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The Epidemiology and Pathophysiology of Breast Cancer

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ABSTRACT: Breast cancer is one complex disease with different molecular and cellular changes. The pathophysiologic features of cancer are based on genetic, hormonal, and environmental influences; thus the disease has several subtypes that differ in behavior and response to treatment. The pathophysiology of breast cancer includes a number of factors that interplay among genetic mutations, hormonal influences, and microenvironment factors. Although these have been greatly elucidated by current research, more detailed understanding is requisite for further enhancement in the outcomes of treatment and development of individualized therapies. New technologies and methodologies are quick to surface; however, they promise better deciphering of breast cancer complexity and consequently better routes for interventions aimed at maximum efficacy. This literature review serves to synthesize the most recent findings on the pathophysiology of breast cancer in light of its complexity, identification of gaps in the current state of knowledge, and suggestions for directions future research should take.

INTRODUCTION

Breast cancer (BC) has come out as a significant public health issue worldwide being the second most common cancer among women and the leading cause of cancer morbidity and death. The worldwide burden of breast cancer is immense, which is reported to make up about 11.6% of the total cancer cases and 18.4% of cancer deaths based on 2018 estimates (Bray et al., 2018). This already alarming number only points further to the dire need for such research and intervention strategies aimed at the prevention and cure of the disease.

Breast cancer is still the most frequent cause of both morbidity and mortality related to cancer among women worldwide. One of the most vital biomarkers in breast cancer is the human epidermal growth factor receptor 2 (HER2), overexpressed in around 20-25% of cases of BC. Presence of HER2 associates with more invasive disease and bad prognosis. The pathophysiology of breast cancer includes a number of factors that interplay among genetic mutations, hormonal influences, and microenvironment factors (DeSantis et al., 2017 ; Keren et al., 2018).

EPIDEMIOLOGY AND MORTALITY RATES

Another trend that has captured much attention is the rise in BC incidence across continents. This year, BC being in front of lung cancer as the most detected cancer worldwide, with an estimated 2.3 million new cases, 11.7% share of all cancer incidences. The flip-flop indicates an epidemiologically dramatic transition and change in risk factors, diagnostic potentials, and probably lifestyle factors affluently affecting the prevalence of BC (Sung et al., 2021).

It is also the most common type of cancer among women when considering just the United States. Statistics have it that in 2013 alone just over 232,340 new cases of invasive BC were to be expected, along with 39,620 deaths resulting from BC (DeSantis et al., 2019). This trend would go on into the following year as an estimated new 231,840 cases and 40,290 deaths were forecast for 2015 (Xia et al., 2022). The persistent high incidences and mortalities thus reiterate the fact that BC keeps to be a threat to women's health. The epidemiological landscape is in constant transition for BC. For example, reports in 2011 said that BC at that time was 23% of all confirmedly diagnosed cancer records and 14% of cancer deaths (Jemal et al., 2011). These figures represent quite a marked increase in BC incidence over the past decade and justify continuous monitoring and studying to apprehend the reasons for this phenomenon. Additionally, the rise of BC as the major site of cancer diagnosis especially among women is a disturbing trend repeated consistently (Feng et al., 2019). The increased incidence is associated with changes in lifestyle, reproductive factors, and environmental exposures. These relationships are worthy of more detailed consideration in the future (DeSantis et al., 2014).

Geographic disparities characterize BC epidemiology; particularly, between developed and less developed countries. It is the most common cancer of females worldwide with highest incidence rates in less developed regions. The higher mortality rates that are

seen in these regions may be due to limited access to healthcare, diagnosis done at an advanced stage and scant treatment modalities (Torre et al., 2015).

Conversely, developed countries tend to report higher incidence rates but relatively lower mortality rates. The convergence of incidence rates between White and Black females in the U.S. suggests changing dynamics in risk exposure and practices for early detection. This disparity in outcomes indicates a complex interplay of socio-economic, racial, healthcare related factors that require further investigation - not one excerpted verbatim from any single source, but these were the instructions given for each transformation (DeSantis et al., 2016).

PATHOPHYSIOLOGY AND RISK FACTORS

The association between hormone therapy and BC incidence is well known. According to Beral et al. (2011), women using current hormonal therapies face an excess risk of BC, predominantly those using oestrogen–progestin formulations, especially when therapy starts around the menopausal time. This indicates the importance of hormonal components in the development of BC. Further, as per Hershman et al. (2010), the side effects accompanying hormonal therapies have implications for diseases of the breast and heart, guiding that the benefits of treatment be weighed against potential risks.

Mutation in the ESR1 ligand-binding domain has been associated with hormone-resistant BC, as identified in this study (Toy et al., 2013). Whether such mutations have a role in the development of resistance by 'genuine' BC has enormous therapeutic implications in the management of hormone receptor-positive BC. Identification of mechanisms through which such mutations lead to resistance will ensure the development of appropriate targeted therapies.

Breast cancer is a group of subtypes based on hormone receptor positivity, HER2 overexpression, or overamplification and triple negativity for the disease to progress (Keren et al., 2018). Each of these subtypes has different molecular features that add to the heterogeneity of the disease. Łukasiewicz et al. (2021) have stated that triple-negative BC is usually with damaging mutations in predisposition genes, indicating a major role of inheritance in its pathophysiology. Besides, it has been revealed by Couch et al.(2015) that new areas of clonal evolution and driver mutations are connected with resistance to advanced estrogen receptor-positive BCs, thereby representing changing genes' dynamic and evolving landscape.

Indeed, the tumor microenvironment has a very vital influence on BC progression. Now among the recognized key factors that affect tumor behavior are changes in immune cell composition and extracellular matrix alterations . This had recorded the source for the previous sentence. According to Keren et al. (2018), using multiplexed ion beam imaging one could uncovered a structured tumor-immune microenvironment in triple-negative BC, which may better indicate the prognostic relevance of the interplay between tumor cells and the immune system.

Indeed, recent studies have also delved into immune-priming strategies for improving efficacy in metastatic triple-negative BC (Voorwerk et al., 2019). It is aimed at using the immune microenvironment for increasing response rates of immunotherapy, especially in resistant cases, to elicit better responses. Signaling Pathways and Resistance Mechanisms.

Proper treatment of BC requires the correct determination of HER2 status. According to Wolff et al. (2013), assessment for HER2 status should be done in all patients with invasive BC. This recommendation serves to underline the independent value of HER2 as a prognostic factor and, at the same time, a predictive factor for treatment decisions. (Wolff et al., 2013).

It has been proved that patients with HER2-positive BC have a better prognosis compared to those with HER2-negative disease. For example, Minckwitz et al. in 2017 stated that women with HER2-positive disease who had received trastuzumab featured a much better prognosis than those with HER2-negative diseases, thus indicating the key place of HER2 in stratification of treatments.

Another critical component of BC pathophysiology is the PI3K/AKT/mTOR signaling pathway, which regulates cell proliferation and survival (Almeida et al., 2017). Since active participation by this pathway is found, it results in abnormal growth of the tumor as well as resistance against therapies, underlining the very urgent need for interventions that can specifically modulate these signaling cascades in their competence in clinical practice. According to Semenza (2016), the hypoxic tumor microenvironment commands the progression of BC. The metabolic alterations elicited by hypoxia are indeed pro-oncogenic and resistance-promoting, thereby offering future prospective areas for studying new dimensions of developing therapeutics against the disease.

With the development of targeted therapies, the scenario has completely changed for HER2-positive BC treatment. The use of the monoclonal antibody reactive to HER2, trastuzumab, as adjuvant-based therapy is documented to considerably improve disease-free and overall survival rates (Slamon et al., 2011). Further, among patients left with residual invasive disease after neoadjuvant therapy (Minckwitz et al, 2017). Note a 50% decrease in the risk for relapse upon adding another 1 of a kind, T-DM1 (trastuzumab emtansine), relative to giving trastuzumab only (2019). The data suggests that upon efficaciously reversing resistance with brain-penetrant HER2-targeted therapies such as tucatinib, continuous therapy with an anti-HER2 agent plus chemotherapy could be useful. Furthermore, based on single-arm studies in relapsed settings, T-DM1 emerged as one of the standards as well, though Modi discussed this in heavily pretreated patients. This has also been underscored by being a choice for treatment. Research into HER2-low metastatic BC also indicates a changing perspective on the role of HER2 as new treatment paradigms develop (Modi et al., 2022).

After treatment studies have continued to portray the advantages of T-DM1. As proven by Verma et al. (2012) T-DM1 prolonged progression-free and overall survival more significantly with reduced toxicity as compared with lapatinib plus capecitabine among the advanced stages of HER2-positive BC. Dawood et al. (2010) reiterated this by observing better outcomes in patients receiving T-DM1 hence, further solidifying its efficacy and safety profile in heavily pretreated populations. Vogel et al. (2023) reported the effectiveness and good tolerability of single-agent trastuzumab as first-line therapy in patients with overexpression HER2 3+. This finding reflects the place of trastuzumab as a cornerstone in the management of metastatic BC.

CONCLUSION

This is a phylogeny for BC that can span genetic mutations, hormonal influences and microenvironmental factors. Up to today research has done very intensive work towards understanding these interactions that drive this pathophysiology. It will yet require more informed details to improve upon the results in treatment and developing personalized therapies. The technologies and new approaches are therefor claimed to have the ability to demystify the secrets of BC complexities hence effective interventions. HER2 over-expression in BC remains an area that has attracted extensive research with manifold achievements in detection and treatment. The role of HER2 in the pathogenesis is evolving with numerous therapeutic options that gives many possible interventions improving the outcomes of the patients. However, more targeted research aimed at addressing existing knowledge gaps would go a long way in better handling of HER2 positive breast cancer, thus enhancing patient care.

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