EPIDEMIOLOGICAL AND CLINICAL PROFILE OF BREAST CANCER: CAUSES AND ETIOLOGICAL INSIGHTS

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ABSTRACT:

Breast cancer continues to be a major global health burden and represents one of the most frequently diagnosed malignancies among women. Its biological diversity and varied clinical behavior make diagnosis and management complex. This study focuses on understanding the spectrum of breast cancer by examining its major pathological types, epidemiological trends, etiological factors, clinical features, and current diagnostic practices, with particular attention to breast lesions of uncertain malignant potential, inflammatory breast cancer, Paget's disease, and hormone-based subtypes.

Information was gathered through an extensive review of published clinical and scientific literature, emphasizing recent advancements in imaging, histopathological evaluation, immunohistochemistry, and molecular profiling. Risk assessment models and emerging technologies, including artificial intelligence-based diagnostic systems, were also evaluated for their contribution to early detection and accurate classification.

The analysis demonstrates that genetic predisposition, hormonal exposure, lifestyle factors, and reproductive history play significant roles in disease development. Receptor status (ER, PR, HER2) was identified as a crucial determinant of prognosis and therapeutic strategy. Aggressive forms such as triple-negative and inflammatory breast cancer were found to be associated with poorer outcomes and limited treatment options.

The study concludes that an integrated understanding of breast cancer biology and improved diagnostic precision are essential for timely intervention, personalized treatment planning, and better overall patient outcomes.

KEYWORDS: Breast cancer, B3 lesions, hormone receptors, epidemiology, diagnostic methods.

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INTRODUCTION:

Despite improvements in early identification and treatment, breast cancer is still one of the most common cancers affecting women globally and a significant public health concern. It is a diverse collection of illnesses with unique clinical, molecular, and histopathological characteristics. Breast cancer is a major cause of cancer-related morbidity and mortality among women, and its prevalence has been continuously rising globally. Breast cancer has a complicated etiology that involves the interaction of genetic, hormonal, environmental, and lifestyle variables. Disease development has been linked to mutations in genes such BRCA1 and BRCA2, long-term exposure to estrogen, obesity, alcohol use, and reproductive history. Implementing successful risk reduction and focused preventative initiatives requires an understanding of these risk variables. Clinically, breast cancer can appear in a variety of ways, from palpable lumps, nipple discharge, or skin changes in advanced cases to asymptomatic lesions found on screening mammography. To identify the tumor subtype and direct treatment choices, the diagnostic technique combines imaging modalities, cytological or histological analysis, and molecular testing. Prognostication and treatment planning depend heavily on classification according to histological type and receptor status (estrogen, progesterone, and HER2).

A) Types of breast cancer:

1) Breast lesions of uncertain malignant potential [b3] lesion:

Atypical ductal and lobular hyperplasia, lobular carcinoma in situ, and other uncommon miscellaneous lesions are examples of breast lesions with unknown malignant potential (B3). Online predictive models, such as the International Breast Cancer Intervention Study (IBIS Tyrer Cuzick) model or the Breast Cancer Risk Assessment Tool (BCRAT, based on the Gail model) [2], may help estimate risk for women with B3 lesions. Improvements in radiological imaging and better image-guided sampling have altered the diagnosis and treatment of B3 lesions. [1]

1) Atypical ductal hyperplasia (ADH): One of the most common B3 lesions of the breast to be diagnosed is ADH. On mammography, it is most frequently linked to masses, asymmetric densities, or clustered calcifications [3,4].A tiny focus of a low-grade, monotonous epithelial intraductal proliferation with a maximum diameter of 2 mm is known as ADH [5,6]. After the needle biopsy diagnosis of ADH, no combination of criteria has been shown to predict a low enough upgrade rate to avoid further intervention. The goal of a meta-analysis of 93 publications was to identify the imaging and patient characteristics that provide enough assurance of no-upgrade to prevent surgery. 5911 of the 6458 ADH cases in the study were treated with surgical excision, while 547 were treated with imaging follow-up. Despite the highly variable findings, they concluded that excision is advised for all individuals with ADH discovered during needle biopsy.

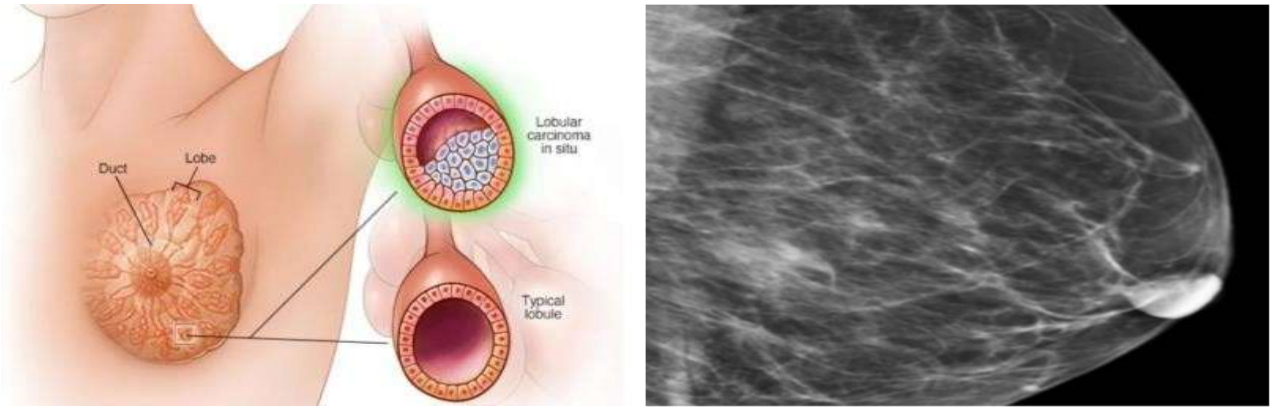

Fig.1: Lobular carcinoma in situ and atypical lobular hyperplasia

2) Lobular carcinoma in situ and atypical lobular hyperplasia: The WHO classifies classical lobular neoplasia (LN) as either atypical lobular hyperplasia (ALH) or classical LCIS, both of which are B3 lesions. DCIS is thought to be similar to pleomorphic LCIS (PLCIS) and florid LCIS. Both are either nonobligate precursor lesions (increased chance of cancer) or risk factor lesions (increased risk of BC developing in either breast), providing an 8–10 times relative risk in comparison to the general population [8]. Histologically, the lobular cells exhibit intracytoplasmic vacuoles, eccentric nuclei, and a lack of cohesiveness. Women with LCIS who did not receive additional surgery (as reported to the SEER registry) had a subsequent 10-year incidence of cancer development of 13.9% in a prospective multi-institutional trial (TBCRC 20) to determine the rate of upgrade to cancer after excision for pure LCIS on CNB. The choice of surgical procedure had no effect on BC-specific survival.[9]

2) Inflammatory breast cancer:

Since Haagsen's criteria were initially published in 1956, IBC has been defined using a number of classification schemes. [10] Despite being relatively uncommon (2% of newly diagnosed breast cancers), inflammatory breast cancer (IBC) is the deadliest type of the disease and accounts for a disproportionate number of deaths (up to 7% of all breast cancer-specific mortality). The Tumor-Node-Metastasis (TNM) classification of breast cancer provides clinical characteristics that are necessary for the diagnosis of IBC. [11] Compared to non-IBC, IBC patients are three times more likely to exhibit stage IV disease. Stage IV illness is observed in 20% to 30% of IBC patients. [12] Skin thickening and indurated skin were seen in 55% and 73% of women with IBC, respectively, in our cohort. Patients with IBC may also suffer a rapid increase in breast volume nearly concurrently with the skin alterations that are strongly suggestive of IBC. [13] in therapy consist of The first-line treatment for IBC is advised to be primary systemic therapy. Prior to systemic therapy, a surgical opinion evaluating the viability of primary resection should be acquired. All tumors that are operable or successfully downstaged should be removed after primary systemic therapy. Radiation therapy after surgery is nearly always recommended (Yamauchi et al, 2012). [14]

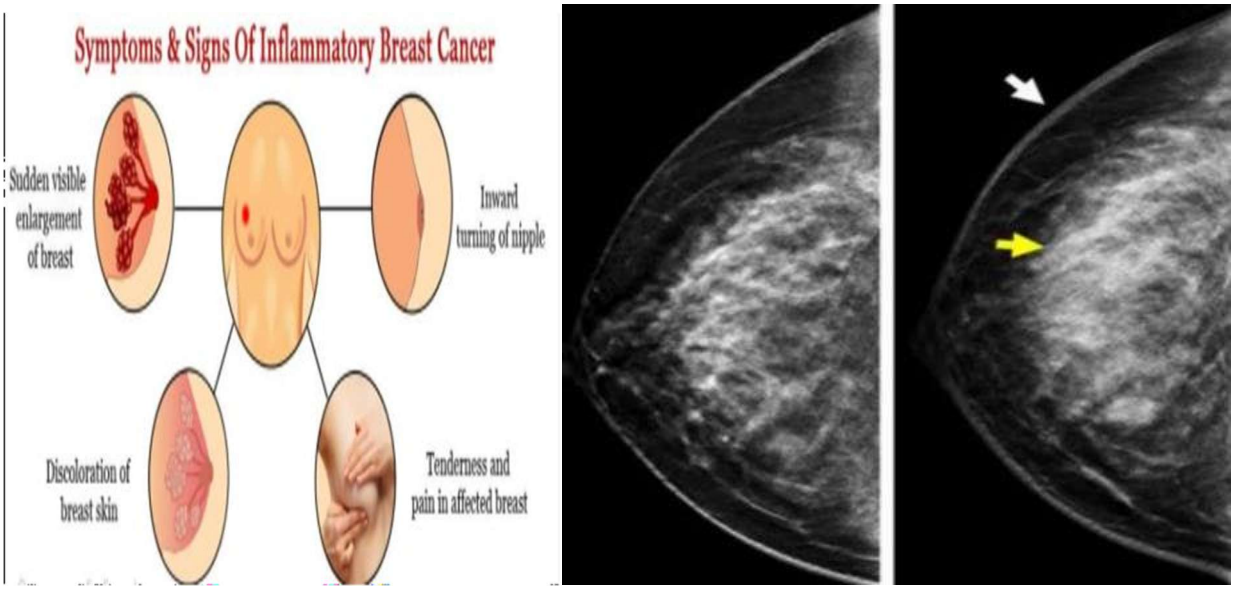

Fig.2: Inflammatory Breast Cancer

Paget's disease of breast cancer:

James Paget initially described Paget's disease of the breast (PDB), a rare skin cancer, as "an eczematous nipple changes before latent invasive breast cancer" in 1874. One Only 0.7%–4.3%2 of all new breast cancers are PDB. Histologically, PDB is defined by an infiltration of Paget cells (PCs) with many pale cytoplasm and nuclei centrally situated in the epidermal layer of the nipple-areolar complex (NAC). 3 PDB typically manifests clinically as eczematous changes or ulceration of NAC with scaling, bleeding, crusting, or leaking, frequently accompanied by discomfort or pruritus in most patients. [15] The most reliable diagnostic method is histologic examination. Although breast lesions have been verified, optical coherence tomography (OCT) and reflectance confocal microscopy (RCM) have recently surfaced as additional diagnostic tools for cases with cutaneous alterations. This could lead to new insights into the non-invasive diagnosis of MPD. [16] Anatomopathological analysis and immunohistochemistry are used to confirm the diagnosis. The mainstay of treatment is surgery, which can be conservative or aggressive depending on the degree of Paget's disease and whether there is associated with malignancy. [17]Based on hormone types:

The identification of human epidermal growth factor receptor 2 (HER-2), progesterone receptor (PR), and estrogen receptor (ER) is crucial for the classification of breast cancer and the choice of treatment approaches. The objective of this work was to use immunohistochemistry to quantify the expression of ER, PR, and HER-2 and to correlate these results with quantitative baseline Ct values determined by quantitative polymerase chain reaction (PCR). Immunotherapy can help patients with TNBC.

1) Hormone receptor positive breast cancer:

More than two-thirds of all breast cancers (BC) are caused by the expression of the estrogen receptor (ER) α and the signaling that goes along with it. Particularly in females who are perimenopausal or postmenopausal, estrogen is a well-known independent stimulator of BC development and progression. [18] Baseline is driven by progestogen, estrogen, and corticoid hormones. Androgens are the primary cause of changes in mammographic density throughout time. Additionally, a significant risk factor for breast cancer is mammographic density (MD). [19]

2) Human epidermal growth factor receptor positive breast cancer:

Changes in the epidermal growth factor receptor (EGFR) are hypothesized to encourage the migration and invasion of cancer cells, and they happen at an advanced stage of malignancy marked by metastatic competence. In this work, we have demonstrated that in two separate groups of patients with HER2-positive primary breast cancer, EGFR overexpression is a poor prognostic marker. Patients with EGFR-overexpressing tumors had poor disease-free survival in the first set, and the subgroup not receiving trastuzumab similarly had a poor prognostic impact from EGFR overexpression

(3 [1]). Additionally, in the second group of patients receiving adjuvant trastuzumab, EGFR overexpression was linked to poor overall and

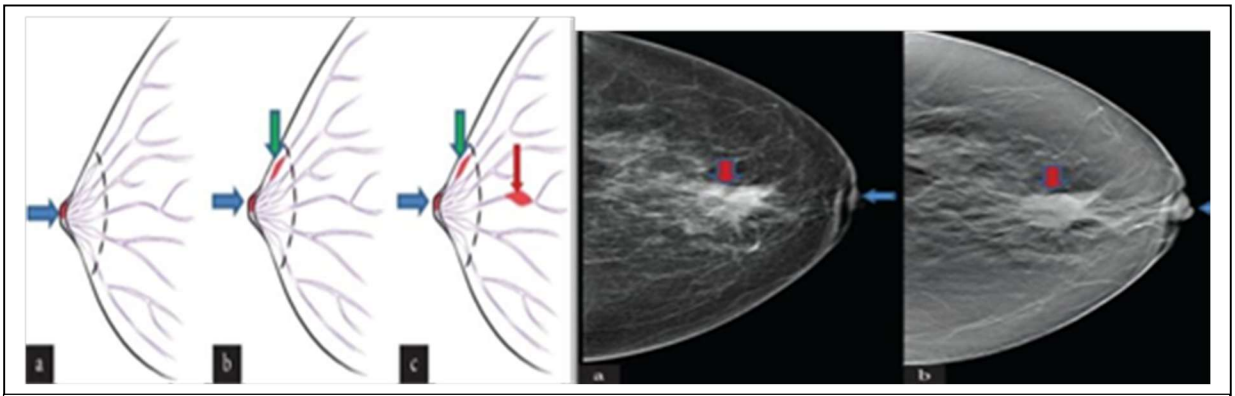

Fig.3: Paget's disease

disease-free survival. Consequently, these findings suggest that EGFR overexpression in HER2-positive primary breast tumors has predictive and prognostic relevance. [20] Trastuzumab is a very successful treatment for early-stage HER2-positive breast cancer. [21] For the majority of women with early HER2 positive breast cancer, a 12-month course of trastuzumab treatment was the standard of care; however, the majority of important RCTs mostly concentrated on patients who had a high risk of recurrence, and the 1-year duration was chosen at random. PEPDG278D is very successful in addressing the sensitivity of trastuzumab-resistant HER2- positive BC to targeted degradation of both HER2 and EGFR. According to our findings, PEPDG278D has great promise in treating individuals with HER2-positive BC who are not responding to the available HER2 inhibitors. [22, 23]

3) Triple negative breast cancer:

15–20% of all cases of breast cancer are triple negative breast cancer (TNBC). Because of its extremely aggressive characteristics, high recurrence rate, high metastatic potential, and poor overall survival, TNBC continues to be the most difficult subtype of breast cancer to treat. [26] Tumor cells can evade immune recognition and eradication, but the immune system can identify and regulate tumor progression. [27] Understanding tumor immune evasion has advanced significantly in recent decades, resulting in new strategies to prevent tumor immune escape and guarantee the eradication of cancer cells. [28] Tumor immunotherapy is the use of biological substances to either stimulate and improve the immune system or control the immune response in order to treat malignancies.[29, 30] The severe side effects of cytotoxic chemotherapy drugs, which have a substantial impact on the prognosis of triple-negative breast cancer, are intolerable to some patients. The anticancer effects are improved when the non-cytotoxic medications are used together. [31] Metformin and hemin were utilized by Lee et al. to treat triple-negative breast cancer, and by blocking mitochondrial metabolism, the combination successfully inhibited tumor growth. [32] Parthenolide and indocyanine green have complementary antitumor actions. The tumor suppression rate of indocyanine green- parthenolide thermosensitive liposomes was about 2.08 times higher than that of paclitaxel in the nude mice xenograft MDA-MB-231 tumor model, and it showed a positive preliminary safety assessment. [31]

2) Epidemiology:

In 157 out of 185 nations, breast cancer is the most common cancer among women, accounting for 670,000 deaths worldwide in 2022. Beyond individuals, children, families, communities, healthcare systems, and survivors coping with ongoing health issues and the possibility of recurrence are all affected by the wide-ranging effects of breast cancer, including its varied costs and challenges across financial, physical, emotional, and societal spheres [32]. An estimated 20 million new cases of cancer and 9.7 million fatalities were reported in 2022. 53.5 million people were predicted to be living five years after receiving a cancer diagnosis. Approximately 1 in 5 people will get cancer at some point in their lives, and 1 in 12 women and 1 in 9 men will die from the illness. [33] According to current data, breast cancer was the most frequent cancer in the world in 2020, with an incidence of 11.7% and a 6.9% global fatality rate (Siegel et al., 2020). [47]

3) Etiology:

Breast cancer affects women's quality of life and survival to varied degrees because it is the most prevalent type and the leading cause of death for women with cancer [34, 35]. Previous studies have noted that several neurological conditions, such multiple sclerosis and Alzheimer's disease, may influence the risk of breast cancer. It is unclear, nevertheless, whether these neurological disorders and breast cancer are causally related. [36] Certain neurological conditions, such as multiple sclerosis and Alzheimer's disease, have been linked to cancer [37, 38]. According to earlier research, Alzheimer's disease can lower the incidence of breast cancer [39, 40]. Furthermore, a number of factors play a crucial role in the development of breast cancer, including age, family medical history, reproductive patterns, gynecological aspects, menarche onset timing, oral

contraceptive use, hormone replacement therapy, excessive drinking, high consumption of saturated fat, and smoking. [48]

4) Clinical manifestation of breast cancer:

Breast pain affects up to 70% of women over 16 at some point in their life, with severe occurrences occurring in 10% to 20% of cases [42]. According to research, breast discomfort alone is not linked to breast cancer [43–44]. Cancer survivors frequently experience persistent discomfort. It could be brought on by cancer treatment or a painful comorbidity that already existed. [45] Although aches, pains, and stiffness in the joints and muscles are prevalent, their natural history, cause, and effects remain unknown. Oestrogen deficiency, however, has been proposed as a potentialreason. [46] Interestingly, compared to patients with other malignancies including prostate, gynecology, head and neck, urinary tract, or gastrointestinal tract, patients with breast cancer have the highest rate of sleeplessness (Savard et al., 2011). There is growing agreement that sleep disruption is linked to sadness, pain, exhaustion, and the advancement of illness. [47]

5) Diagnosis:

The most prevalent malignant tumor in women is breast cancer. Worldwide, 1.33 million women have been diagnosed with breast cancer during the last five years. In addition to physical and clinical evaluations, imaging tests including ultrasonography (US), mammography, spectral mammography, and, in certain situations, magnetic resonance imaging (MRI) serve as the foundation for diagnosis in the diagnostic procedures for identifying localized lesions in breast glands. Too many times, the core-needle biopsy operation is carried out as an inpatient rather than an outpatient treatment. When cancer is suspected based on imaging studies, the initial diagnostic technique is a core-needle biopsy [49] [50]. The simulations' findings demonstrated that the ADE–LVQ [Adaptive Differential Evolution (ADE) algorithm for feature selection and Learning Vector Quantization (LVQ)] model outperforms comparable and sophisticated models in the diagnosis of breast cancer patients. This approach lowers treatment costs while increasing the speed and accuracy of breast cancer diagnosis and prediction. As a result, using techniques based on data mining and artificial intelligence can aid in a more precise diagnosis of this illness. [51]

CONCLUSION:

Clinicians and researchers must have a thorough understanding of breast cancer kinds, their epidemiological patterns, etiology, diagnostic modalities, and clinical manifestations due to the variety of biological behavior and clinical presentation. In order to provide an updated understanding that aids early detection and successful care options for breast cancer, this study attempts to highlight current insights into these features.

REFERENCES:

1. Rubio, I. T., Wyld, L., Marotti, L., Athanasiou, A., Regitnig, P., Catanuto, G., Schoones, J. W., Zambon, M., Camps, J., Santini, D., Dietz, J., Sardanelli, F., Varga, Z., Smidt, M., Sharma, N., Shaaban, A. M., & Gilbert,
F. (2024). European guidelines for the diagnosis, treatment and follow-up of breast lesions with uncertain malignant potential (B3 lesions) developed jointly by EUSOMA, EUSOBI, ESP (BWG), and ESSO. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 50(1), 107292. https://doi.org/10.1016/j.ejso.2023.107292
2. Gail, M. H., Brinton, L. A., Byar, D. P., Corle, D. K., Green, S. B., Schairer, C., & Mulvihill, J. J. (1989). Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. Journal of the National Cancer Institute, 81(24), 1879–1886. https://doi.org/10.1093/jnci/81.24.1879
3. Cullinane, C., Byrne, J., Kelly, L., O Sullivan, M., Antony Corrigan, M., & Paul Redmond, H. (2022). The positive predictive

value of vacuum assisted biopsy (VAB) in predicting final histological diagnosis for breast lesions of uncertain malignancy (B3 lesions): A systematic review & meta-analysis. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 48(7), 1464–1474. https://doi.org/10.1016/j.ejso.2022.04.005

4. McMahon, M. A., Haigh, I., Chen, Y., Millican-Slater, R. A., & Sharma, N. (2020). Role of vacuum assisted excision in minimizing overtreatment of ductal atypia's. European Journal of Radiology, 131, 109258. https://doi.org/10.1016/j.ejrad.2020.109258
5. Rageth, C. J., O'Flynn, E. A. M., Pinker, K., Kubik-Huch, R. A., Mundinger, A., Decker, T., Tausch, C., Dammann, F., Baltzer, P. A., Fallenberg, E. M., Foschini, M. P., Dellas, S., Knauer, M., Malhaire, C., Sonnenschein, M., Boos, A., Morris, E., & Varga, Z. (2019). Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Breast cancer research and treatment, 174(2), 279–296. https://doi.org/10.1007/s10549-018-05071-1
6. WHO. Breast tumours WHO classification of tumours. Fifth ed. 2019.
7. Schiaffino, S., Calabrese, M., Melani, E. F., Trimboli, R. M., Cozzi, A., Carbonaro, L. A., Di Leo, G., & Sardanelli, F. (2020). Upgrade Rate of Percutaneously Diagnosed Pure Atypical Ductal Hyperplasia: Systematic Review and Meta-Analysis of 6458 Lesions. Radiology, 294(1), 76–86. https://doi.org/10.1148/radiol.2019190748
8. King, T. A., Pilewskie, M., Muhsen, S., Patil, S., Mautner, S. K., Park, A., Oskar, S., Guerini-Rocco, E.,Boafo, C., Gooch, J. C., De Brot, M., Reis-Filho, J. S., Morrogh, M., Andrade, V. P., Sakr, R. A., & Morrow,M. (2015). Lobular Carcinoma in Situ: A 29-Year Longitudinal Experience Evaluating Clinicopathologic Features and Breast Cancer Risk. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 33(33), 3945–3952. https://doi.org/10.1200/JCO.2015.61.4743
9. Nakhlis, F., Gilmore, L., Gelman, R., Bedrosian, I., Ludwig, K., Hwang, E. S., Willey, S., Hudis, C., Iglehart, J. D., Lawler, E., Ryabin, N. Y., Golshan, M., Schnitt, S. J., & King, T. A. (2016). Incidence of Adjacent Synchronous Invasive Carcinoma and/or Ductal Carcinoma In-situ in Patients with Lobular Neoplasia on Core Biopsy: Results from a Prospective Multi-Institutional Registry (TBCRC 020). Annals of surgical oncology, 23(3), 722–728. https://doi.org/10.1245/s10434-015-4922-4
10. HAAGENSEN C. D. (1956). Diseases of the female breast. Transactions of the New England Obstetrical and Gynecological Society, 10, 141–156.
11. Wingo, P. A., Jamison, P. M., Young, J. L., & Gargiullo, P. (2004). Population-based statistics for women diagnosed with inflammatory breast cancer (United States). Cancer causes & control: CCC, 15(3), 321–328. https://doi.org/10.1023/B:CACO.0000024222.61114.18
12. Jagsi, R., Mason, G., Overmoyer, B. A., Woodward, W. A., Badve, S., Schneider, R. J., Lang, J. E., Alpaugh, M., Williams, K. P., Vaught, D., Smith, A., Smith, K., Miller, K. D., & Susan G. Komen-IBCRF IBC Collaborative in partnership with the Milburn Foundation (2022). Inflammatory breast cancer defined: proposed common diagnostic criteria to guide treatment and research. Breast cancer research and treatment, 192(2), 235–243. https://doi.org/10.1007/s10549-021-06434-x
13. Dabi, Y., Darrigues, L., Pons, K., Mabille, M., Abd Alsamad, I., Mitri, R., Skalli, D., Haddad, B., & Touboul, C. (2017). Incidence of inflammatory breast cancer in patients with clinical inflammatory breast symptoms. PloS one, 12(12), e0189385. https://doi.org/10.1371/journal.pone.0189385
14. Rea, D., Francis, A., Hanby, A. M., Speirs, V., Rakha, E., Shaaban, A., Chan, S., Vinnicombe, S., Ellis, I. O., Martin, S. G., Jones, L. J., Berditchevski, F., & UK Inflammatory Breast Cancer Working Group (2015). Inflammatory breast cancer: time to standardise diagnosis assessment and

management, and for the joining of forces to facilitate effective research. British journal of cancer, 112(9), 1613–1615. https://doi.org/10.1038/bjc.2015.115

15. Cai, Y., Cheng, Z., Nangong, J., Zheng, X., & Yuan, Z. (2023). Using immunohistochemistry to classify the molecular subtypes of Paget's disease of the breast. Cancer Medicine, 12(13), 14104–14111. https://doi.org/10.1002/cam4.6066
16. Cantisani, C., Taliano, A., Longo, C., Astorino, S., Gomes, V., Caruso, G., Suppa, M., Guida, S., Pogorzelska-Antkowiak, A., & Pellacani, G. (2024). Reflectance Confocal Microscopy Can Help in Detecting Clinically Silent Mammary Paget's Disease. Diagnostics (Basel, Switzerland), 14(23), 2717. https://doi.org/10.3390/diagnostics14232717
17. Younes, B., Zakaria, B., Meriem, N., Benhessou, M., Ennachit, S., & El Karroumi, M. (2023). Extensive Paget's disease of the nipple: Case report. International Journal of Surgery Case Reports, 109, 108586. https://doi.org/10.1016/j.ijscr.2023.108586
18. Wahdan-Alaswad, R. S., Edgerton, S. M., Kim, H. M., Tan, A. C., Haugen, B. R., Liu, B., & Thor, A. D. (2024). Thyroid hormone enhances estrogen-mediated proliferation and cell cycle regulatory pathways in steroid receptor-positive breast Cancer. Cell cycle (Georgetown, Tex.), 23(7-8), 747–766. https://doi.org/10.1080/15384101.2023.2249702
19. Gabrielson, M., Azam, S., Hardell, E., Holm, M., Ubhayasekera, K. A., Eriksson, M., Bäcklund, M., Bergquist, J., Czene, K., & Hall, P. (2020). Hormonal determinants of mammographic density and density change. Breast cancer research: BCR, 22(1), 95. https://doi.org/10.1186/s13058-020-01332-4
20. Lee, H. J., Seo, A. N., Kim, E. J., Jang, M. H., Kim, Y. J., Kim, J. H., Kim, S. W., Ryu, H. S., Park, I. A., Im,
S. A., Gong, G., Jung, K. H., Kim, H. J., & Park, S. Y. (2015). Prognostic and predictive values of EGFR overexpression and EGFR copy number alteration in HER2-positive breast cancer. British journal of cancer, 112(1), 103–111. https://doi.org/10.1038/bjc.2014.556
21. Hu, Q., Wang, X., Chen, Y., Li, X., Luo, T., & Cao, D. (2020). Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomised controlled trials. BMJ open, 10(11), e035802. https://doi.org/10.1136/bmjopen-2019-035802
22. Yang, L., Bhattacharya, A., Peterson, D., Li, Y., Liu, X., Marangoni, E., Robila, V., & Zhang, Y. (2024). Targeted dual degradation of HER2 and EGFR obliterates oncogenic signaling, overcomes therapy resistance, and inhibits metastatic lesions in HER2-positive breast cancer models. Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy, 74, 101078. https://doi.org/10.1016/j.drup.2024.101078
23. Kim, C., Gao, R., Sei, E., Brandt, R., Hartman, J., Hatschek, T., Crosetto, N., Foukakis, T., & Navin, N. E. (2018). Chemoresistance Evolution in Triple-Negative Breast Cancer Delineated by Single-Cell Sequencing. Cell, 173(4), 879–893.e13. https://doi.org/10.1016/j.cell.2018.03.041
24. Ge, J., Zuo, W., Chen, Y., Shao, Z., & Yu, K. (2021). The advance of adjuvant treatment for triple-negative breast cancer. Cancer biology & medicine, 19(2), 187–201. https://doi.org/10.20892/j.issn.2095-3941.2020.0752
25. Li, X., Lou, C., Ren, H., Cui, L., & Chen, K. (2025). Fundamental knowledge and research regarding the role of immunity in triple-negative breast cancer from 2014-2024: A bibliometric analysis. Human vaccines & immunotherapeutics, 21(1), 2483022. https://doi.org/10.1080/21645515.2025.2483022
26. Drake, C. G., Jaffee, E., & Pardoll, D. M. (2006). Mechanisms of immune evasion by tumors. Advances in immunology, 90, 51–81. https://doi.org/10.1016/S0065-2776(06)90002-9
27. Yang Y. (2015). Cancer immunotherapy: harnessing the immune system to battle

cancer. The Journal of Clinical Investigation, 125(9), 3335–3337. https://doi.org/10.1172/JCI83871

28. Chen, D. S., & Mellman, I. (2017). Elements of cancer immunity and the cancer immue set point. Nature, 541(7637), 321–330. https://doi.org/10.1038/nature21349
29. Liu, K., Mao, X., Li, T., Xu, Z., & An, R. (2022). Immunotherapy and immunobiomarker in breast cancer: current practice and future perspectives. American journal of cancer research, 12(8), 3532–3547.
30. Jin, X., Lu, X., Zhang, Z., & Lv, H. (2020). Indocyanine Green-Parthenolide Thermosensitive Liposome Combination Treatment for Triple-Negative Breast Cancer. International Journal of Nanomedicine, 15, 3193–3206. https://doi.org/10.2147/IJN.S245289
31. Lee, J., Yesilkanal, A. E., Wynne, J. P., Frankenberger, C., Liu, J., Yan, J., Elbaz, M., Rabe, D. C., Rustandy,
F. D., Tiwari, P., Grossman, E. A., Hart, P. C., Kang, C., Sanderson, S. M., Andrade, J., Nomura, D. K., Bonini, M. G., Locasale, J. W., & Rosner, M. R. (2019). Effective breast cancer combination therapy targeting BACH1 and mitochondrial metabolism. Nature, 568(7751), 254–258. https://doi.org/10.1038/s41586-019-1005-x
32. Liao L. (2025). Inequality in breast cancer: Global statistics from 2022 to 2050. Breast (Edinburgh, Scotland), 79, 103851. https://doi.org/10.1016/j.breast.2024.103851
33. Morgan, E., Soerjomataram, I., & Joshi, S. (2024, May). Burden and trends of breast cancer worldwide: Opportunities for prevention? (Webinar presentation/summary of findings). International Agency for Research on Cancer (IARC).
34. Papadimitriou, N., Dimou, N., Gill, D., Tzoulaki, I., Murphy, N., Riboli, E., Lewis, S. J., Martin, R. M., Gunter, M. J., & Tsilidis, K. K. (2021). Genetically predicted circulating concentrations of micronutrients and risk of breast cancer: A Mendelian randomization study. International journal of cancer, 148(3), 646– 653. https://doi.org/10.1002/ijc.33246
35. Johnson, K. E., Siewert, K. M., Klarin, D., Damrauer, S. M., VA Million Veteran Program, Chang, K. M., Tsao, P. S., Assimes, T. L., Maxwell, K. N., & Voight, B. F. (2020). The relationship between circulating lipids and breast cancer risk: A Mendelian randomization study. PLoS medicine, 17(9), e1003302. https://doi.org/10.1371/journal.pmed.1003302
36. Ren, F., Yang, C., Feng, K., Shang, Q., Liu, J., Kang, X., Wang, X., & Wang, X. (2024). An exploration of causal relationships between nine neurological diseases and the risk of breast cancer: a Mendelian randomization study. Aging, 16(8), 7101–7118. https://doi.org/10.18632/aging.205745
37. Dong, Z., Xu, M., Sun, X., & Wang, X. (2023). Mendelian randomization and transcriptomic analysis reveal an inverse causal relationship between Alzheimer's disease and cancer. Journal of translational medicine, 21(1), 527. https://doi.org/10.1186/s12967-023-04357-3
38. Melamed, E., & Lee, M. W. (2020). Multiple Sclerosis and Cancer: The Ying-Yang Effect of Disease Modifying Therapies. Frontiers in immunology, 10, 2954. https://doi.org/10.3389/fimmu.2019.02954
39. Driver J. A. (2014). Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence. Biogerontology, 15(6), 547–557. https://doi.org/10.1007/s10522-014-9523-2
40. Freedman, D. M., Wu, J., Chen, H., Kuncl, R. W., Enewold, L. R., Engels, E. A., Freedman, N. D., & Pfeiffer,
R. M. (2016). Associations between cancer and Alzheimer's disease in a U.S. Medicare population. Cancer medicine, 5(10), 2965–2976. https://doi.org/10.1002/cam4.850
41. Hongell, K., Kurki, S., Sumelahti, M. L., & Soilu-Hänninen, M. (2019). Risk of cancer among Finnish multiple sclerosis patients. Multiple sclerosis and related disorders, 35, 221–227. https://doi.org/10.1016/j.msard.2019.08.005
42. Kataria, K., Dhar, A., Srivastava, A., Kumar, S., & Goyal, A. (2014). A systematic review

of current understanding and management of mastalgia. The Indian journal of surgery, 76(3), 217–222. https://doi.org/10.1007/s12262-013-0813-8

43. Neal, R. D., & Morley, S. (1999). Value of breast imaging in women with painful breasts. Negative results are not reassuring. BMJ (Clinical research ed.), 318(7189), 1009.
44. Mohallem Fonseca, M., Lamb, L. R., Verma, R., Ogunkinle, O., & Seely, J. M. (2019). Breast pain and cancer: should we continue to work-up isolated breast pain?. Breast cancer research and treatment, 177(3), 619–627. https://doi.org/10.1007/s10549-019-05354-1
45. Glare, P. A., Costa, D. J., & Nicholas, M. K. (2022). Psychosocial characteristics of chronic pain in cancer survivors referred to an Australian multidisciplinary pain clinic. Psycho-oncology, 31(11), 1895–1903. https://doi.org/10.1002/pon.5975
46. Fenlon, D., Powers, C., Simmonds, P., Clough, J., & Addington-Hall, J. (2014). The JACS prospective cohort study of newly diagnosed women with breast cancer investigating joint and muscle pain, aches, and stiffness: pain and quality of life after primary surgery and before adjuvant treatment. BMC cancer, 14, 467. https://doi.org/10.1186/1471-2407-14-467
47. Zhu, W., Li, W., Gao, J., Wang, L., Guo, J., & Yang, H. (2023). Factors associated with the sleep disturbances of people with breast cancer during chemotherapy in China: A cross-sectional study. Nursing open, 10(8), 5453–5461. https://doi.org/10.1002/nop2.1784
48. Yao, L. X., Zhou, Y. B., Yuan, Y. X., Li, X. F., & Li, X. F. (2024). Network meta-analysis evaluating the impact of diverse exercise regimens on quality of life in women post-breast cancer surgery. Medicine, 103(42), e40009. https://doi.org/10.1097/MD.0000000000040009
49. Lorek, A., Śliwczyński, A., Więckowska, B., Stawowski, B., Dagiel, J., & Gawrychowski, J. (2018). Analysis of Diagnostic Methods for Focal Lesions in Breast Glands with Use of Open Surgical Biopsies and Core- Needle Biopsies in Poland. Medical science monitor : international medical journal of experimental and clinical research, 24, 4974–4981. https://doi.org/10.12659/MSM.908658
50. Linebarger, J. H., Landercasper, J., Ellis, R. L., Gundrum, J. D., Marcou, K. A., De Maiffe, B. M., Hudak, J. M., & Andersen, J. J. (2012). Core needle biopsy rate for new cancer diagnosis in an interdisciplinary breast center: evaluation of quality of care 2007-2008. Annals of surgery, 255(1), 38–43. https://doi.org/10.1097/SLA.0b013e31823e00bf
51. Wang D. (2023). Toward improving the performance of learning by joining feature selection and ensemble classification techniques: an application for cancer diagnosis. Journal of cancer research and clinical oncology, 149(19), 16993–17006. https://doi.org/10.1007/s00432-023-05422-6

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