REVIEW ARTICLE

CURRENT CONCEPTS

Triple-Negative Breast Cancer

William D. Foulkes, M.B., B.S., Ph.D., Ian E. Smith, M.D., and Jorge S. Reis-Filho, M.D., Ph.D.

From the Program in Cancer Genetics, the Research Institute of the McGill University Health Centre, and the Lady Davis Institute of the Jewish General Hospital (W.D.F.); McGill University, Montreal; and the Breast Unit, Royal Marsden Hospital and Institute of Cancer Research (I.E.S.), and the Breakthrough Breast Cancer Research Centre, Institute of Cancer Research (J.S.R.-F.) — both in London. Address reprint requests to Dr. Foulkes at the Program in Cancer Genetics, Departments of Oncology and Human Genetics, Gerald Bronfman Centre for Clinical Research in Oncology, McGill University, 546 Pine Ave. W., Montreal, QC H2W 1S6, Canada, or at william.foulkes@mcgill.ca.

N Engl J Med 2010;363:1938-48.

A PUBMED SEARCH OF THE MEDICAL LITERATURE SHOWS THAT THE FIRST mention of "triple-negative" breast cancer was in October 2005; since then, the term has appeared in more than 600 publications.[1] This increase reflects the growing recognition of the importance of triple-negative breast cancer (see the Glossary for this and other key terms) by oncologists, pathologists, and geneticists, as well as by the approximately 12 to 17% of women with breast cancer who have triple-negative breast cancer. As a group, patients with triple-negative tumors have a relatively poor outcome and cannot be treated with endocrine therapy or therapies targeted to human epidermal growth factor receptor type 2 (HER2).

A close cousin of triple-negative breast cancer is basal-like breast cancer (synonymous terms include "basal-type," "basal-epithelial phenotype," "basal breast cancer," and "basaloid breast cancer"). This molecular subtype of breast cancer is characterized by a gene-expression profile that is similar to that of the basal–myoepithelial layer of the normal breast.[2] Immunohistochemical markers have been used as a surrogate for this profile. The multiplicity of names reflects an underlying uncertainty as to the true nature of this entity.

TRIPLE-NEGATIVE VERSUS BASAL-LIKE BREAST CANCERS

Triple-negative breast cancers are defined as tumors that lack expression of estrogen receptor (ER), progesterone receptor (PR), and HER2. Basal-like breast cancers constitute one of five intrinsic subgroups of breast cancer, the existence of which was revealed by microarray-based expression profiling studies.[2] This subgroup is characterized by an absence or low levels of expression of ER, an absence of HER2 overexpression, and expression of genes usually found in basal or myoepithelial cells of the normal breast (Fig. 1).[2,3] Many cancers meet the definitions of both triple-negative breast cancers and basal-like breast cancers.

Although appreciation of the significance of basal-like breast cancers predated gene-expression studies by some years,[4,5] this term did not come into widespread use until after the publication of these studies.[2] There is still no internationally accepted definition for these tumors.[3] Because a majority of basal-like cancers are also triple-negative breast cancers and the majority of triple-negative breast cancers (approximately 80%) are also basal-like breast cancers,[6] it has been claimed that the triple-negative and basal-like phenotypes are effectively synonymous,[7,8] but clinical, microarray, and immunohistochemical data show that this is not the case (Table 1).

Triple-negative breast cancers encompass other molecular subtypes of breast cancer. These include the so-called claudin-low tumors, which are reported to be enriched with cells that have properties similar to those of stem cells and to have

Glossary

Basal-like breast cancer: A subtype of breast cancer defined by unsupervised analysis of microarray gene-expression data. This subtype comprises a heterogeneous group of tumors characterized by the absence of or low levels of expression of estrogen receptors, very low prevalence of HER2 overexpression, and expression of genes usually found in the basal or myoepithelial cells of the human breast.

BRCA1-related breast cancer: A breast cancer occurring in a woman who carries a deleterious germline mutation in the breast-cancer susceptibility gene *BRCA1*. These tumors usually show a loss of heterozygosity of the wild-type allele and possess a triple-negative and a basal-like phenotype.

Breast-cancer subtypes: A way of classifying breast cancers according to the similarities in their gene-expression profiles, as defined by hierarchical clustering analysis based on an "intrinsic gene list" (i.e., a list of genes that vary more when comparing samples of distinct tumors than when repeated samples of the same tumor are compared). This is a working classification, which is likely to undergo further refinement.

Epithelial-to-mesenchymal transition: Loss of epithelial characteristics and acquisition of mesenchymal features. This process has been well documented in embryogenesis, wound healing and regeneration, and models of cancer. Definitions of epithelial-to-mesenchymal transition in cancer remain controversial; however, examples of this phenomenon in human cancers have been documented.

Human epidermal growth factor receptor type 2 (HER2): A member of a family of cell-membrane–bound receptor tyrosine kinases (HER1 through HER4). *HER2* is amplified in 15 to 20% of breast cancers and when overexpressed is the target of the humanized monoclonal antibody trastuzumab.

Medullary breast cancer: A rare subtype of breast cancer accounting for less than 1% of invasive breast neoplasms that is usually manifested as a well-circumscribed mass. Histologically, typical medullary carcinomas are composed of high-grade, poorly differentiated cells arranged in coalescing sheets. The tumors have scant stroma, pushing borders (the edge of the tumor appears to be pushing into normal tissue), and brisk lymphocytic infiltrate. Prognosis is usually good.

Metaplastic breast cancer: An umbrella term that refers to a heterogeneous group of breast cancers composed of an admixture of adenocarcinoma, with dominant areas of spindle cells, squamous cells, or malignant mesenchymal differentiation.

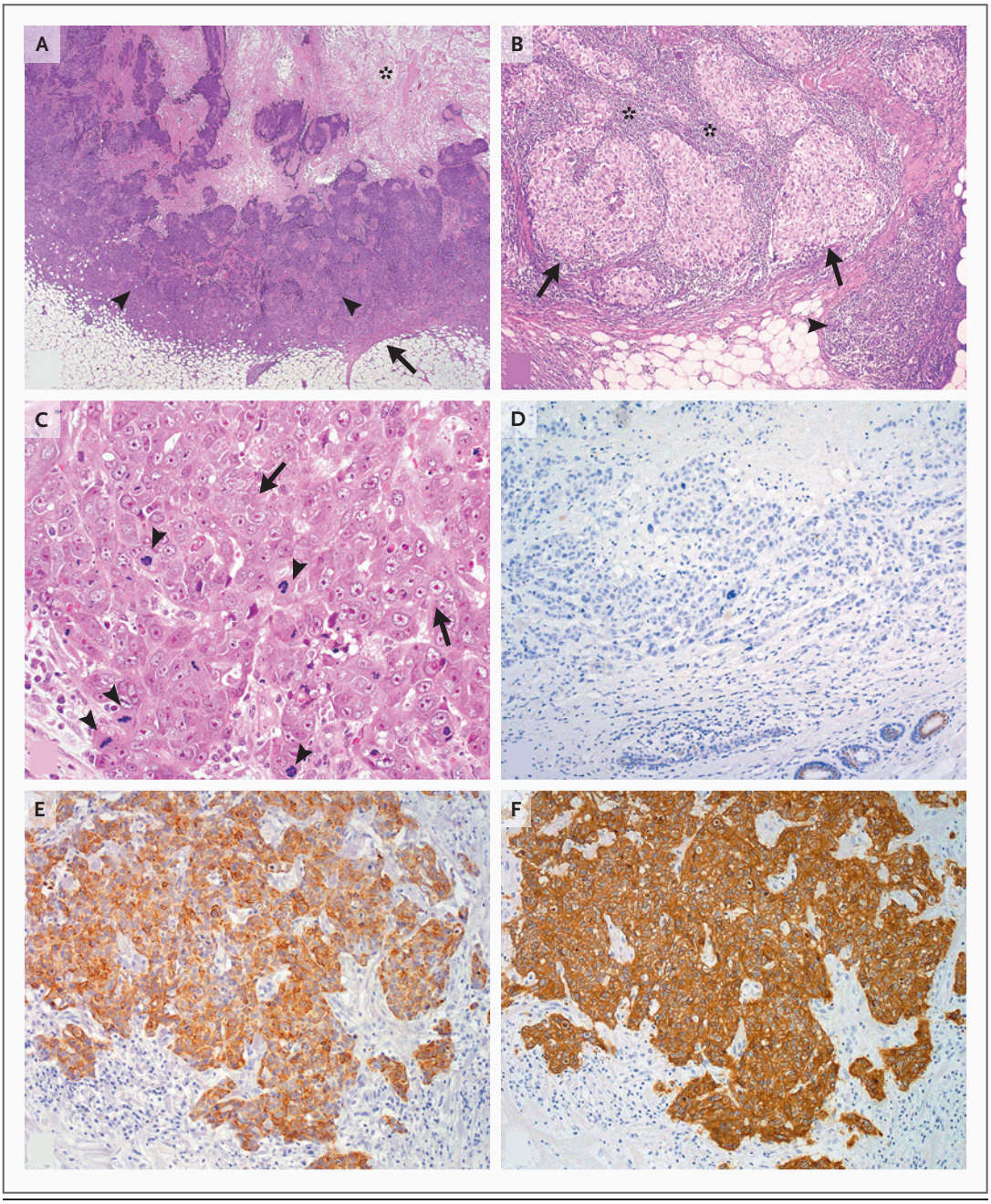
Special histologic type of breast cancer: A tumor characterized by histologic features consistent with those of one of the 17 histopathological types of breast cancer classified by the World Health Organization as a distinct entity in more than 90% of its area.

Triple-negative breast cancer: A tumor characterized by lack of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. Some investigators accept tumors as being negative for expression of ER or PR only if less than 1% of the cells are positive for ER or PR expression; others consider tumors to be negative for ER and PR when up to 10% of cells are positive for expression. Different definitions of HER2-negativity have been used. The two most frequently adopted include tumors with immunohistochemical scores of 0/1+ or tumors with scores of 0/1+ or 2+ that are lacking HER2 gene amplification after in situ hybridization.

Unsupervised hierarchical clustering analysis: A statistical term from the field of machine learning that refers to a computer program that searches for similarities and differences in observations. In unsupervised learning, no attempt is made to guide the analysis in any particular direction. Clustering is a form of unsupervised learning in which observations are clustered in subsets such that observations within each subset resemble each other to a greater degree than observations in other subsets. Such clustering is referred to as hierarchical when new clusters are found in previously established clusters. This hierarchy is usually represented as a tree structure, or dendrogram.

X-chromosome inactivation: During the embryonic development of female mammals, the repression of one of the two X chromosomes takes place in order to compensate for this extra chromosome. As a result of this random process, an inactive X chromosome, or Barr body, is present in every nucleus. All female mammals are therefore mosaics in that some cells express only the paternal X chromosome and others only the maternal X chromosome.

features of epithelial-to-mesenchymal transition; the interferon-rich subgroup, which encompasses tumors with a considerably better prognosis than that associated with other triple-negative breast cancers; and the normal-breast–like subgroup, which may be an artifact (i.e., it may comprise samples enriched with a disproportionately high content of stromal and normal cells).[6,7] Similarly, 18 to 40% of basal-like cancers do not have a triple-negative phenotype on immunohistochemical analysis.[9] Up to 20% of basal-like cancers express ER or overexpress



HER2. At the genetic level, triple-negative and basal-like cancers are remarkably heterogeneous. Amplification of numerous genetic regions has been documented, but the prevalence of each of these amplified regions is low.[10]

Triple-negative and basal-like tumors account for about 15% of all invasive breast cancers, and they usually have a high histologic grade.[3,11] Both triple-negative[12] and basal-like[13] breast cancer occur more frequently in young black and Hispanic women than in young women of other racial or ethnic groups. *BRCA1* is an important breast-cancer susceptibility gene; more than 75% of tumors arising in women carrying a mutation in this gene have a triple-negative phenotype, a basal-like phenotype, or both.[3,11]

As compared with women without cancer, women in whom basal-like breast cancer devel-

Figure 1 (facing page). Histologic and Immunohistochemical Features of Triple-Negative and Core Basal-like Breast Cancers.

Triple-negative tumors (Panels A through D) typically have pushing borders (the edge of the tumor appears to be pushing into normal tissue) (Panel A, arrow; hematoxylin and eosin) and central necrotic areas (Panel A, asterisk). Neoplastic cells are arranged in solid sheets (Panel A, arrowheads) or nests (Panel B, arrows; hematoxylin and eosin). A prominent lymphocytic infiltrate can sometimes be seen at the periphery of the tumor (Panel B, arrowhead) and within the bulk of the tumor (Panel B, asterisks). The neoplastic cells are atypical and pleomorphic (Panel C, arrows; hematoxylin and eosin), and numerous mitotic figures can be detected at high-power magnification (Panel C, arrowheads). The absence of both estrogen receptors (Panel D, upper portion, with normal lobules and ducts containing estrogen-receptor–positive cells present in the bottom right corner; immunohistochemical staining, anti–estrogen-receptor antibody; chromogen, 3,3′-diaminobenzidine; counterstaining, hematoxylin) and progesterone receptors and the expression of HER2 is diagnostic of triple-negative breast cancer. Core basal-like breast cancers are characterized by this same triple-negative phenotype and by the expression of cytokeratin 5 (Panel E; immunohistochemical staining, anti–cytokeratin-5 antibody; chromogen, 3,3′-diaminobenzidine; counterstaining, hematoxylin), EGFR (Panel F; immunohistochemical staining, anti-EGFR antibody; chromogen, 3,3′-diaminobenzidine; counterstaining, hematoxylin), or both cytokeratin 5 and EGFR.

ops reach menarche at an earlier age than do women without cancer[13,14] and have a higher body-mass index during their premenopausal years,[13,14] higher parity,[13] and a lower lifetime duration of breast-feeding.[13] The risk factors for triple-negative and basal-like tumors may differ from those usually associated with other types of breast cancer. For example, in contrast with the risk of the more common low-grade, ER-positive (luminal A) breast cancer, the risk of basal-like breast cancer rises with increasing parity and an increasing ratio of waist-to-hip circumference.[13] Thus, there appears to be a complex interplay of genetic and societal factors that together put black and Hispanic women at increased risk for both triple-negative and basal-like breast cancer.

The term "core basal phenotype"[15,16] has been used in efforts to define a clinically relevant subtype of breast cancer — that is, a tumor that has a triple-negative status but also expresses cytokeratin 5, the epidermal growth factor receptor (EGFR), or both (Fig. 1). Because tumors with a core basal phenotype may have a worse outcome than breast cancers that are negative for all five of these markers,[16] this term could have some clinical value.

CELLULAR ORIGIN OF BASAL-LIKE BREAST CANCERS

The question of whether there is a specific, identifiable cell in the normal breast from which basal-like breast cancers arise is controversial. Basal-like cancer cells possess some phenotypic characteristics that are consistent with those of breast stem cells. Despite these similarities, there is strong evidence that basal-like breast cancers arise from the luminal progenitor compartment.[17,18] Consequently, one possible implication of the term "basal-like breast cancer" — the idea that these cancers arise from normal basal breast cells or basal-like stem cells[19] — appears to be incorrect. Proponents of the "breast cancer stem cell hypothesis" argue that cancer stem cells are ultimately responsible for the maintenance of a population of malignant cells with metastatic potential.[20] Cancer cells from triple-negative and basal-like breast cancers display a profile of cell-surface markers that is similar to that of breast-cancer stem cells, characterized by the phenotype CD44+CD24− (in which CD44 is expressed at high levels but levels of CD24 are low or undetectable) and the expression of aldehyde dehydrogenase 1 (ALDH1A1).[21] Although the population of cells expressing these markers is enriched with cells that have tumorigenic potential, not every cancer cell with this profile has the properties of cancer stem cells.

Cancer stem cells do not necessarily arise from tissue stem cells themselves. They may arise from a differentiated cancer cell that has acquired the property of self-renewal[22]; the phenotypic plasticity of cancer cells is a well-documented phenomenon. Notably, breast-cancer cells that undergo epithelial-to-mesenchymal transition display properties that can be all but indistinguishable from those of breast-cancer stem cells.[23] (This transition from epithelial to mesenchymal characteristics is a natural process that occurs during embryogenesis, wound healing, and tissue regeneration. It can arguably be regarded as a key step in conferring metastatic potential to carcinomas). Basal-like breast cancers often display gene-expression patterns that

Table 1. Key Features of Triple-Negative, Basal-like, and BRCA1-Related Breast Cancers as Compared with All Other Breast-Cancer Subtypes.*

Characteristic	Subtype of Breast Cancer			
	Triple-Negative†	Basal-like‡	BRCA1-Related§	All Other Subtypes
Morphologic features				
Histologic type	Ductal carcinoma of no special type is most common; special types also seen	Ductal carcinoma of no special type is most common; special types also seen	Ductal carcinoma of no special type is most common	Variable
Histologic grade	Mostly grade 3, some grade 2	Mostly grade 3	Mostly grade 3	Variable
Medullary or atypical medullary	Occasional	Occasional	Found in one-eighth of cases	Very rare
Metaplastic elements	Occasional	Occasional	Reported but rare	Very rare
Immunohistochemical expression				
Estrogen receptor	Negative (by definition)	Usually negative	Usually negative	Usually positive
Progesterone receptor	Negative (by definition)	Almost always negative	Usually negative	Usually positive
HER2	Negative (by definition)	Usually negative	Usually negative	Usually negative
EGFR	Often positive	Usually positive¶	Usually positive	Usually negative
CK5 or CK17	Often positive	Almost always positive¶	Usually positive	Usually negative
Cyclin E	Often positive	Usually positive	Usually positive	Usually negative
Molecular features				
TP53 mutations	Sometimes present, often truncating	Usually present, often truncating	Nearly always present, nearly always truncating	Not often present, rarely truncating
Degree of aneuploidy	Usually high	High	Very high	Variable
Gene-expression profile	Often basal-like and occasionally claudin-low	Basal-like, by definition	Usually basal-like	Not basal-like, by definition
Prognosis				
Prognosis in first 5 yr after diagnosis	Intermediate	Generally adverse	Generally adverse	Generally good
Distant relapse 10 yr after diagnosis	Rare	Very rare	Rare, but high risk of second primary cancers	Highly variable
Therapeutic options				
Hormonal therapy	No	No	Usually no	Usually yes
Trastuzumab	No	No	Usually no	Usually no
Chemotherapy	Yes; no clear consensus, but regimens containing doxorubicin or taxane favored	Yes; no consensus on regimen	Yes; DNA-damaging agents are likely to be effective	Usually yes; benefit may be reduced in patients with ER-positive cancers
Other agents likely to be effective	Antiangiogenic agents, platinum salts, PARP inhibitors	Antiangiogenic agents, platinum salts, PARP inhibitors	PARP inhibitors, antiangiogenic agents, platinum salts	Many types of agents; dependent on tumor profile

* CK denotes cytokeratin, EGFR epidermal growth factor receptor, HER2 human epidermal growth factor receptor type 2, PARP poly(adenosine diphosphate–ribose) polymerase, and *TP53* the gene encoding tumor protein 53.
† Cancers are defined as triple-negative on the basis of immunohistochemical test results (absence of staining for estrogen receptor, progesterone receptor, and HER2).
‡ Cancers are defined as basal-like on the basis of gene-expression profiling, although the definition of "basal-like" is controversial, which is one reason why this term has not been accepted in routine clinical use. For example, laboratories use various cytokeratins and cutoff points to define positivity.
§ Cancers are defined as BRCA1-related if a deleterious germline mutation in *BRCA1* is present.
¶ To meet the immunohistochemical definition for the core basal phenotype, the tumor must be positive for EGFR or CK5, as well as having a triple-negative status.

are consistent with those of cells undergoing epithelial-to-mesenchymal transition.[24] It is therefore unclear whether all basal-like cancers are enriched with cancer stem cells or have a disproportionately high content of cells undergoing epithelial-to-mesenchymal transition.

MUTANT BRCA1 AND TRIPLE-NEGATIVE OR BASAL-LIKE BREAST CANCERS

There is a link between the BRCA1 pathway and basal-like breast cancers. The great majority of tumors arising in women carrying a germline *BRCA1* mutation, in particular those receiving a diagnosis before reaching 50 years of age, have morphologic features very similar to those of nonhereditary basal-like cancers and often display a basal-like phenotype as defined by immunohistochemical studies[25,26] or expression arrays.[19]

The immunohistochemical similarities between *BRCA1* tumors and basal-like breast carcinomas extend beyond the expression of high-molecular-weight (i.e., basal) cytokeratins (e.g., cytokeratins 5, 14, and 17) to genes affecting the cell cycle. Both basal-like breast cancers and tumors arising in carriers of a germline *BRCA1* mutation rarely harbor amplifications of the cyclin D1 gene (*CCND1*), and both express lower levels of p27 and higher levels of S-phase kinase-associated protein 2 (SKP2), cyclin E, fascin, caveolins 1 and 2, osteonectin, and caspase 3 than do nonhereditary breast carcinomas or *BRCA2*-related tumors.[27,28] In one study, a common factor seen in both basal-like breast cancer and *BRCA1*-related breast cancer was a defect in the maintenance of normal chromosome X inactivation,[29] suggesting that chromatin modification could be a key to the similarity between *BRCA1*-related and nonhereditary basal-like breast cancer. In other studies, a subgroup of basal-like breast cancers with low levels of BRCA1 expression were characterized by high levels of expression of *ID4* (inhibitor of DNA binding 4), a *BRCA1* silencer.[28,30] (Key features of triple-negative, basal-like, and *BRCA1*-related breast cancers are outlined in Table 1.)

Despite the absence of somatic *BRCA1* mutations in breast cancers, the BRCA1 pathway may be dysfunctional in nonhereditary basal-like tumors.[28] Levels of the BRCA1 protein, measured by means of immunohistochemical studies, may be lower in grade 3 tumors that do not express ER or PR and that possess a basal-like phenotype than in other types of breast cancer.[31] This down-regulation could be mediated by epigenetic mechanisms, and indeed, the *BRCA1* promoter is methylated in more than half of all medullary[32] and metaplastic[28] breast cancers, relatively rare types of breast cancer.[33] However, high-grade invasive ductal breast cancers have a relatively low prevalence of *BRCA1* promoter methylation, regardless of whether they are basal-like cancers.[28,34] Overall, the role of BRCA1 inactivation in nonhereditary basal-like breast cancer remains uncertain and controversial.

Mice deficient in both Brca1 and tumor-suppressor protein p53 in mammary epithelial cells develop tumors that are both triple-negative and basal-like and are remarkably similar to those occurring in human carriers of the *BRCA1* mutation.[18] This finding suggests that BRCA1 plays a permissive role in the transition of undifferentiated breast cells to their more mature counterparts.[35] On the basis of these data and data derived from studies in humans, however, the target cell of this effect seems likely to be a cell that expresses luminal markers or coexpresses luminal and basal markers (i.e., a luminal progenitor).[17,18,36]

Clinically, the triple-negative or the basal-like phenotype indicates the possible presence of a germline *BRCA1* mutation.[25,26] However, the additional usefulness of assays that measure the expression of cytokeratins and other "basal-associated" markers in determining *BRCA1* mutation status remains unclear,[25,37] given the substantial overlap between basal-like and triple-negative cancers. As *BRCA1* mutation carriers age, ER-positive breast cancers become more common.[38] It is unclear, however, whether this tendency reflects the occurrence of nonhereditary cancers in older carriers of the mutation or is a result of the changing role of BRCA1 in the breast as a woman ages.[30,39]

NATURAL HISTORY

Triple-negative[15,40,41] and basal-like[42] breast cancers tend to be larger than other subtypes of breast cancer and are usually high-grade, invasive ductal carcinomas of no special type.[16] Differences in nodal status are less clear-cut, but a large study has shown that basal-like breast cancers are more likely than other types of breast cancer to be node-negative.[16] Both triple-negative and basal-like breast cancers are characterized

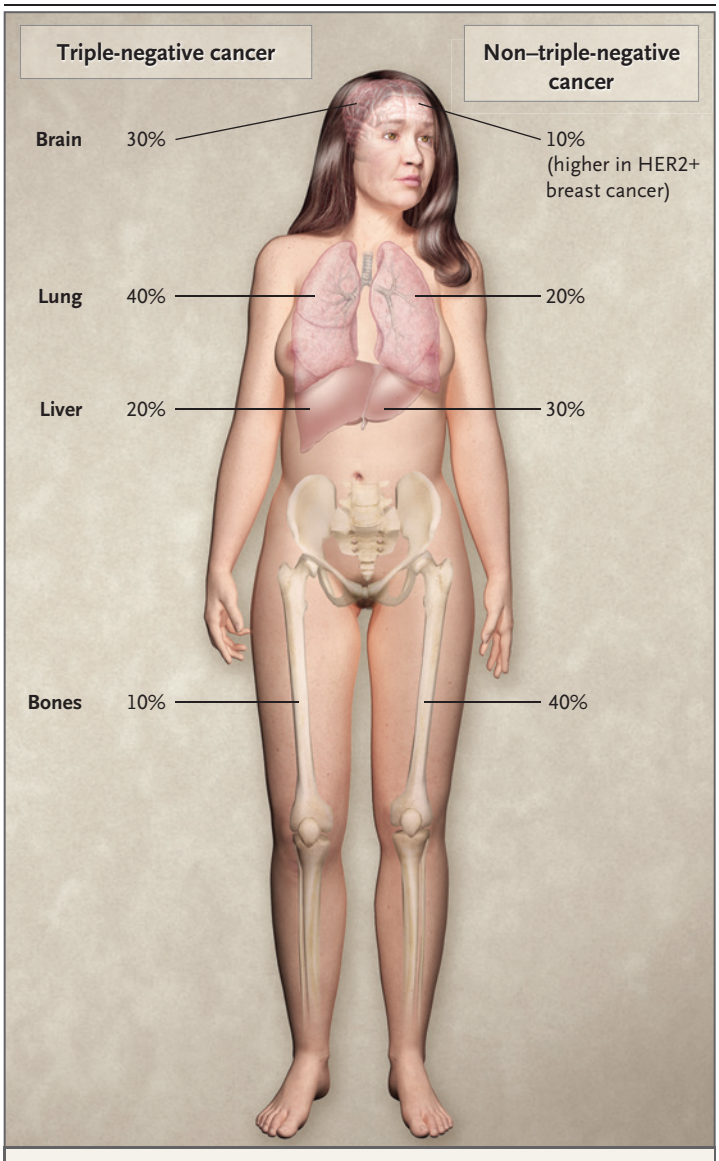


Figure 2. Sites of First Distant Recurrence in Cases of Metastatic Triple-Negative Breast Cancer as Compared with Non–Triple-Negative Breast Cancer.

The percentages shown are approximate percentages of women with a first distant recurrence among women in whom metastases develop. Data are from Dent et al.,[47] Rodríguez-Pinilla et al.,[48] and Liedtke et al.[49]

by an unusually attenuated relationship between the size of the primary tumor and the probability of survival.[40,43] Their rapid growth and frequent occurrence in young women can make mammographic detection difficult. In a nested case–control study carried out as part of a national mammographic screening program, these cancers were over-represented among women with interval breast cancers.[44] Unlike cancers that are ER-positive, PR-positive, and HER2-negative, however, they may reveal specific features on magnetic resonance imaging, such as rim enhancement and a very high intratumor signal intensity on T_2-weighted images.[45] Breast cancers with a core basal phenotype, unlike nonbasal triple-negative cancers, may be more likely than ER-positive breast cancers to recur locally.[46] In addition, both triple-negative and basal-like breast cancers are more likely than other types of breast cancer to metastasize to viscera, particularly to the lungs and brain, and are less likely to metastasize to bone (Fig. 2).[47-49]

Multiple studies have indicated that triple-negative and basal-like breast cancers, as a group, are associated with an adverse prognosis. HER2-positive breast cancers were also associated with a poor prognosis until targeted antibody therapy with trastuzumab came into use. No such biologic therapy is available for triple-negative or basal-like breast cancer.

The shape of the survival curve for patients with triple-negative or basal-like breast cancer differs from that for patients with other types of breast cancer: there is a sharp decrease in survival during the first 3 to 5 years after diagnosis, but distant relapse after this time is much less common (Fig. 3).[15,16,40,49] After 10 years, relapse is more likely among patients with ER-positive cancers than among patients with ER-negative cancers.[16] Thus, although as a group triple-negative and basal-like breast cancers are biologically aggressive, many are potentially curable, reflecting their heterogeneity.

TREATMENT

Women with triple-negative breast cancer do not benefit from endocrine therapy or trastuzumab. Chemotherapy is currently the mainstay of systemic medical treatment, although patients with triple-negative disease, when considered as a group, have a worse outcome after chemotherapy than patients with breast cancers of other subtypes,[49,50] a finding that reflects the intrinsically adverse prognosis associated with the disease. Chemotherapy nevertheless improves the outcome to a greater extent when used in patients with triple-negative breast cancer than when used in patients with the much more common ER-positive subtype (at least among those with node-negative disease).[41] There may be a similar relative gain with taxane chemotherapy. Neoadjuvant studies involving the administration of chemotherapy before surgery suggest that this treatment is very effective in the

minority of women with triple-negative cancer who have a complete pathological response and thus an excellent outcome; in contrast, the outcome for the majority who still have residual disease after treatment is relatively poor (Table 2).[49] These observations suggest that there is a subgroup of women with triple-negative disease whose tumors are extremely sensitive to chemotherapy, but there are many women for whom chemotherapy is of uncertain benefit.

Currently, there is no preferred standard form of chemotherapy for triple-negative breast cancer, and treatment should be selected as it is for other cancer subtypes. Retrospective analyses suggest that the addition of docetaxel or paclitaxel to anthracycline-containing adjuvant regimens may be of greater benefit for the treatment of ER-negative and HER2-negative cancers than for the treatment of ER-positive, HER2-negative cancers, which are much more common.[51,52] A meta-analysis of trials comparing the effects of cyclophosphamide, methotrexate, and fluorouracil with anthracycline-containing regimens suggests that the latter are more effective against triple-negative disease,[53] although confusingly, a retrospective analysis of one trial suggests the opposite for basal-like breast cancers.[54] The use of cisplatin and carboplatin to treat triple-negative breast cancers is currently being assessed in clinical trials, on the basis that dysfunction of BRCA1 and its pathway is associated with a specific DNA-repair defect that sensitizes cells to these agents in animal models. Initial findings suggest that neoadjuvant use of cisplatin results in high rates of complete pathological response in patients with breast cancer who have *BRCA1* mutations[55] and perhaps also in patients with triple-negative cancer.[56] Newer cytotoxic agents, including ixabepilone, have shown early promise in the treatment of triple-negative disease.[57]

The use of targeted agents against triple-negative breast cancer is currently being investigated. The addition of the angiogenesis inhibitor bevacizumab to paclitaxel as first-line treatment for metastatic breast cancer has resulted in at least as much of a benefit with respect to progression-free survival in the women with ER-negative and PR-negative cancers (virtually all of which were also HER2-negative) as it has in the overall study group (hazard ratio, 0.53 and 0.60, respectively),[58] and bevacizumab is now being assessed as an adjuvant therapy against triple-negative disease. Overexpression of EGFR is more common in

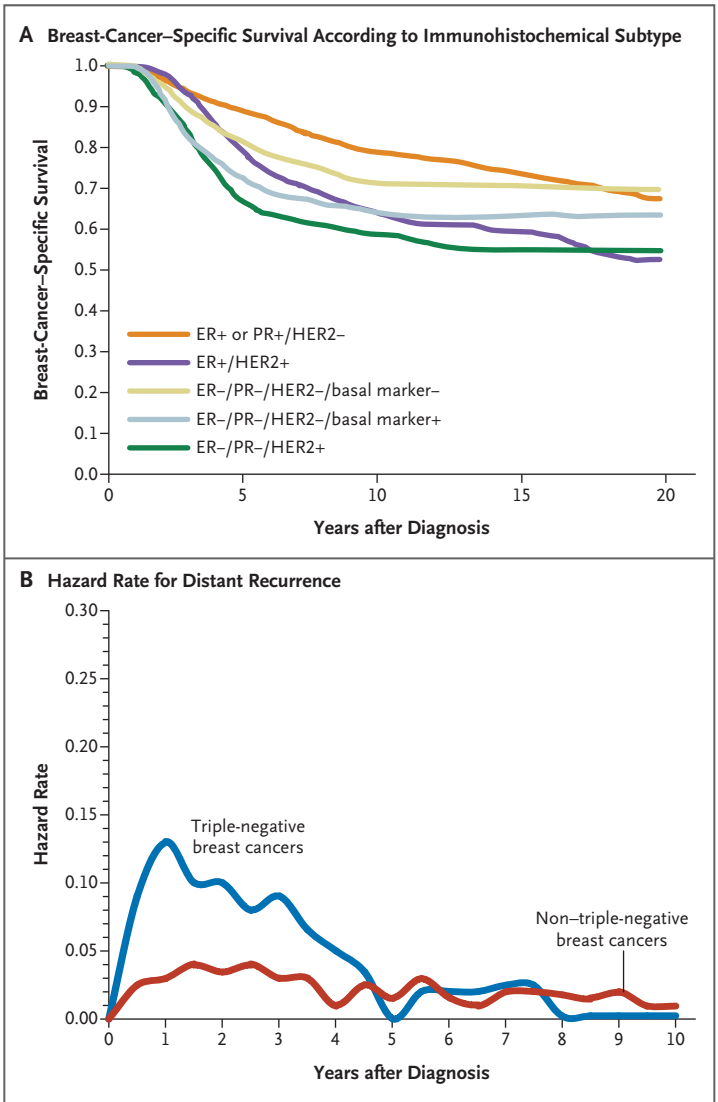


Figure 3. Survival after a Diagnosis of Breast Cancer.

Panel A shows the survival rate in a series of 3744 patients according to immunohistochemical subtype.[16] Among women with ER-positive or PR-positive and HER2-negative tumors, or so-called luminal A cancer (2625 patients), there was a consistent decline in survival over time. Women with ER-positive and HER2-positive tumors, or luminal B cancer (222 patients), had a steeper and more prolonged drop in survival than women with luminal A cancer. Women with ER-negative, PR-negative, and HER2-positive tumors (258 patients) had a uniformly poor survival rate (because these patients did not receive trastuzumab, their survival rate would be inferior to that of any current cohort of patients). The 639 women with triple-negative breast cancer were divided into two groups — those in whom basal markers were expressed (cytokeratin 5 or EGFR, core basal phenotype; 336 patients) and the outcome was poor and those in whom expression of these markers was absent (303 patients) and the 20-year outcome was not different from that seen in patients with luminal A breast cancer. (Immunohistochemical subtype was not assigned in 302 patients.) Panel B shows the hazard rates for distant recurrence of triple-negative breast cancer and non–triple-negative breast cancer.[40] Data in Panel A are from Cheang et al.,[16] and data in Panel B are from Dent et al.[40]

Table 2. Overall Survival Rate after Neoadjuvant Chemotherapy in Women with Triple-Negative Breast Cancer and Those with Non–Triple-Negative Breast Cancer.

Variable	Triple-Negative Breast Cancer (N=225)	Non–Triple-Negative Breast Cancer (N=863)	P Value
	percent of women		
Complete pathological response*	22	11	0.03
3-Yr overall survival with complete pathological response	94	98	0.24
3-Yr overall survival after less than complete pathological response	68	88	0.001

* Complete pathological response was determined on the basis of examination of breast tissue removed at the time of definitive surgery. Data are from Liedtke et al.[49]

triple-negative breast cancers than in other subtypes, and use of the monoclonal antibody cetuximab, targeted against EGFR, is being further studied in combination with carboplatin.[59] However, triple-negative and basal-like breast cancers often display abnormalities in *PTEN*[60] (the gene encoding the phosphatase and tensin homologue), which are frequently associated with resistance to anti-EGFR therapies. Currently, the most interesting clinical target in triple-negative breast cancer is the enzyme poly(adenosine diphosphate–ribose) polymerase (PARP), which is involved in base-excision repair after DNA damage. PARP inhibitors have recently shown very encouraging clinical activity in early trials of tumors arising in *BRCA* mutation carriers[61] and in sporadic triple-negative cancers. One of these inhibitors, iniparib (also known as BSI-201), was recently used in a randomized phase 2 trial involving patients with triple-negative cancer (ClinicalTrials.gov number, NCT00540358). When the inhibitor was added to a chemotherapy combination of gemcitabine and carboplatin, there were significant improvements in the rate of tumor regression (48% vs. 16%, P=0.002), median progression-free survival (6.9 months vs. 3.3 months; hazard ratio, 0.34; P<0.001), and median overall survival (9.2 months vs. 5.7 months; hazard ratio, 0.35; P<0.001).[62] An updated analysis showed a median overall survival rate of 12.2 months versus 7.2 months (hazard ratio, 0.5; P=0.005).[63] Similarly, the use of an oral PARP inhibitor, olaparib, often after chemotherapy had failed, resulted in tumor regression in up to 41% of patients carrying *BRCA* mutations, most of whom had triple-negative breast cancer.[64] In both instances, these benefits were achieved with minimal toxicity. PARP inhibitors and other targeted agents are now at the forefront of clinical research on the treatment of triple-negative breast cancer.

CONCLUSIONS

Taken in their entirety, triple-negative and basal-like breast cancers show aggressive clinical behavior, but a subgroup of these cancers is markedly sensitive to chemotherapy and is associated with a good prognosis when treated with conventional chemotherapy regimens. Furthermore, some triple-negative and basal-like cancers may harbor a dysfunctional BRCA1 pathway and thus may be sensitive to agents such as platinum salts and inhibitors of the PARP enzyme that selectively target cells deficient in homologous recombination DNA repair. It seems very likely that neither triple-negative nor basal-like breast cancers are single entities but rather are a collection of different diseases. Hence, studies that address the molecular underpinning of this heterogeneity and attempt to identify the drivers of therapeutically relevant subgroups of triple-negative and basal-like breast cancers are warranted.

A diagnosis of triple-negative disease has currently important implications for the choice of systemic therapies. Given the lack of an internationally accepted definition of basal-like breast cancer, it is not surprising that this diagnosis has no clinical implications — especially since a substantive portion of these cancers may be ER-positive or may overexpress HER2. It could be argued that instead of identifying descriptive and prognostic molecular subgroups (e.g., basal-like and claudin-low) within the triple-negative group, it would be more clinically relevant to identify those patients whose triple-negative tumors are sensi-

tive to specific chemotherapy agents (or combinations thereof) and targeted therapies. The expressions "triple-negative" and "basal-like" are essentially operational rather than diagnostic. In time, they will probably be replaced by other, more specific terminology.

Supported by grants from Susan G. Komen for the Cure (to Dr. Foulkes) and Breakthrough Breast Cancer (to Dr. Reis-Filho).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Virginia Manning for help with an earlier version of Figure 2 and Britta Weigelt for her critical reading of an earlier version of the manuscript.

REFERENCES

1. Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? J Clin Oncol 2005;23:7350-60.
2. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000;406:747-52.
3. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. J Clin Oncol 2008;26:2568-81.
4. Dairkee SH, Mayall BH, Smith HS, Hackett AJ. Monoclonal marker that predicts early recurrence of breast cancer. Lancet 1987;1:514.
5. Malzahn K, Mitze M, Thoenes M, Moll R. Biological and prognostic significance of stratified epithelial cytokeratins in infiltrating ductal breast carcinomas. Virchows Arch 1998;433:119-29.
6. Weigelt B, Baehner FL, Reis-Filho JS. The contribution of gene expression profiling to breast cancer classification, prognostication and prediction: a retrospective of the last decade. J Pathol 2010;220:263-80.
7. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med 2009;360:790-800.
8. Kreike B, van Kouwenhove M, Horlings H, et al. Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. Breast Cancer Res 2007;9:R65.
9. Bertucci F, Finetti P, Cervera N, et al. How basal are triple-negative breast cancers? Int J Cancer 2008;123:236-40.
10. Turner N, Lambros MB, Horlings HM, et al. Integrative molecular profiling of triple negative breast cancers identifies amplicon drivers and potential therapeutic targets. Oncogene 2010;29:2013-23.
11. Reis-Filho JS, Tutt AN. Triple negative tumours: a critical review. Histopathology 2008;52:108-18.
12. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. Cancer 2007;109:1721-8.
13. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat 2008;109:123-39.
14. Yang XR, Sherman ME, Rimm DL, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev 2007;16:439-43.
15. Tischkowitz M, Brunet JS, Bégin LR, et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC Cancer 2007;7:134.
16. Cheang MC, Voduc D, Bajdik C, et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res 2008;14:1368-76.
17. Lim E, Vaillant F, Wu D, et al. Aberrant luminal progenitors as the candidate target population for basal tumor development in BRCA1 mutation carriers. Nat Med 2009;15:907-13.
18. Molyneux G, Geyer FC, Magnay FA, et al. BRCA1 basal-like breast cancers originate from luminal epithelial progenitors and not from basal stem cells. Cell Stem Cell 2010;7:403-17.
19. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100:8418-23.
20. Wicha MS, Liu S, Dontu G. Cancer stem cells: an old idea — a paradigm shift. Cancer Res 2006;66:1883-90.
21. Morrison BJ, Schmidt CW, Lakhani SR, Reynolds BA, Lopez JA. Breast cancer stem cells: implications for therapy of breast cancer. Breast Cancer Res 2008;10:210.
22. Visvader JE, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. Nat Rev Cancer 2008;8:755-68.
23. Mani SA, Guo W, Liao MJ, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell 2008;133:704-15.
24. Sarrió D, Rodriguez-Pinilla SM, Hardisson D, Cano A, Moreno-Bueno G, Palacios J. Epithelial-mesenchymal transition in breast cancer relates to the basal-like phenotype. Cancer Res 2008;68:989-97.
25. Foulkes WD, Stefansson IM, Chappuis PO, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst 2003;95:1482-5.
26. Lakhani SR, Reis-Filho JS, Fulford L, et al. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 2005;11:5175-80.
27. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 2004;4:814-9.
28. Turner NC, Reis-Filho JS, Russell AM, et al. BRCA1 dysfunction in sporadic basal-like breast cancer. Oncogene 2007;26:2126-32.
29. Richardson AL, Wang ZC, De Nicolo A, et al. X chromosomal abnormalities in basal-like human breast cancer. Cancer Cell 2006;9:121-32.
30. Manié E, Vincent-Salomon A, Lehmann-Che J, et al. High frequency of TP53 mutation in BRCA1 and sporadic basal-like carcinomas but not in BRCA1 luminal breast tumors. Cancer Res 2009;69:663-71.
31. Abd El-Rehim DM, Ball G, Pinder SE, et al. High-throughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses. Int J Cancer 2005;116:340-50.
32. Esteller M, Silva JM, Dominguez G, et al. Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors. J Natl Cancer Inst 2000;92:564-9.
33. Weigelt B, Reis-Filho JS. Histological and molecular types of breast cancer: is there a unifying taxonomy? Nat Rev Clin Oncol 2009;6:718-30.
34. Matros E, Wang ZC, Lodeiro G, Miron A, Iglehart JD, Richardson AL. BRCA1 promoter methylation in sporadic breast tumors: relationship to gene expression profiles. Breast Cancer Res Treat 2005;91:179-86.
35. Foulkes WD. BRCA1 functions as a breast stem cell regulator. J Med Genet 2004;41:1-5.
36. Gorski JJ, James CR, Quinn JE, et al. BRCA1 transcriptionally regulates genes associated with the basal-like phenotype in breast cancer. Breast Cancer Res Treat 2010;122:721-31.
37. Collins LC, Martyniak A, Kandel MJ, et al. Basal cytokeratin and epidermal growth factor receptor expression are not predictive of BRCA1 mutation status in women with triple-negative breast cancers. Am J Surg Pathol 2009;33:1093-7.
38. Foulkes WD, Metcalfe K, Sun P, et al. Estrogen receptor status in *BRCA1*- and *BRCA2*-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res 2004;10:2029-34.
39. Tung N, Wang Y, Collins LC, et al. Es-

trogen receptor positive breast cancers in BRCA1 mutation carriers: clinical risk factors and pathologic features. Breast Cancer Res 2010;12:R12.
40. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429-34.
41. Colleoni M, Cole BF, Viale G et al. Classical cyclophosphamide, methotrexate, and fluorouracil chemotherapy is more effective in triple-negative, node-negative breast cancer: results from two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. J Clin Oncol 2010;28:2966-73.
42. Abd El-Rehim DM, Pinder SE, Paish CE, et al. Expression of luminal and basal cytokeratins in human breast carcinoma. J Pathol 2004;203:661-71.
43. Foulkes WD, Grainge MJ, Rakha EA, Green AR, Ellis IO. Tumor size is an unreliable predictor of prognosis in basal-like breast cancers and does not correlate closely with lymph node status. Breast Cancer Res Treat 2009;117:199-204.
44. Collett K, Stefansson IM, Eide J, et al. A basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. Cancer Epidemiol Biomarkers Prev 2005;14:1108-12.
45. Uematsu T, Kasami M, Yuen S. Triple-negative breast cancer: correlation between MR imaging and pathologic findings. Radiology 2009;250:638-47.
46. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 2010;28:1684-91.
47. Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA. Pattern of metastatic spread in triple-negative breast cancer. Breast Cancer Res Treat 2009;115:423-8.
48. Rodríguez-Pinilla SM, Sarrió D, Honrado E, et al. Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. Clin Cancer Res 2006;12:1533-9.
49. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26:1275-81.
50. Tan DS, Marchío C, Jones RL, et al. Triple negative breast cancer: molecular profiling and prognostic impact in adjuvant anthracycline-treated patients. Breast Cancer Res Treat 2008;111:27-44.
51. Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 2007;357:1496-506.
52. Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. Lancet 2009;373:1681-92.
53. Di Leo A, Isola J, Piette F, et al. A meta-analysis of phase III trials evaluating the predictive value of HER2 and topoisomerase alpha in early breast cancer patients treated with CMF or anthracycline-based adjuvant therapy. Breast Cancer Res Treat 2008;107:Suppl:24s. abstract.
54. Cheang M, Chia SK, Tu D, et al. Anthracycline in basal breast cancer: the NCIC-CTG trial MA5 comparing adjuvant CMF to CEF. J Clin Oncol 2009;27:Suppl:15s. abstract.
55. Byrski T, Huzarski T, Dent R, et al. Response to neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 2009;115:359-63.
56. Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. J Clin Oncol 2010;28:1145-53.
57. Baselga J, Zambetti M, Llombart-Cussac A, et al. Phase II genomics study of ixabepilone as neoadjuvant treatment for breast cancer. J Clin Oncol 2009;27:526-34.
58. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666-76.
59. Carey LA, Rugo HS, Markom PK, et al. TBCRC 001: EGFR inhibition with cetuximab added to carboplatin in metastatic triple-negative (basal-like) breast cancer. J Clin Oncol 2008;26:Suppl:15s. abstract.
60. Marty B, Maire V, Gravier E, et al. Frequent PTEN genomic alterations and activated phosphatidylinositol 3-kinase pathway in basal-like breast cancer cells. Breast Cancer Res 2008;10:R101.
61. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med 2009;361:123-34.
62. O'Shaughnessy J, Osborne C, Pippen J, et al. Efficacy of BSI-201, a poly(ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): results of a randomized phase II trial. J Clin Oncol 2009;27:Suppl:15s. abstract.
63. O'Shaughnessy J, Osborne C, Pippen J, et al. Final results of a randomized phase II study demonstrating efficacy and safety of BSI-201, a poly (ADP-ribose) polymerase (PARP) inhibitor, in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). Cancer Res 2009;69:Suppl:24s. abstract.
64. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010;376:235-44.