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Understanding Breast Cancer: A Key Emphasis on Molecular Signalling Pathways and Phytotherapy

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Abstract

Globally, 2.3 million women have been diagnosed with breast cancer, making it a significant global public health concern [1]. By 2040, the annual rate of new cases is projected to reach 3 million, an increase of nearly 40 percent from 2020 [2]. Lifelong exposures to a variety of endogenous and exogenous variables, as well as the interaction of genetic elements, contribute to the complexity of breast cancerogenesis [3]. Normal human growth is strictly regulated by the signalling pathways that allow cells to communicate with one another and their surroundings. Breast carcinoma is caused by alterations in signalling networks that regulate cell motility, differentiation, cell proliferation, and cell apoptosis. Surgery, radiotherapy, chemotherapy, hormonal therapy, and targeted therapy are the primary forms of breast cancer treatment [4]. However, phytotherapy have shown promise because they are more effective, safer, and have a lower resistance rate than hormone-targeting and chemotherapeutics [5]. Alternatively, plant-derived natural compounds that have anti-cancer potential by targeting impaired signalling pathways such as Wnt/β-Catenin, NF-κB, PI3K/Akt/mTOR, and epithelial-to-mesenchymal-related pathways. This comprehensive review discusses the actual incidence of breast cancer, its risk factors, diagnostic methods, associated pathogenesis theories, and the universal classification of malignant breast tumours. Finally, we accentuate on the role of phytocompounds to reverse the associated molecular abnormalities, for more effective therapy and a better management of breast carcinomas.

Keyword: Breast cancer; Phytotherapy; Signalling pathways; Management

Introduction

As the most prevalent disease among women worldwide, breast cancer poses a major global public health issue. Globally, a 2.3 million instances of breast cancer in women are identified [1]. The annual rate of new instances of breast cancer is expected to approach 3 million by 2040, an increase of almost 40% from 2020. Similarly, mortality from breast cancer is set out to grow more than 50%, from 685,000 in 2020 to 1 million in 2040 [2]. Breast cancerogenesis is among the most complex of all malignancies due to lifelong exposures to a variety of endogenous and exogenous variables, as well as the interaction of genetic elements [6]. Complex signalling pathways, which enable cells to communicate with one another and with their environment, tightly regulate normal human growth [6-10]. Unsurprisingly, signalling pathways may become hyper-activated as a result of proto-oncogene activating mutations, or significantly hypo-activated when tumour suppressors are inactivated. In general, genetic and epigenetic changes that enable cells to bypass the mechanisms that ordinarily regulate their proliferation, survival, and migration are responsible in cancer development [7-9]. Numerous of these changes correspond to signalling networks that control cell motility, cell differentiation, cell proliferation, and cell death [11].

The main types of treatment for breast cancer are surgery, radiotherapy, chemotherapy, hormonal therapy, and targeted therapy. Surgery is used in the treatment of localized breast cancer, followed by neoadjuvant therapy and adjuvant therapy. Radiotherapy is used after surgery to reduce the risk of local recurrence of cancer [12]. Natural products as cancer treatments have been promising, as they are more effective, safer, and have a lower incidence of resistance than hormone-targeting and chemotherapeutics [13-15]. Alkaloids, flavonoids, and polyphenols are only few of the many plant-derived natural chemicals that have anti-cancer potential by targeting defective signalling pathways like Wnt/β-Catenin, NF-κB, and PI3K/Akt/m-TOR. Plant-based compounds can inhibit cell growth and proliferation, angiogenesis, epithelial-to-mesenchymal transition, and migration and metastasis. In this comprehensive review, we detail the actual prevalence of breast cancer cases, the intrinsic and extrinsic risk factors, the diagnosis modalities, associated pathogenesis theories, and the universal classification of breast malign tumours. We highlight the main impaired signalling pathways implicated in breast cancer development and progression. Finally, we accentuate on the role of phytocompounds to reverse the molecular impairments of breast carcinomas.

Prevalence of Breast Cancer

In women, Breast Cancer (BC) is the most common form of cancer, with 2.3 million new cases, accounting for 11.7% of all cancer cases in both sexes, and 24.5% within females, have been diagnosed worldwide [1]. BC has surpassed lung cancer (11.4% for both sexes, and 8.4% for females), as the top cause of cancer incidence [16]. Even though only 8.3% of breast cancer cases were diagnosed in Africa, the death rate was higher at 12.5% [2,16,17]. Estimates put the annual rate of new instances of breast cancer at around 3 million by 2040, an increase of over 40% from 2020. The projected number of fatalities attributable to breast cancer is also projected to rise by over 50%, from 685,000 in 2020 to 1 million in 2040 [2]. It is projected that the incidence of breast cancer in Africa would rise by 49% faster than in any other region in 2040 [2,17]. This incidence remains under-reported due to a lack of infrastructure for cancer detection in resource-constrained countries in sub-Saharan Africa, as only 20 of 46 sub-Saharan African nations are represented in cancer incidence report by the International Association of Cancer Registries [16-18].

Risk Factors

The multifactorial origin of breast cancer explains the persistence of the etiopathological problem of breast carcinogenesis with the orientation increasingly towards research and the incrimination of several risk factors [19-20].

Intrinsic Factors

Genetic predisposition: Family history plays a significant role in breast cancer risk [21]. Most breast cancer patients (between 3 and 10 percent) have a hereditary propensity that they pass on to their daughters [3]. A woman's risk of acquiring breast cancer nearly doubles if she has a first degree relative (mother, sister, or daughter) who has been diagnosed with breast cancer. While having two first-degree relatives with the disease increases the woman's risk about 3-fold [3]. 85% of them are connected to breast cancer-related gene 1 and 2 mutations (BRCA1 and BRCA2). High frequencies of mutations in BRCA1 and BRCA2 have been observed in breast cancer patients of African ancestry [22-24]. These mutations have been associated with moderate or high risk of breast cancer in African American women [23,25], who have a higher incidence of breast cancer at young ages, a higher incidence of aggressive mammary tumours, and a 42% higher breast cancer mortality rate than non-Hispanic white women [26,27]. A woman who carries a mutation in one of these genes during the course of her lifetime has a 40% to 80% chance of developing breast cancer. Studies suggest that the type of gene in question, family history of breast cancer, and age all have a role [3,21,28].

Age: Since breast cancer is almost one hundred times more common in women than in men, merely being a woman is the biggest risk factor. The older the woman, the higher the risk of getting breast cancer [29,30]. Increases in serum free estradiol concentrations are likely responsible for the estimated 50% increase in breast cancer risk in postmenopausal women [29].

Race/Ethnicity: Outcomes vary among racial and ethnic minority populations, as well as other underserved populations, both of which experience health disparities [31]. In general, white non-Hispanic women continue to have the highest breast cancer incidence rate. In contrast, the mortality rate associated with this cancer is much higher in black women, who also have the lowest survival rates [28,32,33]. Disparities in incidence and mortality rates include socioeconomic status, late stage of breast cancer at diagnosis, biologic and genetic differences in tumours, differential access to health care, and disease-related molecular mechanistic differences [33].

Reproductive factors: Reproductive risk factors associated with breast cancer risk include age at menarche, number of pregnancies, age at first birth, duration of breastfeeding, and age at menopause [34]. Early menarche, late menopause, or lack of breastfeeding is associated with a higher risk of developing breast cancer due to a longer period of exposure to oestrogen activity [35]. Early age at menarche is possibly also associated with an overall poorer prognosis (high tumor grade and lymph node involvement) [36]. On the other hand, oestrogen deficiency, premature menopause, castration, duration of breastfeeding, late age of first menstruation and use of anti-oestrogens are accompanied by a reduced risk of breast cancer [37]. Aberrant hormonal exposure before puberty may also increase the risk, but high oestrogen levels during pregnancy decrease it [35]. Women with a history of preeclampsia during pregnancy or children born to a preeclamptic pregnancy are at lower risk of developing breast cancer, where the deregulated hormone levels during preeclampsia show a protective effect preventing from breast carcinogenesis [38]. No association between the increased breast cancer risk and abortion was stated so far [39]. Moreover, the incidence of breast cancer is significantly lower in populations where breastfeeding was frequent and prolonged [40]. Breastfeeding for 12 months can reduce the risk of developing breast cancer by 4.3% to 4.5% [41] with no significant difference depending on the age of the patients [34].

Mammary tissue density: Greater breast density is seen in women who are younger and have lower Body-Mass Index (BMI), who are pregnant or breastfeeding, as well as while taking hormone replacement treatment. In general, the risk of breast cancer increases with breast tissue density [41-44].

Personal antecedent

i. History of breast cancer: A woman, who has had breast cancer, has a 2.9% risk of breast cancer recurrence in the treated breast if she has a family history, and 1.45% with no family history [45].

ii. Breast conditions: non-proliferative or minimally proliferating lesions, including simple cystic changes, mild degrees of hyperplasia or Fibroadenoma, are not associated with an increased risk of cancer [46]. However, proliferative lesions without atypia increase this risk up to two times; while atypical lobular or ductal hyperplasia is at risk of 7 to 10 times [21,47,48].

iii. Exposure to medical radiation: chest irradiation and repeated mammography examinations increase the risk of breast cancer. The incidence of this risk is influenced by the age at which screening begins and its frequency. In addition, this risk is higher in women with high breast density because they receive larger doses [49].

iv. Previous radiotherapy: Patients who get radiation therapy before the age of 30 have an increased risk of developing breast cancer [50]. Patients, who undergo radiotherapy, with a history of breast cancer in their family, have an increased risk of developing the disease themselves [51].

Extrinsic Factors

Physical activity and BMI: A decrease in body mass, another risk factor for breast cancer, may result with increased physical activity [52]. Therefore, it has been challenging to identify the separate contribution of physical activity and BMI to breast cancer risk. When it comes to hormones, being overweight is linked to an environment that encourages tumour growth in the breast. In addition, getting regular exercise reduces the negative effects of oestrogen, shortening the luteal phase of the ovulation cycle, and decreases cumulative exposure to ovarian hormone [53]. Moreover, women in office jobs and those who spend long periods of time sitting at work are at high risk of developing breast cancer [53,54].

Alcohol consumption: Excessive alcohol intake increases the level of oestrogen, arouses hormonal imbalance, cause fat gain and elicits high BMI levels, thus increase the risk of breast cancer [20]. Its consumption before the first pregnancy induces carcinogenic events and morphological alteration in mammary glands, leading to 7-10% increase in breast cancer risk [55].

Smoking: Carcinogens found in tobacco, from direct and indirect smoking, increase the rate of mutations in tumour suppressor genes, mainly P53 [20]. Moreover, long time smoking before the first full-term pregnancy increase the risk of breast cancer in females with family history [56].

Diagnosis of Breast Cancer

Imaging

Image examination is an important method in early diagnosis of breast cancer. It includes two-dimensional ultrasonography and magnetic resonance imaging, which both have good sensitivity and specificity [57]. However, in contrast to ultrasonography, magnetic resonance imaging is complicated, time-consuming and insensitive to calcification [58]. Furthermore, For the purpose of diagnosing calcifications in lesions and displaying the shape and border of breast lumps, mammography examinations are commonly utilized and widely applied for breast disease screening due to their low cost, ease of use, low invasiveness, and high accuracy [59]. However, mammary tumours could not be detected in dense-tissue breasts using these imaging techniques. Therefore, the introduction of digital mammography, called "scintimammography" or "Molecular breast imaging", provides high-resolution functional images of the breast. It utilizes small semiconductor-based γ-cameras in a mammographic configuration to detect small breast lesions after injection Tc-99m sestamibi [60,61].

Breast Biopsy

To improve the diagnostic accuracy, one of the two types of needle biopsies are used simultaneously with breast imaging [60]:

i. Fine needle aspiration cytology: A small needle is used to remove cells and/or fluid from the suspicious lesion in the breast [62].

ii. Core needle biopsy: using a larger needle, small cylinders of tissues are removed, and analysed by a pathologist for malignant cells [63].

Immunohistochemistry

Immunohistochemistry (IHC) could be used to differentiate the histological type of breast cancers. Hematoxylin and eosin stained sections provide for quick and easy detection to differentiate ductal from lobular carcinomas [64-66]. However, in cases when the morphology is unclear, IHC can be useful to distinguish between ductal and lobular carcinomas using E-cadherin, high molecular weight cytokeratin, P120, and β-catenin, as a molecular marker, where membrane staining is positive (for all this markers) in ductal carcinomas, while it is negative in lobular carcinomas [64,67].

In addition, IHC could be used to differentiate between in situ (confined with confined by a basement membrane) and invasive mammary carcinomas (break through the basement membrane and spreads throughout the surrounding stroma). Histologically, the absence of myoepithelial cells around a lesion is typical of invasion [68], hence, absence of myoepithelial cells markers, including calponin, smooth muscle myosin heavy chain, and p63, is a marker of invasiveness [69]. Moreover, hormone receptors (oestrogen and progesterone receptors) can be informative for prognosis, mainly to predict endocrine therapy response [64,70,71]. Immunohistochemistry reactions to HER2/neu is another marker for sensitivity to Herceptin (trastuzumab), and resistance to Tamoxifen [70-73]. IHC could also be used to assess markers of apoptosis, cell proliferation, angiogenesis and metastasis [71].

Pathogenesis and Classification of Breast Cancers

The two leading models accounting for breast carcinogenesis are the sporadic clonal evolution model, also called stochastic model, and the cancer stem cell model, also called hierarchical model [74,75]. According to the sporadic clonal evolution hypothesis, any breast epithelial cell with advantageous genetic and epigenetic alterations is selected over time to contribute to tumour progression. However, the alternative hierarchical model postulates that only stem and progenitor cells can initiate and maintain tumour progression. Nevertheless, stem cells might undergo clonal evolution, providing a dynamic link between the two models [74]. There are numerous forms of breast cancer that can develop in various parts of the mammary gland, including the ducts, lobules, and tissue in between. For this reason, the type of breast cancer is determined by the damaged cells. Cancers of the breast are divided into carcinomas and sarcomas [3]. 95% of all cancers are adenocarcinomas: breast cancers that arise from the mammary epithelium include in situ or non-invasive and invasive carcinomas. Sarcomas, on the other hand, are a rarer type of breast cancer (1% of breast cancer) caused by changes and transformations of stromal cells. Histologically, there are over 20 kinds of invasive malignancies. Intra-ductal carcinoma of the non-specific form is the most prevalent. This kind accounts for 70% to 80% of all invasive cancers, followed by invasive lobular carcinomas (about 10% of breast cancers) [76]. Less common histological forms include mucinous, cribriform, micropapillary, papillary, tubular, medullary, metaplastic, and apocrine carcinomas.

At a molecular level, human epidermal growth factor 2 (HER2), oestrogen and progesterone hormone receptors status allow for sub categorization of breast cancer, which is otherwise a highly heterogeneous disease [77-80]. Consequently, there are four distinct types of breast tumours based on the presence or absence of the aforementioned receptors: (1) Luminal A, which expresses both hormone receptors and HER2-negative; (2) Luminal B, which expresses both hormone receptors and HER2; (3) HER2 enriched, which does not expresses hormone receptors but it is HER2-positive; and (4) Triple-Negative Tumours (TNBC), which express none of these receptors [6,81]. TNBC is notoriously linked to a worse prognosis, shorter overall survival time, and a shorter time until the cancer recurs [82]. These tumours can adapt novel molecular aberrations and network alteration in order to utilise biochemical pathways that are not affected by typical pharmaceutical treatments. Based on its aggressive clinicopathological features, TNBC treatment typically combines chemotherapy, surgery, and radiation therapy [83-85]. The lack of targeted medications designed particularly for triple-negative breast cancers, in contrast to the other subtypes, has increased the need for developing novel therapeutic approaches beyond chemotherapy.

Luminal Breast Cancer

Luminal A tumours (40% to 50% of invasive breast cancers) are associated with low grade and a good prognosis, while luminal B cancers tend to be of higher grade and associated with worse prognosis due

to the lower expression of ER-related genes, but higher expression in proliferation-related genes [6,76,86,87].

HER2+ Enriched Breast Cancer

The HER2-overexpressing subtype, comprising 15% of all invasive breast cancers, is characterized by the overexpression of HER2 signalling-associated genes and genes located in HER2 amplicon on chromosome 17q12. HER2-overexpressing tumours are likely to be high grade, ER and PR-, and run an aggressive clinical course. A minority of HER2-positive cancers coexpress ER and are classified as luminal B [6,76,86,87].

Triple-Negative Breast Cancer

Triple-Negative Breast Cancer (TNBC) is a heterogeneous group of breast tumours characterised by the absence of the ER, PR, and HER2 proteins. They account for around 20% of all breast cancers. TNBC is more prevalent among African-American women and women younger than 40 [70,81,88]. The vast majority (about 80%) of breast tumours resulting from BRCA1 germline mutations are TNBC, whereas 11-16% of all TNBC carry BRCA1 or BRCA2 germline mutations. TNBC tends to be aggressive on a biological level and is frequently associated with a poorer prognosis [6,76,86,87].

Main Signalling Pathways Involved in Breast Cancerogenesis

Epidermal growth factor signalling pathway is one of the major players in breast cancer. Epidermal Growth Factor Receptors (EGFRs), consist of four members (HER1, HER2, HER3, and HER4) are overexpressed in breast cancer tissues and is associated with higher aggressiveness and poor clinical outcomes [89]. EGFRs possess seven different ligands including Epidermal Growth Factor (EGF), tumour growth factor-alpha (TGFα), betacellulin, heparin-binding EGF, amphiregulin, and epiregulin [89,90]. The ability to influence many cellular activities via several routes is a hallmark of the constitutively active form of HER2, which also makes it the ideal component to form dimers with other molecules [73,91,92]. Multiple downstream signalling pathways, including the Mitogen-Activated Protein Kinase (MAPK) and the phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) pathways, are activated by ligand binding and subsequent dimerization of HER2 [93,94], leading to cell survival, cell growth, and tumour progression [89].

Oestrogen signalling pathway interacts with several oncogenic signalling pathways such as epidermal growth factor pathway. Oestrogen receptors consist of membrane G protein-coupled receptors and nuclear oestrogen receptors (ERa, ERb), which are the transcriptional factors that regulate the expression of target genes upon ligand binding. These two types of nuclear hormone receptors form homo- or heterodimers upon ligand binding and translocate into the cell nucleus for transcriptional regulation, which is the main function of ERs. ER dimers bind to the ERE region of target genes and recruit co-regulators to achieve the regulation of transcriptional activity. Another mechanism by which ERs control the expression of target genes is acting as a co-regulator for other transcription factors [3].

Furthermore, about 17-20% of newly diagnosed breast cancers are of triple negative profile, which are characterised by a lack of expression of the oestrogen receptor, the progesterone receptor, and the human epidermal growth factor receptor 2 [83]. Its incidence is the highest in younger African women, and it is characterised by frequent relapses and metastases, and rapid progression to death [95-97]. To yet, no treatment has been shown to mitigate this type of breast cancer aggressiveness. High mortality rates are a direct reflection of the poor prognosis and the ineffective application of unspecific treatments, like chemotherapy that might exacerbate patients' health problems. TNBC-associated tumorigenic signalling pathways are mainly Receptor Tyrosine Kinases (RTKs) and downstream signalling pathways [98-100].

RTKs are important components of signal transduction pathways in the regulation of proliferation, and are associated with two downstream signalling pathways in particular: The Ras/Mitogen-Activated Protein Kinase (MAPK) pathway, and the phosphoinositide 3-kinase (PI3K)/AKT/Mechanistic Target of Rapamycin (mTOR) pathway [101-103]. Epithelial-to-Mesenchymal Transition (EMT) and associated pathways are crucial in TNBC pathogenesis, development and progression. During EMT, epithelial cells lose the expression of E-cadherin and acquire mesenchymal markers, including vimentin [104]. There is evidence to indicate that a number of RTKs, including EGFR, IGF1R, hepatocyte growth factor receptor and c-Met, non-RTKs, including Src, and embryonic transcription factors, including Twist and Slug, can induce EMT. Diverse signalling pathways, including MAPKs, PI3K and nuclear factor-κB, also promote EMT [105-107]. Other pathways, including Notch and Wnt/β-catenin signalling pathways, are also associated with EMT.

Phytotherapy in the Management of Breast Cancer

The main types of treatment for breast cancer are surgery, radiotherapy, chemotherapy, hormonal therapy, and targeted therapy [4]. Surgery is used in the treatment of localized breast cancer, preceded by neoadjuvant therapy to shrink tumour bulk, and followed by adjuvant therapy to ensure full recovery and minimize the risk of metastases. Radiotherapy could be used after surgery to reduce the risk of local recurrence of cancer [60,108]. Resistance, tumour relapse, and metastasis remain the primary causes of mortality for individuals with breast cancer despite widespread successful use of conventional approaches for treatment [5]. The outcomes of using natural products as cancer treatments have been promising. They are more effective, safer, and have a lower incidence of resistance than hormone-targeting and chemotherapeutics. Synergistic relationships between plant-derived substances and various chemotherapy regimens show promise [92]. Because of their selectivity, they are less likely to negatively impact normal human cells, natural materials are also favoured over conventional medicines. Quercetin, catechin, formononetin, calycosin, and carotenoids are only few of the many plant-derived natural chemicals that have anti-cancer potential. Targeting defective signalling pathways like Wnt/β-Catenin, NF-κB, PI3K/Akt/m-TOR, and hedgehog pathways, plant-based drugs can inhibit cell growth and proliferation, angiogenesis, epithelial-to-mesenchymal transition, and migration and metastasis.

Polyphenols, including quercetin, resveratrol, and catechin exert an anti-cancer activity against many types of tumours. Seo, et al. [109] have demonstrated that quercetin induces apoptosis, intrinsically via the mitochondrial pathway, and extrinsically via the activation of caspases through the inhibition of Signal Transducer and Activator of Transcription 3 (STAT3) factor in breast cancer. It arrests the cell cycle, inhibits the expression of metalloproteases, and induces autophagy in breast cancer [110]. In addition, quercetin inhibits the overexpression of HER2 and promotes its ubiquitination [111,112]. This phytocompound attenuates PI3K-Akt signalling pathway in breast cancer, leads to a reduced capacity of metastasis, down-regulates matrix metalloproteinase 2/9 and VEGF [110]. Jia, et al. [110] have also studied the effect of quercetin on the metabolism of cancerous cells. Quercetin blocks glucose intake, glycolysis, and the production of lactic acid through reduced expression glucose transporter 1 and Lactate dehydrogenase A, leading to a lower state of hypoxia, acidity, and migration, in consequences [110.112].

Resveratrol, another polyphenol, is shown to exert its anti-cancer effect by induction autophagy, and inhibiting stemness-like and EMT characteristics of breast cancer cells [113]. Another study established

that resveratrol inverse resistance to doxorubicin and inhibit breast cancer cells' migration capacity through the regulation of β-catenin signalling pathway [114]. Similarly, resveratrol was revealed to attenuate cells capacity of migration through the inactivation of Yes-Associated Protein 1 (YAP1). Resveratrol inactivates RhoA, leading to the activation of lats1, which in turn phosphorylates and inactivates the proto-oncogene YAP1 [115]. This nuclear transcription factor is significantly correlated with the overexpression of EMT-related pathways, the occurrence of distant metastasis of breast cancer, and poor prognosis; therefore, targeting YAP1 may improve patients' survival [116].

Panepoxydone is also known for its anti-cancer effects. It attenuates NF-κB signalling pathway and the TNFα-induced activation of NF-κB by inhibiting the phosphorylation and promoting the degradation of IκB [117,118]. Panepoxydone attenuates cell growth, and reverse EMT in breast cancer through FOXM1 downregulating, a transcription factor of NF-κB. In addition, this phytocompound enables the downregulation of vimentin, slug and zeb1, and the upregulation of N-cadherin, reversing therefore EMT features [119].

Conclusion

Active research in breast cancer therapy focuses on the use of plant-derived chemicals. Phytocompounds have a wide spectrum of anti-cancer properties, such as the ability to inhibit the growth and spread of cancer cells, induce cell death, and enhance the efficacy of conventional cancer therapies by targeting impaired signalling pathways such as Wnt/β-catenin, NF-κB, PI3K/Akt/mTOR, and EMT-related pathways. Overall, the use of phytocompounds in cancer therapy is a subject that requires additional study. While these compounds may have potential as complementary or alternative cancer therapies, additional research is required to fully comprehend their mechanisms of action and potential interactions/synergies with conventional cancer therapies.

Authors' Contributions

All authors have contributed equally to the paper conceptualisation, writing and editing.

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