Observational Study

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2025, Vol. 53(5) 1–10
© The Author(s) 2025
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/03000605251342508
journals.sagepub.com/home/imr
Sage

Prevalence and clinicopathological features of human epidermal growth factor receptor-2–low breast cancers: A single-center experience

ılkay Cinar

Abstract

Objective: Human epidermal growth factor receptor-2–low breast cancer, characterized by low-level human epidermal growth factor receptor-2 expression and immunohistochemistry score 1+ or immunohistochemistry score 2+ without amplification, has been proposed as a distinct subgroup. This study investigated the prevalence and clinicopathological characteristics of human epidermal growth factor receptor-2–low breast cancers.

Methods: A retrospective observational cohort study was conducted on patients diagnosed with invasive breast carcinoma between 2021 and 2023 at a single tertiary center. Data on histological type, tumor grade, human epidermal growth factor receptor-2 status, and Ki-67 proliferation index were collected.

Results: Among the 181 patients who were included, 54.7% were classified as human epidermal growth factor receptor-2–low, 27.6% as human epidermal growth factor receptor-2–negative, and 17.7% as human epidermal growth factor receptor-2–positive. Human epidermal growth factor receptor-2–low tumors were predominantly those classified into grade 2 (69.7%). The mean age of patients with human epidermal growth factor receptor-2–low tumors was 60 years. The Ki-67 index was significantly lower in human epidermal growth factor receptor-2–low tumors than in human epidermal growth factor receptor-2–positive and human epidermal growth factor receptor-2–negative groups ($p = 0.001$). No significant differences were observed in the rates of axillary lymph node metastasis among the groups ($p = 0.13$).

Department of Pathology, Faculty of Medicine, Giresun University, Türkiye

Corresponding author:
Ilkay Cinar, Department of Pathology, Faculty of Medicine, Giresun University, Gazipaşa Yerleşkesi Debboy Mevki, Merkez-Giresun/Türkiye.
Email: a.ilkaycinar@gmail.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Conclusion: Human epidermal growth factor receptor-2–low breast cancers constitute a significant proportion of breast cancer cases and are associated with distinct clinicopathological features, including high estrogen reception positivity and lower Ki-67 proliferation rates.

Keywords
Human epidermal growth factor receptor-2–low, breast cancers, estrogen receptor, progesterone receptor, Ki-67 antigen

Date received: 4 February 2025; accepted: 29 April 2025

Introduction

Breast cancer is the most commonly diagnosed malignancy in women and a leading cause of cancer-related death worldwide.[1] Human epidermal growth factor receptor 2 (HER-2) plays an important role in the biology of breast cancer. HER-2 gene amplification is associated with a poorer prognosis and a more aggressive disease course.[2] Furthermore, it is critical for determining targeted treatment options. HER-2 status in breast cancer is routinely assessed and reported in pathology reports. Guidelines published by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommend that HER-2 expression be evaluated using immunohistochemistry (IHC) and in situ hybridization (ISH).[3]

Conventionally, HER-2 status has been classified as "positive" or "negative." However, approximately 50% of tumors previously categorized as HER-2–negative exhibit low levels of HER-2 expression, defined as an IHC score of 1+ or an IHC score of 2+ without amplification.[4] The diagnosis of HER-2–low breast cancer is usually made using pathological tests, such as IHC and ISH. IHC assesses cell surface HER-2 protein expression, while ISH assesses ERBB2 gene amplification. HER-2 status is determined using the IHC scoring system, and tumors scoring 1+ or 2+ are classified as HER-2–low.[5]

This observation has led to the hypothesis that tumors with low HER-2 expression may now represent a distinct biologic subgroup categorized as "HER-2–low." This new classification has gained significant popularity owing to the clinical benefits demonstrated by antibody-drug conjugates (ADCs), such as trastuzumab deruxtecan (T-DXd) in HER-2–low tumors.[6] HER-2–low tumors are predominantly hormone receptor–positive, exhibit low proliferation rates, and show well-differentiated features.[7] However, their biological and clinical positioning between HER-2–positive and HER-2–negative tumors is yet to be fully elucidated.[8]

The biological heterogeneity of HER-2–low breast cancers and their relationship to clinical outcomes have not yet been clearly defined.[9,10] Recognition of HER-2–low tumors plays a critical role in guiding treatment strategies. These tumors require different approaches to patient management considering their hormone receptor status. This study investigated the prevalence and clinicopathological features of HER-2–low breast cancers and compared the findings with those reported in the literature. The results aimed to contribute to a better understanding of HER-2–low tumors and optimize treatment strategies.

Methods

This retrospective observational cohort study was conducted as per the ethical principles outlined in the Declaration of Helsinki (as revised in 2024). It was approved by the Ethics Committee of Giresun University (Approval Number: 11.12.2024/08). As the study was retrospective, written informed consent from individual patients was not required, and all data were anonymized to ensure patient confidentiality. The reporting of this study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[11]

Case selection

This study evaluated invasive breast carcinoma patients diagnosed at the Giresun University Education and Research Hospital Pathology Laboratory between 2021 and 2023. Patients were selected consecutively, and core biopsy materials obtained from the pathology laboratory archives and diagnosed as invasive breast carcinoma were included in the study. Inclusion criteria were the availability of clinicopathological data and reported HER-2 status. Patients with missing data were excluded.

Data collection and management

Clinical and histopathological data. Patient age, tumor location, histological type and grade, estrogen receptor (ER), progesterone receptor (PR), HER-2, and Ki-67 data were obtained from hematoxylin–eosin (HE) slides, pathology reports, and electronic records.

Histomorphological evaluation. HE-stained slides were prepared using routine laboratory protocols: fixation in 10% buffered formaldehyde, paraffin embedding, 5-μm sectioning, and staining. HER-2, ER, PR, and Ki-67 evaluations were performed under a light microscope (Nikon Eclipse). IHC was performed using monoclonal antibodies, including HER-2 (Ventana anti–HER-2, 4B5), ER (Ventana anti-ER, SP1), PR (Ventana anti-PR, 1E2), and Ki-67 (Ventana anti-ki67, 30-9). Fluorescence in situ hybridization and ISH evaluations were performed externally in the majority of cases, and the results were obtained from patient pathology reports. In a subset of cases, dual ISH analysis was performed at our institution (Ventana HER-2 dual ISH DNA probe cocktail).

Classification of HER-2 status

The HER-2 status was categorized according to the ASCO and CAP guidelines as follows:[12]

HER-2–negative: HER-2 IHC score 0;
HER-2–low: HER-2 IHC score 1+ or IHC score 2+ without ISH amplification;
HER-2–positive: HER-2 IHC score 3+ or IHC score 2+ with ISH amplification.

Ki-67 proliferation index

Ki-67 expression was categorized as follows:[12,13]

Low proliferation: ≤20% nuclear staining in tumor cells;
Moderate proliferation: 21%–40% nuclear staining;
High proliferation: >40% nuclear staining.

Hormone receptor status

The hormone receptor status was classified according to the ASCO/CAP guidelines:[12]

Negative:<1% of tumor cells showing immunoreactivity;

Low: 1%–10% immunoreactive tumor cells;
Positive: >10% immunoreactive tumor cells.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences package. Group differences were assessed using Chi-square and Fisher's exact tests. Continuous variables are presented as mean ± SD values, and categorical variables are expressed as frequencies and percentages. A p-value of less than 0.05 was considered statistically significant.

Results

In total, 181 invasive breast carcinoma cases were evaluated. The mean age of the overall cohort was 58 ± 12.3 years. The most common histological subtype was invasive carcinoma of no special type, accounting for 92.8% of the cases (n = 168). In terms of tumor grade, the majority of cases (66.3%, n =120) were classified as grade 2, followed by grade 1 (20.4%, n = 37) and grade 3 (13.3%, n = 24). Tumor laterality was nearly evenly distributed, with 50.8% of tumors located in the right breast (n = 92), 48.1% in the left breast (n = 87), and 1.1% showing bilateral involvement (n = 2). Axillary lymph node metastasis was observed in 33 patients (18.2%) at diagnosis. ER expression was positive (>10%) in 77.3% of the overall cohort, low (1%–10%) in 18.2%, and negative (<1%) in 4.5% of the subjects. PR positivity was noted in 61.9% of the cases, while 23.8% had low expression and 14.4% were PR negative. The Ki-67 proliferation index showed low proliferation (≤20%) in 58.5% of the cases, moderate proliferation (20%–40%) in 19.5% of the cases, and high proliferation (>40%) in 22% of the cases. Regarding HER-2 status, 27.6% of tumors were HER-2-0 (n = 50), 54.7% were HER-2–low (n = 99) (Figures 1 and 2), and 17.7% were HER-2–positive (n = 32) (Figure 3). Among HER-2–low tumors, 40.4% (n = 40) had an IHC score of 1+, while 59.6% (n = 59) had a score of 2+ with ISH-negative status.

The HER-2–low subgroup consisted of 99 patients with a mean age of 60.4 ± 12.8 years. The majority of tumors were grade 2 (69.7%, n = 69), followed by grade 1 (21.2%) and grade 3 (9.1%). There was no statistically significant difference in the

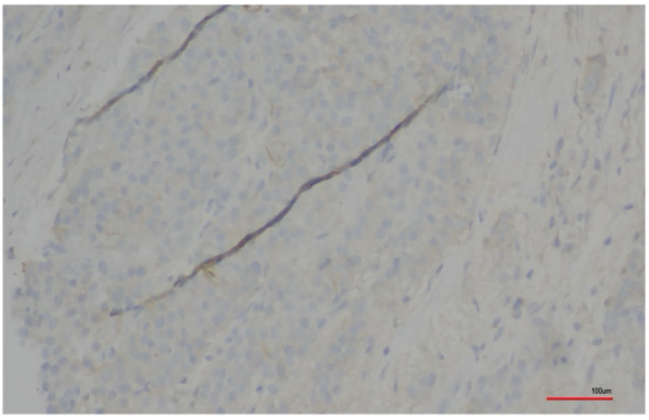

Figure 1. HER-2 immunohistochemistry staining score 1+ (Ventana anti–HER-2, 4B5, 20 × 100). HER-2: human epidermal growth factor receptor 2.

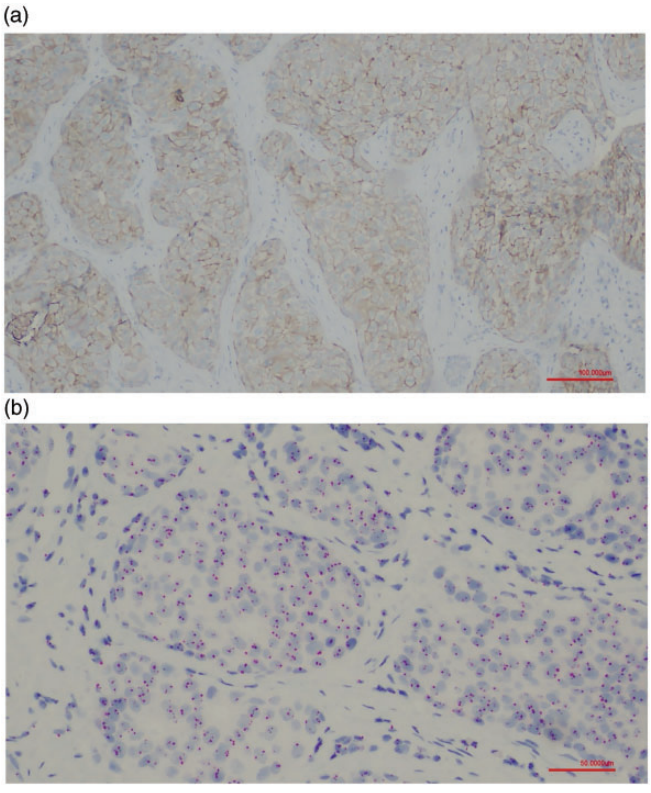

Figure 2. (a) HER-2 immunohistochemistry staining score 2+ (Ventana anti–HER-2, 4B5, 10 × 100) and (b) HER-2 Dual ISH (Ventana Dual ISH DNA probe cocktail) in the same case no amplification (20 × 100).

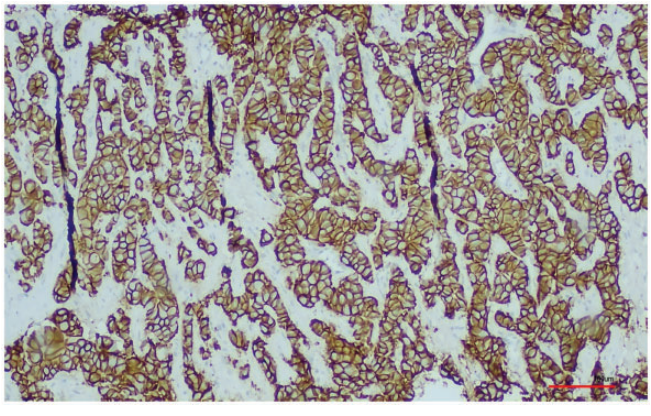

Figure 3. HER-2 immunohistochemistry staining score 3+ (Ventana anti–HER-2, 4B5, 10 × 100).

tumor grade between the HER-2–low group and the HER-2–negative or HER-2–positive groups ($p = 0.10$). Tumor laterality in the HER-2–low group showed a slight predominance of the left breast (50.5%) over the right (47.5%), and two patients (2%) exhibited bilateral involvement. Axillary lymph node metastasis at diagnosis was present in 17 HER-2–low patients (17.2%), with no statistically significant difference among HER-2 groups ($p = 0.13$). ER positivity was remarkably high in HER-2–low tumors, with 90% of the patients showing >10% expression, 5% showing low expression, and 5% showing negative expression. This distribution showed a statistically significant difference compared to the HER-2–negative and HER-2–positive groups ($p < 0.001$). Similarly, PR positivity was seen in 70.7% of HER-2–low patients, with 12.1% showing low expression and 17.2% showing negative expression; this difference was statistically significant ($p < 0.001$). The Ki-67 proliferation index in HER-2–low tumors revealed low proliferation in 67.7%, moderate proliferation in 22.2%, and high proliferation in only 10% of the study population. The Ki-67 distribution was significantly different from that of the HER-2–negative and HER-2–positive groups ($p = 0.001$).

A detailed summary of clinicopathological features s per HER-2 status is presented in Table 1 and Figure 4.

Discussion

In this study, we evaluated the prevalence and clinicopathological characteristics of HER-2–low breast cancers and examined the position of this subgroup within the broader spectrum of breast cancer. Our findings indicate that HER-2–low tumors accounted for 54.7% of all cases, were predominantly ER-positive, and exhibited a low-grade proliferative profile. Additionally, the rate of lymph node metastasis at diagnosis was 17.2%.

Previous studies have reported a prevalence of 31%–55% for HER-2–low breast cancer. Zhang et al. reported a prevalence of 31% for HER-2–low tumors,[14] while Marchió et al. indicated that they

Table 1. Comparison of clinical and pathological features based on HER-2 status.

	All cases (n = 181)	HER-2–Low (n = 99)	HER-2–negative (n = 50)	HER-2–positive (n = 32)
Age (mean)	58 ± 12.3	60.4 ± 12.8	56.9 ± 13.7	57.2 ± 14.3
ER positivity (%) (>10%)	90	96.0	66.0	87.5
PR positivity (%) (>10%)	76.7	88.8	60.0	78.1
Tumor grade (%)				
Grade 1	20.4	21.2	22.0	18.8
Grade 2	66.3	69.7	54.0	71.9
Grade 3	13.3	9.1	24.0	9.4
Ki-67 proliferation Index (%)				
<15 (low)	31.5	39.8	28.0	18.8
15–30 (intermediate)	28.2	29.1	26.0	31.3
>30 (high)	40.3	31.1	46.0	50.0
Laterality (%)				
Right	50.8	47.5	50	62.5
Left	48.1	50.5	50	37.5
Bilateral	2	2	0	0

HER-2: human epidermal growth factor receptor 2.

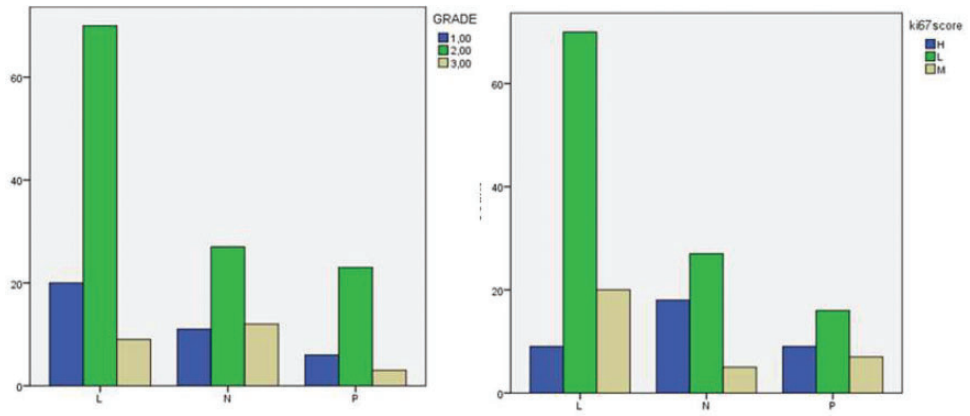

Figure 4. Comparison of histological grade and Ki-67 proliferation index among HER-2 status groups. Bar charts illustrate the distribution of histological grade (left) and Ki-67 proliferation index (right) in breast cancer cases categorized by HER-2 status. For grade, most HER 2-low tumors were grade 2, while grade 1 and grade 3 were less common. Regarding Ki-67, HER-2–low tumors predominantly showed low proliferation (L), in contrast to HER-2–negative and HER-2–positive tumors, which had higher proportions of medium (M) and high (H) proliferation indices. (L: HER-2–low; N: HER-2–negative; P: HER-2–positive).

comprised approximately 55% of all breast cancers.[15] In our cohort, the prevalence was 54.7%, aligning closely with the upper limit of previously reported ranges. These findings suggest that HER-2–low tumors represent a substantial proportion (approximately 50%) of all breast cancers, underscoring the importance of recognizing and evaluating this subgroup in clinical settings. The median age at breast cancer diagnosis in the general population has been reported as 61.8 years.[16] In this study, the age ranged from 30–94 years, with a median age of 58 years and an interquartile range (IQR) of 49.0–67.5 years for the overall cohort. In the HER-2–low group, the median age was 61 years with an IQR of 51.0–70.0. Although the age distribution was broadly consistent with that reported in the literature, the HER-2–low group demonstrated a slightly older median age than the other subgroups. Bidoli et al. suggested that regional variations in age at diagnosis may be influenced by differential exposure to risk factors, awareness levels, and screening practices.[17] Tumor laterality has been explored in prior studies, with some reporting a slight predominance of left-sided breast cancers. Ruszkowska-Ciastek et al. reported a left-to-right ratio of 1.04,[17] while as per Al Saad et al., 50.44% of tumors were left-sided and 47.37% were right-sided.[18] Furthermore, left-sided tumors have been associated with marginally worse long-term outcomes.[19] Gadhia et al. reported a 64.95% prevalence of left-sided breast cancer, particularly in triple-negative and grade III tumors. A tendency toward left laterality has also been observed in HER-2–negative tumors.[20] In our study, right-sided tumors were slightly more common in the overall cohort (50.8% vs. 48.1%). However, among HER-2–low cases, left-sided involvement was marginally more prevalent (50.5% vs. 47.5%). Interestingly, both bilateral cases in our cohort were from the HER-2–low group. To the best of our knowledge, no studies have specifically addressed laterality in HER-2–low tumors, highlighting an area for future investigation. Consistent with the literature, the majority of HER-2–low tumors in our cohort were low-to-intermediate

grade.[7,14,21] In particular, 69.7% of HER-2–low tumors were grade 2 and 21.2% were grade 1. Previous studies have also indicated that HER-2–low tumors are frequently diagnosed at early clinical stages (I–II) and tend to be well-to-moderately differentiated.[14] Regarding proliferative activity, earlier research has demonstrated that HER-2–low tumors generally have lower Ki-67 indices compared to both HER-2–negative and HER-2–positive tumors.[4,9,21,22] Our findings are in agreement with these reports, with low proliferation rates ($\leq$20%) observed in 67.7% of HER-2–low patients, representing a statistically significant difference ($p < 0.001$). These results support the notion that HER-2–low tumors may possess a less aggressive biological phenotype. Hormone receptor positivity has been consistently reported to be higher in HER-2–low tumors than in HER-2–negative tumors, with many classified within the Luminal B molecular subtype.[14,23,24] Our study reinforces these observations, demonstrating ER positivity in 90% and PR positivity in 70.7% of HER-2–low patients. These rates were significantly higher than those observed in the HER-2–negative and HER-2–positive groups ($p < 0.001$).

Finally, lymph node metastasis was identified in 17% of HER-2–low patients at diagnosis, with no significant difference when compared to the HER-2–negative or HER-2–positive groups ($p = 0.13$). These results are consistent with those reported by Zhang et al.; they noted similar metastatic behavior in HER-2–low tumors.[14] This suggests that HER-2–low tumors may generally carry a relatively low metastatic potential.

The limitations of our study include its retrospective design and relatively limited sample size. Additionally, the lack of long-term follow-up and survival data restricts our ability to assess prognostic outcomes. These limitations should be considered when interpreting the findings, and larger, multicenter prospective studies are needed to validate our results.

Conclusion

This study aimed to describe the prevalence and clinicopathological features of HER-2–low breast cancers, a subgroup of breast cancer with increasing clinical importance in the management of breast cancer. The findings suggest that HER-2–low tumors constitute a significant portion of breast cancers, generally exhibit higher hormone receptor positivity, tend to be low-to-intermediate grade, and exhibit low proliferative activity. Although there are currently no targeted therapies specifically approved for HER-2–low breast cancers, ADCs such as T-DXd have shown encouraging clinical benefits in this group. Given that response to treatment may vary according to the level of HER-2 expression, the management of HER-2–low breast cancers may require a more personalized approach.

In summary, HER-2–low breast cancers represent a distinct and clinically important subgroup within the spectrum of breast malignancies, characterized by unique biological behaviors and emerging therapeutic potential. Nevertheless, larger, prospective studies are warranted to further elucidate their molecular heterogeneity and treatment responsiveness. Such investigations are crucial for the advancement of more precise and effective therapeutic strategies and may ultimately contribute to establishing a new paradigm in breast cancer care.

Acknowledgement

None.

Author contributions

IC: conceptualization, methodology, data curation, writing, original draft, writing—review and editing.

Data availability statement

The dataset supporting this study is available from the corresponding author upon reasonable request.

Declaration of conflicting interests

No conflict of interest was declared by the authors.

Ethics approval and consent to participate

The study was conducted following the Declaration of Helsinki and was approved by the Ethics Committee of Giresun University (Approval Number: 11.12.2024/08).

Funding

No funding disclosure.

ORCID iD

ılkay Cinar https://orcid.org/0000-0002-2632-3209

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: worldwide GLOBOCAN incidence and mortality estimates for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: association between amplification of the HER-2/neu oncogene and recurrence and survival. *Science* 1987; 235: 177–182.
3. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: focused update of the American society of clinical oncology/college of American pathologists clinical practice guideline. *Arch Pathol Lab Med* 2018; 142: 1364–1382.
4. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: the pathologic and clinical landscape. *J Clin Oncol* 2020; 38: 1951–1962.
5. Tarantino P, Viale G, Press MF, et al. ESMO expert consensus statements (ECS) on the definition, diagnosis and management of HER2-low breast cancer. *Ann Oncol* 2023; 34: 645–659.
6. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med* 2022; 387: 9–20.
7. Schettini F, Chic N, Brasó-Maristany F, et al. Clinical, pathological and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer* 2021; 7: 1–10.
8. Denkert C, Seither F, Schneeweiss A, et al. Clinical and molecular characteristics of HER2- low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. *Lancet Oncol* 2021; 22: 51–61.
9. Schettini F and Prat A. Dissecting the biological heterogeneity of HER2-positive breast cancer. *Breast* 2021; 59: 339–350.
10. Corti C, Giugliano F, Nicolò E, et al. HER2-low breast cancer: a new subtype? *Curr Treat Options Oncol* 2023; 24: 468–478.
11. Von Elm E, Altman DG, Egger M; STROBE Initiative, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
12. College of American Pathologists. Breast Cancer Protocol Documents. CAP website. https://documents.cap.org/documents/Breast. (accessed 15 January 2025).
13. Davey MG, Hynes SO, Kerin MJ, et al. Ki-67 as a prognostic biomarker in invasive breast cancer. *Cancers (Basel)* 2021; 13: 4455.
14. Zhang H, Katerji H, Turner BM, et al. HER2-low breast cancers: new opportunities and challenges. *Mod Pathol* 2022; 35: 1075–1082.
15. Marchiò C, Annaratone L, Marques A, et al. Emerging concepts in HER2 assessment in breast cancer: heterogeneity, HER2-low carcinomas and beyond. *Semin Cancer Biol* 2021; 72: 123–135.
16. Bidoli E, Virdone S, Hamdi-Cherif M, et al. Age of onset of breast cancer in women: a 25-year population-based cancer registry study. *Sci Rep* 2019; 9: 14111.

17. Ruszkowska-Ciastek B, Rhone P, Bielawski K, et al. Differential impact of breast cancer laterality on clinicopathological, angiogenic, and hemostatic profiles: potential role of tumor localization in future outcomes. *J Clin Med* 2020; 9: 1708.
18. Al Saad S, Al Shenawi H, Almarabheh A, et al. Laterality of breast cancer in Bahraini women: a retrospective study. *BMC Cancer* 2022; 22: 968.
19. Abdou Y, Gupta M, Asaoka M, et al. Left breast cancer is associated with aggressive biology and worse outcomes than right breast cancer. *Sci Rep* 2022; 12: 13377.
20. Gadhia P, Joshi N, Vaniawala S, et al. Evaluation of HER2 suspicious cases after laterality in breast cancer. *Asian Pac J Cancer Biol* 2024; 9: 191–196.
21. Denkert C, Lebeau A, Schildhaus HU, et al. New therapies for metastasized HER2-low mammacarcinoma: consequences for histopathological diagnostics. *Pathologie* 2022; 43: 457–466.
22. Chen C, Li W, Wu W, et al. Characteristics of HER2 low-expression breast cancer: a Chinese single-center real-world data analysis. *Breast Cancer Manag* 2023; 12: BMT71.
23. Kang S and Kim SB. HER2-low breast cancer: now and in the future. *Cancer Res Treat* 2024; 56: 700–720.
24. Won HS, Ahn J, Kim Y, et al. Clinical significance of HER2-low expression in early breast cancer: a nationwide study from the Korean Breast Cancer Society. *Breast Cancer Res* 2022; 24: 22.