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Solid Tumour Section

Review

Breast: Ductal carcinoma

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Identity

Other names

Infiltrating/invasive ductal carcinoma (IDC)
Carcinoma of no special type (NST) or not otherwise specified (NOS)

Classification

Note

IDC represents 65 to 85 percent of all breast cancers. IDC originates in the transition between the breast's milk ducts and lobuli and invades surrounding breast tissue.

Classification

Invasive ductal carcinoma is a heterogeneous group with many different subtypes, some of them extremely rare. Each of these variants is associated with another pathological presentation and with a different prognosis compared to invasive ductal carcinoma of no special type (NST). As shown in Figure 1, some of the most important subclassifications are:

- Medullary carcinoma: younger age, association with BRCA1 mutation, 1-5% of breast carcinomas, rarely lymph node metastases, bad prognosis
- Metaplastic carcinoma: <1% of breast carcinomas, association with BRCA1 mutation, bad prognosis
- Mucinous/colloid carcinoma: older age, 1-6% of breast carcinomas, better prognosis
- Inverted papillary carcinoma: 1% of all breast carcinomas, better prognosis, striking lymphovascular invasion
- Tubular carcinoma: younger age, about 5% of breast carcinomas, excellent prognosis
- Cribriform carcinoma: younger age, good prognosis.

Clinics and pathology

Disease

Carcinoma of the breast is more common in the left breast than in the right, in a ratio of 110/100. Approximately 50% arise in the upper outer quadrant, 10% in each of the remaining quadrants, and 20% in the central or subareolar region. While the overwhelming majority of breast cancer cases in humans are women, men can also develop breast cancer.

Progression: One of the earliest detectable changes is loss of normal regulation of cell growth and polarity, resulting in early morphological changes such as atypical ductal hyperplasia (ADH) and columnar cell lesions (CCL). Next, genomic instability results in the formation of ductal carcinoma in situ (DCIS) lesions.

In the most popular model to explain the development of IDC, low-grade DCIS lesions tend to progress to low-grade IDC, and high-grade DCIS tends to progress to high-grade IDC by accumulation of fairly specific chromosomal and gene alterations (Buerger et al., 2000; Hwang et al., 2004).

The majority of molecular changes that are observed in breast cancer seem to be already evident in the DCIS stage (Mommers et al., 2001).

Also, epigenetic changes such as methylation and microRNAs are believed to play role in the disease progression and occur early as well (O'Day and Lal, 2010; Jovanovic et al., 2010).

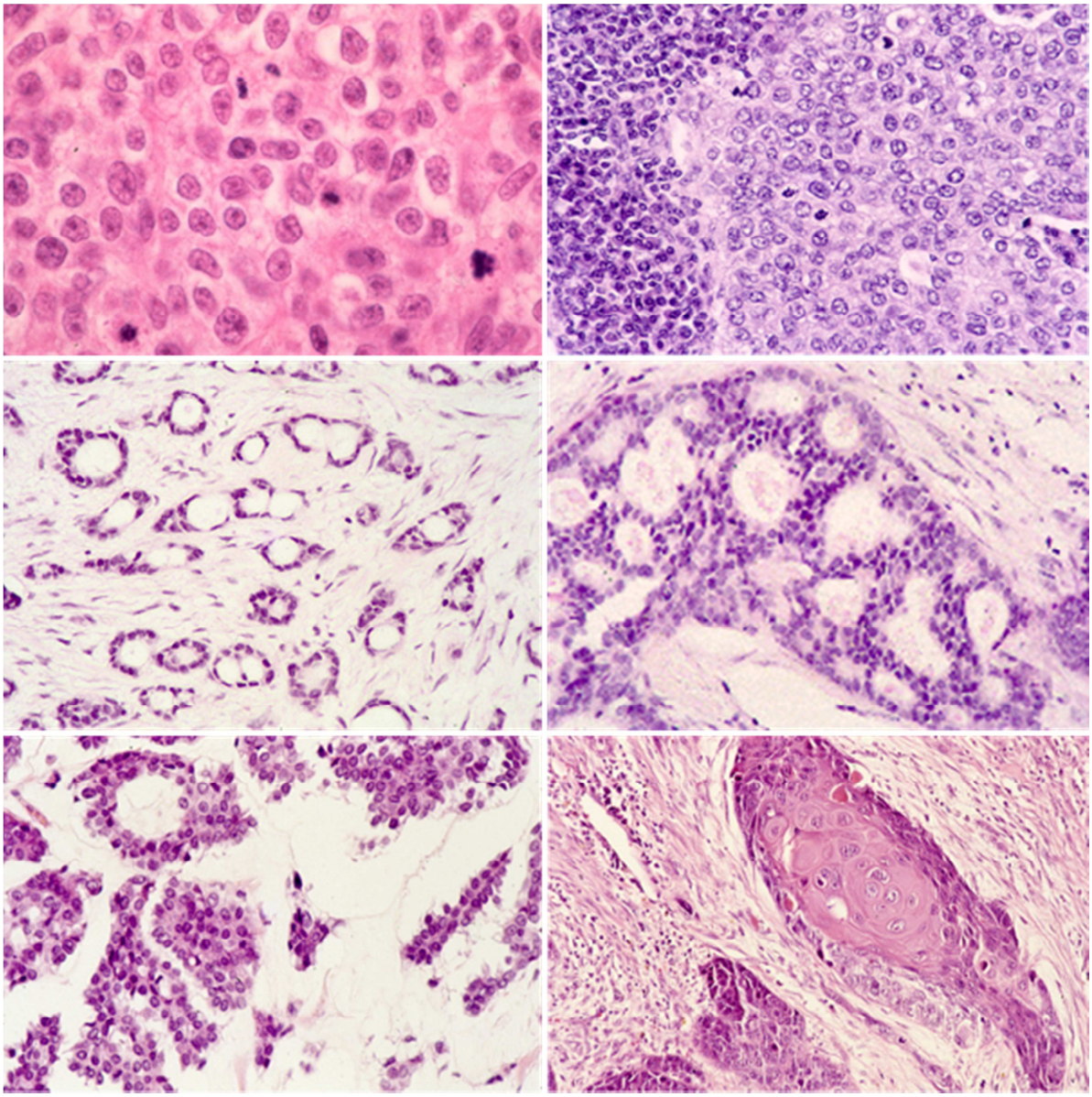

Figure 1. Main breast cancer histological types. From top left to bottom right: ductal NST, medullary, tubular, cribriform, mucinous and (squamous) metaplastic breast cancer.

Etiology

The etiology is multifactorial with three major contributors to the development of breast cancer: 1) genetic factors, 2) hormonal influences and 3) environmental factors. Less than 10% of women with breast cancer have a family history of the disease (BRCA1/BRCA2 mutations, ATM, TP53). Hormonal influences include early menstruation, late menopause, nulliparity, and late age at first childbirth. Environmental risk factors include alcohol consumption and dietary fat intake. Cigarette smoking and caffeine consumption have not been implicated in breast cancer.

Epidemiology

Worldwide, breast cancer is the most common invasive cancer in women. Incidence and mortality data on breast cancer can be found at the International Agency for Research on Cancer Globocan website and at the SEER database of the U.S. National Cancer Institute. Based on rates from 2006-2008, 12.29% (1/8) of women born today will be diagnosed with breast cancer at some time during their lifetime. Breast cancer is rarely found before the age of 25 years (except in familial cases). The incidence then increases with age, with most women being 60 years old when diagnosed.
The main risk factors are genetic predisposition, increasing age, proliferative breast disease, carcinoma of the contralateral breast or endometrium, radiation exposure (Hodgkin lymphoma), geographic influences, race, length of reproductive life, parity, age of first child (older than 30 years), obesity, and exogeneous estrogens (hormonal replacement therapy, oral contraceptives).

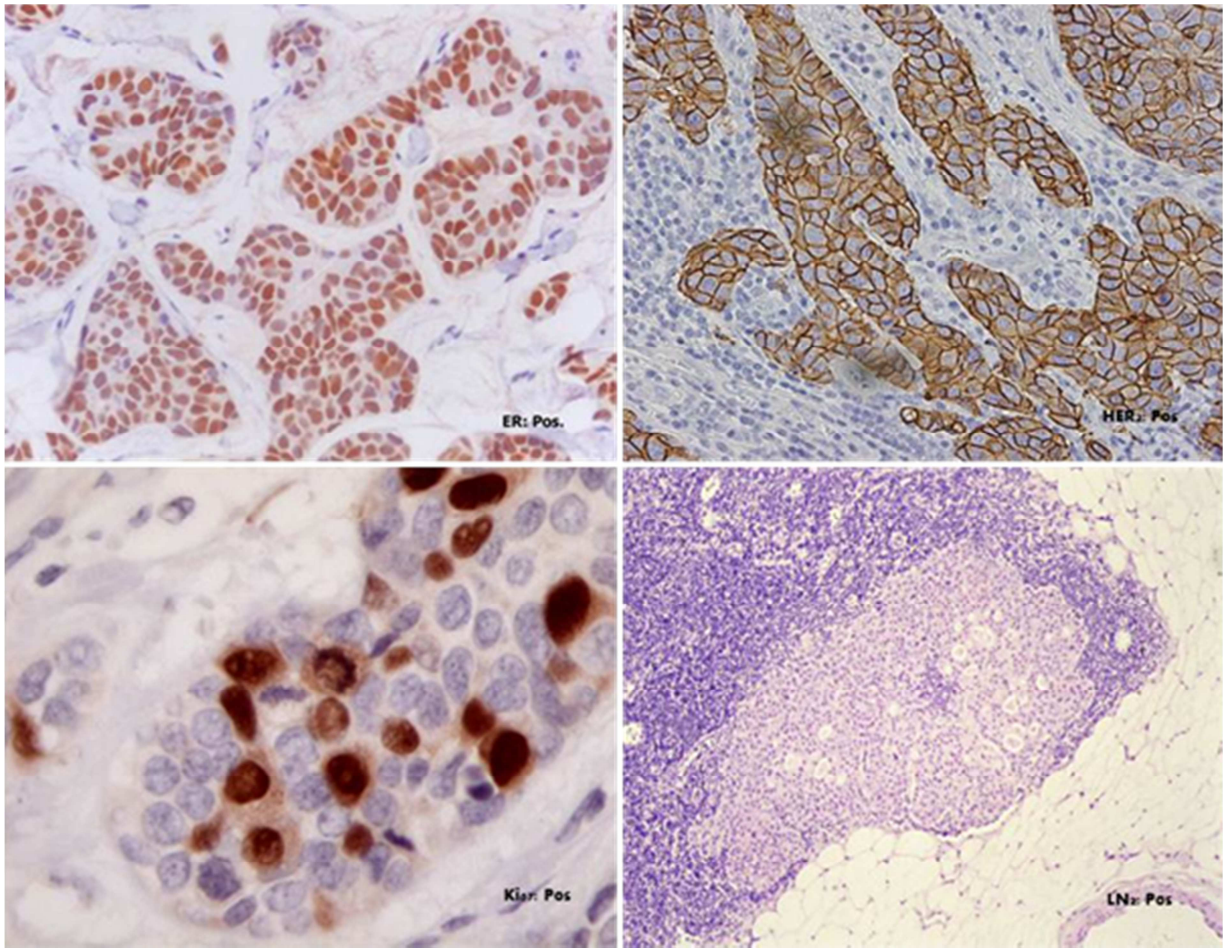

Figure 2: Breast cancer biomarkers. Top left: ERα expression. Top right: HER2 receptor overexpression (3+). Bottom left: Ki67/MIB1 nuclear expression. Bottom right: lymph node metastasis.

Clinics

Cancers of the breast are usually first discovered by women or their physician as a solitary painless mass. The use of mammography, sonography and MRI has increased the detection of ductal carcinoma in situ (DCIS) and small invasive tumors before they reach palpable size. These non-palpable lesions can then be sampled by image-guided core needle biopsies. These lesions are usually <1 cm in size and less than 1/5th will have axillary metastases. Palpable lesions, in contrast, are usually 2-3 cm in size when first found, and approximately 1/3 has already spread to axillary or other lymph nodes. Lymph node status is generally assessed through the sentinel node procedure.

Clinical staging:

The American Joint Committee on Cancer (AJCC) staging system provides a strategy for grouping patients with respect to prognosis. Therapeutic decisions are formulated in part according to staging categories but primarily according to tumor size, lymph node status, estrogen-receptor and progesterone-receptor levels in the tumor tissue, human epidermal growth factor receptor 2 (HER-2/neu) status, menopausal status, and the general health of the patient (Edge et al., 2010). Stages are subdivided as follows:

- Stage 0: Ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS); 5-year survival rate 93%
- Stage 1: Invasive carcinoma 2 cm or less without nodal involvement and no distant metastases; 5-year survival rate 88%
- Stage 2: Invasive carcinoma 5 cm or less with involved but movable axillary lymph nodes and no distant metastases, or a tumor > 5 cm without nodal involvement or distant metastases (5-year survival rate 74-81%)
- Stage 3 (locally advanced): Breast cancer > 5 cm with nodal involvement; or any breast cancer with fixed axillary nodes; or any breast cancer with involvement of the ipsilateral internal mammary lymph nodes; or any breast cancer with skin involvement, pectoral and chest wall fixation, edema, or clinical inflammatory carcinoma, if distant metastases are absent (5-year survival rate 41-67%)
- Stage 4: any form of breast cancer with distant metastases (including ipsilateral supraclavicular lymph nodes); 5-year survival rate 15%.

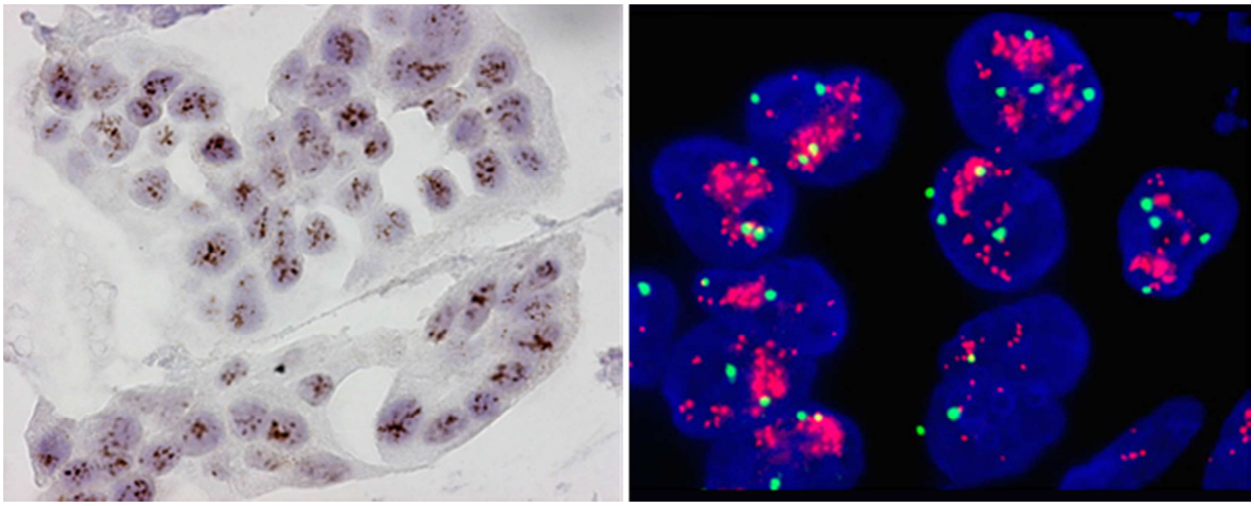

Figure 3. Left: invasive breast carcinoma with HER2 amplification by CISH; Right: FISH showing invasive breast carcinoma with HER2 amplification (red) and CEP17 gain (green).

Pathology

The pathologist assesses resection margins, lymph node status, tumor size, tumor grade, mitotic activity, histological subtype, lymphovascular invasion, hormonal receptor status (by immunohistochemistry) and HER2 status.

Treatment

Surgery (mastectomy or lumpectomy, axillary node dissection), radiation, hormonal therapy, chemotherapy or combinations. A very important therapeutic strategy since 1998 is targeted therapy with trastuzumab, a humanized monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2, amplified and overexpressed in 10-15% of breast cancers) (Romond et al., 2005).

Prognosis

Prognosis and survival rates vary greatly depending on cancer type, grade, proliferation rate (van Diest et al., 2004), staging and treatment. Prognosis of breast tumors without distant metastases depends on a number of histopathological factors (upon distant metastases, cure is unlikely):

- Locally advanced disease (skin or skeletal muscle invasion)
- Presence and number of lymph node metastases, including the size of metastatic deposit and invasion through the capsule
- Tumor size
- Histological subtype (NST/medullary/metaplastic vs. tubular, cribriform, mucinous)
- Tumor grade (Bloom and Richardson grading system combines tubule formation, mitotic rate and nuclear atypia)
- Hormonal receptor status (estrogen and progesterone receptor positivity confers better prognosis; 70-80% of breast cancers are positive for ER/PR)
- Proliferative rate (mitotic index, Ki-67 staining)
- Expression of certain oncogenes (HER2, MYC) or loss of tumor suppressor genes (TP53, CDH1).

Genetics

Note

Most breast cancer cases are sporadic, with many different oncogenes and tumor suppressor genes involved, while 5-10% are estimated to be due to an inherited predisposition.

Autosomal dominant alterations in two genes, BRCA1 and BRCA2, are likely to account for most familial cases of early-onset breast cancer, and for 3-4% of all breast cancers.

Mutations in several other genes, including TP53, PTEN, STK11/LKB1, CDH1, CHEK2, ATM, MLH1, and MSH2, have also been associated with hereditary breast tumors (Campeau et al., 2008; Walsh et al., 2006).

Cytogenetics

Cytogenetics Molecular

Although traditionally classical karyotyping and chromosome based comparative genomic hybridization (CGH) have yielded information on chromosomal loci and genes involved in breast carcinogenesis, nowadays molecular and cytogenetic techniques such as fluorescence in situ hybridization (FISH, see Figure 3 right), (q)PCR, multiplex ligation-dependent probe amplification (MLPA, see Figure 4), next generation sequencing, and array techniques for CGH, gene expression, methylation and microRNAs are frequently used in breast cancer diagnostics and research.

FISH, as well as its chromogenic counterparts C(hromogenic)ISH and S(ilver)ISH, but also MLPA are currently used to analyze HER2 gene amplification status, an important prognostic factor and predictor of trastuzumab, chemotherapy and hormonal therapy response in breast cancer.

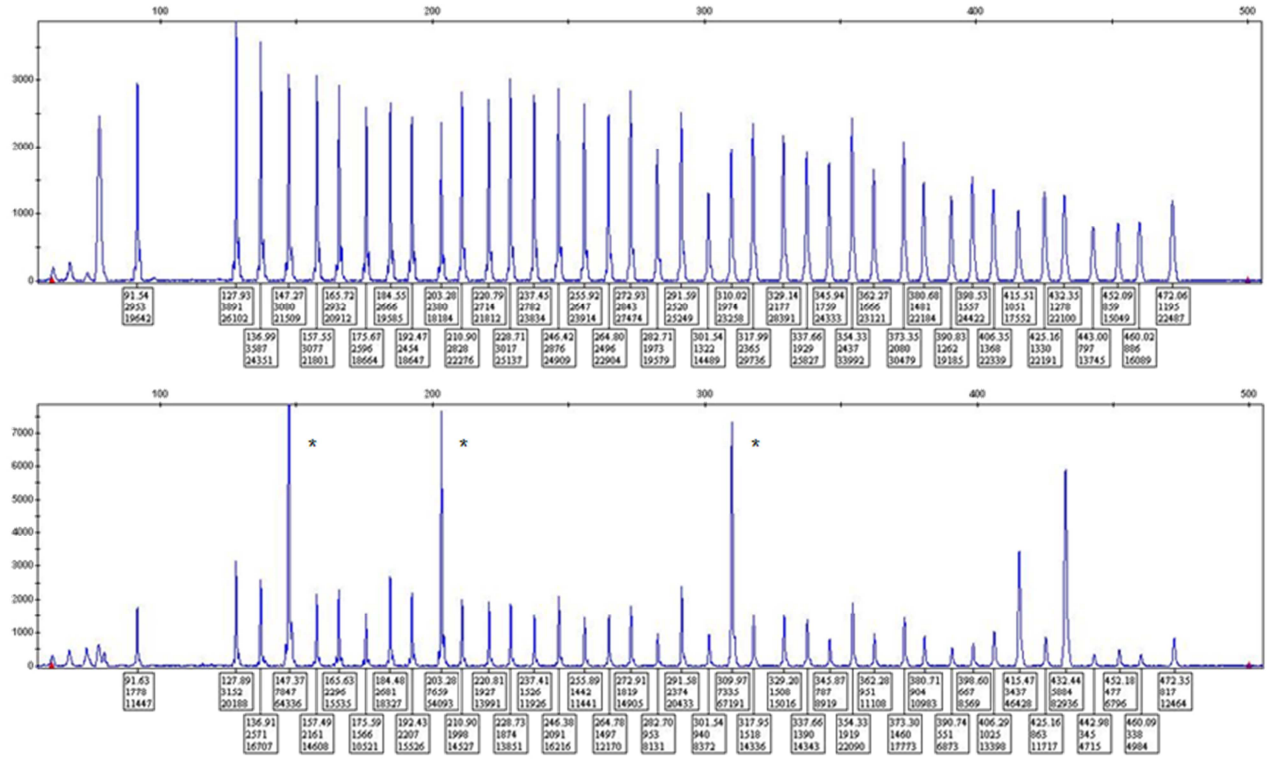

Figure 4. Top: HER2 non-amplified case by multiplex ligation-dependent probe amplification (MLPA). Bottom: HER2-amplified case by MLPA; notice the increased peak height for 5 probes (* = HER2 probes).

ISH and MLPA are generally performed as a second-line gene amplification test in tumors for which the immunohistochemistry (protein expression) status for HER2 is equivocal (so-called 2+). Amplification of HER2 is usually determined as ratio of HER2 on CEP17, the centromere of chromosome 17 (where HER2 resides), to correct for a phenomenon called polysomy 17. However, several groups have questioned the value of CEP17 correction since it does not seem to be correlated to chromosome 17 polysomy, which in fact is very rare (Moelans et al., 2011).

CGH has mainly been used in the research setting because of its high costs and difficulty of interpretation. Results of CGH have extensively been described here, with most frequent alterations (mainly gains and amplifications) on chromosomes 8, 11 and 17. A graphical representation of the chromosomal aberrations found in breast tumors can be found here. A possible application for CGH in diagnostics in the future could be the differential diagnosis metastasis/new primary tumor. Genetic alterations in the primary tumor are believed to be fairly conserved throughout the metastatic process and as such, comparison of the chromosomal profiles of primary tumors and metastases should show high similarity.

Sequencing projects provide us with more insight in breast cancer genomic rearrangements (copy number alterations, breakpoints, intra- and inter-chromosomal rearrangements (Edgren et al., 2011). A graphical (Circos plot) representation of chromosomal rearrangements in the MCF7 breast cancer cell line can be found here, and illustrates the complexity of the breast cancer genome. A series of recent next-generation sequencing manuscripts have further underlined the genetic diversity of breast cancer. Beyond confirming recurrent somatic mutations in PIK3CA, TP53, AKT1, GATA3 and MAP3K1, potential driver mutations were identified in several new cancer genes including AKT2, ARID1B, CASP8, CDKN1B, MAP3K1, MAP3K13, NCOR1, SMARCD1, TBX3, MTAP, PPP2R2A, CBFB and MAP2K3 (Stephens et al., 2012; Banerji et al., 2012; Curtis et al., 2012). Next to recurrent mutations and deletions, recurrent fusion products have also been shown (Banerji et al., 2012) to be more or less present in certain subtypes of breast cancer. Analysis of paired DNA-RNA profiles revealed novel subgroups with distinct clinical outcomes (Curtis et al., 2012).

Additional anomalies

As for most human cancers, aneuploidy is frequently present in breast tumors. The predictive value of nuclear DNA content in mammary carcinoma is still under debate in spite of several reports indicating a relationship between DNA ploidy and prognosis.

Chromosomal translocations that form fusion products and/or activate gene expression by promoter insertion are key events in hematological malignancies, but have been reported to be less common in epithelial cancers such as breast cancer. However, that view is currently

being challenged by array painting and next generation sequencing studies.
Reciprocal and more complex balanced translocations seem to be far more frequent than expected. The NRG1 gene on 8p12 seems to be translocated in 6% of breast cancers (Huang et al., 2004; Chua et al., 2009) and furthermore, several translocation break points are located within genes, including known cancer-critical genes such as EP300/p300 and CTCF (Howarth et al., 2008; Edwards, 2010).
One of the best known translocations in a specific subtype of breast cancer (secretory type) is a recurrent chromosomal translocation t(12;15)(p13;q25), leading to the formation of the ETV6-NTRK3 fusion gene (Vasudev and Onuma, 2011). Another well-known recurrent translocation in adenoid cystic carcinoma (ACC) of the breast, t(6;9)(q22-23;p23-24), resulting in a fusion of the two transcription factor genes MYB and NFIB (Persson et al., 2009). The fusion results in loss of the 3'-end of MYB, including several conserved binding sites for microRNAs that regulate MYB expression negatively.

Genes involved and proteins

Note
The number of genetic alterations in breast cancer is immense and it is therefore not possible to elaborate on all of them.
A selection was made based on the amount of evidence/literature present. Several of the genes/proteins involved in invasive ductal carcinoma have already been described in "Breast tumors: an overview". These will not be repeated here (TP53, HER2/ERBB2, CCND1, FGFR1, BRCA1, BRCA2, BRCA3, PTEN, ATM, MSH2, MLH1, PMS1, MSH3, CDH1, HRAS, NRAS and KRAS).

BIRC5

Location
17q25

Protein
The encoded protein (baculoviral IAP repeat containing 5), also called survivin, is an adapter molecule involved in signal transduction, cell communication and cell survival. It is a component of the chromosomal passenger complex (CPC), a complex that acts as a key regulator of mitosis. The BIRC5 gene is a member of the inhibitor of apoptosis (IAP) gene family, which encodes negative regulatory proteins that prevent apoptotic cell death. Amplification of the BIRC5 region (in 15-30% of breast cancers) has been shown to predict distant recurrence (Davis et al., 2007) and an altered cytoplasmic to nuclear ratio of BIRC5 was shown to be an independent prognostic factor in breast cancer (Brennan et al., 2008).

EGFR

Location
7p11

Protein
The epidermal growth factor receptor 1 (EGFR, ERBB1) is one of the four members of the ErbB family. EGFR is a receptor tyrosine kinase protein that binds to EGF. Binding to its ligand induces receptor dimerization, tyrosine autophosphorylation and leads to cell proliferation. EGFR is amplified in a small percentage (5-10%) of sporadic breast tumors but a broad range of amplification frequencies has been reported in literature (7-65%) (Lambros et al., 2007). EGFR amplification/overexpression is however more frequent in hereditary, triple negative (ER, PR and HER2 negative) and basal-like breast tumors (Livasy et al., 2006; van der Groep et al., 2004). As for IGFR1 (see below), one of the mechanisms of resistance to the HER2-targeted antibody trastuzumab is cross-talk between EGFR and HER2, which has lead to the development of a dual (oral) tyrosine kinase inhibitor of HER2 and EGFR, called lapatinib (Montemurro et al., 2007).

EMSY (C11orf30)

Location
11q13

Protein
Its protein can repress transcription, possibly via its interaction with a multiprotein chromatin remodeling complex that modifies the chromatin. Its interaction with BRCA2 suggests that it may play a central role in the DNA repair function of BRCA2. It is amplified in 7-13% of breast tumors (Hughes-Davies et al., 2003; Kirkegaard et al., 2008; Moelans et al., 2010). Co-amplification of CCND1 and EMSY was shown to be associated with an adverse outcome in ER-positive tamoxifen-treated breast cancers (Brown et al., 2010). On the other hand, a recent study suggested that EMSY is unlikely to be a driver of the 11q13-q14 amplicon and does not have a dominant role in modulating the response to agents targeting cells with defective homologous recombination (Wilkerson et al., 2011).

ESR1

Location
6q25.1

Protein
This gene encodes an estrogen receptor (ER alpha), a ligand-activated transcription factor. Upon ligand binding the estrogen receptor undergoes a conformational change allowing dimerization to form either homo- or heterodimers. As a dimer, the estrogen receptor binds to the estrogen response element (ERE) in the promoter region of target genes.

Initial reports showed an ESR1 amplification frequency of 20.6% in breast cancer (Holst et al., 2007) but subsequent studies reported considerably lower amplification frequencies, ranging between 5 and 10% (Albertson, 2008; Moelans et al., 2012). Studies have been contradictory with respect to its correlation with ER alpha protein overexpression, prognostic value as well as predictive value (tamoxifen response or resistance). ER alpha protein overexpression is present in 70-80% of breast cancers and is predictive of response to endocrine therapy (Wolmark and Dunn, 2001).

HIF1A

Location
14q23.2

Protein
This gene encodes the alpha subunit of transcription factor hypoxia-inducible factor-1 (HIF-1), which is a heterodimer composed of an alpha and a beta subunit. HIF-1 functions as a regulator of cellular response to hypoxia by activating transcription of many genes, including those involved in energy metabolism, angiogenesis and apoptosis. HIF-1 thus plays an essential role in tumor angiogenesis and survival (Semenza, 2000). Although no amplifications are involved (Vleugel et al., 2004), HIF1 alpha has been shown to be overexpressed in sporadic breast cancer, and even more in BRCA1-related hereditary breast cancer (van der Groep et al., 2008). Increased levels of HIF1 alpha have been associated independently with poor prognosis in lymph node negative breast carcinoma (Bos et al., 2003).

IGF1R

Location
15q26.3

Protein
Its protein is a receptor with tyrosine kinase activity. IGFRs mediate their intracellular actions through the PI3-K and RAS/RAF/MAPK signaling pathways. Many tumors have altered expression of IGF1R and its ligands and this constitutes an early event in tumorigenesis. IGF1R overexpression is predominantly seen in ER-positive breast tumors. The HER2 group (ER/PR negative, HER2 positive) generally shows reduced expression and the expression is somewhat heterogeneous in the triple-negative group (ER, PR and HER2 negative) (Bhargava et al., 2011).
One of the mechanisms of resistance to the HER2-targeted antibody trastuzumab is cross-talk between the insulin-like growth factor-I receptor and HER2 (Jin and Esteva, 2008). In addition to its therapeutic potential in HER2-positive trastuzumab-resistant tumors, targeting the IGF1R also shows therapeutic potential in basal-like breast cancers, a group of aggressive tumors of poor prognosis for which there is no effective targeted therapy currently available (Klinakis et al., 2009).

MYC

Location
8q24

Protein
c-myc is a nuclear protein that plays a role in cell cycle progression, apoptosis and cellular transformation. It functions as a transcription factor that regulates transcription of specific target genes. It is amplified in 9-15% of breast cancers but a broad range of amplification frequencies has been reported (between 1 and 94%) (Lambros et al., 2007; Jensen et al., 2009). MYC amplification has generally been associated with a worse prognosis, with higher mitotic activity and larger tumor size (Moelans et al., 2010). In human breast tumors, MYC amplification has been associated with HER2 amplification and HER2-amplified breast tumors were shown to have a 2.5-fold or greater increased likelihood of having MYC amplification (Al-Kuraya et al., 2004). Patients with MYC/HER2 co-amplification were observed to have substantially worse outcomes than patients who had single-gene amplification, even after standard chemotherapy. However, it was subsequently shown that patients with MYC/HER2 co-amplification in their primary breast tumors benefited significantly more from trastuzumab than did patients with only HER2 amplification. This could, however, not be confirmed in a later study (Perez et al., 2011).

NOTCH1

Location
9q34.3

Protein
Functions as a receptor for membrane-bound ligands Jagged1, Jagged2 and Delta1. Upon ligand activation through the released NOTCH1 intracellular domain (NICD) it forms a transcriptional activator complex. NOTCH1 affects multiple cellular processes including stem cell maintenance, cell fate, differentiation, proliferation, motility and survival (Reedijk, 2012). Aberrant NOTCH1 activity influences breast cancer progression through these processes and NOTCH1 activity seems to participate in cancer metastasis by modulating the EMT, angiogenesis, and anoikis-resistance of tumor cells (Hu et al., 2012). Aberrant NOTCH signaling can induce breast carcinoma in transgenic mice, and high expression of NOTCH receptors and ligands has been linked to poor clinical outcomes in patients with breast cancer (Han et al., 2011).

PIK3CA

Location
3q26.3

Protein
PI 3-Kinases (phosphoinositide 3-kinases, PI3Ks) coordinate a diverse range of cell functions including

proliferation, cell survival, degranulation, vesicular trafficking and cell migration. PIK3CA activating mutations show a high prevalence in breast cancer (34%) (Cizkova et al., 2012) and are associated with higher age at diagnosis, hormone receptor positivity, HER2 negativity, lower tumor grade and stage, and lymph node negativity. PIK3CA mutations have been associated with significantly longer metastasis-free survival, especially in the PR-positive and HER2-positive subgroups (Cizkova et al., 2012). The majority of mutations occur at three hotspots, making these ideal targets for therapeutic development.

PTEN

Location
10q23

Protein
This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase that antagonizes the PI3K-AKT/PKB signaling pathway and thereby modulates cell cycle progression and cell survival. About 25-50% of women with Cowden disease, a syndrome associated with germ-line mutations of the PTEN gene (at 10q23), develop breast cancer, but PTEN mutations have been found in only 5% of sporadic breast cancers. However, 29-48% of breast cancers display loss of heterozygosity in 10q23, about 40% of breast cancers show a decrease or absence of PTEN protein levels at the time of diagnosis (Garcia et al., 2004) and PTEN promoter hypermethylation was reported to be a common event in sporadic breast cancer, occurring in 20-50% of breast cancers (Khan et al., 2004).
PTEN not only antagonizes tumorigenesis but also sensitizes breast cancers to targeted therapy with trastuzumab (Pandolfi, 2004). Its loss has therefore been associated with trastuzumab resistance (Nahta and O'Regan, 2010).

RARB

Location
3p24

Protein
This receptor binds retinoic acid, the biologically active form of vitamin A which mediates cellular signalling in embryonic morphogenesis, cell growth and differentiation. RXR-RAR heterodimers act as ligand-dependent transcriptional regulators by binding to the specific retinoic acid response element (RARE) found in the promoter regions of target genes. In the absence of a RAR agonist, RXR-RAR recruits co-repressor proteins and associated factors such as histone deacetylases to maintain a condensed chromatin structure. RAR agonist binding stimulates co-repressor release and co-activator complexes, such as histone acetyltransferase, are recruited to activate transcription. The RARB2 promotor region was shown to be methylated in 20-25% of breast cancers and methylation was shown to be an independent important determinant of breast cancer prognosis (Sharma et al., 2009; Cho et al., 2012).

RASSF1

Location
3p21.3

Protein
This gene encodes a protein similar to the RAS effector proteins. Loss or altered expression of this gene has been associated with a variety of cancers, which suggests a tumor suppressor function. The inactivation of this gene was found to be correlated with the hypermethylation of its CpG-island promoter region. The encoded protein was found to interact with DNA repair proteins and was also shown to inhibit the accumulation of cyclin D1, and thus induce cell cycle arrest. The most important isoform for breast cancer seems to be isoform A. The frequency of RASSF1A methylation in breast tumors is high (65%) and methylation in tumor samples and fine-needle aspirate washings was shown to be an independent predictor of poor prognosis (Sharma et al., 2009; Buhmeida et al., 2011; Martins et al., 2011). RASSF1A methylation is an attractive biomarker for early cancer detection and its methylation analysis is applicable to a range of body fluids including serum and nipple fluid (Suijkerbuijk et al., 2008).

SRC

Location
20q12-q13

Protein
The protein encoded by this gene is a non-receptor protein tyrosine kinase that plays pivotal roles in numerous cellular processes such as proliferation, migration, and transformation. Src kinases are key upstream mediators of both the PI3-K and MAPK signaling pathways, and have been shown to have important roles in cell proliferation, migration and survival. c-SRC (SRC) is a key modulator of trastuzumab response and a common node downstream of multiple trastuzumab resistance pathways (Zhang et al., 2011). SRC is activated in both acquired and de novo trastuzumab-resistant cells and regulation involves dephosphorylation by PTEN. Increased SRC activation conferred considerable trastuzumab resistance in breast cancer cells and correlated with trastuzumab resistance in patients. Targeting SRC in combination with trastuzumab sensitized multiple lines of trastuzumab-resistant cells to trastuzumab and eliminated trastuzumab-resistant tumors in vivo, suggesting the potential clinical application of this strategy to overcome trastuzumab resistance (Zhang et al., 2011). Furthermore, early-phase clinical trials using the src-inhibitors dasatinib and bosutinib have

suggested modest activity as monotherapy in breast cancer, with potentially greater activity in combination regimens. Given the interaction between SRC and the estrogen receptor, ongoing trials are exploring combinations with endocrine therapy. The relationship between SRC and the vascular endothelial growth factor receptor also justifies investigation of combinations with angiogenesis inhibitors (Mayer and Krop, 2010).

TOP2A

Location

17q21-q22

Protein

This gene encodes a DNA topoisomerase, an enzyme that controls and alters the topologic states of DNA during transcription. This nuclear enzyme is involved in processes such as chromosome condensation, chromatid separation, and the relief of torsional stress that occurs during DNA transcription and replication. It catalyzes the transient breaking and rejoining of two strands of duplex DNA which allows the strands to pass through one another, thus altering the topology of DNA. It is amplified in 5-10 % of breast tumors but amplification is not correlated with overexpression (Di Leo et al., 2002; Knoop et al., 2005; Moelans et al., 2010). TOP2A has been suggested to be a predictive marker of anthracyclin benefit (Nielsen et al., 2008) but subsequent studies were controversial (Bartlett et al., 2010).

TWIST1

Location

7p21

Protein

TWIST1 is a basic helix loop helix protein that plays a role both in human development and in cancer biogenesis. It is an anti-apoptotic and pro-metastatic transcription factor that is known to repress E-cadherin expression in breast cancer (Vesuna et al., 2008) as well as ERα expression thereby contributing to the development of hormone resistance (Vesuna et al., 2012). It is overexpressed in many epithelial cancers including breast cancer. Twist overexpression in breast cancer cells can induce angiogenesis, correlates with chromosomal instability, and promotes an epithelial-mesenchymal-like transition (EMT) that is pivotal for the transformation into an aggressive breast cancer phenotype (Mironchik et al., 2005). TWIST1 promoter methylation is significantly more prevalent in malignant compared with healthy breast tissue and is therefore useful as a biomarker in breast cancer diagnosis, although there is no direct correlation with TWIST1 expression (Gort et al., 2008).

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