Chapter 4
Breast Cancer: Current Perspectives on the Disease Status

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Abstract Breast cancer is the most frequently diagnosed cancer in women and ranks second among causes for cancer related death in women. Evidence in literature has shown that the past and ongoing research has an enormous implication in improving the clinical outcome in breast cancer. This has been attributed to the progress made in the realm of screening, diagnosis and therapeutic strategies engaged in breast cancer management. However, poor prognosis in TNBC and drug resistance presents major inhibitions which are also current challenges for containing the disease. Similarly, a focal point of concern is the rising rate of breast cancer incidence and mortality among the population of under developed world. In this chapter, an overview of the current practices for the diagnosis and treatment of breast cancer and associated impediments has been provided.

Keywords Breast carcinoma · Endocrine therapy · Basal like · Metastasis · Drug resistance

4.1 Global Burden: Incidence and Mortality

Cancer is a leading cause of death worldwide in countries across the globe. The existing burden in terms of both the incidence and mortality is expected to grow rapidly due to increased life expectancy and lifestyle issues that increase cancer risk. There were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide as reported by IARC. Over the years the incidence of cancer disease were more pronounced in the developed world as compared to less developed nations. However, the recent trends show such a disparity being closing in as 57% (8 million) of new

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cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5-year prevalent cancer cases occurred in the less developed regions (GLOBACAN 2012) [1]. Consequently, over 20 million new cancer cases are expected annually in less than a decade by 2025 [2]. The burden and patterns in incidence for several common cancers worldwide estimated for more and less developed regions has been shown in Fig. 4.1.

After the lung cancer, breast cancer is estimated to be the second most common cancer overall (1.7 million cases, 11.9%) though it ranks 5th as cause of death (522,000, 6.4%) because of the relatively favorable prognosis. In women, breast cancer is the most common cancer diagnosed in more and less developed regions, with more cases occurring in less developed (883,000 cases) than more developed regions (794,000) as shown in Fig. 4.2 [1, 3].

Earlier the incidence rates of breast cancer increased by about 30% in western countries between 1980 and the late 1990s, primarily due to increased screening, changes in reproductive patterns, and increased use of menopausal hormonal therapy [4, 5]. However, these rapid increases have slowed or plateaued since the early 2000s, probably because of the sensitization of the female population with the associated risk factors. Contrary to the western world, breast cancer incidence rates in many other countries, especially less developed countries, continue to increase due to changing reproductive patterns as well as increased awareness and screening [5, 6].

4.2 Breast Cancer Associated Risk Factors

Considering **age** as a predominant risk factor, compared with lung cancer, the incidence of breast cancer is higher at younger ages with reported incidence doubling about every 10 years until the menopause. Menstrual status also contributes to the age related risk factor with women having menstruation early in life or a late menopause have an increased risk of developing breast cancer. Similarly, the risk of breast cancer in women who have their first child after the age of 30 is about twice that of women who have their first child before the age of 20 and the highest risk groups include women having a first child after the age of 35. Breast cancer susceptibility is generally inherited as an autosomal dominant with limited penetrance (can be transmitted through either sex) and about 10% of breast cancer in Western countries is due to genetic predisposition with higher incidence among close **family** members and first degree relatives. **Lifestyle** issues such as diet (saturated fat), alcohol consumption (excessive intake) and sedentary status leading to abnormal weight (obesity) have also been reported as risk factors. Exposure to **ionizing radiations** at younger age and **hormone replacement therapy** (HRT) also contribute to a higher relative risk. Age adjusted incidence and mortality for breast cancer varies by up to a factor of five between countries with **geographical** variation reporting higher incidence in developed countries (Table 4.1) [7].

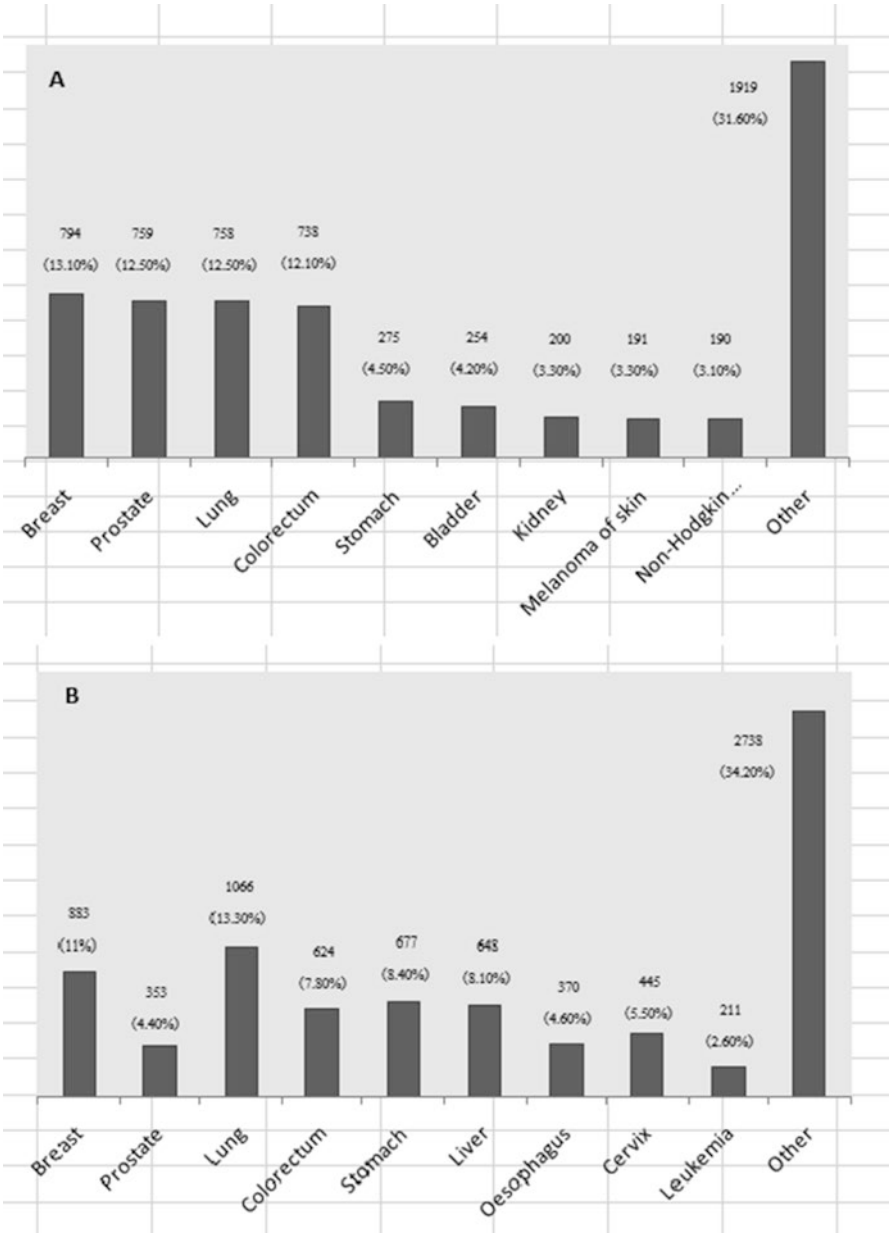

Fig. 4.1 Estimated global numbers of new cases (thousands) of various cancers in populations for (**a**) more developed and (**b**) less developed regions, both sexes combined, 2012

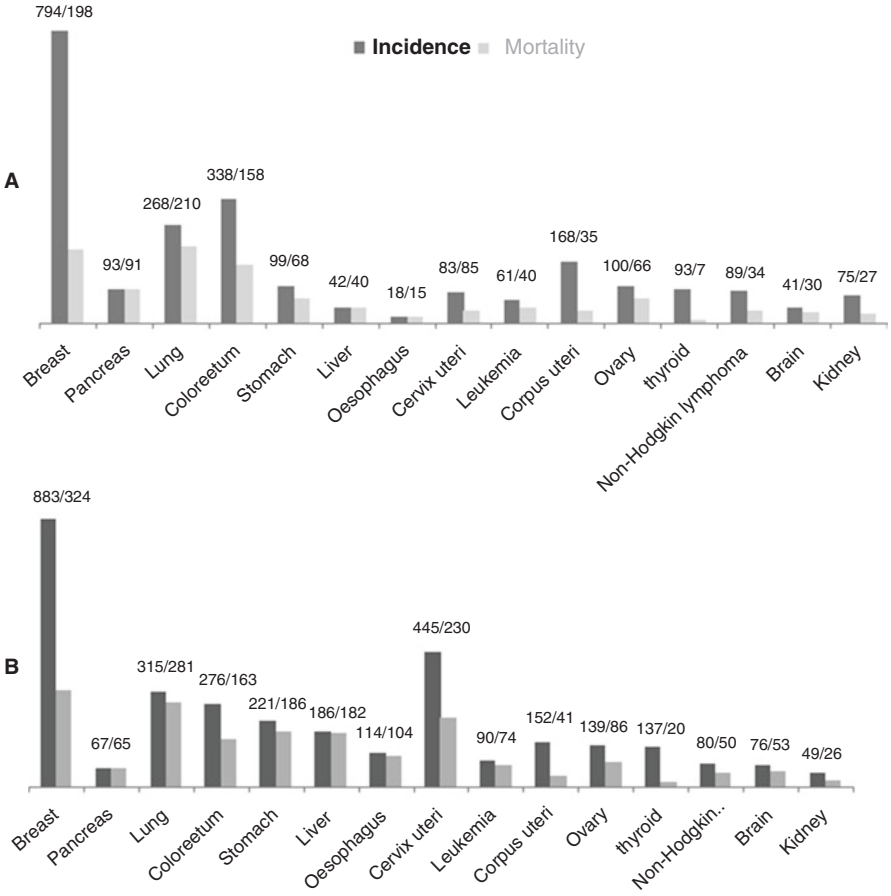

Fig. 4.2 Estimated numbers (thousands) of new cancer cases (incidence) and deaths (mortality) in women in more developed (**a**) and less developed (**b**) regions of the world in 2012

4.3 Classification Based on Histology and Molecular Markers

Breast cancer can be broadly categorized on the basis of histological outcome into in situ carcinoma and *invasive* carcinoma. Breast carcinoma in situ is further sub-classified as either ductal (DCIS; more common) or lobular (LCIS; less common). DCIS has been further sub-classified based on the features of the tumor into five well characterized subtypes: comedo, cribiform, micropapillary, papillary and solid [8, 9]. Similarly, invasive carcinomas are a heterogeneous group of tumors differentiated into histological subtypes that include infiltrating ductal (IDC), invasive

Table 4.1 Common risk factors associated with the incidence of breast cancer

Factors	Relative risk	Exclusive parameters
Age	>10	Beyond 50 years (elderly)
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Delayed pregnancy	3	First child in early 40s
Family history	>2	Breast cancer in first degree relative
Diet	1.5	Rich in saturated fat
Alcohol consumption	1.3	Excessive
Body weight:		
(Premenopausal)	0.7	BMI >35
(Postmenopausal)	2	BMI >35
Hormone replacement therapy	1.35	More than 10 years
Ionizing radiations	3	Abnormal exposure in young age
Geographical area	5	Developed nations

lobular, ductal/lobular, mucinous (colloid), tubular, medullary and papillary carcinomas. Among the invasive carcinomas IDC is the most common subtype accounting for 70–80% of all invasive lesions. IDC is further sub-classified as either well-differentiated (grade 1), moderately differentiated (grade 2) or poorly differentiated (grade 3) based on the levels of nuclear pleomorphism, glandular/tubule formation and mitotic index [9–11].

The prognostic value of certain markers such as ER, PR, ErbB2 (Her2/neu) have been utilized to provide a molecular classification of breast cancer subtypes. The classification has been shown to be of high prognostic and predictive significance for IDC (though not utilized for DCIS) and it is recommended that their status be determined on all invasive carcinomas [11, 12]. Immunohistochemical (IHC) techniques are utilized to measure expression of estrogen receptor (ER), progesterone receptor (PR), and overexpression of human epidermal growth factor receptor 2 (HER2/neu). Breast cancers are then classified with respect to the presence or absence of these receptors as Luminal A (ER and/or PR positive, and HER2 negative); Luminal B (ER and/or PR positive, and HER2 positive); HER2-enriched (ER and PR negative, and HER2 positive) and Basal Like (Triple negative breast cancer-ER, PR and HER2 negative) [13]. Triple-negative breast cancers grow and spread faster than most other types of breast cancer. Patients with luminal A and B, and HER2-enriched subtypes are sensitive to targeted treatments, while patients with triple negative characteristic show poor prognosis. The status of these markers helps determine which patients are likely to respond to targeted therapies (i.e., tamoxifen or aromatase inhibitors for ER+/PR+ patients and trastuzumab or lapatinib for HER2/neu patients) while triple negative patients only have chemotherapy as an alternative [14]. Figure 4.3 summarizes the several subtypes of breast cancer based on histological and molecular characterization.

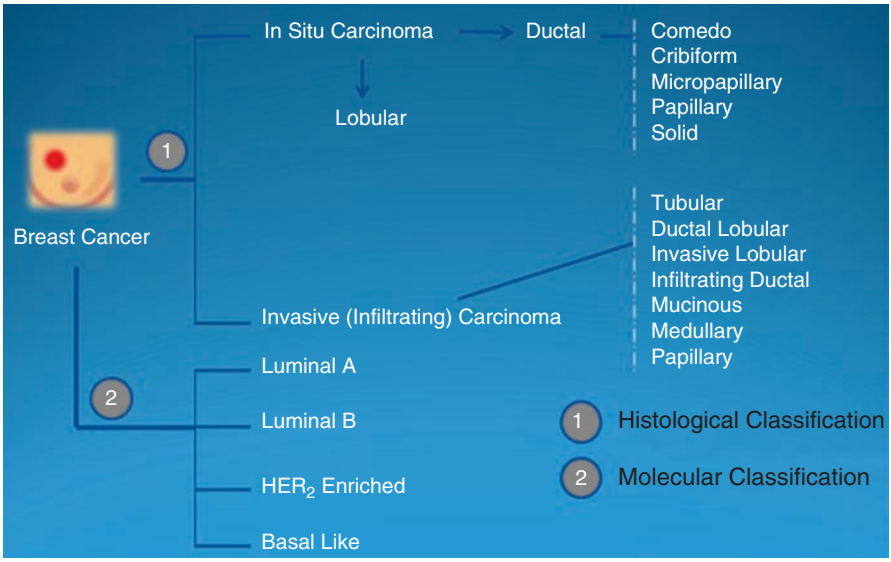

Fig. 4.3 Histological and molecular characterization of breast cancer subtypes

4.4 Tumor Markers in Breast Cancer

Numerous serum tumor markers have been described for breast cancer, including members of the MUC-1family of mucin glycoproteins (e.g., CA 15.3, BR 27.29,MCA, CA 549), carcinoembryonic antigen (CEA), oncoproteins (e.g., HER-2/c-erbB-2) and cytokeratins (e.g. tissue polypeptide antigen and tissue polypeptide-specific antigen). In practice, serum markers in breast cancer are mostly used for monitoring patients with diagnosed disease; tissue based markers are however primarily measured in order to determine prognosis and predict response to therapy. Clinically, the most useful tissue-based markers in breast cancer are estrogen receptor (ER), progesterone receptor (PR) and HER-2 (also known as c-erbB-2 or neu), uPA and PAI-1 [15].

According to the American Society of Clinical Oncology (2007) the following markers showed evidence of clinical utility and were recommended for use in practice: CA 15-3, CA 27.29, carcinoembryonic antigen, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, urokinase plasminogen activator, plasminogen activator inhibitor 1, and certain multi-parameter gene expression assays [16].

Breast cancer metastasis accounts for the majority of deaths from breast cancer. Recent method to detect metastasis is the analysis of circulating tumor cells (CTCs). CTCs are tumor cells originating from primary sites or metastases that circulate in the patients' bloodstream and are very rarely found in healthy individuals. CTCs are recognized as critical elements in the metastasis of carcinomas and their analysis enables the prediction of metastatic relapse and progression [17, 18].

4.5 Breast Cancer Metastasis

Breast cancer appears as a disease of mammary epithelial cells which acquire the ability to grow abnormally for years and such a potential remains confined within mammary ducts or lobules (non-invasive breast cancer). This captivity of malignant epithelial cells within the ducto-lobular mesh is an important restraint to breast cancer progression. Since the malignant cells remain contained within the ducts or lobules, the patient survival has been reported to be relatively higher as ~98% of patients diagnosed with localized breast cancer have least probability of cancer recurrence within 5 years. In contrast, breast cancer prognosis markedly deteriorates in the event of cells invading out of the ducto-lobular region into the surrounding stroma (invasive breast cancer). Thus the 5-year survival for regionally invasive breast cancer i.e. breast cancer that has spread to regional lymph nodes, is only 83% (showing a 15% decrease from localized breast cancer). After moving out of the ducts or lobules, cancer cells can metastasize through the blood or lymphatic systems to distant organs such as the lungs, liver, or bones. The presence of distant metastases at the time of diagnosis presents the worst prognosis with only 23% of patients surviving 5 years post-diagnosis [19].

Breast cancer spreads to different distant organs, preferentially to bones, lung, liver and brain. The process of metastasis which includes cell migration and colonization is a multistep cascade of molecular events directed by gene mutations and altered expressions [20]. It is well recognized that metastasis consists of distinct steps in which tumor cells (i) detach and migrate away from the primary tumor site, (ii) invade neighboring tissue and penetrate through basement membrane, (iii) enter the blood or lymphatic vessels, (iv) survive the condition of anoikis while they are detached from the tumor mass and in circulation, (v) exit the blood or lymphatic vessels at a distant organ, (vi) form micrometastatic nodule, (vii) adapt and reprogram the surrounding stroma, and form macrometastases [21]. Metastatic cell migration includes local invasion, intravasation, dissemination and extravasation where as infiltrating distant tissue, evading immune defenses, adapting to supportive niches, surviving as latent tumour-initiating seeds, and eventually breaking out to replace the host tissue, are key steps for metastatic colonization [22].

Changes in cell phenotype between the epithelial and mesenchymal states, defined as the epithelial–mesenchymal transition (EMT; pre-invasion) and mesenchymal–epithelial transition (MET; re-invasion) are recognized as critical events for metastasis of carcinomas. EMT is thought to be critical for the initial transformation from benign to invasive carcinoma, whereas MET (the reverse of EMT) is critical for the later stages of metastasis. In the early stages the cancer cells need to cross its surrounding tissues and also the endothelial cells of the blood vessel in order to get into the blood circulation system. For this a sub-population of cancer cells undergoes EMT. Endothelial-mesenchymal transition is a physiological process characterized by loss of cell-cell adhesion and cytoskeletal alterations, leading to changes in cell morphology and acquisition of invasive and migratory properties [23]. Once accessing into the blood or lymphatic system, these cancer cells migrate to all parts

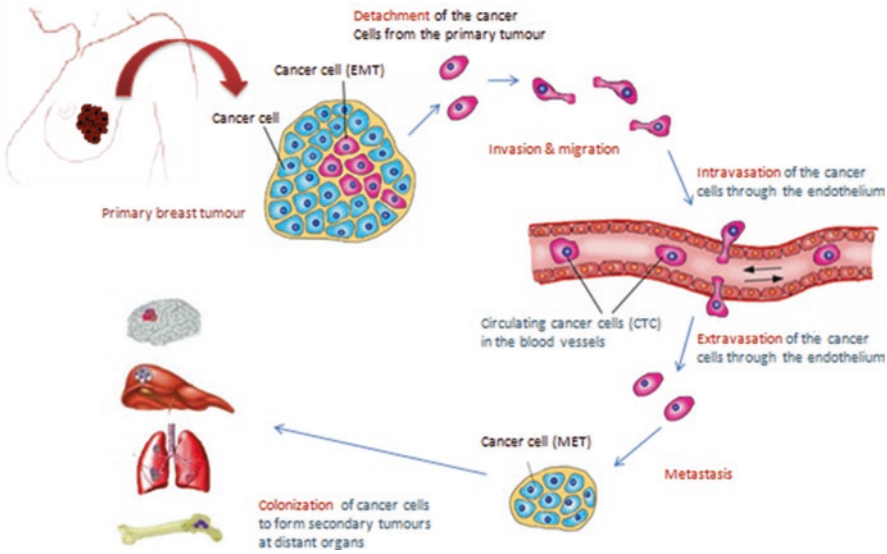

Fig. 4.4 Schematic overview of metastatic cascade

of the body to invade the new tissues by crossing the endothelial cells of the blood vessel. Subsequently, the disseminated mesenchymal tumor cells undergo the reverse transition, MET, at the site of metastases. Figure 4.4 provides a simplistic overview of the metastatic cascade of the breast cancer.

4.6 Therapeutic Strategies

The therapeutic approaches that are employed for breast cancer management include cytoreductive surgery, radiation treatment, targeted endocrine/molecular therapy and chemotherapy [24]. Due to the heterogeneity of the disease the treatment protocol requires rationalized therapy in individual cases according to the characterization and stage of the disease. Traditionally, radical mastectomy and modified radical mastectomy were the mainstream procedures for locoregional management which were eventually replaced by breast conserving surgery with breast radiation as preferred protocols [25]. Subsequently, neoadjuvant (preoperative) chemotherapy for locally advanced and operable breast cancer has been a major development with important implications for locoregional management [26]. Systemic chemotherapy at the time of locoregional recurrence also demonstrated significant improvement in disease-free survival and overall survival for poor-prognosis group [27].

One of the developments that have caused a paradigm shift with global impact in breast cancer prevention is the targeted therapy for estrogen receptor (+ve) and Her2

enriched cancer types [28]. Five years of adjuvant endocrine therapy with the selective estrogen receptor modulator tamoxifen or aromatase inhibitors (AIs, which cause estrogen depletion) reduces breast cancer recurrence and improves overall survival in women with ER-positive early-stage breast cancer [25]. Tamoxifen is a selective estrogen receptor modulator which is antagonist of ER in breast tissue (tamoxifen has agonist actions in other tissues) binds to estrogen receptor and inhibits the proliferative activities of estrogen on mammary epithelium [29], with reports suggesting a decline in the risk of ER+ breast cancer recurrence to 50% and a 28% decrease in morbidity rates [30]. Aromatase (which transforms androstenedione into esterone and testosterone to estrogen) is the chief estrogen source in post-menopausal females and its inhibitors lead to estrogen depletion. As a substitute to tamoxifen in post-menopausal women, (especially in ER+ breast cancer), third generation aromatase inhibitors i.e. letrozole, anastrozole and exemestane, are generally used [31]. It needs a mention that resistance to endocrine therapies that require beyond 5 years of extended therapy remains a clinical challenge. However, gene expression assays on ER expression patterns have implication to identify which patients with ER-positive breast cancers warrant chemotherapy in addition to endocrine therapy and which can be treated adequately with endocrine therapy alone [32].

Trastuzumab is a biologically active, humanized monoclonal antibody which has been reported to improve the survival rates for HER2/neu positive breast cancer patients [33]. It is considered clinically safe and effective in mono-therapy regime of every 3 weeks or in combination with paclitaxel, gemcitabine, vinorelbine or carboplatin [33, 34]. Protein tyrosine kinase inhibitor lapatinib, an orally active, reversible blocker of the HER2 tyrosine kinase is also used for HER2-positive metastatic breast cancer in combination with letrozole as first-line treatment and in patients presenting with trastuzumab resistance [35, 36].

Patients with triple negative breast cancer do not benefit from hormonal or trastuzumab-based therapy because of the loss of target receptors such as ER, PGR, and HER-2. Hence, surgery and chemotherapy, individually or in combination, appear to be the only available modalities [37]. The current highest pathologic complete response (pCR) rates, about 40–45%, are achieved by taxane/anthracycline sequential chemotherapy regimens and inclusion of platinum drugs with the taxane component [38]. Moreover, the addition of platinum agents, under various schedules, to anthracycline/taxane neoadjuvant chemotherapy also demonstrated statistically significantly higher pCR rates (41% *vs* 54%; 37% *vs* 53%; 26% *vs* 51%) [39]. Few novel therapies for TNBC include inhibition of Poly ADP-ribose polymerase enzymes (PARP inhibitor) which are critical for the repair of DNA breaks. Anti-VEGF monoclonal antibody (bevacizumab) targeting angiogensis in tumour region is also under research as tumour VEGF expression is significantly higher in TNBC compared with non TNBC presentations. In patients with metastatic TNBC, a cetuximab (anti-EGFR monoclonal antibody) plus cisplatin combination (BALI-I Trial) has demonstrated an overall better response rate of 20% when compared to a 10% overall better response rate with cisplatin alone. The serine-threonine kinase mammalian target of rapamycin (mTOR) promotes protein translation, angiogenesis,

Table 4.2 Anti-cancer drugs in breast cancer therapy

Natural product	Vinorelbine (vinca alkaloid), paclitaxel (taxane), doxorubicin (antibiotic)
Anti-metabolite analogues	Methotrexate (folic acid analogue), 5-fluorouracil and Capacitabine (pyramidine analogues)
Platinum salts	Carboplatin, cisplatin
Alkylating agent	Cyclophosphamide (nitrogen mustard)
Hormone antagonist	Tamoxifen (anti-estrogen)
Enzyme inhibitors	Letrozole and anastrazole (aromatase inhibitors)
PARP inhibitors	Olaparib
Monoclonal antibody	Trastuzumab (anti-HER2), cetuximab (anti-EGFR). Bevacizumab (anti-VEGF; angiogenesis inhibitor)
Histone deacetylase inhibition (HDAC)	Vorinostat
Protein tyrosine kinase inhibitor	Lapatinib (HER2), Neratinib (EGFR)

proliferation & migration and therapeutic strategies engaging mTOR inhibitors (everolimus) are under investigation. Additional targeted therapies for TNBC include HDAC (histone deacetylase) inhibitors, such as vorinostat which suppress cancer-cell proliferation by inducing cell-cycle arrest and/or apoptosis [40].

Table 4.2 shows anticancer drugs used in treatment regimens for chemotherapy and targeted therapy against breast cancer.

4.7 Drug Resistance in Breast Cancer

Despite numerous drug combinations and regimens, most of the patients with advanced breast cancer inevitably develop resistance to treatment [41]. Drug resistance mechanisms include intracellular drug metabolism/efflux and target modulations as well as extracellular elements of crosstalk between tumor cells and microenvironment [42, 43]. Malignant cells that survive primary treatment continue to evolve, thereby presenting a resistant clone population, which leads to constraint free progression responsible for worst prognosis and death. Estrogen, HER2 signaling, and the PI3K/Akt pathway in drug-resistant breast cancer has been summarized in Fig. 4.5 [44]. It is thus believed that even if ER/HER2 signaling is effectively blocked, cancer proliferation may continue, as downstream pathways may be activated by alternative routes.

Patients with metastatic ER-positive disease develop resistance to endocrine therapy such as against frontline drug tamoxifen. Tamoxifen is a prodrug and to be active against ER it requires bioactivation to the major metabolite, endoxifen [45]. The metabolism involves two members of the cytochrome P450 (CYP) family, CYP2D6 and CYP3A4. The polymorphisms of CYP2D6 is implicated in its catalytic activity and altered drug metabolism as CYP2D6 metabolizer status has been

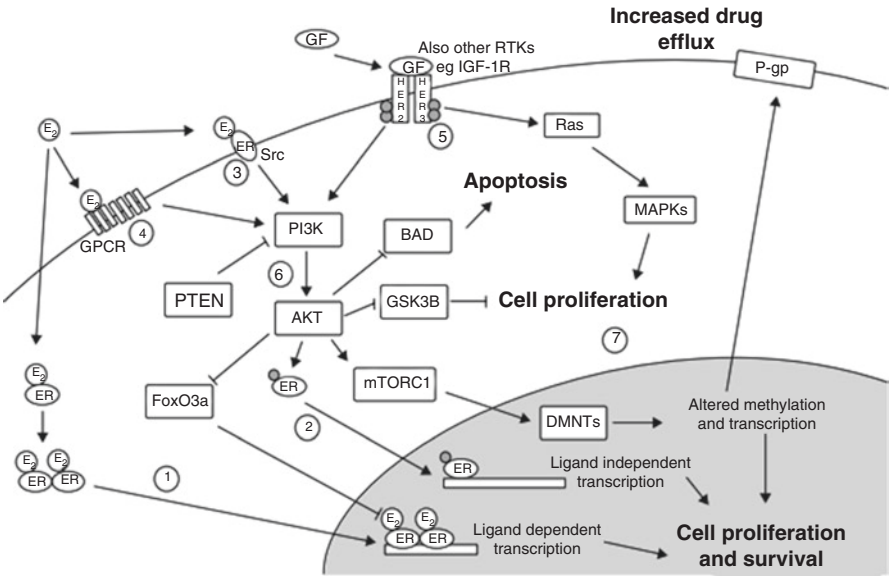

Fig. 4.5 Estrogen, HER2 signalling, and the PI3K/Akt pathway in drug-resistant breast cancer. Notes: ER can activate gene transcription by nuclear translocatin following ligand binding (1) or as a result of receptor phosphorylation in the absence of ligand (2). ERs may also be found associated with the plasma membrane in the presence of SRC and other adaptor proteins. Here, ligand binding triggers nongenomic effects via activation of signaling pathways, including the PI3K/Akt and the Ras/MAPK pathways (not shown) (3). These pathways are also activated by ligand binding to the GPR30 (4) and by growth factor binding to receptor tyrosine kinases, including HER2, inducing autophosphorylation and downstream signalling (5). The PI3K/Akt pathway (6) as indicated is a covergence point in the mechanisms implicated in drug resistance in the three types of breast cancer discussed here, as pathway hyperactivity frequently occurs with multiple downstream effects (7). (Reproduced from the original source [44] under the terms of Creative Common Attribution License)

correlated with response to tamoxifen treatment, with poor metabolizers having greater tumor progression than extensive metabolizers [46]. Moreover, it is known that phosphorylation regulates ERα activity and plays a role in tamoxifen resistance where phosphorylation by protein kinase A or p21-activated kinase-1 modifies the action of tamoxifen from antagonist to agonist. Reports have shown an enhanced activity of these kinases in tamoxifen-resistant breast cancer [47].

Trastuzumab (Herceptin), a monoclonal antibody that binds HER2, has been in use for patients with HER2-positive breast cancer. However, studies have reported de novo resistance to trastuzumab in approximately 65% of cases and induced resistance in approximately 70% of initially sensitive patients [48]. One of the mechanisms of resistance include epitope masking involving mucin 4, a large O-glycosylated membrane-associated protein and CD44/hyaluronan polymer complex which masks the epitope, sterically hindering trastuzumab binding and thereby preventing trastuzumab induced inhibition of HER2 signaling [49]. Trastuzumab resistance has also been reported by activation of downstream signaling *via* alternate

routes. For instance trastuzumab treatment also induces upregulation of a number of miRNAs (miR-21) and c-Met leading to the activation of Akt signaling [50, 51]. It has also been reported that in up to 30% of HER2-enriched breast cancers, an amino-terminal truncated form of HER2 is expressed (p95-HER2). The p95-HER2 possesses constitutive kinase activity, triggering downstream signaling, but lacks the trastuzumab binding site, thus generating trastuzumab resistance [44, 52].

Therapeutic options for women presenting with triple negative breast cancer are limited due to the lack of a therapeutic target and as a result, are managed with standard chemotherapy such as paclitaxel (Taxol). Although TNBCs are generally very susceptible to chemotherapy initially, the risk of relapse for TNBC patients in the first 3–5 years is significantly higher than for women presenting with hormone positive breast cancer [53]. ATP-binding cassette (ABC) transporters involved in chemoresistance in TNBC include (a) multidrug-resistant protein-1 (MRP1) which confers resistance to agents such as vinca alkaloids, anthracyclines, and high-dose methotrexate but not paclitaxel or mitoxantrone, (b) breast cancer resistance protein (ABCG2) which is responsible for the efflux of drugs such as doxorubicin, and (c) the P-glycoprotein (MDR1) pump which pumps a wide array of chemotherapeutics out of cancer cells, including paclitaxel [54–56].

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