Solid Tumour Section
Review

Breast tumors: an overview

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Classification

Benign epithelial lesions with no significant tendency to malignant transformation include:
- adenoma:
-- Ductal
-- lactating
-- Tubular
- adenosis:
-- apocrine
-- blunt duct
-- microglandular
-- sclerosing
- fibroadenoma
- radial scar/complex sclerosing lesions

Invasive breast carcinomas are divided into two major categories on the basis of their cytoarchitectural features:
- Invasive ductal carcinoma:
-- acinic cell carcinoma
-- adenoid cystic carcinoma
-- apocrine carcinoma
-- cribriform carcinoma
-- glycogen-rich/clear cell
-- inflammatory carcinoma
-- lipid-rich carcinoma
-- medullary carcinoma
-- metaplastic carcinoma
-- micropapillary carcinoma
-- mucinous carcinoma
-- neuroendocrine carcinoma
-- oncocytic carcinoma
-- papillary carcinoma
-- sebaceous carcinoma
-- Secretory Breast Carcinoma
-- tubular carcinoma
- lobular carcinoma
-- pleomorphic
-- signet ring cell

The recognized precursor lesions of invasive breast carcinoma are:
- intraductal proliferative lesions:
-- atypical ductal hyperplasia
-- ductal carcinoma in situ
-- florid
-- usual
- lobular neoplasia/atypical lobular.

The terminology Invasive ductal/lobular carcinoma does not imply an origin form ducts and lobules, respectively, but the presence of cytoarchitectural and phenotypical features of ductal-type and lobular-type, respectively.

Ductal adenocarcinoma is the most common. Lobular carcinoma is the second malignant breast tumour.

Medullary carcinoma is rare.

Hyperplasia is a proliferation without criteria of malignancy.

Fibroadenomas are benign breast tumours.

Clinics and pathology

Etiology

The etiology is multifactorial. It involves diet, genetic and reproductive factors, and related hormone imbalances.

Epidemiology

The annual incidence of breast cancer is about 43/100 000 per year in France, and the mortality rate is about 18/100 000 per year. Invasive breast cancer is the most common carcinoma in women, accounting for 22% of

all female cancers. One million women worldwide are diagnosed with breast cancer every year.

The main factors of risk are:

Gender: women's risk for the development of invasive breast carcinoma is approximately 400 times that of men.

Age: breast cancer incidence increases rapidly with age. The mean age at diagnosis is around 60 yrs.

Genetic factors: rare (3 to 5% of cancers and 1/500-800 women) but highly predictive of the disease.

The areas of higher risk are the affluent populations of North America, Europa and Australia, where 6% of women develop invasive breast carcinoma before age 75.

Pathology

The most common histologic type of invasive breast carcinoma is designated as **ductal**, NOS (not otherwise specified). It comprises about 80% of all cases. It is a proliferation of epithelial cells from galactophoral ducts; it may be preceded and accompanied by an in situ component characterized by a proliferation of cells within the ducts without interuption of the basal membrane; when this membrane is altered, the carcinoma is invasive. It can be graded on the basis of the architecture (amount of tubule formations), nuclear atypia and mitotic activity. The score resulting from the sum of these criteria (NottinghamÕs score) has been show to be an important prognostic indicator. A 3-grade system has been developed for in situ ductal carcinoma. Grade III in situ ductal carcinoma corresponds to the classic comedocarcinoma, whereas Grade I in situ ductal carcinoma merges with atypical ductal hyperplasia, to the point that some authors regard the two process as one and the same. Recently, a proposal has been made to embrace all of the various types of intraductal proliferative lesions under the term ductal intraepithelial neoplasia (DIN) and to divide this into 3 grades, having increasingly higher risk for the development of invasive carcinoma.

Many morphologic variants of invasive ductal carcinoma exist, some of them extremely rare. They include: tubular, cribriform, medullary, mucinous, neuroendocrine, papillary, micropapillary, apocrine, metaplastic, lipid-rich, secretory, oncocytic, adenoid cystic, acinic cell, glycogen-rich (clear cell), sebaceous, and inflammatory carcinoma. The prognosis of these subtypes varies, some of them having a better and some a worse outcome than invasive ductal carcinoma, NOS.

Invasive lobular carcinoma is the second major type (5-10%) of breast cancer. Like its ductal counterpart, it may be preceded or accompanied by an in situ component. It is histologically more homogeneous than ductal carcinoma, but some morphologic variation exist, such as pleomorphic and signet ring cell.

Medullary carcinoma, already mentioned above as a rare subtype of invasive ductal carcinoma (1%) with a better prognosis, it has a very distinctive form: sharply circumscribed, accompanied by a heavy lymphoid infiltrate, of high nuclear grade, with a syncytial pattern of growth, and lacking in situ or microglandular features. When one of these features is lacking, the tumor is referred to as Òatypical medullary carcinoma". A high frequency of medullary carcinoma has been reported in patients with BRCA1 germ line mutation.

The different steps in the progression of breast cancer are not well individualized.

Hyperplasia is a proliferation of ductal or lobular epithelial cells, without criteria of malignancy; in contrast, atypical hyperplasia has incomplete malignant features and can be difficult to distinguish from in situ carcinoma.

Fibroadenomas are the most common form of benign breast tumors.

These different forms of breast cancer may occur with (hereditary or familial forms) or without (sporadic forms) a familial background.

Prognosis

There are over 100 factors that have been identified as having prognostic significance in breast carcinoma, but only a minority of them will retain this property when subjected to a multivariate analysis. The most important prognostic factors are: presence and number of positive lymph nodes; tumor size; microscopic grade; and presence of lymphovascular invasion. Other parameters examined pathologically - such as hormone receptors and ERBB2/Neu - have more of a predictive than a prognostic value, in the sense of anticipating a certain type of response to specific forms of therapy.

Upon diagnosis, the different presentations are classified upon morphological study, and the gravity and prognosis of the disease is estimated with several parameters that are:

tumor size,

tumor grade: it is calculated from assessment of tubular differentiation, number of mitoses, and nuclear polymorphism,

the absence of estrogen and progesterone receptors,

the presence of lymph node metastasis,

peritumoral vascular invasion. Other parameters such as the proliferating index (Ki 67, S-phase), the ploidy, and the presence of P53 or ERBB2 alteration may also be useful for prognostic evaluation or as predictive factors for therapeutic response.

Genetics

Note

Familial breast cancers are thought to represent about 5 to 10% of all breast cancers.

Cytogenetics

Morphological cytogenetics

Many of the chromosomal aberrations observed in breast carcinomas are not specific of this type of tumour; karyotypes of breast tumours frequently show multiclonality, suggesting the existence of a high degree of intratumoural heterogeneity.

Alterations of chromosome arms 1q, 3p, 6q, 8p are often present; i(1q) and der t(1;16) are frequent as sole anomalies; +7, +8 and +20 are also frequent; cytogenetic signs of DNA amplification, such as homogeneously staining regions (HSR), are commonly observed in breast carcinomas and seem preferentially associated to 8p.

Molecular cytogenetics

LOH studies: loss of heterozygosity (LOH) has been associated with physical deletion of large genomic segments containing tumour suppressor genes; common regions of LOH in breast cancer are located on several chromosomes: 1p, 1q, 3p, 6q, 8p, 11q, 13q, 16q, 17p, 17q; almost all breast tumours show LOH in one or several regions; some regions are lost in more than 50% of tumors: 8p, 16q, 17p; precancerous lesions also show LOH.

CGH: Comparative genomic hybridization (CGH) is a molecular cytogenetics method designed to detect and map chromosomal regions showing abnormal copy numbers in tumors; theoretically, it is possible to detect equally copy number gains (DNA amplification or polyploidies) or losses using this approach; it appears, however, that CGH has a greater sensitivity for gains than for losses; this could be related to the fact that gains are generally of higher magnitude than losses and that losses can be obscured by intratumoral heterogeneity.

Overall CGH data show that breast tumor genomes undergo severe rearrangements; on average, breast tumors show 5-7 copy number changes/tumor; less than 10% of the tumors analyzed by CGH show neither gains nor losses; almost every chromosome presents at least one site with aberrant copy numbers, however, gains or losses are not evenly distributed throughout the genome.

Hot spots for gains are routinely observed at 1q (50-55% of the tumors), 8q (60%), 17q (25-30%), 20q (20-25%); gains generally involve subregions of each chromosomal arm and most prevalent regions are 1q31-q32, 8q12 and 8q24 (with MYC and other genes), 17q12 (ERBB2) and 17q23-q24, and 20q13; other regions of recurrent gains are 11q13 (20%, with CCND1), 8p12 (10-15%, and FGFR1), 16p (10-15%); recurrent losses are observed at 1p, 6q, 8p, 11q23-qter, 13q, 16q, 17p and 22q.

CGH has revealed that copy number gains are common

in breast tumors and involve 26 (!) chromosomal arms; these data somewhat contradict karyotypical analysis and LOH studies which indicate that losses are more frequent that gains; furthermore, it appears from CGH data that the number of events (gains and losses) increases in advanced cancer.

Genes involved and proteins

HRAS

Location
11p15.5

KRAS

Location
12p12.1

NRAS

Location
1p13.2

Protein
H, K, and NRAS genes are a subfamily of the huge RAS/RHO/RAB superfamily and encode ubiquitous cytoplasmic GTP binding p21 proteins involved in signal transduction.

Somatic mutations
RAS genes are mutated at codons 12, 13 and 61in different types of cancers; the frequency of mutations in breast cancer is rather low (<10%) compared to colorectal cancer or pancreatic cancer for instance.

P53

Location
17p13

DNA / RNA
11 exons

Protein
The tumor suppressor gene P53 encodes an ubiquitous nuclear protein involved in the control of genome integrity by preventing cells from dividing before DNA damage is repaired; it has 5 conserved regions containing a transactivation domain, a DNA-binding domain, a tetramerization domain.

Somatic mutations
20-25% of breast cancers show P53 mutations and these correspond to aggressive breast tumors (loss of estrogen receptor expression).

90% of P53 mutations are found within exons 5 through 9, portions correspondig to codons 165-185 (exon 5) and 235-252 (exon 7) concentrating 50% of the mutations (mutational hot spots); most frequently involved are codons 175, 248 and 273; mutations affecting residues 165-185 and 235-252 bear worse prognostic significance than others; these amino acid residues are located in the L2 and L3 domains of the

p53 protein; both these domains bind a Zinc atom and convey contact to DNA; it may thus be of greater phenotypic significance.

The majority of P53 mutations (80%) in breast cancer are missense, while nonsense mutations, deletions, insertions or, splice site mutations, which result in the truncation of the protein, make the rest (20%). Prolonged half-life of the protein can also be detected by immunohistochemistry and shows correlation with missense mutations.

ERBB2

Location
17q21.2

Protein
The ERBB2 (also called HER2 or NEU) gene encodes an integral type I protein of 185 kDa with a cysteine-rich extracellular region, a transmembrane domain and an intracellular region endowed with a tyrosine kinase activity.

Somatic mutations
HER2 somatic mutations are reported in lung cancer, glioblastoma and ovarian tumor. No somatic mutations in human breast carcinoma are described.

Amplification : the ERBB2 gene is amplified and overexpressed in 20-25% of breast tumors; tumors showing ERBB2 amplification have predominantly lost estrogen receptor expression (ER-) and are of ductal invasive type; interestingly, 70% of intraductal comedo carcinomas show ERBB2 expression, suggesting a role of this gene in the etiology of this breast tumor subtype; Although ERBB2 amplification and overexpression are related to a worsened course of the disease, they do not represent independent prognostic indicators;
However, the p185-ERBB2 protein being a transmembrane receptor with low levels of expression in normal tissues has turned out to be a very interesting target for therapeutical approaches; several protocols using engineered anti-ERBB2 antibodies have shown a good success rate.

CCND1

Location
11q13.3

Protein
The CCND1 gene codes for a cell cycle protein specifically acting in the G1 phase; upon interaction with cyclin dependent kinases (CDK4 or CDK6) cyclin D1 phosphorylates the p105-RB protein and thereby promotes progression in late G1 thus favoring entry into S phase; ectopic overexpression of CCND1 has been shown to result in shortened G1 phase and increased genetic instability, possibly due to a bypass of cell cycle checkpoints.

Somatic mutations
Amplification: the CCND1 gene is amplified in approximately 15% breast cancers; CCND1

amplification is strongly correlated to expression of ER and is prevalent in invasive lobular carcinomas; univariate analysis and Cox model studies show that CCND1 amplification is an independent prognostic factor, however, it bears greatest significance in node positive patients.

FGFR1

Location
8p11-12

Protein
The FGFR1 gene encodes an integral type I protein of 145 kDa with an extracellular region made of three immunoglobulin-like domains, a transmembrane domain and an intracellular region endowed with a tyrosine kinase activity; alternative splicing create a large number of isoforms; it is a receptor for different members of the fibroblast growth factor family (FGF), which has about 20 members known to date.

Somatic mutations
Amplification: the 8p11-12 region is amplified in about 10% of breast carcinomas; the FGFR1 gene is overexpressed as a consequence of the amplification, and is a good candidate for being the driver gene of the 8p11-12 amplicon; FGFR1 is frequently amplified concomitantly with CCND1 (40% of FGFR1 amplified tumors also show CCND1 amplification); this coamplification of FGFR1 and CCND1 chromosomal regions results in the formation of a hybrid chromosomal structure in which amplified FGFR1 and CCND1 sequences are sequentially arranged.

BRCA1

Location
17q21

DNA/RNA
Large gene of 22 coding exons spaning more than 70 kb of genomic DNA; exon 11 corresponds to almost 50% of the total coding sequence (5592 nucleotides); the BRCA1 mRNA has a size of 7.8 kb, and a complex pattern of alternative splicing has been reported; it is expressed in numerous tissues (breast, ovary, testis, spleen, thymus).

Protein
The corresponding protein has 1863 amino acids, and 190-220 kDa; BRCA1 is not a member of any known gene family; there is only two stretches of evolutionary conserved sequences between humans and mice: at the N-terminus (the RING finger motif), and at the C-terminus (the BRCT domain); the function of BRCA1 is still unknown but it seems to act as a tumor suppressor gene with transcriptional activity; it is involved in cell proliferation processes of mammary epithelial cells in response to hormonal stimulation, in apoptosis, control of recombination and genome integrity after binding to proteins involved in these activities.

Germinal mutations

More than 300 sequence variations at the germline level have been reported; a list is available on the BIC website:

the germline mutations are dispersed throughout the coding sequence; although a majority of these variations are unique, recurrent mutations such as 185delAG and 5382insC are observed; they were initially described in the Ashkenazy Jewish population; more than 80% of the sequence variants lead to a truncated protein; in contrast, the majority of missense mutations are of unknown clinical significance, excepted those in the RING finger region; in the BRCA1 families, an excess of breast, ovarian, and prostate cancers are seen; all mutations combined, penetrance at age 70 years works out at 56% to 87% in the case of breast cancer, and 16% to 63% in that of ovarian cancer BRCA1-associated breast cancers have specific morphological features; they are more frequently of histoprognostic grade 3, highly proliferating and poorly differentiated tumors with a very pleomorphotic nuclear pattern; high frequencies of P53 alterations and negativity of steroid receptors are found in these tumors; a high rate of medullary breast carcinomas is observed among BRCA1-associated breast cancers; evidence for possible genotype-phenotype correlations have been provided concerning the tumor spectrum (breast/ ovarian cancer incidence rate), the penetrance, and the proliferation rate of tumors.

Somatic mutations

In contrast, somatic mutations of BRCA1 coding sequence are rare in breast/ovarian cancers.

BRCA2

Location

13q12-13

DNA / RNA

Like BRCA1 it is a large gene spanning more than 70 kb of genomic DNA; the coding sequence comprises 26 exons (10254 nucleotides) with three large ones (exons 10, 11, 27); the mRNA is of 11-12 Kb long; like BRCA1, it is expressed in various tissues.

Protein

The coresponding protein has 3418 amino acid residues (384 kDa), and is poorly conserved, exepted for the BRC repeats region in exon 11 (8 copies of 20-30 aa); like BRCA1, its function remains unknown; however, it acts as a tumor suppressor gene; transcriptional activation properties have been reported as well as involvement in the DNA repair system.

Germinal mutations

More than 100 unique germ-line mutations are reported and are dispersed throughout the coding sequence (cf the BIC website, address above); recurrent mutations are seen: 6174delT (of Ashkenazy Jewish origin),

999del5 (Icelandic), and 6503delTT (in France and in the UK); the majority lead to a truncated protein and are considered as disease-associated mutations, except for a polymorphic stop codon in exon 27; missense mutations are of uncertain clinical significance.

BRCA2 germline mutations are associated with a high risk of male and female breast cancer; initially, the breast cancer risk was considered as equivalent to that of BRCA1, but in a recent work based only on the Icelandic recurrent BRCA2 999del5 mutation, the estimated risk of breast cancer at age 70 years is considered of only 37%; the ovarian cancer risk is lower than that of BRCA1; in addition, an excess of prostate and pancreas cancers is also seen at the morphological level, BRCA2 breast cancers seem to be different from both BRCA1-associated breast cancers and sporadic cases, with a poor differentiation but no high proliferation rate; evidence for possible genotype-phenotype correlation has been provided concerning the tumor spectrum (breast/ovarian cancer incidence rate).

Somatic mutations

Somatic mutations of BRCA2 coding sequence are rare in breast/ovarian cancers.

BRCA3

Location

An important breakthrough in the understanding of breast carcinogenesis came with the identification of the two major genes BRCA1 and BRCA2, correponding to 52% and 32% of hereditary breast cancer families, respectively; however, the germline mutations of these genes do not account for all familial cases; additional genes may be involved.

One such gene might be located on chromosome arm 8p; a positive linkage has first been found in a small set of French families, and then a lod score of almost 3 was obtained in one German family; in addition, the chromosome 8p12-22 region seems to be frequently involved in breast carcinogenesis as well as in different types od tumors (lung, prostate, ovarian); while the 8p12-22 region remain a strong candidate locus, whole-genome linkage studies are in progress to identify the other gene(s) that predispose to breast cancer.

PTEN

Location

10q23

DNA / RNA

9 exons

Protein

The PTEN protein (also called MMAC1) is an evolutionary conserved dual-specificity phosphatase sharing extensive similarity with the cytoskeletal protein tensin; PTEN appears to be a tumor suppressor since biallelic inactivations are observed in several types of tumors; inactivating germline mutations are

responsible for a cancer prone syndrome, the Cowden disease (see below); also, PTEN -/- ES cells are highly tumorigenic in syngeneic mice whereas PTEN +/- are not.

Germinal mutations

Heterozygous germline mutations are responsible for the Cowden disease, a cancer prone syndrome with high susceptibility to breast carcinoma, and, to a lesser degree, to thyroid carcinoma; most of the mutations are inactivating mutations, either by leading to protein truncation, or by introducing alterations in the phosphatase catalytic domain; germline mutations are also seen in the Bannayan-Riley-Ruvalcaba syndrome.

Somatic mutations

In spite of the initial description of PTEN homozygous deletion in two breast tumor xenografts and biallelic inactivation of PTEN in two breast carcinoma cell lines, very few PTEN mutations have been observed in sporadic breast carcinoma (1 described mutation in more than 100 analyzed tumors).

ATM

Location

11q23

DNA / RNA

The ATM gene covers 150 kb of DNA and is spread over 64 exons. It codes for a 13.000 bp transcript, translated into a 3500 aa protein.

Protein

Nuclear protein showing homology at its carboxy terminus with PI-3 kinase; belongs to a family of DNA damage signaling proteins characterized in either yeast or Drosophila; ATM interacts with the ABL protein and is known to transmit a signal to the P53 protein. ATM activity seems restricted to double strand DNA breaks induced by ionising radiations or radio-mimetics; it is noteworthy that the phenotype of Atm KO mice is very similar to that of ATM patients, but that heterozygous Atm +/- mutant mice do not show an increased incidence of cancer.

Germinal mutations

The ATM gene is the genetic determinant to ataxia telangiectasia, a rare recessive disorder, which among other clinical signs, is characterized by an extreme sensitivity to ionising radiations; it has been hypothesized that ATM could play a role in cancer predisposition because AT patients show a 100 fold increased risk of cancer, particularly hematological malignancies; furthermore, epidemiological studies have suggested that AT heterozygotes were also at increased risk of developing cancer, specially breast cancer in women; this, added to the fact that the ATM gene maps to 11q23, a region frequently affected by losses of heterozygosity, suggested that heterozygous mutations in the ATM gene may favor breast cancer development; ATM heterozygotes have been estimated to represent 1% of the total population.
Most mutations reported in ATM kindreds result in the truncation of the protein.

Mismatch repair genes

Note

MSH2 (2p21), MLH1 (3p21), PMS1 (2q31-33), PMS2 /GTBP/MSH6 (7p22), MSH3 (5q).

Protein

The proteins encoded by the mismatch repair genes are analogues of the bacteria Mut HLS system which is involved in the reparation of DNA replication errors; their defect leads to genomic instability, the most visible consequence of which is the presence of additional alleles at microsatellite markers; the latter are prone to replication errors; their alteration is a hallmark of genomic instability, also called RER (replication error) or MSI (microsatellite instability) phenotype.

Somatic mutations

Frequencies of genomic instability varies from 0 to 40% in breast cancer, depending on studies; however, mutations of mismatch repair genes are uncommon in breast cancer; thus, the high frequencies observed may be due to unknown genes involved in the control of DNA integrity.

E-Cadherin

Location

16q22.1

Somatic mutations

Mutations and loss of expression of the E-cadherin gene, located on chromosome arm 16q, is very frequentlly observed in breast lobular carcinomas.

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