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Clinical and biomarker predictors of early and late recurrence in hormone receptor-positive breast cancer

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Research article

Title: Clinical and Biomarker Predictors of Early and Late Recurrence in Hormone Receptor-Positive Breast Cancer

Running head: Clinical predictors of recurrence in breast cancer

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Abstract

Background: Hormone receptor-positive (HR+) breast cancer (BC) is characterized by a persistent risk of recurrence that continues for decades. Although many factors have been linked to recurrence, the clinical features associated with late relapse and patterns of distant metastases are less understood. Our study aimed to identify factors associated with early (<5 years) and late (5-10 years) recurrence in a real-world cohort of HR+/human epidermal growth factor receptor type2-negative (HER2-) BC patients.

Methods: Our study performed a retrospective analysis of stage I-III HR+/HER2- BC cases diagnosed between 1981-2022. Assessed variables included metastatic sites, early and late invasive recurrences.

Results: A total of 4,367 women with HR+/HER2- were included; 81.2% were stage I/II, 41,4% had nodal involvement; 42.0% received neoadjuvant chemotherapy and 94.0% adjuvant endocrine therapy (ET). Five- and ten-year invasive disease-free survival (iDFS) rates were 85.0% and 70.0%, respectively. Of the 847 invasive events (19.4%), 54.3% were early and 45.7% late recurrences. Compared with late recurrences, early recurrences were associated with fewer stage I tumors, higher nodal involvement, higher grade, and elevated Ki-67. In multivariate analysis, higher stage was the only independent factor linked to both early and late recurrence; older age correlated with late relapse. Distant metastases occurred in 70.2% of recurrences and were associated with higher tumor burden, grade 3, and elevated Ki-67; 47.5% involved visceral sites.

Conclusion: Late recurrences may occur even in patients clinically classified as low risk. Early recurrences reflect higher tumor burden and proliferative activity, with implications for treatment and follow-up strategies

Keywords: Breast neoplasm, prognosis, treatment outcome, recurrence, hormone receptor

Background

Localized hormone receptor-positive (HR+) breast cancer (BC) carries a persistent risk of recurrence after treatment [1], with over half of recurrences occurring more than five years after diagnosis [2]. This risk extends beyond 20 years, with 15 year-recurrence rates ranging from 13% to 41%, after 5-year adjuvant endocrine therapy (ET) [1]. However, the underlying mechanisms for micro metastatic

dormancy and re-activation remain unknown [3]. Clinical factors and prognostic biomarkers can identify high-risk patients that may benefit from specific treatment strategies, such as extended ET [4], or adjuvant cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors [5,6]. In this context, widely available biomarkers such as Ki-67 and histological grade (HG), have proven useful for risk stratification and therapeutic decision-making [7].

Nevertheless, there is growing interest in further refining the assessment of late recurrence risk, given the toxicity profiles and quality-of-life implications of prolonged therapies [8]. Improving our understanding and characterization of accessible clinico-pathological factors, along with these key biomarkers, and their association with early and late recurrence is of critical importance. This knowledge could facilitate better prognostication, enable more individualized treatment strategies, and ultimately inform the development of optimal long-term surveillance protocols.

Historically, 5-year ET has been the cornerstone of systemic treatment in early HR+ BC. The selective estrogen receptor (ER) modulator tamoxifen has been shown to reduce recurrence risk by almost half during the first five years after diagnosis and by approximately one-third over the subsequent five years, while also reducing BC mortality by nearly one-third over the first 15 years [9]. In postmenopausal women, aromatase inhibitors (AIs) have demonstrated further reductions in recurrence and mortality risks by 30% and 15%, respectively, versus tamoxifen [10]. Moreover, early studies such as the aTTom and ATLAS trials have also confirmed a survival benefit by extended tamoxifen [11,12]. More recently, trials using extended AI have shown further improvements in disease-free survival (DFS) in postmenopausal women, albeit with substantial non-adherence and significant adverse effects [13–15]. As a result, current consensus recommends maintaining adjuvant ET (tamoxifen or AI) plus ovarian function suppression for premenopausal women, for five years in lower-risk patients with stage I disease, and up to ten years for stage III disease. For stage II patients, the recommended duration varies between 7 and 8 years, depending on nodal involvement, and up to ten years for very high-risk patients [16]. Additionally, CDK4/6 inhibitors, namely ribociclib and abemaciclib, have further reduced recurrence risk with a carry-on effect after 2-3 years of therapy for intermediate and high-risk patients, with recent data even confirming an overall survival benefit among those patients with the highest risk [17,18].

Previously, the Clinical Treatment Score 5 (CTS5), a prognostic tool, was validated as a predictive model for late recurrence (≥ 5y) in postmenopausal patients [19]. However, data addressing late distant metastatic recurrence, specifically distinguishing between visceral and non-visceral disease, remains limited. In recent years, molecular assays such as the Breast Cancer Index (BCI) and the Molecular Grade Index (MGI) have emerged as promising risk stratification tools, demonstrating prognostic and predictive capacity for late recurrence in early-stage HR+ BC. Notably, when assessed after 5-year ET, BCI can estimate the likelihood of benefit from extended therapy, thereby helping to identify patients who may safely discontinue treatment versus those who may benefit from continued ET [20,21]. Unfortunately, limited access and high costs have hindered the widespread implementation of genomic predictive tools, especially in low- and middle-income countries. On the other hand, most predictive models have been validated using phase III trial populations usually from high-income settings, which may not adequately reflect the patient populations and resource constraints of more diverse healthcare systems. Consequently, there remains an unmet need to develop accessible and broadly applicable tools to identify patients at risk for distant recurrence.

Herein, we assess the predictive value of clinico-pathological characteristics by comparing early versus late recurrence patients. We also characterize differences in locoregional and distant metastatic disease patterns.

Methods

Patient Cohort

Clinicopathological data were retrieved from a prospectively maintained institutional database containing treatment and outcomes information for stage I-III HR+/epidermal growth factor receptor 2-negative (HER2-) BC patients diagnosed between January 1981 and December 2022. Patients were treated at four cancer centers in Santiago, Chile; HG, ER, progesterone receptor (PR), and HER2 expression were extracted from pathology reports. Tumor staging was determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) Manual [22]. ER positivity was defined as ≥1% staining on immunohistochemistry (IHC), and similarly, PR positivity was defined as ≥1% staining on IHC, following the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP)

guidelines [23]. Tumor size/T-stage, quantitative ER/PR, and histologic subtype were not uniformly available across the entire study period. Whenever available, Ki-67 values were recorded as a continuous value. Treatment was indicated according to standard clinical practices. ET use was registered as "recommended/indicated". Additional data on ET type (tamoxifen or aromatase inhibitors), duration, adherence, ovarian function suppression, switching strategies, or early discontinuation were inconsistent/incomplete across the study period and therefore were not analyzed. Recurrence events were required to occur at least six months after completion of local therapy to avoid misclassification of metastatic patients at diagnosis.

Endpoints

Invasive DFS (iDFS) was defined according to STEEP 2.0 criteria [24]. Early recurrence was defined as the occurrence of invasive recurrent disease between 6 and <60 months after diagnosis, to avoid including misclassified metastatic patients, and late recurrence was defined as invasive disease recurrence ≥60 months after initial diagnosis until 120 months (10 years). Distant recurrence-free survival (DRFS) was defined as the time from diagnosis to the first occurrence of distant metastasis. Metastatic sites were classified as follows: liver, lung, and brain metastases were defined as visceral recurrence, while bone, serous membranes, skin, and distant lymph nodes were considered non-visceral metastases.

Statistical Methods

Descriptive statistics were used to summarize demographic, clinical, and pathological characteristics of the entire cohort, as well as 10-year iDFS, and to compare clinico-pathological features of patients with early versus late recurrence and those who developed distant metastasis. Univariate and multivariate logistic regression models were applied to assess which clinico-pathological variables were associated with early or late recurrence. Variables with a p-value <0.05 in univariate analyses were included in the multivariate models. Considering AJCC clinical stage (I–III) incorporates both tumor extent and nodal status, stage and lymph node involvement were not entered simultaneously. Clinical stage was retained in the final multivariate models as the primary measure of baseline disease burden due to its standard clinical use and interpretability. Survival analyses were performed using the Kaplan-Meier method. All p-values

were two-sided, and statistical significance was set at $p<0.05$. To evaluate late recurrence conditional on surviving the initial high-risk period, we performed a prespecified 5-year landmark analysis. Only patients who remained alive and free of any invasive recurrence at 60 months after diagnosis were included. Time-to-event calculations were re-anchored at the 5-year mark, and cumulative invasive recurrence was estimated from year 5 onward using Kaplan-Meier methods. Stratified analyses according to stage at diagnosis (I-III) were conducted to quantify the conditional risk of recurrence in patients who were disease-free at the landmark time point. To account for temporal changes in diagnostic procedures, pathology reporting, systemic therapies, and follow-up across the study period, time period analysis were performed: 1981–1999, 2000–2009, and 2010–2022, and incorporated in the primary multivariable Cox models. Additionally, given temporal variability in Ki-67 we performed sensitivity analyses excluding Ki-67 from multivariable Cox model. Statistical analyses were performed using Stata/IC version 16.1 and R version 4.2.2 (The R Project for Statistical Computing, www.r-project.org).

Results

A total of 9,227 non-metastatic (stages I/II/III) BC patients diagnosed between 1981 and 2022 were analyzed. Of these, 4,367 had early-stage HR+/HER2- BC and sufficient data regarding iDFS and a minimum follow-up of six months. Patients' basic characteristics are summarized in Table 1. Briefly, median age was 57 years (range: 18–97), and nodal involvement was present in 44.2 %. While 49% received (neo)adjuvant chemotherapy (CT), 94% received adjuvant ET.

With a median follow-up of 67 months, 847 patients (19.4%) experienced an invasive recurrence, with 595 (70.2%) presenting as distant metastases. The 5- and 10-year iDFS rates for the entire cohort were 85.0% (95% CI: 84-86%) and 70.0% (95% CI: 68-73%), respectively (Supplementary Figure S1). When stratified by stage, 5-year iDFS was 93.4% (95% CI: 91.8-94.7) for stage I, 87.2% (95% CI: 85.2-88.9) for stage II, and 65.1% (95% CI: 61.1-68.8) for stage III. Comparatively, at 10 years, iDFS reached 84.6% (95% CI: 81.7-87.0), 69.9% (95% CI: 66.3-73.2), and 45.1% (95% CI: 40.0-50.0), respectively ($p<0.001$; Figure 1A). According to nodal status, the 5- and 10-year iDFS rates were 78.1% (75-80%) and 59.1% (55-62%) for lymph node positive disease, and 91.9% (90-93%) and 81.2% (78-83%) for N0 disease ($p<0.001$; Figure 1B). Patients who experienced invasive recurrence were younger (median age 53 vs. 57

years, $p<0.001$), less frequently diagnosed through mammography screenings (22.8% vs. 39.7%, $p<0.0001$), more likely to present with locally advanced disease (stage III: 37.4% vs. 16.3%, $p<0.001$), had higher HG (Grade 3: 41.9% vs. 26.6%, $p<0.001$), and higher baseline Ki-67 levels (median 25% vs. 18%, $p<0.001$) (Table 2, Supplementary Table S1). Among patients who were alive and disease-free at 5 years, the conditional risk of subsequent invasive recurrence continued to increase over time. Using the landmark cohort, the cumulative invasive recurrence from years 5 to 10 reached 9.4% in stage I**,** 19.8% in stage II**,** and 30.7% in stage III. By 15 years after diagnosis (10 years after the 5-year landmark), the cumulative risks continued to rise to 22.3%**,** 40.3%**,** and 52.4%**,** respectively (Figure 1C).

Multivariate analyses found that stage and baseline Ki67 remained significantly associated with invasive recurrence (Supplementary Figure S2 and supplementary Table S2). In multivariate Cox models stratified by time period, stage remained the strongest predictor of invasive recurrence, and Ki-67 was also independently associated with recurrence risk (Supplementary Tables S3, S4 and S5). When excluding Ki-67 from the model, stage and grade remained significantly associated with recurrence (Supplementary Tables S6 and S7). To address the variability in Ki-67 across decades, we repeated the multivariate analyses but restricted to 2010–2022, obtaining consistent estimates for stage and Ki-67 (Supplementary Table S8). Finally, replacing stage with lymph node involvement yielded similar inferences for the main covariates. (Supplementary Table S9).

As shown in Table 3, only stage and nodal status were significant predictors of early recurrence (see Supplementary Table S10). In contrast to early recurrence, late recurrence was observed in patients with earlier-stage at diagnosis (Stage I-II: 74.1% vs. 52.7%, $p<0.0001$), lower nodal involvement (N-positive: 41% vs. 58%, $p=0.001$), predominantly lower HG (1-2: 67% vs. 48%, $p<0.001$), and lower Ki-67 at diagnosis (median 20% vs. 30%, $p=0.0008$) (Supplementary Table S11). In the multivariate model for late recurrence, only age (with a 2% increase in late recurrence risk per year of age at diagnosis, $p<0.0001$) and stage III at diagnosis (HR 1.49, $p=0.018$) remained statistically significant (Supplementary Table S12, Supplementary Figure S3). Overall, main associations remained unchanged after adjusting for time periods.

Regarding distant recurrence, 5- and 10-year DRFS rates were 88.0% (95% CI 87–89%) and 77.0% (95% CI 75–79%), respectively (Figure 2A). Between years 5 and 10, cumulative distant recurrence

reached 4.1% for stage I, 14.9% for stage II, and 28.7% for stage III. At 15 years from diagnosis, these risks increased to 9.9%, 27.7%, and 44.5%, respectively (Figure 2B).

When comparing distant to locoregional recurrence (ipsilateral or contralateral recurrence), higher stage, nodal involvement, HG, and elevated Ki-67 were significantly associated with distant metastasis in univariate analysis. Notably, fewer patients who developed distant metastases had received CT (24.9% vs. 45.6%, $p<0.001$) (Supplementary Tables S13 and S14). In the multivariate analysis, both stage II and stage III were associated with increased distant metastasis risk: HR 2.3; 95% CI: 1.37-7.97, $p=0.007$, HR 12.8; 95% CI: 5.20-31.6, $p=0.001$; respectively. Higher Ki-67 values also conferred greater risk (HR 1.01 per unit increase; 95% CI: 1.00-1.02, $p=0.004$), as did HG 3 (HR 3.55; 95% CI: 1.07-11.8, $p=0.0038$) (Supplementary figure S4, supplementary table S15). Since lymph nodal status was not directly included in our main multivariate model, an alternative nodal-based specification was evaluated as part of a sensitivity analysis; again confirming Ki67, grade and now nodal status (HR 4.41 95% CI 2.65-7.33; $p<0.001$) as significantly associated with distant recurrence (Supplementary Table S16).

Of the 595 patients with distant recurrence, 60.9% (n=364) recurred within the first 5 years, while 39.0% (n=233) recurred between 5 and 10 years after diagnosis. Specific metastatic site data were available for 570 patients. Of these, 47.5% (n=271) presented with visceral metastases as the first site of recurrence, with the majority (59.0% [n=160]) diagnosed within the first 5 years. In contrast, 52.4% (n=299) initially presented with non-visceral metastases, again with a higher proportion, 57.8% (n=173), occurring within 5 years and 42.1% (n=126) after 5 years; p=0.081) (Supplementary Table S17). Finally, in patients with distant recurrence, 6.8% (n=39) experienced brain metastases, with 76.0% (n=29) classified as early recurrence, where within these patients, 34% (n=10) presented with exclusive brain involvement. Among late recurrences, 9 out of 39 patients (34%) developed brain metastases, but only one patient experienced brain metastasis as the sole site of late (≥5 year) recurrence.

Discussion

Our real-world study assessed clinico-pathological variables associated with early and late invasive recurrence in non-metastatic HR+/HER2- BC patients, focusing on distant recurrence patterns. Our findings confirm a persistent risk of recurrence in HR+ BC, with nearly one-third of patients experiencing invasive

recurrence at 10 years. Notably, most events were distant metastases (70%), which ultimately drive patient survival outcomes [25]. Classical prognostic factors, locally advanced disease (stage III), nodal involvement, higher HG (HG 3), and elevated Ki-67, were also confirmed as strong predictors of early recurrence and are still essential to guide treatments in the absence of more advanced biomarkers such as genomic platforms.

While early recurrence was associated with advanced stage at diagnosis, late recurrence predominantly occurred in early-stage patients with less aggressive features like lower HG and Ki-67 levels. However, advanced stage at diagnosis remained the most relevant risk factor for recurrence in both early and late events; 10-year recurrence risks ranged from 15% in stage I to 55% in stage III. Furthermore, our 5-year landmark analysis reinforces the persistent late risk characteristic of HR+ disease. Among patients that were disease-free at 60 months, conditional invasive recurrence between years 5 and 10 ranged from 22% in stage I to over 50% in stage III, with distant recurrence reaching from 10 to 45% across stages. Even though we used a limit of 10 years for our late-recurrence analyses, our results are in line with the 2017 EBCTCG report that demonstrated steady distant recurrence rates within 5–20 years (13–41% according to tumor and nodal status). The use of a 5-year landmark to estimate subsequent recurrence parallels the CTS5 framework, which assesses risk after completion of initial ET, typically within years 5–10. Again, our findings were consistent with an EBCTCG meta-analysis confirming a sustained hazard of distant recurrence beyond 5 years. However, unlike EBCTCG, our real-world dataset did not capture the full 10–20 year follow-up interval, and therefore these results should be interpreted within the 5–10 year window analyzed.

These conditional risks emphasize the need for treatment strategies that address not only the biology of early recurrence but also the residual hazard characteristic of endocrine-sensitive disease. Hence, an accurate estimation of risk at diagnosis is key to guide adjuvant CT, reducing the risk of early recurrence and improving survival [26]. This also helps to make more informed decisions regarding the duration of ET with higher-risk patients deriving benefit from extended treatment (up to 10 years) [27]. Obviously, the potential benefit of prolonged ET should be balanced with long-term toxicities, including menopausal symptoms, fatigue, sexual dysfunction, and osteoporotic complications [28–30].

The introduction of CDK4/6 inhibitors have further reduced both early and late recurrences in high-risk HR+ disease. The MonarchE and NATALEE trials demonstrated clinically meaningful reductions in invasive recurrence, with emerging overall survival benefit in abemaciclib and a durable carry-over effect seen with ribociclib [31,32].

Recently, genomic assays, such as PAM50, have been adopted as predictors of late recurrence [33,34]. This assay estimates 10-year recurrence risk post-ET, classifying patients into low, intermediate, and high-risk categories, guiding decisions on CT, extended ET [35], or the addition of CDK4/6 inhibitors [36]. Similarly, the Breast Cancer Index (BCI) has also demonstrated predictive value for late distant recurrence and the benefit of extended ET, particularly in low clinical risk (N0) patients [37]. On the other hand, dynamic biomarkers, such as early proliferation response measured by Ki-67 ≤10% after 2–4 weeks of ET, are being considered to individualize treatment strategies [38,39]. Despite these advancements, traditional clinico-pathological factors are still central to make treatment decisions. This was reaffirmed by the 2023 St. Gallen Consensus, which recommended ET duration based on stage and nodal status: 5 years for stage I, up to 10 years for stage III, and 7–8 years for stage II with nodal involvement [40].

Dowsett *et al*. [41] validated the Clinical Treatment Score post-5 years (CTS5), a model incorporating stage, nodal status, HG, and age to estimate residual risk of distant recurrence after 5-year ET. This tool, derived from the ATAC trial [42] and validated in BIG 1-98 [43], classifies patients into low, intermediate, and high risk of 5–10-year recurrence, suggesting that low-risk patients with <1% annual recurrence risk derive limited benefit from extended ET. Consistent with these findings, our study identified age, nodal status, and stage as robust predictors of late recurrence. Notably, unlike ATAC and BIG 1-98, which only included postmenopausal women, our cohort also included premenopausal patients. Interestingly, late recurrence risks were similar between age groups, despite the limited use of ovarian function suppression, especially in low- and middle-income countries [44,45]. Similarly, Yamashita *et al*. [46] confirmed that tumors size and lymph node positivity predict late recurrence, even in premenopausal women. Recently, a Spanish multicenter study further confirmed CTS5 as a useful tool to stratify late recurrence risk in HR+/HER2-negative patients; however, it tended to overestimate absolute risk [47]. A recent systematic review evaluated biomarkers for extended ET and identified BCI as the only validated tool to predict >5-year treatment benefit. This analysis found consistent evidence supporting BCI's

predictive capacity for late distant recurrence, particularly in postmenopausal women with early-stage HR+/HER2-negative BC. This reinforces the role of BCI not only as a prognostic marker but also as a decision-making tool to individualize extended endocrine strategies [48]. Despite these promising results, the validation of most predictive models has been limited to high-income countries or controlled clinical trial populations that have better access to advanced therapies, structured follow-up, and higher adherence to ET. Therefore, these findings may not fully apply to patients from low- and middle-income countries, where access to therapies and adherence remain limited. In addition, given that our cohort was drawn from specialized cancer centers from a single healthcare system, the observed recurrence timing patterns may not be directly generalizable or applicable to other settings. Moreover, differences in screening uptake [49] timeliness of diagnosis, ET adherence, access to ovarian function suppression or extended ET [50] and follow-up intensity across regions may shift the relative distribution of early versus late recurrence.

Regarding distant metastatic disease, we observed that nearly two-thirds of distant metastases occurred within the first five years of follow-up, consistent with prior studies. Pedersen *et al*. [51] reported better survival outcomes for patients with late recurrence, partially explained by the higher proportion of locoregional rather than distant relapses among late recurrences. Some of these late locoregional events may represent new primary tumors rather than true recurrences [52], potentially explaining their more favorable outcomes due to the absence of treatment-resistant tumor clones.

Although late distant recurrences also demonstrated better survival, data on recurrence localization were limited. While we observed a trend toward higher non-visceral involvement in late recurrence, no statistically significant differences were found between visceral and non-visceral metastases. Notably, brain metastases were more frequently observed among patients with early recurrence.

These patterns may reflect time-dependent selection, whereby biologically aggressive tumors tend to relapse earlier. However, because detailed information on ET type, duration, ovarian suppression, and adherence was unavailable, we could not fully disentangle intrinsic tumor biology from real-world treatment heterogeneity in shaping late recurrence patterns. Importantly, incomplete ET exposure data could have biased late recurrence estimates in either direction. For example, if adherence, treatment duration, or use of ovarian suppression differed by age group or treatment era, part of the observed association between age and late recurrence may reflect differences in treatment exposure rather than age-related tumor biology

alone. Still, patients who experience late recurrence are enriched for tumors with lower HG, lower Ki-67, and more indolent biology, despite retaining a clinically meaningful risk of relapse. This depletion of high-risk phenotypes over time helps explain why late-recurrence cohorts appear to have more favorable baseline characteristics.

Our study has several limitations. First, its retrospective design precludes definitive causal inferences. In this regard, we observed changes in the incidence of recurrence across time periods that likely reflect changes in surveillance intensity, imaging availability, pathology standardization, and completeness in the capture of events rather than changes in tumor biology and aggressiveness in recent decades. Secondly, tumor size (T component/T stage), histologic subtype, and quantitative ER/PR expression were not consistently registered across the study period; therefore, seeking to avoid substantial missingness and selection bias they were not included in our main multivariate analyses. Consequently, we were unable to assess potential differences between ductal and lobular carcinomas [51,52] or the prognostic contribution of quantitative HR expression beyond positivity thresholds [53]. Although clinical stage and nodal status were included as available surrogates of overall tumor burden, residual confounding by tumor size and lobular histology cannot be excluded, which may particularly impact interpretation of late recurrence risk. [53,54][55]. Third, as pointed earlier, although 94% of patients were recommended for adjuvant ET, data on adherence, duration, and type of ET were unavailable, thus interpretation of early and late recurrence patterns should consider that ET exposure could not be fully characterized. Still, our recurrence estimates reflect outcomes under routine practice conditions and should not be interpreted as biological effects independent of ET intensity or persistence. Finally, our definition of late recurrence was limited to events occurring within 5 to 10 years, therefore very late recurrence events that occurred ≥10 years were not captured. Despite these limitations, this study has important strengths. It included both premenopausal and postmenopausal women, provided detailed information on patterns of metastatic recurrence, and highlighted the continuing relevance of accessible, low-cost biomarkers such as Ki-67 and HG. As pointed earlier, these markers remain critical tools in middle- and low-income settings, where access to advanced molecular tests remains limited.

Conclusions

In summary, compared to early recurrent disease, late relapse tends to occur in patients with initially lower clinical and pathological risk. Nevertheless, even after five years of DFS, the initial stage remains the primary determinant of recurrence, underscoring the importance of early diagnosis. Treatment and follow-up strategies should account for these biological differences to improve long-term outcomes.

Declarations

Abbreviations:
AJCC: American Joint committee on cancer
ASCO/CAP: American society of clinical oncology/College of American pathologists
BC: breast cancer
BCI: breast cancer index
CDK4/6: cyclin-dependent kinases 4 and 6
CI: confidence interval
CT: chemotherapy
CTS5: clinical treatment score 5
DFS: disease-free survival
DRFS: distant recurrence-free survival
EBTCG: early breast cancer trialists collaborative group
ER: estrogen receptor
ET: endocrine therapy
HER2: human epidermal growth factor receptor type 2
HG: histological grade
HR: hormone receptor
iDFS: invasive disease-free survival
IHC: immunohistochemistry
MGI: molecular grade index
OS: overall survival
PR: progesterone receptor

Ethics approval and consent to participate:
This was an observational study. Study was approved by the institutional review board and ethics committee at the Pontificia Universidad Catolica de Chile. According to decree 196/2003 ('Italian Privacy Code') and decree 101/2018 ('Harmonization Decree' harmonizing the Italian data protection laws with the provision of the General Data Protection Regulation 679/2016—GDPR). The scientific & ethics committee at Pontificia Universidad Catolica de Chile ("*Comite etico cientifico de ciencias de la salud*": Scientific ethics committee in Health Sciences) and the Dr. Sotero del Rio Healthcare complex ("*Comité Ético Cientifico del SSMSO*"; Scientific Ethics Committee of the Southeastern Metropolitan Health Service) waived the use of informed consent when processing anonymized data given this study was carried out in the performance of public interest or public powers based on a provision of law. Our study strictly adhered to the principles established in the Declaration of Helsinki.

Consent for publication:
Not applicable

Availability of data and materials:
Analyzed data are not openly available because they contain potentially identifiable information (e.g., dates of diagnoses and treatment) that cannot be shared publicly without patients' approval and data use

agreements, however they are available from the corresponding author (CS) and the research team on reasonable request.

Competing interests:
The authors declare that they have no competing interests

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Authors` contributions:
All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Benjamin Walbaum, Francisco Acevedo, Mauricio P. Pinto and Cesar Sanchez. The first draft of the manuscript was prepared by Benjamin Walbaum, Francisco Acevedo, Mauricio P. Pinto and Cesar Sanchez, and all authors provided critical feedback and revisions to previous versions of the manuscript. All authors read and approved the final manuscript.

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Figure legends

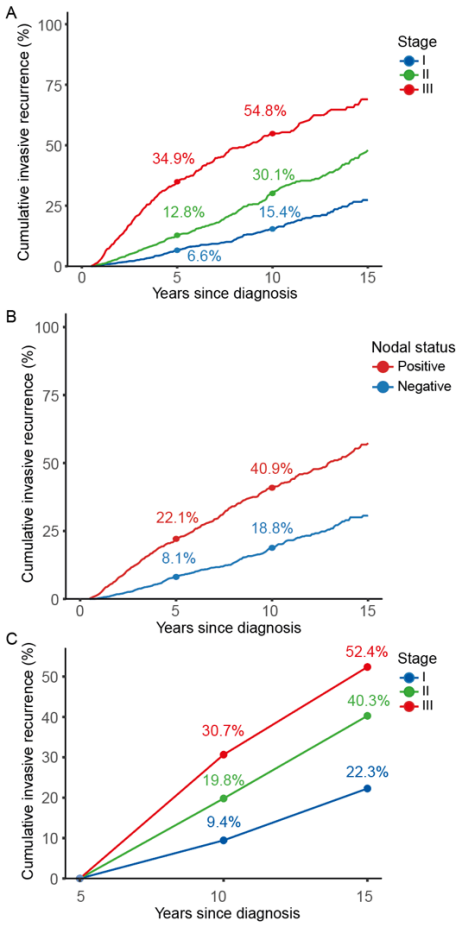

Figure 1. Cumulative risk of invasive recurrence by stage and nodal status. A. Cumulative incidence of invasive recurrence stratified by AJCC stage (I, II, and III) at diagnosis. Estimated cumulative risks at 5 and 10 years were 6.6% and 15.4% for stage I, 12.8% and 30.1% for stage II, and 34.9% and 54.8% for stage III, respectively. B. Cumulative incidence of invasive recurrence by nodal status. Node-positive disease was associated with higher recurrence risk versus node-negative. Estimated cumulative risks at 5 and 10 years were 8.1% and 18.8% for node-negative disease and 22.1% and 40.9% for node-positive disease. C. Five-year landmark analysis stratified by stage, including only patients who remained event-free at 5 years (60 months) after diagnosis. Subsequent cumulative invasive recurrence risk at 10 and 15 years from diagnosis remained stage-dependent: 9.4% and 22.3% for stage I, 19.8% and 40.3% for stage II, and 30.7% and 52.4% for stage III.

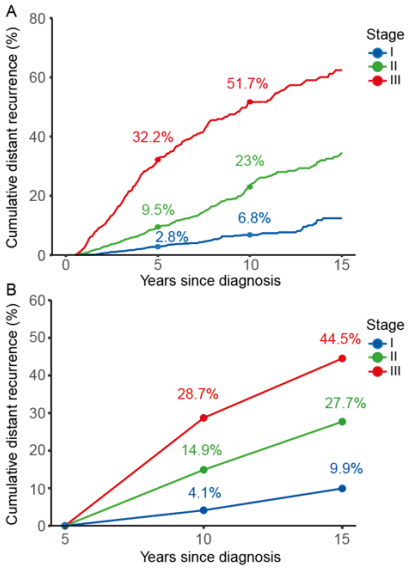

Figure 2. Cumulative distant disease risk by stage. A. Cumulative incidence of distant recurrence stratified by stage (I-III) at diagnosis. Stage III was associated with the highest risk of distant recurrence at all time points. Estimated cumulative distant recurrence rates at 5 years were 2.8% (stage I), 9.5% (stage II), and 32.2% (stage III). At 10 years, corresponding risks were 6.8%, 23.0%, and 51.7%, respectively. B. Five-year landmark analysis stratified by stage, including only patients who remained free of distant recurrence during the first 5 years following diagnosis. At 10 years (5 years after the landmark), cumulative risks were 4.1% (stage I), 14.9% (stage II), and 28.7% (stage III). At 15 years from diagnosis, cumulative risks increased to 9.9%, 27.7%, and 44.5%, respectively

Tables

Table 1. Baseline clinical and pathological characteristics of participants.

Variable; units	**Total (n=4367)**
Median age; y (range)	57.19 (18-97)
Diagnostic method; %	
Mammography	36.79
Symptoms	63.21
Stage; %	
I	37.17
II	42.39
III	20.45
Lymph node status; %	
Negative	55.84

Positive	44.16
Histological grade; %	
1	21.29
2	49.10
3	29.61
Median Ki67; % (range)	20 (1-100)
Use of chemotherapy; %	49.01

Table 2. Clinical and pathological characteristics of participants by invasive recurrence status.

Variable; units	**Invasive recurrence status**		**p-value**
	Negative (n=3520)	**Positive (n=847)**	
Median age; y (range)	57.1 (18-98)	53.8 (19-88)	<0.0001
Diagnostic method; %			
Mammography	39.78	22.80	<0.0001
Symptoms	60.22	77.20	
Stage; %			
I	40.68	22.55	<0.0001
II	42.95	40.02	
III	16.36	37.43	
Lymph node status; %			<0.0001
Negative	60.48	36.31	
Positive	39.52	63.69	
Histological grade; %			
1	23.45	12.48	<0.0001
2	49.95	45.62	
3	26.6	41.90	
Median Ki67; % (range)	18 (1-100)	25 (1-100)	<0.0001
Use of chemotherapy; %	46.44	68.92	<0.0001

Table 3. Clinical characteristics of patients with early (<5 years) or late (5-10 years) invasive recurrence

Variable; units	Invasive recurrence		p-value
	Early; <5 y (n=460)	Late; 5-10 y (n=387)	
Median age; y (range)	54 (19.4-89.0)	53.8 (23.2-84.0)	0.649
Diagnostic method; %			
Mammography	16.79	31.30	<0.0001
Symptoms	83.21	68.69	
Stage; %			
I	16.96	29.20	<0.0001
II	35.87	44.96	
III	47.17	25.84	
Lymph node status; %			
Negative	31.05	42.55	0.001
Positive	68.95	57.45	
Histological grade; %			
1	8.90	16.41	<0.0001
2	39.86	51.95	
3	51.25	31.64	
Median Ki67; % (range)	30 (1-100)	20 (1-90)	0.0008
Distant disease; n (%)	367 (79.70)	234 (60.50)	<0.0001
Visceral disease; n (%)	160 (48.0)	111 (46.80)	0.081
Non-visceral; n (%)	173 (51.90)	126 (53.10)	0.144