Prevalence, Treatment Patterns, and Prognosis of Low Estrogen Receptor–Positive (1% to 10%) Breast Cancer: A Single Institution's Experience in Korea

Yeon Hee Park (yhparkhmo@skku.edu)
Samsung Medical Center https://orcid.org/0000-0003-4156-9212
Vassiliki Karantza
Merck & Co Inc
Shawna R. Calhoun
Merck & Co Inc
Seri Park
Sungkyunkwan University School of Medicine
Sohee Lee
Samsung Medical Center
Ji-Yeon Kim
Samsung Medical Center
Jong Han Yu
Samsung Medical Center
Seok Won Kim
Samsung Medical Center
Jeong Eon Lee
Samsung Medical Center
Seok Jin Nam
Samsung Medical Center
Gursel Aktan
Merck & Co Inc
Mark Marisco
Merck & Co Inc

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Abstract

Purpose: To determine prevalence, clinicopathological characteristics, initial treatments, and outcomes associated with low estrogen receptor (ER)–expressing invasive breast cancer.

Methods: This retrospective, noninterventional database study included patients undergoing surgery with curative intent for invasive ductal or lobular breast cancer. Patients were treated between January 2003-December 2012. Demographics, clinicopathologic characteristics, initial treatments, and outcomes were abstracted from patient records. Patients were categorized using immunohistochemistry to determine ER, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) levels. ER-positive patients were subclassified as ER-Low (1%–10%) and ER-High (>10%) according to Allred Proportion Score. Disease-free survival (DFS) and overall survival (OS) were estimated by the Kaplan-Meier method and compared among groups by log-rank test.

Results: 5930 patients were included (median follow-up, 80.9 months). Of all patients included, 117 (2.0%) had ER-Low tumors, 63 (53.8%) of whom had HER2− tumors and 54 (46.2%) HER2+ tumors. Five-year DFS and OS were highest in the ER-High/HER2− cohort (94.0% and 98.6%, respectively) and lowest in the triple-negative breast cancer (TNBC; 81.3% and 90.1%) and ER-Low/HER2− (85.7% and 92.1%) cohorts. Menopausal status, elevated Ki-67, higher nuclear grade, higher tumor stage, presence of lymphovascular invasion, greater regional lymph node involvement, and larger tumor size were all potential prognostic factors for shorter DFS and OS.

Conclusion: Patients with ER-Low/HER2− breast cancer had similar clinicopathological characteristics, treatments, and outcomes as patients with TNBC irrespective of disease setting. Further research is needed to understand predictive and prognostic factors associated with ER-Low/HER2− disease.

Introduction

Breast cancer was the most common cancer worldwide for women in 2018, comprising 24.2% of cases and 15.0% of deaths [1]. For 2018, it was estimated that there were 626.7 breast cancer deaths per 100,000 women worldwide. In South Korea in 2019, breast cancer was predicted to be the most common cancer in women aged 35 to 64 years [2].

Breast cancer is a heterogeneous disease. Microarray expression data provide the most comprehensive information for breast cancer molecular characterization, but it is impractical for use in the clinical setting [3-5]. Therefore, immunohistochemistry (IHC) is used to categorize tumors into subtypes based on positive or negative status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [6]. These tumor characteristics have been shown to be important prognostic factors [6]. In particular, ER expression status is a key prognostic factor, with lower expression corresponding to a higher risk score [7].

Hormone therapy and trastuzumab have been shown to improve outcomes in patients with ER-positive disease and HER2-positive (HER2+) disease, respectively [8, 9]. ER positivity, as determined by IHC, is used to determine whether a patient will benefit from hormone therapy because, as mentioned above, intrinsic subtyping by microarray expression data cannot be used in the clinical setting. However, patients with primary breast cancers with borderline or low estrogen receptor expression (ER-Low), IHC 1% to 10%, may be less likely to respond to hormone therapy and have a similar prognosis to patients with hormone triple-negative breast cancer (TNBC), particularly with regard to HER2-negative (HER2−) disease [7, 10, 11].

Recently, the American Society of Clinical Oncology/College of American Pathologists updated their recommendations for reporting of ER status: “if 1 to 10% of tumor cell nuclei are immunoreactive, the sample should be reported as ER Low Positive with a recommended comment” [12]. Determining the specific ER value threshold at which hormone therapy provides a benefit has been difficult because the magnitude of benefit is more limited at lower ER expression levels [11].

Data on the prevalence of ER-Low tumor status among patients with breast cancer and their response to hormone therapy and clinical outcomes are limited [7, 10, 13-15]. We conducted a retrospective, noninterventional database study to examine the prevalence, clinicopathological characteristics, treatments, and outcomes according to ER expression levels (ER-High, ER-Low, and ER−) and HER2 status for Korean patients with invasive ductal or lobular breast cancer who underwent surgery with curative intent.

Methods

Study Population and Design

In this retrospective, noninterventional database study, data were collected from patients diagnosed with invasive breast cancer and treated at Samsung Medical Center (SMC), Seoul, South Korea. Patients underwent surgery with curative intent between January 2003 and December 2012. Patients were excluded if they received neoadjuvant chemotherapy, had distant metastases or inflammatory breast cancer on presentation, or other histopathology except invasive ductal or lobular carcinoma. Patients without IHC data (ER, PR, HER2, and Ki-67) or who were lost to follow-up within the first 12 months after surgery were also excluded. Up to 10 years of follow-up data were analyzed. Data were previously collected by researchers at SMC from electronic medical records and the Korean National Statistical Office. Because this was a noninterventional retrospective study of a de-identified database, no informed consent was involved. SMC’s institutional review board reviewed the study.

Categorization of Breast Cancer Subtypes

Breast cancer molecular subtype is reported according to ER/HER2 status, with ER further classified as “high” or “low.” Only ER status was used in this analysis (PR status was not considered for determination of ER-Low vs ER-High); therefore, patients classified as HR+ due to being PR+ alone were not represented in the results that were stratified by ER-Low/High status.

Estrogen receptor status was based on the Allred Proportion Score (APS), which is a categorical measure of the percentage of cells that are immunoreactive. The Allred Total Score is a composite score indicating the strength of estrogen positivity by combining the percentage of cells that stain IHC ER on a scale of 0 to 5, and the intensity of staining (intensity score), on a scale of 0 to 3, for a possible total score ranging from 0 to 8. Patients were categorized by their proportion score only, as follows: ER-negative: APS = 0 or 1; ER-Low: APS = 2; ER-High: APS ≥3 (**Table S1**) [16]. HER2 testing was conducted using immunohistochemistry (**Table S2**) [16]. Of note, a score of 2+ required an in situ hybridization test of the same specimen or a new test of a new specimen, if available, using either immunohistochemistry or in situ hybridization.

Epidemiologic Assessments and Outcomes

The primary objective was to evaluate the distribution of molecular subtypes, particularly ER-Low versus ER-High, as well as describing the baseline demographic, clinical, tumor characteristics, and treatments in the breast cancer population. In addition, both disease-free survival (DFS) and overall survival (OS) were included as clinical outcomes. DFS was defined as the time from surgery to the date of the first of either a disease recurrence event documented in the patient’s chart, second cancer, death, or censored as of December 31, 2017. OS was defined as the time from surgery until death due to any cause or censored as of December 31, 2017. First-line treatments by subtype were reported as hormone, chemotherapy, and radiation.

Statistical Analysis

Descriptive statistics were generated, including mean, median, minimum, and maximum values for continuous variables and frequencies and relative frequencies for categorical variables, overall and by cohort. Breast cancer cohorts were reported as proportions of the full analytical sample according to ER/HER2 status. Exploratory univariate analyses were conducted using Cox proportional hazard regression to identify factors potentially associated with survival endpoints. Point estimates for DFS and OS, along with 95% CIs, were reported overall and by cohort. DFS and OS were estimated according to the Kaplan-Meier method and compared among groups by log-rank test.

Results

Patient Demographics and Baseline Clinical Characteristics

A total of 5930 patients met the criteria to be included in the study. At diagnosis, 2798 (47.2%) were diagnosed with stage I disease, 2426 (40.9%) with stage II disease, and 701 (11.8%) with stage III disease (**Table 1)**. Among the total population, 748 (12.6%) had TNBC, 394 (6.6%) had ER−/HER2+ tumors, 4314 (72.7%) had ER+/HER2− tumors, and 474 (8.0%) had ER+/HER2+ tumors (**Table 1)**. There were 117 (2.0%) patients with ER-Low tumors; of that cohort, 63 (53.8%) patients had HER2− tumors and 54 (46.2%) had HER2+ tumors. Examination of Ki-67 showed a higher percentage with Ki-67 ≥14 in the ER-Low/HER2− (n = 54; 90.0%) cohort than in the ER-High/HER2− cohort (n = 1715; 43.3%). Patients in the TNBC cohort had a similar proportion with Ki-67 ≥14 as the ER-Low/HER2− cohort (n = 653; 92.2%). Similarly, patients in the ER-Low/HER2− cohort had a higher incidence of BRCA1/2 mutations (n = 2; 3.2% and n = 1; 1.6%, respectively) than patients in the ER-High/HER2− cohort (n = 4; 0.1% and n = 44; 1.0%), comparable to patients with TNBC tumors (n = 32; 4.3% and n = 8; 1.1%). Median follow-up time, defined as time from surgery until death due to any cause or censored as of December 31, 2017, across the entire cohort was 80.9 months (interquartile range, 35.3).

Among 5913 patients with complete information on adjuvant treatment, patients with ER-Low/HER2− tumors were more likely to receive adjuvant chemotherapy-based treatment, including trastuzumab, than patients with ER-High/HER2− tumors (59/63; 93.7% vs 2458/4240; 58.0%) and as likely as patients with TNBC (690/746; 92.5%; **Table 2**). Adjuvant hormone therapy, either alone or in combination, was prescribed more often in patients with ER-High/HER2− tumors (4200/4240; 99.1%) than in patients with ER-Low/HER2− tumors (58/63; 92.1%) (**Table 2**), while similar results were observed in patients with ER+/HER2− and ER+/HER2+ tumors (4258/4303; 99.0% vs 464/472; 98.3%, respectively).

5-Year Disease-Free Survival and Overall Survival Rates

Among all patients, the 5-year DFS rate was 91.7% (**Table 3)**. The highest 5-year DFS rate was in patients in the ER-High/HER2− cohort (94.0%), and the lowest 5-year DFS rates were in patients in the TNBC cohort (81.3%) and the ER-Low/HER2− cohort (85.7%). Kaplan-Meier analysis of DFS by molecular subtype is presented in **Figure 1A**.

Overall, 5763 patients survived 5 years (97.2%). The highest rate was again in the ER-High/HER2− cohort (98.6%), and the lowest rates were in the TNBC cohort (90.1%) and the ER-Low/HER2− cohort (92.1%; **Table 3**). Kaplan-Meier analysis of OS by molecular subtype is presented in **Figure 1B**).

Potential Prognostic Factors for OS and DFS

To evaluate potential prognostic factors, univariate analyses were performed for DFS and OS. TNBC and ER-Low/HER2− were grouped together (n = 811) and analyzed along with the overall cohort and ER-High/HER2− cohort. Significant potential prognostic factors for the overall cohort associated with shorter DFS

and OS were postmenopausal status, elevated Ki-67, higher nuclear grade, higher American Joint Committee on Cancer (AJCC) tumor stage, lymphovascular invasion, greater regional lymph node involvement, and larger tumor size (**Tables 4 & 5**). Older age was also a significant prognostic factor for shorter OS (**Table 5**). The significant prognostic factors associated with shorter DFS for the TNBC + ER-Low/HER2− combined cohorts were higher AJCC tumor stage, lymphovascular invasion, greater regional lymph node involvement (4-9 vs. 0 only), and larger tumor size, and for the ER-High/HER2− cohort were elevated Ki-67, higher nuclear grade, higher AJCC tumor stage, lymphovascular invasion, greater regional lymph node involvement, larger tumor size, and multifocal tumors (**Table 4**). These results were similar for OS, with more characteristics being significant prognostic factors in the ER-High/HER2− cohort than in the TNBC + ER-Low/HER2− group (**Table 5**).

Discussion

Treatment decisions regarding hormone therapy and chemotherapy are difficult to make in patients with low ER breast cancer. Microarray expression-based intrinsic subtyping of breast cancer is not feasible in clinical practice at this time, and published data on outcomes in this specific subset of breast cancer patients are limited. Therefore, this analysis aimed to investigate the natural disease course of patients with low ER breast cancer and identify potential prognostic clinicopathological characteristics to help guide appropriate stratification and provide insight to determine the best treatment options.

The majority of patients in our study were diagnosed as having ER+/HER2− tumors. Only 117 patients, 2% of the total and 2.4% of ER+ tumors, had ER-Low tumors as determined by APS. This is consistent with other studies [17-22] and a meta-analysis [15] that found a similarly low percentage of patients with ER-Low tumors. In the largest published individual study (N=9639), Yi et al. found that 250 patients (2.6%) had ER-Low tumors [10], and in the meta-analysis, a rate of 5% (834/16,606) was reported [15]. Although patients with ER-Low tumors may make up a small percentage of the overall population, these patients may benefit from treatment plans tailored to their specific subset of disease characteristics. These patients were not recognized as a breast cancer subgroup until recently; therefore, their response to hormone-based treatment and prognosis have not been widely reported [12].

Several differences in adjuvant treatment regimens were observed across our study cohorts. Adjuvant chemotherapy-based treatment, for example, was received by the vast majority of patients (92%-94%) with ER-Low/HER2− tumors and TNBC, compared with only slightly more than half of patients with ER-High/HER2− tumors. These trends are similar to those previously reported [15] and follow current treatment guidelines [23, 24]. Another difference in treatment regimens was that most patients (92%-93%) with ER-Low tumors received hormone-based adjuvant therapy, compared with few patients with ER− and TNBC tumors (<10%). Interestingly, a systematic review and meta-analysis of a small number of studies found that hormone therapy did not have a significant effect on the 5-year OS rate in patients with ER-Low tumors [15]. While relapse-free survival and DFS were higher in patients who received hormone therapy, the differences were not significant. Further research is needed to determine whether patients with ER-Low tumors may benefit from hormone therapy, perhaps based on other prognostic factors or further stratification within the ER-Low category. If studies of this specific subset of patients show that no clinical benefit is derived from hormone therapy, it may suggest patients should be treated similarly to TNBC.

In our study, univariate analysis identified several potential prognostic factors for shorter DFS and OS. The TNBC and ER-Low/HER2− cohorts were combined for this analysis. Significant characteristics associated with both shorter DFS and OS in this subgroup were higher AJCC tumor stage, lymphovascular invasion, greater regional lymph node involvement, and larger tumor size. Results were generally similar in the ER-High/HER2− cohort, with elevated Ki-67 and higher nuclear grade also achieving significance. Multivariate analysis was not performed due to the small sample size. This analysis, by molecular subtype, of various clinicopathological characteristics as potential prognostic factors has not been widely explored in patients with tumors classified as ER-Low. Although several previous epidemiological studies have reported similar predictors of decreased DFS and OS [25-27], they did not differentiate between patients with ER-Low and ER-High tumors.

Given the similarities of clinical characteristics between TNBC and ER-Low/HER2−, our data suggest that patients with ER-Low/HER2− tumors may benefit from being managed similarly to patients with TNBC. DFS and OS in the ER-Low/HER2− cohort were more similar to the TNBC cohort than those with ER-High/HER2− tumors, which is consistent with previous findings [10, 13, 18, 21]. Landmann, et al. recently concluded that ER-Low tumors are biologically distinct from ER-High tumors, and that patients with ER-Low tumors had similar DFS and OS to a population of patients with predominantly TNBC [18]. The ER-Low molecular subtype needs to be more finely stratified than the current guidance in order to optimize treatment based on the biological characteristics of a patient's tumor type. Lovejoy et al. showed that the mutation frequency and array of mutated genes did not differ between patients with ER-Low/HER2− tumors and those with TNBC, suggesting patients with ER-Low tumors should be eligible for germline testing to assist in determination of treatment course [19]. In our study, patients with ER-Low/HER2− tumors had a similar incidence of mutation in BRCA1/2 as patients with TNBC, suggesting that more consistent BRCA1/2 testing should be implemented in the former group. Taken together, these findings support the recent guideline updates by both ASCO and ESMO specifying that cancers with low ER expression, 1–10%, should be classified as 'low ER.' ESMO further suggests that patients with low ER (1–10% positive cells), progesterone-positive, and HER2− should be considered as patients with TNBC [12, 28].

Aspects of this study that may limit interpretation of the findings include the retrospective design, single-center experience, and variability of the clinical data (eg, heterogeneity of treatment regimens, availability and completeness of treatment response and date of progression, and consistency of follow-up schedules). Additionally, this cohort of patients, who underwent surgery with curative intent, may have a more favorable prognosis than patients with the same molecular subtype at large due to the nature of the initial prognosis. Patients were required to have at least 12 months of follow-up post-surgery, which may have introduced bias for favorable outcomes and thereby overestimated survival outcomes. Descriptive comparisons of clinical outcomes by molecular subtype must be carefully considered as other factors may influence outcomes.

In summary, patients with ER-Low/HER2− breast cancer had similar clinicopathological characteristics, initial treatments, and outcomes as patients with TNBC. Further research is needed to investigate hormone responsiveness and prognosis in patients with ER-Low/HER2− disease.

Declarations

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Conflicts of interest/Competing interests: Yeon Hee Park: Consultancy or advisory board member for AstraZeneca, Pfizer, Eisai, Roche, and Novartis Pharmaceuticals. Research funding from AstraZeneca, Merck, Pfizer, Novartis, Alteogen, and Roche.

Vassiliki Karantza: Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and owns stock in Merck & Co., Inc., Kenilworth, NJ, USA

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Mark Marsico: Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and owns stock in Merck & Co., Inc., Kenilworth, NJ, USA

Availability of data and material: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Code availability: Not applicable

Author contributions: Yeon Hee Park, Vassiliki Karantza, Shawna Calhoun, Jeong Eon Lee, Gursel Aktan, and Mark Marsico were involved in the conception, design or planning of the study.

Gursel Aktan and Mark Marsico were involved in the analysis of the data.

Yeon Hee Park, Shawna Calhoun, Seri Park, Sohee Lee, Ji-Yeon Kim, Jong Han Yu, Seok Won Kim, Jeong Eon Lee, Seok Jin Nam, and Mark Marsico were involved in acquisition of the data.

Yeon Hee Park, Vassiliki Karantza, Shawna Calhoun, Seok Jin Nam, Gursel Aktan, and Mark Marsico were involved in interpretation of the results.

Yeon Hee Park, Gursel Aktan, and Mark Marsico were involved in drafting the manuscript.

All authors reviewed or revised the manuscript for important intellectual content, approved the final version of the manuscript, and are accountable for the work.

Other contributions included provision of study materials/patients (Jong Han Yu, Seok Won Kim, and Jeong Eon Lee) and administrative, logistical or technical support (Shawna Calhoun and Mark Marsico).

Ethics approval: Data were previously collected by researchers at Samsung Medical Center (SMC) from electronic medical records and the Korean National Statistical Office. SMC's institutional review board reviewed the study.

Consent to participate: Because this was a noninterventional retrospective study of a de-identified database, no informed consent was involved.

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Tables

Table 1. Clinical Characteristics at Diagnosis

Category, n (%)	Overall (N = 5930)	ER−/HER2+ (N = 394)	TNBC[a] (N = 748)	ER+/HER2− (N = 4314)	
				ER-Low (N = 63)	ER-Hig (N = 42
Age, years					
<65	5479 (92.4)	361 (91.6)	674 (90.1)	61 (96.8)	3935 (92.6)
≥65	451 (7.6)	33 (8.4)	74 (9.9)	2 (3.2)	316 (7.4)
Menopausal status					
Postmenopausal	2300 (38.8)	215 (54.6)	330 (44.1)	24 (38.1)	1532 (
Premenopausal	3515 (59.3)	164 (41.6)	399 (53.3)	36 (57.1)	2652 (
Pregnancy	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Oophorectomy(total hysterectomy)	110 (1.9)	14 (3.6)	19 (2.5)	3 (4.8)	64 (1.5
Unknown	4 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.0)
gBRCA1					
Not detected	476 (8.0)	23 (5.8)	66 (8.8)	5 (7.9)	352 (8.
Detected	41 (0.7)	2 (0.5)	32 (4.3)	2 (3.2)	4 (0.1)
Equivocal (VUS)	56 (0.9)	0 (0.0)	10 (1.3)	3 (4.8)	38 (0.9
Unknown	5357 (90.3)	369 (93.7)	640 (85.6)	53 (84.1)	3857 (
gBRCA2					
Not detected	414 (7.0)	19 (4.8)	79 (10.6)	6 (9.5)	283 (6.
Detected	56 (0.9)	2 (0.5)	8 (1.1)	1 (1.6)	44 (1.0
Equivocal (VUS)	102 (1.7)	3 (0.8)	18 (2.4)	3 (4.8)	69 (1.6
Unknown	5358 (90.4)	370 (93.9)	643 (86.0)	53 (84.1)	3855 (
Ki-67					
<14	2393 (43.0)	25 (6.6)	55 (7.8)	6 (10.0)	2246 (
≥14	3167 (57.0)	355 (93.4)	653 (92.2)	54 (90.0)	1715 (
Nuclear grade					
Low	1099 (18.5)	4 (1.0)	13 (1.7)	2 (3.2)	1074 (
Intermediate	3023 (51.0)	107 (27.2)	137 (18.3)	9 (14.3)	2557 (
High	1785 (30.1)	283 (71.8)	587 (78.5)	50 (79.4)	613 (1
Unknown	23 (0.4)	0 (0.0)	11 (1.5)	2 (3.2)	7 (0.2)
Lymphovascular invasion					
Not identified	4017 (67.7)	276 (70.1)	528 (70.6)	46 (73.0)	2883 (
Present	1869 (31.5)	115 (29.2)	209 (27.9)	16 (25.4)	1343 (
Unknown	44 (0.7)	3 (0.8)	11 (1.5)	1 (1.6)	25 (0.6
Multiplicity					
Not multifocal tumor	4583 (77.3)	289 (73.4)	645 (86.2)	52 (82.5)	3230 (
Multifocal tumor	1347 (22.7)	105 (26.6)	103 (13.8)	11 (17.5)	1021 (
AJCC stage					
I	2798 (47.2)	164 (41.6)	283 (37.8)	21 (33.3)	2121 (

II	2426 (40.9)	174 (44.2)	400 (53.5)	37 (58.7)	1617 (
III	701 (11.8)	56 (14.2)	65 (8.7)	5 (7.9)	508 (1
Unknown	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)
Tumor size stage					
DCIS, LCIS	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
~2 cm	3558 (60.0)	224 (56.9)	353 (47.2)	29 (46.0)	2680 (
2.1–5 cm	2111 (35.6)	154 (39.1)	364 (48.7)	33 (52.4)	1378 (
≥5.1cm	242 (4.1)	15 (3.8)	27 (3.6)	1 (1.6)	183 (4.
Including chest wall, skin, pectoralis muscle inflammatory	8 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	7 (0.2)
Unknown	9 (0.2)	0 (0.0)	4 (0.5)	0 (0.0)	2 (0.0)
Tumor size (cm), median (IQR)	1.8 (1.3)	1.8 (1.6)	2.1 (1.3)	2.1 (1.0)	1.6 (1.
Regional lymph nodes stage					
0	3644 (61.5)	239 (60.7)	504 (67.4)	40 (63.5)	2586 (
1–3	1653 (27.9)	106 (26.9)	183 (24.5)	19 (30.2)	1205 (
4–9	400 (6.7)	33 (8.4)	33 (4.4)	3 (4.8)	293 (6.
>10	228 (3.8)	16 (4.1)	28 (3.7)	1 (1.6)	162 (3.
Unknown	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)
Surgery type					
Modified radical mastectomy (Total mastectomy)	1687 (28.4)	172 (43.7)	147 (19.7)	16 (25.4)	1176 (
Breast-conserving surgery (Partial mastectomy)	4200 (70.8)	221 (56.1)	592 (79.1)	47 (74.6)	3048 (
Biopsy	43 (0.7)	1 (0.3)	9 (1.2)	0 (0.0)	27 (0.6

Abbreviations: AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor; IQR, interquartile range; LCIS, lobular carcinoma in situ; TNBC, triple-negative breast cancer; VUS, variant of unknown significance.

[a]TNBC defined according to individual estrogen receptor, progesterone receptor, and HER2 status.

Table 2. Adjuvant Treatment Characteristics

Treatment, n (%)	|Overall (N = 5913)[a]	ER−/HER2+ (N = 392)	TNBC[b] (N = 746)	ER+/HER2− (N = 4303)		ER+/HER2+ (N = 472)	
				ER-Low (N = 63)	ER-High (N = 4240)	ER-Low (N = 54)	ER-High (N = 418)
Treatment combination (mutually exclusive)							
Chemotherapy only	216 (3.7)	93 (23.7)	104 (13.9)	4 (6.3)	11 (0.3)	2 (3.7)	2 (0.5)
Radiation only	57 (1.0)	18 (4.6)	33 (4.4)	0 (0.0)	5 (0.1)	1 (1.9)	0 (0.0)
Hormone therapy only	372 (6.3)	4 (1.0)	2 (0.3)	1 (1.6)	340 (8.0)	3 (5.6)	22 (5.3)
Combination of chemotherapy,[c] radiation, and hormone therapy	2359 (39.9)	16 (4.1)	33 (4.4)	47 (74.6)	1950 (46.0)	30 (55.6)	283 (67.7)
Combination of chemotherapy[c] and hormone therapy	617 (10.4)	10 (2.6)	6 (0.8)	7 (11.1)	492 (11.6)	15 (27.8)	87 (20.8)
Combination of radiation and hormone therapy	1454 (24.6)	6 (1.5)	3 (0.4)	3 (4.8)	1418 (33.4)	2 (3.7)	22 (5.3)
Combination of chemotherapy[c] and radiation therapy	774 (13.1)	219 (55.9)	547 (73.3)	1 (1.6)	5 (0.1)	1 (1.9)	1 (0.2)
No treatment	64 (1.1)	26 (6.6)	18 (2.4)	0 (0.0)	19 (0.4)	0 (0.0)	1 (0.2)
Treatment type (not mutually exclusive)							
Adjuvant chemotherapy	3964 (67.0)	337 (86.0)	690 (92.5)	59 (93.7)	2458 (58.0)	48 (88.9)	372 (89.0)
Trastuzumab	879 (14.9)	305 (77.8)	28 (3.8)	7 (11.1)	153 (3.6)	45 (83.3)	341 (81.6)
Adjuvant radiotherapy	4644 (78.5)	259 (66.1)	616 (82.6)	51 (81.0)	3378 (79.7)	34 (63.0)	306 (73.2)
Adjuvant hormone therapy	4802 (81.2)	36 (9.2)	44 (5.9)	58 (92.1)	4200 (99.1)	50 (92.6)	414 (99.0)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor; TNBC, triple-negative breast cancer.

[a]Excludes patients with missing information on adjuvant chemotherapy, radiotherapy, hormone, or trastuzumab therapy.

[b]TNBC defined according to individual estrogen receptor, progesterone receptor, and HER2 status.

[c]Includes use of adjuvant chemotherapy or trastuzumab.

Table 3. 5-Year Disease-Free and Overall Survival

Outcome, n (%)	Overall (N = 5930)	ER−/HER2+ (N = 394)	TNBC[a] (N = 748)	ER+/HER2− (N = 4314)		ER+/HER2+ (N = 474)	
				ER-Low (N = 63)	ER-High (N = 4251)	ER-Low (N = 54)	ER-High (N = 420)
DFS[b]	5438 (91.7)	344 (87.3)	608 (81.3)	54 (85.7)	3997 (94.0)	49 (90.7)	386 (91.9)
OS[c]	5763 (97.2)	374 (94.9)	674 (90.1)	58 (92.1)	4193 (98.6)	53 (98.1)	411 (97.9)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor; TNBC, triple-negative breast cancer.

[a]TNBC defined according to individual estrogen receptor, progesterone receptor, and HER2 status.

[b]DFS defined as the length of time from surgery to the date of the first of either a disease recurrence event documented in the patient's chart, second cancer, or death.

[c]OS defined as the length of time from surgery until death for any cause.

Table 4. Univariate Analyses of Disease-Free Survival for Identification of Potential Prognostic Factors

Baseline Variables	Overall (N = 5930)		TNBC[a] + ER-Low/HER2− (N = 811)		ER-High/HER2− (N = 4251)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years						
≥65 vs <65	1.27 (0.96–1.66)	0.090	0.98 (0.58–1.63)	0.928	1.27 (0.88–1.84)	0.206
Menopausal status						
Postmenopausal vs premenopausal	1.19 (1.01–1.40)	0.037	1.07 (0.79–1.45)	0.667	1.18 (0.95–1.47)	0.141
Ki-67						
≥14 vs <14	2.45 (2.02–2.98)	<0.001	1.17 (0.63–2.16)	0.620	2.29 (1.83–2.88)	<0.001
Nuclear grade						
High vs intermediate	1.79 (1.52–2.11)	<0.001	1.08 (0.73–1.60)	0.710	1.80 (1.41–2.30)	<0.001
Low vs intermediate	0.44 (0.32–0.60)	<0.001	0.59 (0.14–2.45)	0.464	0.47 (0.34–0.65)	<0.001
AJCC stage						
III vs II	2.01 (1.65–2.46)	<0.001	1.90 (1.23–2.94)	0.004	2.36 (1.82–3.06)	<0.001
Lymphovascular invasion						
Present vs not present	2.26 (1.93–2.65)	<0.001	2.43 (1.79–3.29)	<0.001	2.46 (1.99–3.04)	<0.001
Regional lymph nodes stage						
1–3 vs. 0	1.46 (1.22–1.76)	<0.001	1.37 (0.97–1.94)	0.073	1.66 (1.30–2.13)	<0.001
4–9 vs. 0	2.24 (1.72–2.92)	<0.001	2.92 (1.74–4.88)	<0.001	2.47 (1.73–3.52)	<0.001
>10 vs. 0	4.58 (3.54–5.92)	<0.001	1.61 (0.78–3.30)	0.198	6.58 (4.79–9.04)	<0.001
Tumor size, cm						
≥5.1 vs 2.1–5	1.73 (1.29–2.31)	<0.001	2.49 (1.36–4.56)	0.003	1.83 (1.27–2.62)	0.001
Multiplicity						
Multifocal vs not multifocal	1.16 (0.97–1.39)	0.113	1.07 (0.70–1.63)	0.772	1.31 (1.04–1.66)	0.025

Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor; HR, hazard ratio; TNBC, triple-negative breast cancer.

[a]TNBC defined according to individual estrogen receptor, progesterone receptor, and HER2 status.

Table 5. Univariate Analyses of Overall Survival for Identification of Potential Prognostic Factors

Subgroups	Overall (N = 5930)		TNBC[a] + ER-Low/HER2− (N = 811)		ER-High/HER2− (N = 4251)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years						
≥65 vs <65	2.34 (1.64–3.34)	<0.001	1.26 (0.67–2.35)	0.479	3.20 (1.91–5.35)	<0.001
Menopausal status						
Postmenopausal vs premenopausal	1.77 (1.35–2.31)	<0.001	1.26 (0.83–1.90)	0.272	2.00 (1.31–3.04)	0.001
Ki-67						
≥14 vs <14	3.33 (2.33–4.76)	<0.001	1.13 (0.49–2.59)	0.778	2.39 (1.53–3.72)	<0.001
Nuclear grade						
High vs intermediate	2.82 (2.13–3.73)	<0.001	1.56 (0.85–2.86)	0.154	2.40 (1.52–3.80)	<0.001
Low vs intermediate	0.45 (0.25–0.80)	0.007	0.78 (0.10–6.02)	0.813	0.56 (0.30–1.06)	0.075
AJCC stage						
III vs II	2.37 (1.76–3.20)	<0.001	2.35 (1.41–3.93)	0.001	3.31 (2.09–5.23)	<0.001
Lymphovascular invasion						
Present vs. not present	2.58 (1.99–3.36)	<0.001	3.17 (2.10–4.77)	<0.001	2.28 (1.51–3.44)	<0.001
Regional lymph nodes stage						
1–3 vs. 0	1.98 (1.45–2.70)	<0.001	2.15 (1.37–3.38)	0.001	2.20 (1.31–3.70)	0.003
4-9 vs. 0	4.02 (2.73–5.91)	<0.001	4.94 (2.65–9.18)	<0.001	5.34 (2.92–9.76)	<0.001
>10 vs. 0	5.80 (3.82–8.79)	<0.001	2.71 (1.15–6.36)	0.022	9.635 (5.27–17.59)	<0.001
Tumor size, cm						
≥5.1 vs 2.1–5	1.81 (1.17–2.81)	0.008	2.69 (1.33–5.44)	0.006	1.79 (0.93–3.45)	0.083
Multiplicity						
Multifocal vs not multifocal	1.04 (0.76–1.42)	0.819	0.89 (0.49–1.64)	0.718	1.30 (0.82–2.06)	0.263

Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor; HR, hazard ratio; TNBC, triple-negative breast cancer.

[a]TNBC defined according to individual estrogen receptor, progesterone receptor, and HER2 status.

Figures

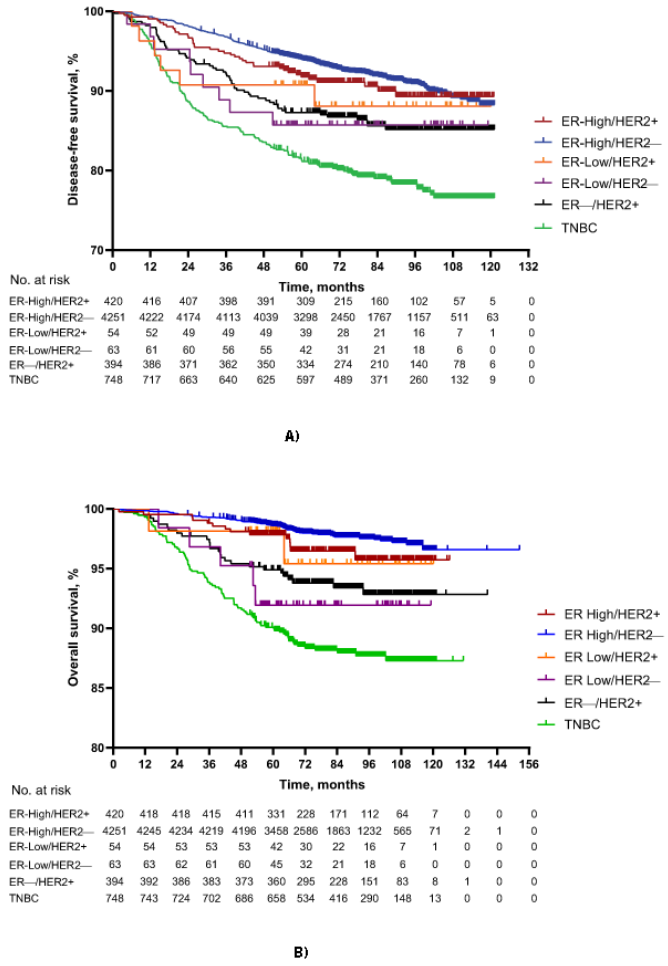

Figure 1

Kaplan-Meier Estimates of Disease-Free Survival and Overall Survival by Molecular Subtype (N = 5930). Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor; TNBC, triple-negative breast cancer. (a) Disease-Free Survival by Molecular Subtype; (b) Overall Survival by Molecular Subtype

Supplementary Files

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