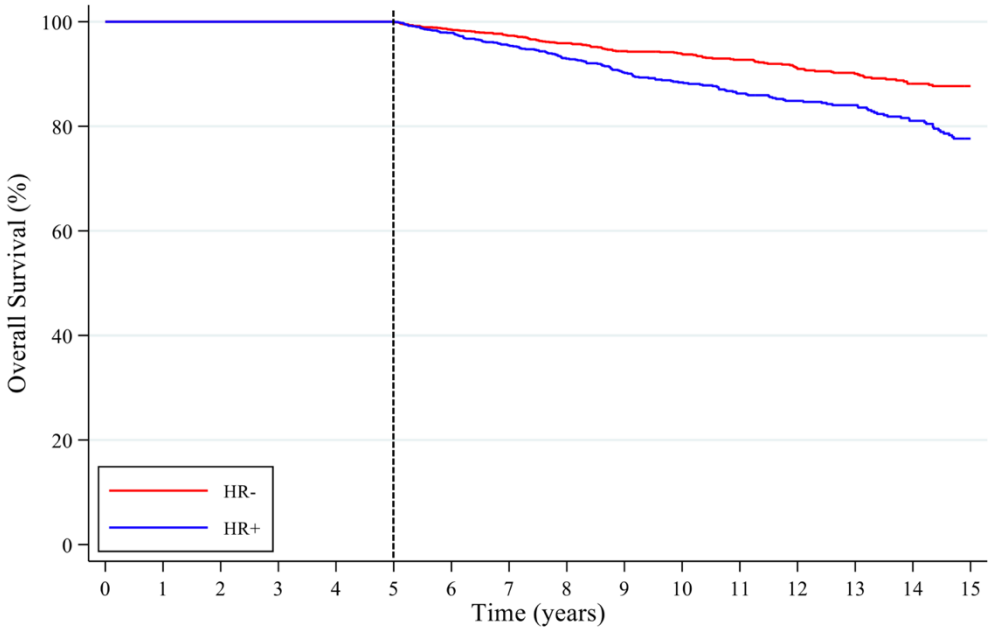


Number at risk

HR-	2566	2504	2329	2080	1856	1645	
HR+	2143	2109	1977	1791	1632	1442	

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

C) Overall survival (years >5)



Number at risk

HR-	1468	1284	1126	991	869	761	642	527	406	324
HR+	1249	1064	892	744	637	532	450	363	292	219

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

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 (Table 3).

Table 3. Results of the adjusted cox-models according to time intervals in patients harboring *BRCA1* pathogenic variants only

BRCA1	**Hazard Ratio (HR+ vs HR-)**					
	Model 1* (N=3,018)			**Model 2** (N=2,887)**		
	Analysis time ≤5 years HR (95% CI)	**Analysis time >5 years HR (95% CI)**	**All time HR (95% CI)**	**Analysis time ≤5 years HR (95% CI)**	**Analysis time >5 years HR (95% CI)**	**All time HR (95% CI)**
DFS	0.81 (0.67-0.98)	0.88 (0.68-1.15)	0.83 (0.71-0.97)	0.83 (0.68-1.03)	0.80 (0.60-1.08)	0.82 (0.69-0.98)
BCSS	0.85 (0.61-1.19)	0.98 (0.63-1.51)	0.89 (0.68-1.15)	0.84 (0.54-1.28)	0.87 (0.51-1.49)	0.85 (0.61-1.19)
OS	0.87 (0.63-1.20)	1.05 (0.70-1.56)	0.93 (0.72-1.19)	0.83 (0.55-1.27)	1.01 (0.62-1.64)	0.90 (0.66-1.24)

*adjusted for age, year of diagnosis, country, histology, tumor size, grade, nodal status, HER2 expression, type of breast surgery, chemotherapy use
**adjusted for age, year of diagnosis, country, histology, tumor size, grade, nodal status, HER2 expression, type of breast surgery, chemotherapy use and uptake of prophylactic mastectomy
Abbreviations: DFS, disease-free survival; BCSS, breast cancer specific survival; OS, overall survival; HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease; HR, hazard ratio.

For patients harboring *BRCA2* PV, those with hormone receptor-positive disease had a better prognosis in the first 5 years and a worse prognosis afterwards, in terms of BCSS with an adjusted HR of 2.23 (95%CI 1.11-4.49) for years >5 (Table 4).

Table 4. Results of the adjusted cox-models according to time intervals in patients harboring *BRCA2* pathogenic variants only

BRCA2	**Hazard Ratio (HR+ vs HR-)**					
	Model 1* (N=1,655)			**Model 2** (N=1,576)**		
	Analysis time ≤5 years HR (95% CI)	**Analysis time >5 years HR (95% CI)**	**All time HR (95% CI)**	**Analysis time ≤5 years HR (95% CI)**	**Analysis time >5 years HR (95% CI)**	**All time HR (95% CI)**
DFS	0.70 (0.52-0.94)	1.02 (0.68-1.53)	0.81 (0.63-1.03)	0.71 (0.51-0.99)	0.98 (0.62-1.55)	0.81 (0.62-1.06)
BCSS	0.31 (0.17-0.57)	2.23 (1.11-4.49)	0.89 (0.58-1.35)	0.30 (0.13-0.68)	2.79 (0.98-7.92)	0.87 (0.55-1.38)
OS	0.31 (0.17-0.55)	1.37 (0.78-2.41)	0.73 (0.50-1.07)	0.24 (0.12-0.45)	1.33 (0.74-2.39)	0.69 (0.46-1.04)

*adjusted for age, year of diagnosis, country, histology, tumor size, grade, nodal status, HER2 expression, type of breast surgery, chemotherapy use
**adjusted for age, year of diagnosis, country, histology, tumor size, grade, nodal status, HER2 expression, type of breast surgery, chemotherapy use and uptake of prophylactic mastectomy
Abbreviations: DFS, disease-free survival; BCSS, breast cancer specific survival; OS, overall survival; HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease; HR, hazard ratio.

Sensitivity analyses were conducted by including only patients for whom the 1% cut-off for ER and/or PgR receptor expression was used, and then only in patients with known HER2-negative disease, and results were consistent with those reported in the main analyses (Supplementary Figure S1, Supplementary Figure S2 A-D and Supplementary Tables S2-S6). Among the 4,497 patients with available information on uptake of risk-reducing mastectomy, results were consistent with those reported in the main analysis (Supplementary Tables S2-S6).

3.2 Analyses by tumor subtype

Among the 4,363 young *BRCA* carriers eligible for this analysis, 612 (14.0%) were classified as having luminal A-like, 1,038 (23.8%) as luminal B-like, 2,373 (54.4%) as triple-negative and 340 (7.8%) HER2-positive disease. Baseline characteristics of the patients according with tumor subtype are reported in Table 5.

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 if compared with all the other breast cancer subtypes (Table 5).

Patients with luminal A-like disease had 90.8% of cases with grade 2 tumors, more than half (53.3%) had T1 stage, 76.8% were harboring *BRCA2* PV, and received chemotherapy in 75.0% of the cases, while those with luminal B-like disease had 89.2% of cases grade 3 diseases, T1 stage in 38.8% and ≥ T2 in 57.5% of the cases, 56.8% were harboring *BRCA2* PV, and 93.2% of the cases received chemotherapy (Table 5).

Table 5. Patient, tumor, and treatment characteristics between all cancer subtypes

	Luminal A-like N (%) N=612	Luminal B-like N (%) N=1,038	Triple-negative N (%) N=2,373	HER2-positive N (%) N=340	P value[a]
Age at diagnosis, median (IQR) years	35 (32 to 38)	35 (32 to 38)	34 (31 to 37)	35 (32 to 38)	0.01
Country:					<0.001
North America	65 (10.6)	128 (12.3)	220 (9.3)	62 (18.2)	
South-Center America	17 (2.8)	24 (2.3)	97 (4.1)	6 (1.8)	
Asia + Israel	65 (10.6)	122 (11.7)	427 (18.0)	57 (16.8)	
Oceania	17 (2.8)	50 (4.8)	74 (3.1)	9 (2.6)	
North Europe	115 (18.8)	161 (15.5)	394 (16.6)	40 (11.8)	
South Europe	284 (46.4)	496 (47.8)	989 (41.7)	149 (43.8)	
East Europe	49 (8.0)	57 (5.5)	172 (7.2)	17 (5.0)	
Year at diagnosis:					0.38
2000-2005	76 (12.4)	135 (13.0)	351 (14.8)	51 (15.0)	
2006-2010	140 (22.9)	257 (24.8)	611 (25.7)	80 (23.5)	
2011-2015	175 (28.6)	314 (30.2)	668 (28.1)	98 (28.8)	
2016-2020	221 (36.1)	332 (32.0)	743 (31.3)	111 (32.6)	
Age at diagnosis:					<0.001
≤ 30 years	93 (15.2)	194 (18.7)	558 (23.5)	63 (18.5)	
31-35 years	229 (37.4)	384 (37.0)	841 (35.4)	118 (34.7)	
36-40 years	290 (47.4)	460 (44.3)	974 (41.0)	159 (46.8)	
Histology:					<0.001
Ductal carcinoma	484 (79.1)	865 (83.3)	2049 (86.3)	282 (82.9)	
Lobular carcinoma	57 (9.3)	33 (3.2)	19 (0.8)	8 (2.3)	
Invasive not specified	17 (2.8)	50 (4.8)	101 (4.3)	18 (5.3)	
Others	41 (6.7)	53 (5.1)	139 (5.9)	17 (5.0)	
Missing	13 (2.1)	37 (3.6)	65 (2.7)	15 (4.4)	
Tumor grade:					
G1	56 (9.1)	7 (0.7)	10 (0.4)	2 (0.6)	NA
G2	556 (90.8)	105 (10.1)	210 (8.8)	95 (27.9)	
G3	0 (0.0)	926 (89.2)	1968 (82.9)	210 (61.8)	
Missing	0 (0.0)	0 (0.0)	185 (7.8)	33 (9.7)	
Tumor size:					<0.001
T1	326 (53.3)	403 (38.8)	832 (35.1)	129 (37.9)	
T2	191 (31.2)	452 (43.5)	1121 (47.2)	151 (44.4)	
T3-T4	83 (13.6)	145 (14.0)	327 (13.8)	46 (13.5)	
Missing	12 (2.0)	38 (3.7)	93 (3.9)	14 (4.1)	
Nodal status:					<0.001
N0	279 (45.6)	504 (48.5)	1365 (57.5)	147 (43.2)	
N1	244 (39.9)	353 (34.0)	721 (30.4)	122 (35.9)	
N2-N3	81 (13.2)	158 (15.2)	226 (9.5)	56 (16.5)	
Missing	8 (1.3)	23 (2.2)	61 (2.6)	15 (4.4)	
BRCA cohort:					<0.001
BRCA1	140 (22.9)	444 (42.8)	2133 (89.9)	147 (43.2)	
BRCA2	470 (76.8)	590 (56.8)	218 (9.2)	187 (55.0)	
BRCA1 + *BRCA2*	2 (0.3)	2 (0.2)	17 (0.7)	4 (1.2)	
*BRCA*mut (unknow if *BRCA1* or *BRCA2*)	0 (0.0)	2 (0.2)	5 (0.2)	2 (0.6)	
Time from diagnosis to BRCA testing, median (IQR) months	5.4 (1.0-20.7)	5.2 (0.8-23.5)	4.7 (0.9-23.4)	7.5 (1.4-35.5)	0.115
Missing	90 (14.7)	169 (16.3)	315 (13.3)	66 (19.4)	
Breast surgery:					<0.001
Not done	0 (0.0)	3 (0.3)	10 (0.4)	1 (0.3)	
Breast conserving surgery					
Mastectomy	198 (32.3)	349 (33.6)	1037 (43.7)	108 (31.8)	
Missing	410 (67.0)	677 (65.2)	1304 (54.9)	222 (65.3)	
	4 (0.6)	9 (0.9)	22 (0.9)	9 (2.6)	

Use of chemotherapy:					<0.001
No	148 (24.2)	66 (6.4)	68 (2.9)	8 (2.3)	
Yes	459 (75.0)	967 (93.2)	2295 (96.7)	327 (96.2)	
Missing	5 (0.8)	5 (0.5)	10 (0.4)	5 (1.5)	
Type of chemotherapy*:					<0.001
Anthracycline- and taxane-based	344 (74.9)	695 (71.9)	1675 (73.0)	218 (66.7)	
Anthracycline-based	70 (15.2)	180 (18.6)	417 (18.2)	36 (11.0)	
Taxane-based	25 (5.4)	34 (3.5)	67 (2.9)	51 (15.6)	
Others	11 (2.4)	30 (3.1)	73 (3.2)	11 (3.4)	
Missing	9 (2.0)	28 (2.9)	63 (2.7)	11 (3.4)	
Use of endocrine therapy**:					
No	20 (3.3)	67 (6.4)	NA	14 (5.9)	NA
Yes	586 (95.7)	957 (92.2)		217 (91.9)	
Missing	6 (1.0)	14 (1.3)		5 (2.1)	
Type of endocrine therapy***:					
Tamoxifen alone	195 (33.3)	345 (36.0)		70 (32.3)	
Tamoxifen + LHRHa	185 (31.6)	236 (24.7)		48 (22.1)	
LHRHa alone	6 (1.0)	24 (2.5)	NA	9 (4.1)	NA
AI ± LHRHa	114 (19.4)	172 (18.0)		54 (24.9)	
Tamoxifen and AI (± LHRHa)	75 (12.8)	157 (16.4)		31 (14.3)	
Others	7 (1.2)	14 (1.5)		2 (0.9)	
Missing	4 (0.7)	9 (0.9)		3 (1.4)	
Duration of endocrine therapy, median (IQR) months	54 (25 to 60)	60 (26 to 60)	NA	60 (30 to 60)	NA

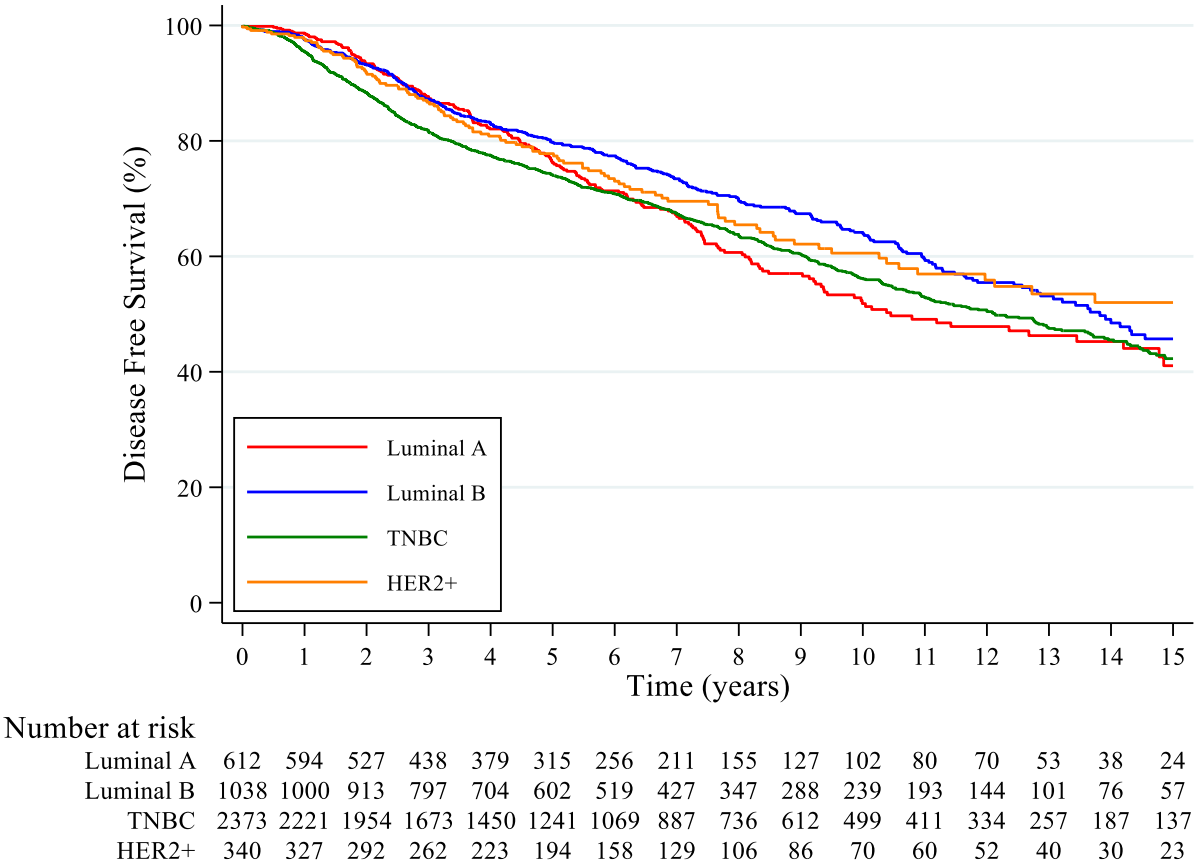
[a] Calculated after exclusion of missing values
* Calculated among patients who received chemotherapy
** Calculated among patients with hormone receptor-positive breast cancer
*** Calculated among patients with hormone receptor-positive breast cancer who received endocrine therapy

Abbreviations: IQR, interquartile range; G, tumor grade; T, tumor size; N, nodal status; ER, estrogen receptor; PR, progesterone receptor; LHRHa, luteinizing hormone-releasing hormone agonists; AI, aromatase inhibitors; NA, not assessed.

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 higher rate of distant and loco-regional recurrences (Supplementary Table S7).

The 8-years DFS was 60.8% (95%CI, 55.7%-65.4%) in patients with luminal A-like, 69.7% (95%CI, 66.2%-72.8%) in luminal B-like, 63.5% (95%CI, 61.1%-65.7%) in triple-negative and 65.5% (95%CI, 59.1%-71.1%) in HER2-positive disease (Figure 7A).

Figure 7A. Prognosis in terms of disease-free survival of patients according to breast cancer subtypes



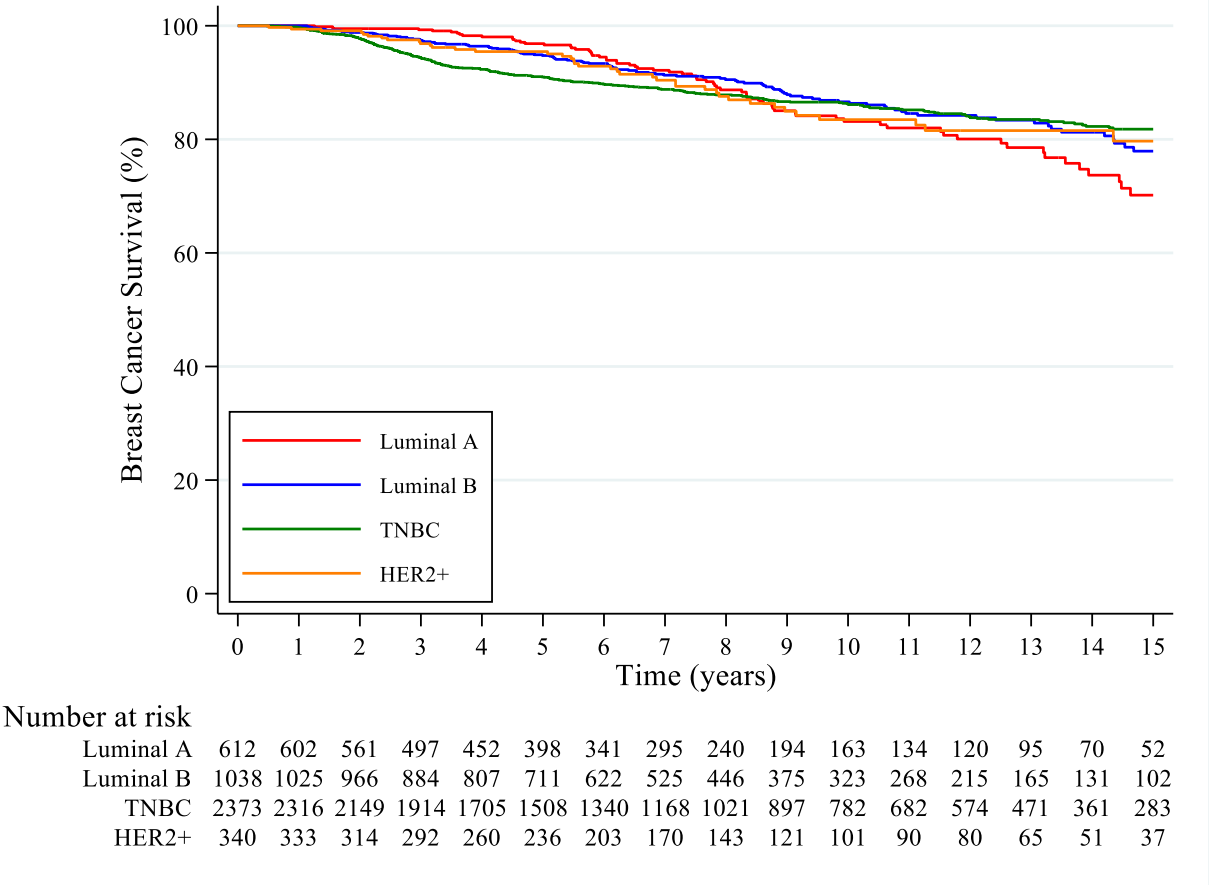
Number at risk

Luminal A	612	594	527	438	379	315	256	211	155	127	102	80	70	53	38	24
Luminal B	1038	1000	913	797	704	602	519	427	347	288	239	193	144	101	76	57
TNBC	2373	2221	1954	1673	1450	1241	1069	887	736	612	499	411	334	257	187	137
HER2+	340	327	292	262	223	194	158	129	106	86	70	60	52	40	30	23

Abbreviations: TNBC, triple-negative breast cancer; HER2+, HER2-positive breast cancer

The 8-years BCSS was 88.7% (95%CI, 84.9%-91.6%) in patients with luminal A-like, 90.5% (95%CI, 88.2%-92.4%) in luminal B-like, 87.8% (95%CI, 86.2%-89.2%) in triple-negative, and 87.6% (95%CI, 82.5%-91.2%) in HER2-positive disease (Figure 7B).

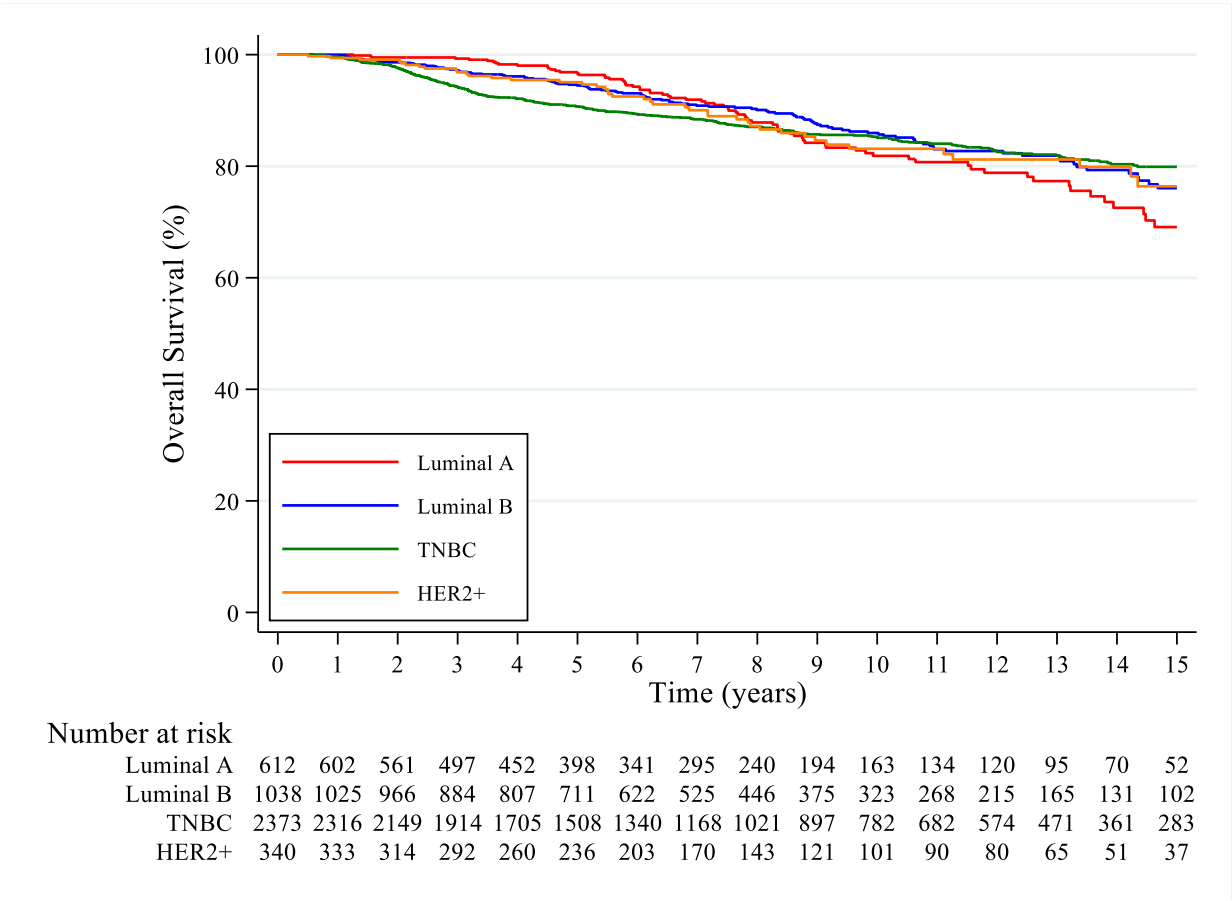
Figure 7B. Prognosis in terms of breast cancer-specific survival of patients according to breast cancer subtypes



Abbreviations: TNBC, triple-negative breast cancer; HER2+, HER2-positive breast cancer

The 8-years OS was 87.8% (95%CI, 83.9%-90.8%) in patients with luminal A-like, 90.1% (95%CI, 87.7%-92.0%) in luminal B-like, 87.0% (95%CI, 85.4%-88.5%) in triple-negative and 87.2% (95%CI, 82.1%-90.9%) in patients with HER2-positive disease (Figure 7C).

Figure 7C. Prognosis in terms of overall survival of patients according to breast cancer subtypes



Number at risk

Luminal A	612	602	561	497	452	398	341	295	240	194	163	134	120	95	70	52
Luminal B	1038	1025	966	884	807	711	622	525	446	375	323	268	215	165	131	102
TNBC	2373	2316	2149	1914	1705	1508	1340	1168	1021	897	782	682	574	471	361	283
HER2+	340	333	314	292	260	236	203	170	143	121	101	90	80	65	51	37

Abbreviations: TNBC, triple-negative breast cancer; HER2+, HER2-positive breast cancer

4. DISCUSSION

To our knowledge, this is the largest study including young women with breast cancer carrying germline *BRCA* PV 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 strong positive prognostic factor in young *BRCA* carriers with breast cancer; time and patterns of recurrence differed according to hormone receptor status and to 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 recurrences in patients with hormone receptor-negative tends to have a peak in the first two/three years after diagnosis and then a reduction in later relapses, in those with hormone receptor-positive disease the rates of tumor recurrences (including distant metastases) remain constantly higher 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] and in patients harboring *BRCA* PV, hormone receptor-positive diseases appears to be biologically more aggressive than in sporadic diseases.[14,17,18]

In our analysis, patients with hormone receptor-positive disease harboring *BRCA* PV 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-years DFS, with a DFS of 65.8% and of 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 that in those with hormone receptor-negative, but no differences were observed afterwards.

We also observed that patients with hormone receptor-negative disease had a progressive increase in the HRs of late DFS events at longer follow-up. However, in patients who do not carry germline

BRCA PV,[24,27,28] hormone receptor-negative disease is known to have peak in DFS events in the first two to three 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 more than 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 almost 9 years of follow-up between patients with hormone receptor-positive and negative disease, while afterwards the prognosis of patients with hormone receptor-positive disease appears to be worse than those with hormone receptor-negative disease. This appeared to occur earlier than what 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 about 14-15 years.[25]

All these observations may have relevant implications from a clinical perspective: whereas recurrences in hormone receptor-positive breast cancer patients 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 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 higher biological aggressiveness in luminal-like disease than sporadic diseases[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 diseases)[31]. Assuming a greater biological aggressiveness of luminal-like disease in patients harboring *BRCA* PV, 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 abemaciclib and olaparib, could further lower recurrence risk for 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 performed in accordance with local practice. Furthermore, date of germline *BRCA* testing was unknown for 703 (14.9%) of 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]

5. CONCLUSIONS

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 strong positive prognostic value in these patients, particularly in those with Luminal A-like disease and in those harboring *BRCA2* PV. Addressing clinical behavior and outcomes of young patients with breast cancer is crucial, especially for those harboring *BRCA* PV 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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7. SUPPLEMENTARY MATERIAL

8.1 Supplementary Tables

Table S1. Results of the adjusted cox-models according to time intervals in the overall population

Overall	Hazard Ratio (HR+ vs HR-)					
	Model 1* (N=4,709)			Model 2** (N=4,497)		
	Analysis time ≤5 years HR (95% CI)	Analysis time >5 years HR (95% CI)	All time HR (95% CI)	Analysis time ≤5 years HR (95% CI)	Analysis time >5 years HR (95% CI)	All time HR (95% CI)
DFS	0.77 (0.65-0.91)	0.91 (0.75-1.12)	0.82 (0.72-0.93)	0.79 (0.66-0.95)	0.86 (0.68-1.08)	0.82 (0.71-0.94)
BCSS	0.65 (0.47-0.89)	1.22 (0.88-1.68)	0.87 (0.70-1.09)	0.65 (0.43-0.98)	1.17 (0.78-1.76)	0.85 (0.64-1.13)
OS	0.66 (0.48-0.89)	1.12 (0.82-1.51)	0.85 (0.69-1.05)	0.64 (0.43-0.96)	1.08 (0.74-1.59)	0.84 (0.67-1.05)

*adjusted for age, year of diagnosis, country, histology, tumor size, grade, nodal status, HER2 expression, type of breast surgery, chemotherapy use

**adjusted for age, year of diagnosis, country, histology, tumor size, grade, nodal status, HER2 expression, type of breast surgery, chemotherapy use and uptake of prophylactic mastectomy

Abbreviations: DFS, disease-free survival; BCSS, breast cancer specific survival; OS, overall survival; HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease; HR, hazard ratio.

Table S2. Patient, tumor, and treatment characteristics between patients with hormone receptor-positive and negative breast cancer (by including only patients for whom the 1% cut-off for estrogen and/or progesterone receptor expression in their tumor was used to define hormone receptor-positive status).

	Hormone receptor-positive N (%) N=1753	Hormone receptor-negative N (%) N=2020	P value[a]
Country:			<0.001
North America	48 (2.7)	98 (4.8)	
South-Center America	96 (5.5)	94 (4.6)	
Asia + Israel	188 (10.7)	229 (11.3)	
Oceania	127 (7.2)	181 (9.0)	
North Europe	260 (14.8)	260 (12.9)	
South Europe	708 (40.4)	707 (35.0)	
East Europe	326 (18.6)	451 (22.3)	
Year at diagnosis:			0.02
2000-2005	259 (14.8)	343 (17.0)	
2006-2010	376 (21.4)	490 (24.3)	
2011-2015	498 (28.4)	538 (26.6)	
2016-2020	620 (35.4)	649 (32.1)	
Age at diagnosis, median (IQR) years	35 (32 to 38)	34 (31 to 37)	0.02
Age at diagnosis:			<0.001
≤ 30 years	304 (17.3)	463 (22.9)	
31-35 years	651 (37.1)	712 (35.2)	
36-40 years	798 (45.5)	845 (41.8)	
Histology:			<0.001
Ductal carcinoma	1381 (78.8)	1717 (85.0)	
Lobular carcinoma	93 (5.3)	17 (0.8)	
Invasive not specified	92 (5.2)	95 (4.7)	
Others	109 (6.2)	125 (6.2)	
Missing	78 (4.4)	66 (3.3)	
Tumor grade:			<0.001
G1	59 (3.4)	10 (0.5)	
G2	609 (34.7)	184 (9.1)	
G3	892 (50.9)	1649 (81.6)	
Missing	193 (11.0)	177 (8.8)	
Tumor size:			<0.001
T1	739 (42.2)	714 (35.3)	
T2	701 (40.0)	942 (46.6)	
T3-T4	231 (13.2)	276 (13.7)	
Missing	82 (4.7)	88 (4.4)	
Nodal status:			<0.001
N0	764 (43.6)	1143 (56.6)	
N1	649 (37.0)	616 (30.5)	
N2-N3	275 (15.7)	203 (10.0)	
Missing	65 (3.7)	58 (2.9)	
BRCA cohort:			<0.001
*BRCA*1	623 (35.5)	1792 (88.7)	
*BRCA*2	1119 (63.8)	206 (10.2)	
BRCA 1 + *BRCA*2	6 (0.3)	17 (0.8)	
*BRCA*mut (unknow if *BRCA*1 or *BRCA*2)	5 (0.3)	5 (0.2)	
Time from diagnosis to *BRCA* testing, median (IQR) months	4.9 (0.7-26.2)	5.2 (0.8-29.3)	0.359
Missing	266 (15.2)	266 (13.2)	

HER2 status: HER2 negative HER2 positive Missing	 1474 (84.1) 210 (12.0) 69 (3.9)	 1869 (92.5) 86 (4.3) 65 (3.2)	<0.001
Breast surgery: Not done Breast conserving surgery Mastectomy Missing	 4 (0.2) 578 (33.0) 1150 (65.6) 21 (1.2)	 6 (0.3) 882 (43.7) 1113 (55.1) 19 (0.9)	<0.001
Use of chemotherapy: No Yes Missing	 228 (13.0) 1509 (86.1) 16 (0.9)	 68 (3.4) 1937 (95.9) 15 (0.7)	<0.001
Type of chemotherapy*: Anthracycline- and taxane-based Anthracycline-based Taxane-based Others Missing	 1044 (69.2) 243 (16.1) 100 (6.6) 50 (3.3) 72 (4.8)	 1369 (70.7) 344 (17.8) 78 (4.0) 75 (3.9) 71 (3.7)	0.01
Use of endocrine therapy**: No Yes Missing	 87 (5.0) 1637 (93.4) 29 (1.6)	NA	NA
Type of endocrine therapy***: Tamoxifen alone Tamoxifen + LHRHa LHRHa alone AI ± LHRHa Tamoxifen and AI (± LHRHa) Others Missing	 498 (30.4) 489 (29.9) 34 (2.1) 330 (20.2) 244 (14.9) 22 (1.3) 20 (1.2)	NA	NA
Duration of endocrine therapy, median (IQR) months	60 (26 to 60)	NA	NA

[a] Calculated after exclusion of missing values
* Calculated among patients who received chemotherapy
** Calculated among patients with hormone receptor-positive breast cancer
*** Calculated among patients with hormone receptor-positive breast cancer who received endocrine therapy

Abbreviations: IQR, interquartile range; G, tumor grade; T, tumor size; N, nodal status; ER, estrogen receptor; PR, progesterone receptor; LHRHa, luteinizing hormone-releasing hormone agonists; AI, aromatase inhibitors.

Table S3. Pattern of disease-free survival events according to hormone receptor status (by including only patients for whom the 1% cut-off for estrogen and/or progesterone receptor expression in their tumor was used to define hormone receptor-positive status).

	Hormone receptor-positive N (%) N=1,753	Hormone receptor-negative N (%) N=2,020	*P* value[a]
Follow-up, median (IQR)	7.5 (4.3-12.0)	8.0 (4.4-13.0)	0.48
No events	1,176 (67.1)	1,262 (62.5)	0.01
Loco-regional recurrence	119 (6.8)	160 (7.9)	0.21
Distant recurrences	220 (12.6)	180 (8.9)	0.01
Second primary malignancy	66 (3.8)	93 (4.6)	0.25
Ovaries	22 (1.3)	50 (2.5)	
Pancreas	6 (0.3)	3 (0.2)	
Cervix	3 (0.2)	5 (0.3)	
Colon-rectal-anal	3 (0.2)	5 (0.3)	
Haematological	3 (0.2)	3 (0.2)	
Skin	7 (0.4)	8 (0.4)	
Thyroid	2 (0.1)	4 (0.2)	
Endometrial	5 (0.3)	2 (0.1)	
Upper Gastrointestinal	2 (0.1)	3 (0.2)	
Others	13 (0.7)	10 (0.5)	
Second primary breast cancer	150 (8.6)	308 (15.3)	<0.0001
Death without any disease-free survival event	22 (1.3)	17 (0.8)	0.29

[a] P-values for time-dependent events estimated by means of the Log-rank test.

Abbreviations: IQR, interquartile range.

Table S4. Patient, tumor, and treatment characteristics between patients with hormone receptor-positive and hormone receptor-negative breast cancer in patients with known HER2-negative disease only

	Hormone receptor-positive N (%) N=1821	Hormone receptor-negative N (%) N=2373	P value[a]
Country:			0.01
North America	43 (2.4)	97 (4.1)	
South-Center America	71 (3.9)	74 (3.1)	
Asia + Israel	285 (15.6)	394 (16.6)	
Oceania	113 (6.2)	172 (7.2)	
North Europe	201 (11.0)	220 (9.3)	
South Europe	823 (45.2)	989 (41.7)	
East Europe	285 (15.6)	427 (18.0)	
Year at diagnosis:			0.03
2000-2005	238 (13.1)	351 (14.8)	
2006-2010	421 (23.1)	611 (25.7)	
2011-2015	530 (29.1)	668 (28.1)	
2016-2020	632 (34.7)	743 (31.3)	
Age at diagnosis, median (IQR) years	35 (32 to 38)	34 (31 to 37)	0.01
Age at diagnosis:			<0.001
≤ 30 years	308 (16.9)	558 (23.5)	
31-35 years	677 (37.2)	841 (35.4)	
36-40 years	836 (45.9)	974 (41.0)	
Histology:			<0.001
Ductal carcinoma	1479 (81.2)	2049 (86.3)	
Lobular carcinoma	103 (5.7)	19 (0.8)	
Invasive not specified	76 (4.2)	101 (4.3)	
Others	101 (5.5)	139 (5.9)	
Missing	62 (3.4)	65 (2.7)	
Tumor grade:			<0.001
G1	63 (3.5)	10 (0.4)	
G2	661 (36.3)	210 (8.8)	
G3	928 (51.0)	1968 (82.9)	
Missing	169 (9.3)	185 (7.8)	
Tumor size:			<0.001
T1	781 (42.9)	832 (35.1)	
T2	718 (39.4)	1121 (47.2)	
T3-T4	249 (13.7)	327 (13.8)	
Missing	73 (4.0)	93 (3.9)	
Nodal status:			<0.001
N0	848 (46.6)	1365 (57.5)	
N1	663 (36.4)	721 (30.4)	
N2-N3	264 (14.5)	226 (9.5)	
Missing	46 (2.5)	61 (2.6)	
BRCA cohort:			<0.001
*BRCA*1	635 (34.9)	2133 (89.9)	
*BRCA*2	1179 (64.7)	218 (9.2)	
BRCA 1 + *BRCA*2	4 (0.2)	17 (0.7)	
*BRCA*mut (unknow if *BRCA*1 or *BRCA*2)	3 (0.2)	5 (0.2)	
Time from diagnosis to *BRCA* testing, median (IQR) months	4.9 (0.8-23.4)	4.7 (0.9-23.4)	0.661
Missing	281 (15.4)	315 (13.3)	
Breast surgery:			<0.001
Not done	4 (0.2)	10 (0.4)	
Breast conserving surgery	619 (34.0)	1037 (43.7)	
Mastectomy	1184 (65.0)	1304 (54.9)	
Missing	14 (0.8)	22 (0.9)	

Use of chemotherapy: No Yes Missing	 240 (13.2) 1571 (86.3) 10 (0.5)	 68 (2.9) 2295 (96.7) 10 (0.4)	<0.001
Type of chemotherapy*: Anthracycline- and taxane-based Anthracycline-based Taxane-based Others Missing	 1128 (71.8) 282 (17.9) 66 (4.2) 43 (2.7) 52 (3.3)	 1675 (73.0) 417 (18.2) 67 (2.9) 73 (3.2) 63 (2.7)	0.16
Use of endocrine therapy**: No Yes Missing	 91 (5.0) 1707 (93.7) 23 (1.3)	NA	NA
Type of endocrine therapy***: Tamoxifen alone Tamoxifen + LHRHa LHRHa alone AI ± LHRHa Tamoxifen and AI (± LHRHa) Others Missing	 593 (34.7) 494 (28.9) 31 (1.8) 298 (17.5) 253 (14.8) 23 (1.3) 15 (0.9)	NA	NA
Duration of endocrine therapy, median (IQR) months	60 (26 to 60)	NA	NA

[a] Calculated after exclusion of missing values
* Calculated among patients who received chemotherapy
** Calculated among patients with hormone receptor-positive breast cancer
*** Calculated among patients with hormone receptor-positive breast cancer who received endocrine therapy

Abbreviations: IQR, interquartile range; G, tumor grade; T, tumor size; N, nodal status; ER, estrogen receptor; PR, progesterone receptor; LHRHa, luteinizing hormone-releasing hormone agonists; AI, aromatase inhibitors; NA, not assessed.

Table S5. Pattern of first disease-free survival event according to hormone receptor status in patients with known HER2-negative disease only

	Hormone receptor-positive N (%) 1,821 (43.4)	Hormone receptor-negative N (%) 2,373 (56.6)	*P* value[a]
Follow-up, median (IQR)	7.4 (4.3-11.9)	8.0 (4.4-12.8)	0.53
No events	1,224 (67.2)	1,483 (62.5)	0.01
Loco-regional recurrence	124 (6.8)	198 (8.3)	0.10
Distant recurrence	230 (12.6)	230 (9.7)	0.01
Second primary malignancy	59 (3.2)	106 (4.5)	0.08
Ovaries	20 (1.1)	56 (2.4)	
Pancreas	4 (0.2)	3 (0.1)	
Cervix	2 (0.1)	6 (0.3)	
Colon-rectal-anal	3 (0.2)	6 (0.3)	
Haematological	3 (0.2)	4 (0.2)	
Skin	6 (0.3)	9 (0.4)	
Thyroid	2 (0.1)	4 (0.2)	
Endometrial	4 (0.2)	3 (0.1)	
Upper-gastrointestinal	2 (0.1)	3 (0.1)	
Others	13 (0.7)	12 (0.5)	
Second primary breast cancer	166 (9.1)	342 (14.4)	<0.0001
Death without any disease-free survival event	18 (1.0)	14 (0.6)	0.14

[a] P-values for time-dependent events estimated by means of the Log-rank test.

Abbreviations: IQR, interquartile range.

Table S6. Results of the adjusted cox-model according to time intervals in patients with known HER2-negative disease only

HER2-negative only	Hazard Ratio (HR+ vs HR-)					
	Model 1* (N=4,194)			Model 2** (N=4,005)		
	Analysis time ≤5 years HR (95% CI)	Analysis time >5 years HR (95% CI)	All time HR (95% CI)	Analysis time ≤5 years HR (95% CI)	Analysis time >5 years HR (95% CI)	All time HR (95% CI)
DFS	0.75 (0.63-0.89)	0.91 (0.73-1.14)	0.81 (0.71-0.93)	0.77 0.63-0.93	0.85 0.66-1.09	0.81 0.69-0.94
BCSS	0.69 (0.49-0.96)	1.35 (0.94-1.92)	0.93 (0.74-1.18)	0.78 0.51-1.19	1.25 0.80-1.95	0.96 0.71-1.29
OS	0.68 (0.49-0.95)	1.16 (0.83-1.62)	0.88 (0.70-1.11)	0.76 0.50-1.15	1.06 0.69-1.62	0.89 0.67-1.19

*adjusted for age, year of diagnosis, country, histology, tumor size, grade, nodal status, type of breast surgery, chemotherapy use

**adjusted for age, year of diagnosis, country, histology, tumor size, grade, nodal status, type of breast surgery, chemotherapy use and uptake of prophylactic mastectomy

Abbreviations: DFS, disease-free survival; BCSS, breast cancer specific survival; OS, overall survival; HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease; HR, hazard ratio.

Table S7. Pattern of first disease-free survival event according to different cancer subtypes

	Luminal A-like N (%) N=612	Luminal B-like N (%) N=1,038	Triple-negative N (%) N=2,373	HER2-positive N (%) N=340	P value[a]
Follow-up, median (IQR)	7.3 (4.0-11.9)	7.6 (4.7-12.0)	8.0 (4.4-12.8)	7.8 (4.6-12.5)	
No events	401 (65.5)	706 (68.0)	1483 (62.5)	228 (67.1)	0.01
Loco-regional recurrence	57 (9.3)	59 (5.7)	198 (8.3)	22 (6.5)	0.01
Distant recurrence	86 (14.0)	112 (10.8)	230 (9.7)	47 (13.8)	0.01
Second primary malignancy	16 (2.6)	38 (3.7)	106 (4.5)	14 (4.1)	0.19
Ovaries	4 (0.7)	15 (1.4)	56 (2.4)	4 (1.2)	
Pancreas	2 (0.3)	2 (0.2)	3 (0.1)	2 (0.6)	
Cervix	0 (0.0)	2 (0.2)	6 (0.3)	1 (0.3)	
Colon-rectal-anal	1 (0.2)	1 (0.1)	6 (0.3)	0 (0.0)	
Haematological	1 (0.2)	2 (0.2)	4 (0.2)	0 (0.0)	
Skin	4 (0.7)	2 (0.2)	9 (0.4)	1 (0.3)	
Thyroid	0 (0.0)	2 (0.2)	4 (0.2)	1 (0.3)	
Endometrial	1 (0.2)	2 (0.2)	3 (0.1)	1 (0.3)	
Upper-gastrointestinal	0 (0.0)	2 (0.2)	3 (0.1)	0 (0.0)	
Others	3 (0.5)	8 (0.8)	12 (0.5)	4 (1.2)	
Second primary breast cancer	45 (7.3)	111 (10.7)	341 (14.4)	28 (8.2)	<0.001
Death without any disease-free survival event	7 (1.1)	12 (1.2)	15 (0.6)	1 (0.3)	0.21

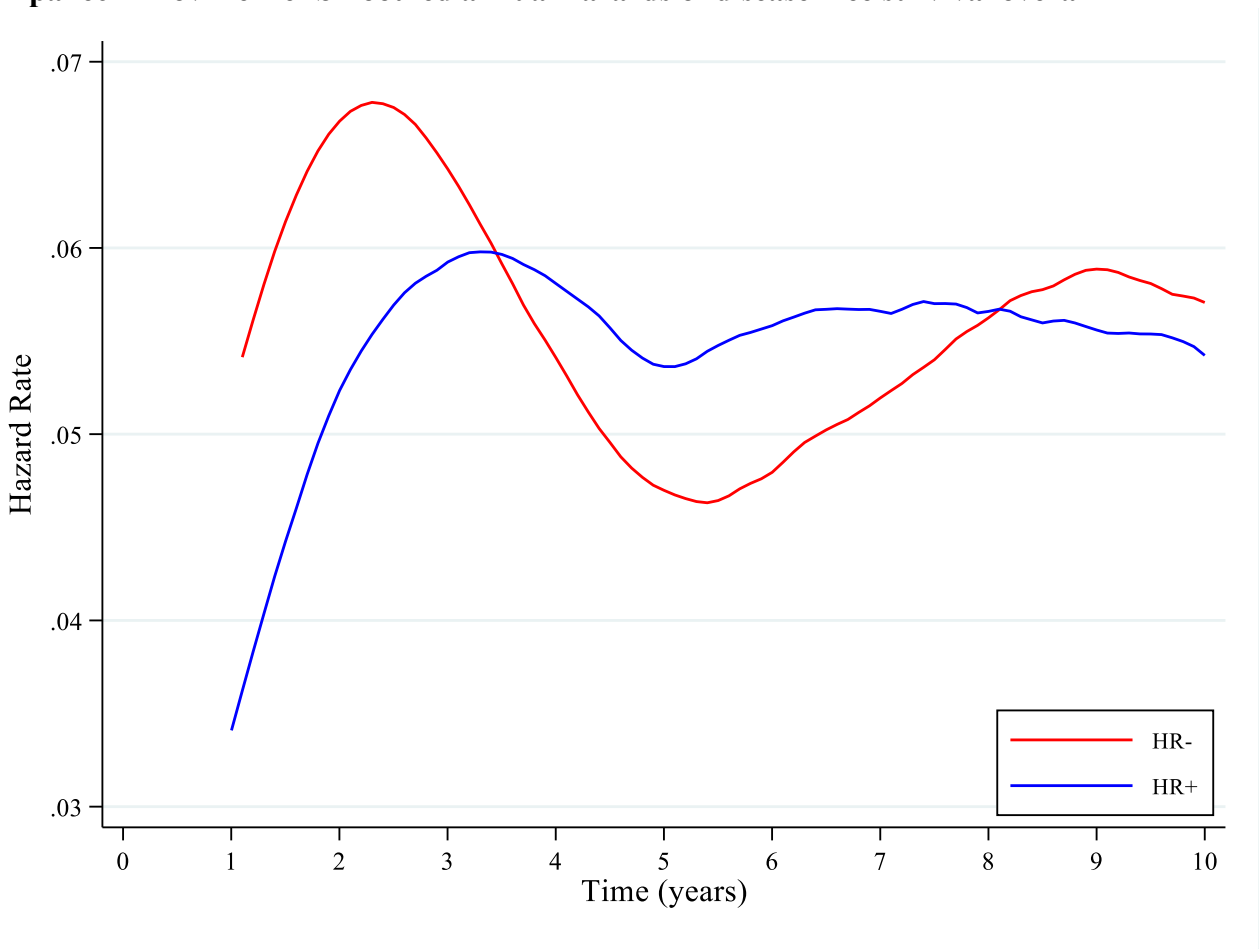
[a] P-values for time-dependent events estimated by means of the Log-rank test.

Abbreviations: IQR, interquartile range.

8.2 Supplementary Figures

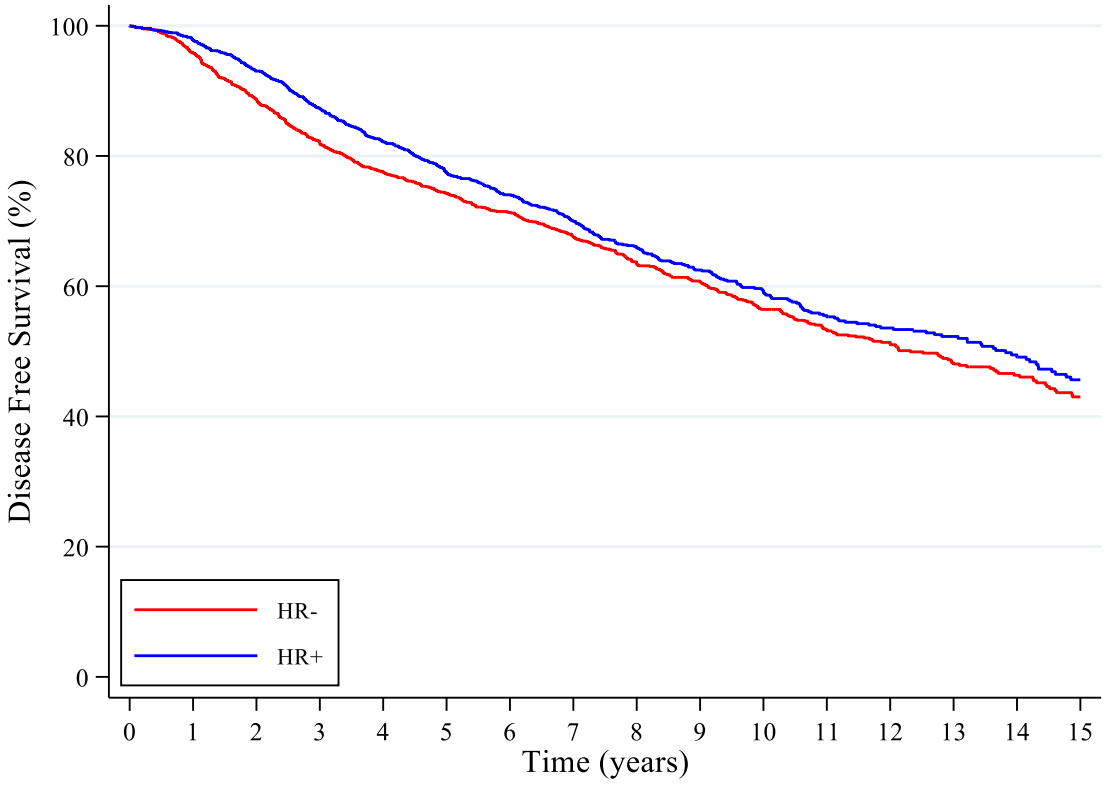
Figure S1. Comparison between patients with hormone receptor-positive and negative disease (by including only patients for whom the 1% cut-off for estrogen and/or progesterone receptor expression in their tumor was used to define hormone receptor-positive status)

A) Epanechnikov Kernel-Smoothed annual hazards of disease-free survival overall



Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

B) Disease-free survival

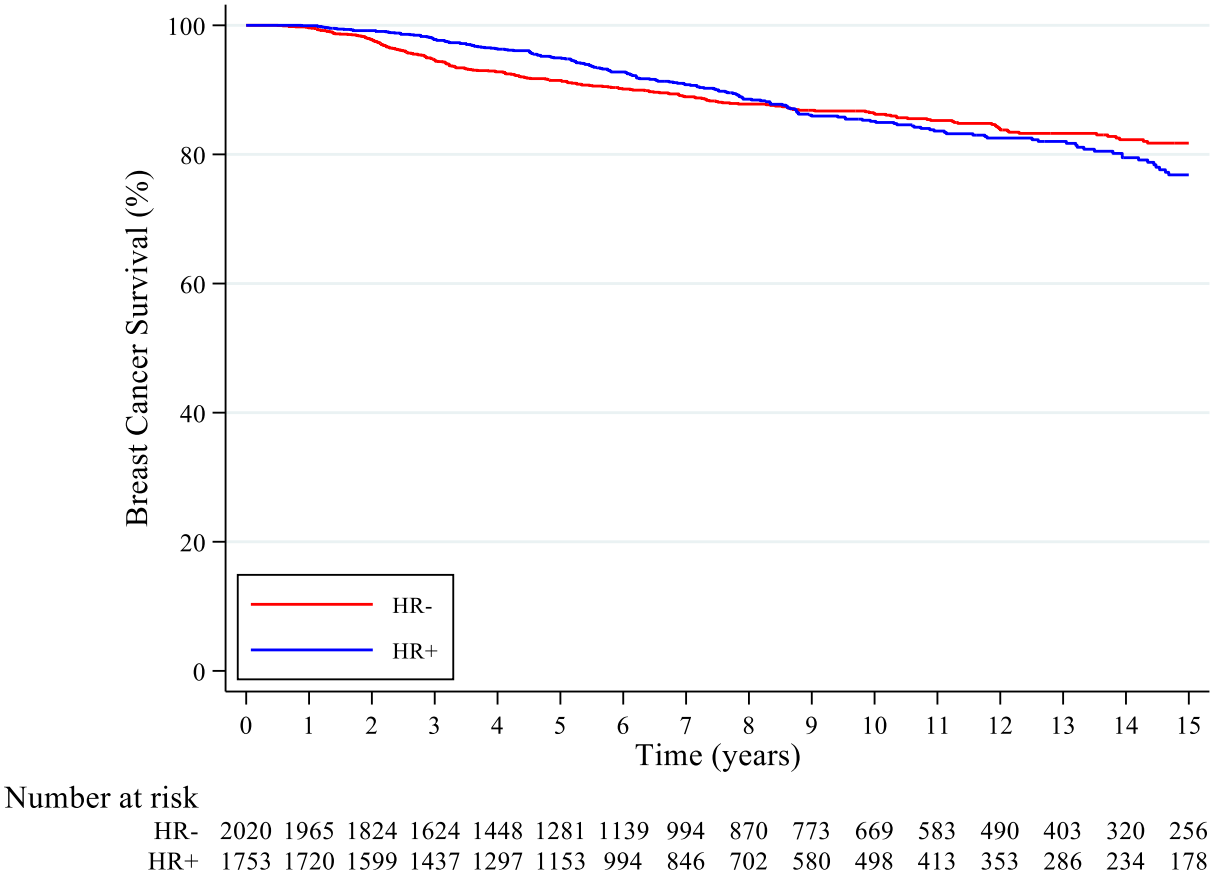


Number at risk

HR-	2020	1894	1668	1426	1229	1054	913	759	629	532	427	354	289	226	168	126
HR+	1753	1683	1505	1286	1115	951	797	659	522	421	349	280	233	181	143	101

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

C) Breast cancer specific survival

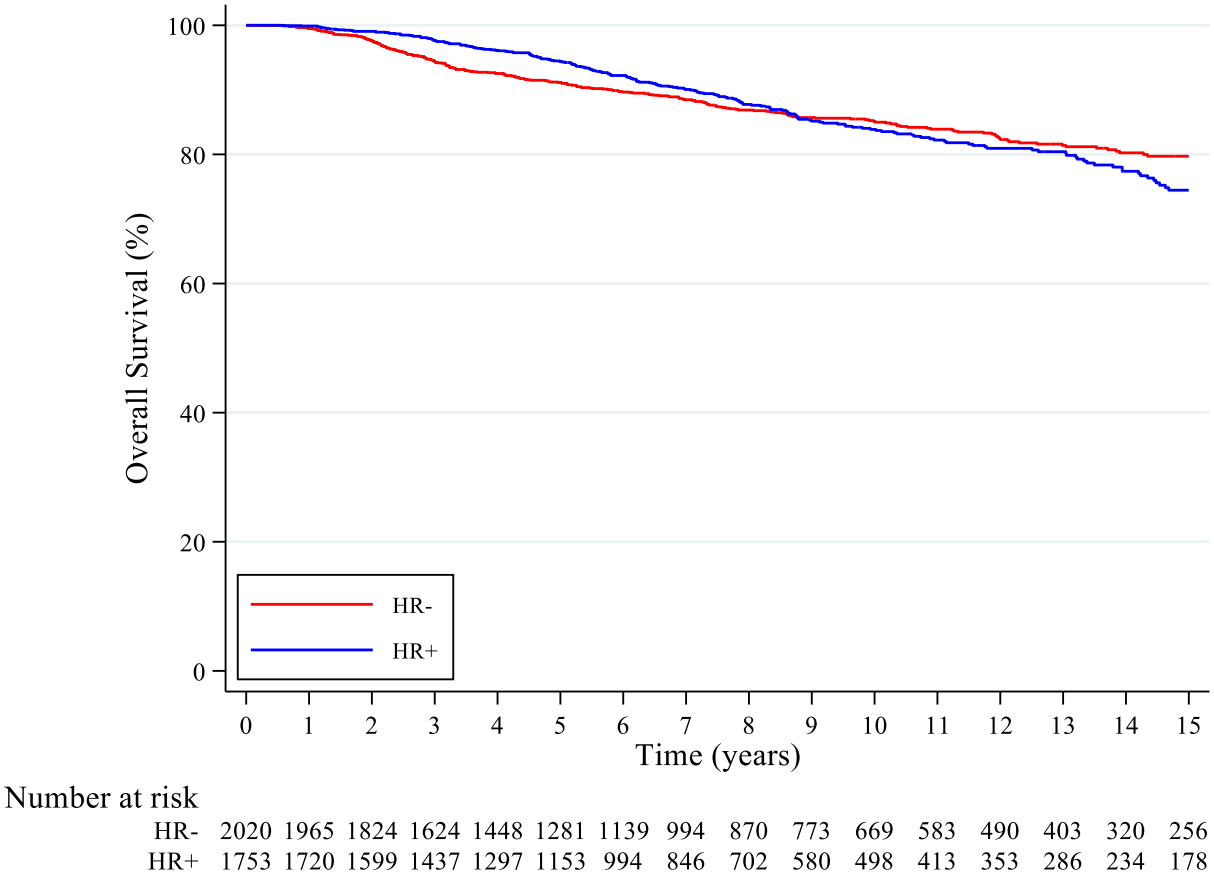


Number at risk

HR-	2020	1965	1824	1624	1448	1281	1139	994	870	773	669	583	490	403	320	256
HR+	1753	1720	1599	1437	1297	1153	994	846	702	580	498	413	353	286	234	178

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

D) Overall survival



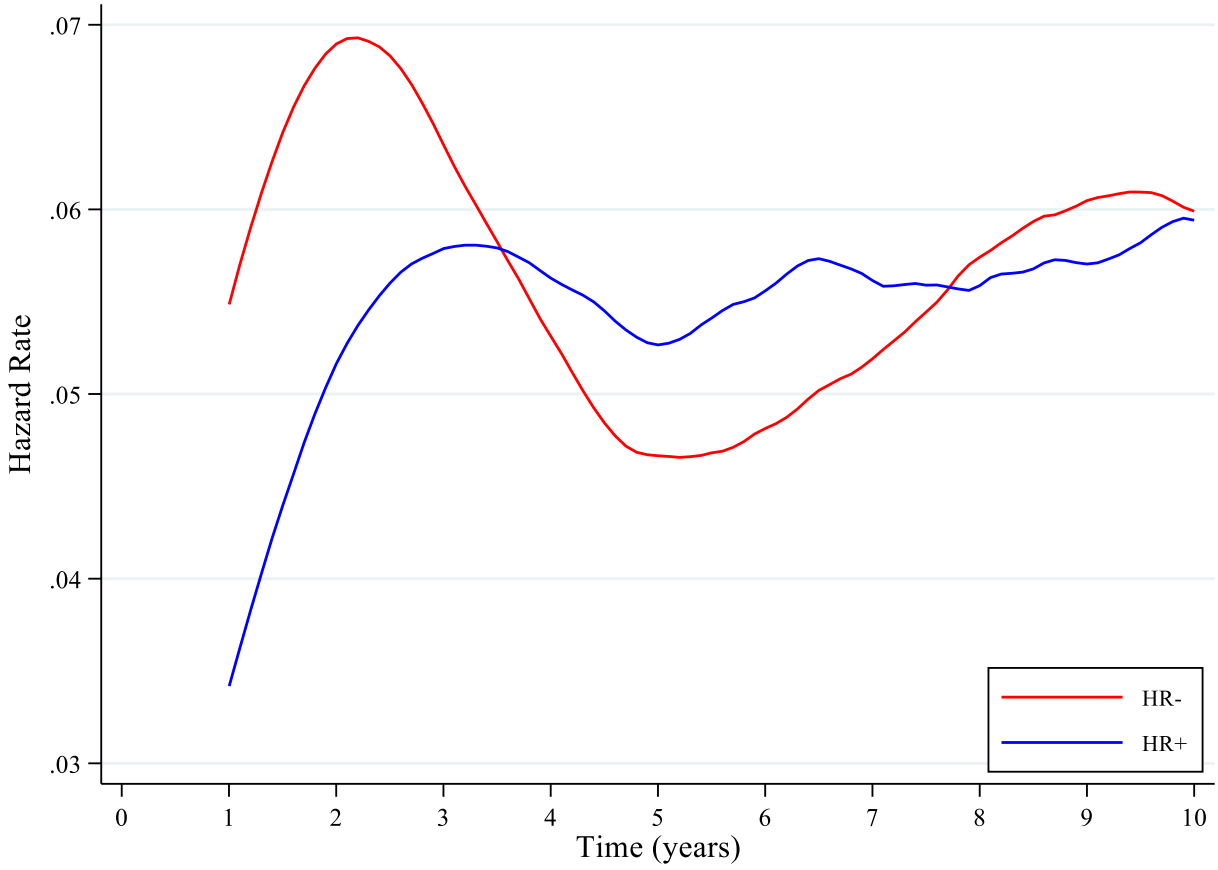
Number at risk

HR-	2020	1965	1824	1624	1448	1281	1139	994	870	773	669	583	490	403	320	256
HR+	1753	1720	1599	1437	1297	1153	994	846	702	580	498	413	353	286	234	178

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

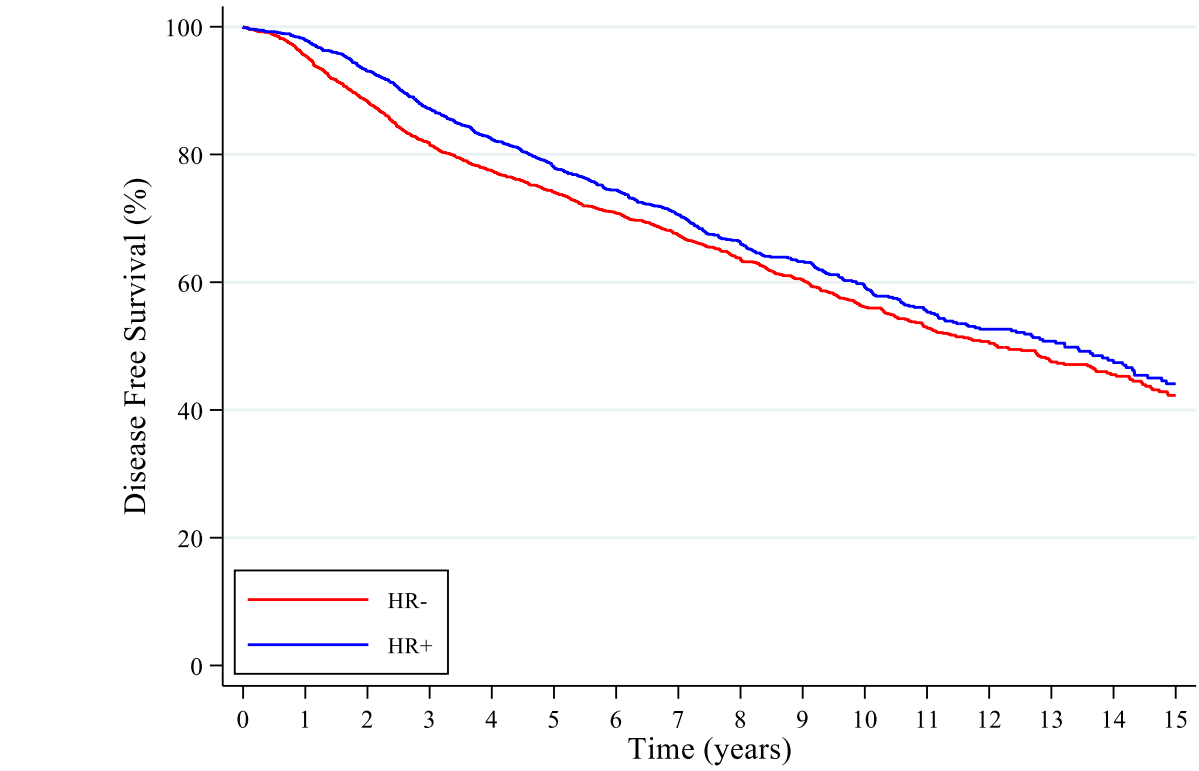
Figure S2. Epanechnikov Kernel-Smoothed annual hazards of recurrence between patients with hormone receptor-positive and negative disease only in patients with known HER2-negative disease

A) Epanechnikov Kernel-Smoothed annual hazards of disease-free survival overall



Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

B) Disease-free survival

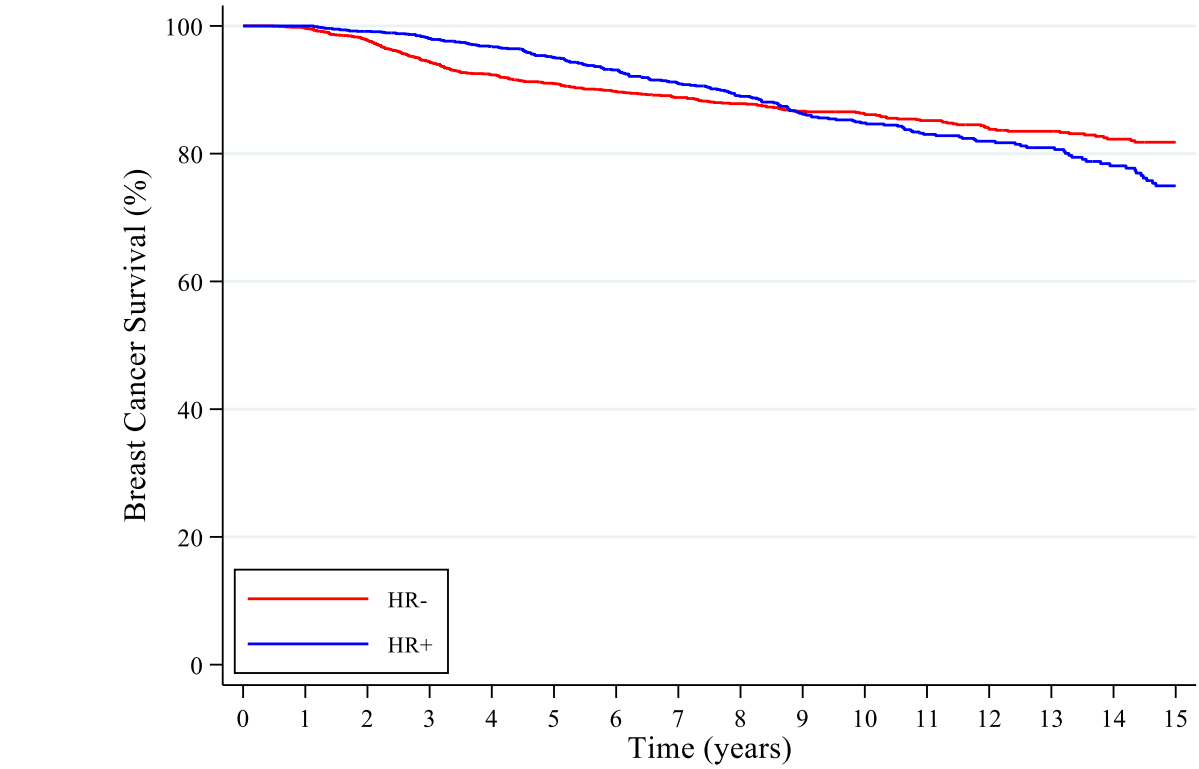


Number at risk

HR-	2373	2221	1954	1673	1450	1241	1069	887	736	612	499	411	334	257	187	137
HR+	1821	1755	1573	1341	1172	989	829	684	542	445	366	294	232	170	129	90

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

C) Breast cancer specific survival

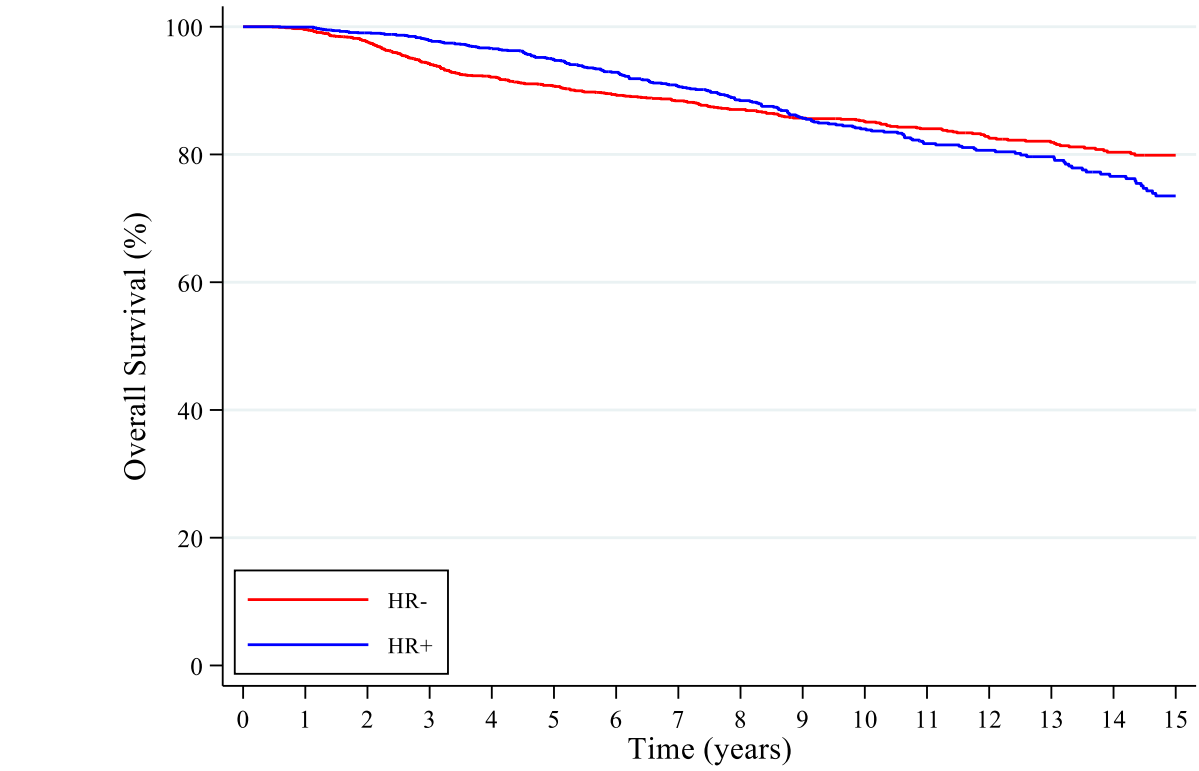


Number at risk

HR-	2373	2316	2149	1914	1705	1508	1340	1168	1021	897	782	682	574	471	361	283
HR+	1821	1792	1673	1503	1366	1198	1035	880	734	609	522	431	358	281	221	168

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease

D) Overall survival



Number at risk

HR-	2373	2316	2149	1914	1705	1508	1340	1168	1021	897	782	682	574	471	361	283
HR+	1821	1792	1673	1503	1366	1198	1035	880	734	609	522	431	358	281	221	168

Abbreviations: HR+, hormone receptor-positive disease; HR-, hormone receptor-negative disease