Biomarkers in Breast Cancer

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Abstract

Biomarkers offer great promise in the care of patients who have cancer. They can establish a more accurate and definitive diagnosis, and help identify patients most likely to respond to therapy, those most likely to experience disease recurrence, or those most likely to suffer toxicity. Predictive markers are associated with response, or lack thereof, to a particular treatment. Prognostic markers are baseline measurements that project a disease trajectory. No longer limited to measurement of serum-based proteins, the types of biomarkers now available in oncology practice are exceedingly diverse, ranging from assays of circulating factors in the peripheral blood of patients who have cancer to specialized molecular or genetic analyses of the tumor tissue itself. In 2007 the American Society of Clinical Oncology (ASCO) updated their recommendations for the use of tumor marker tests in the prevention, screening, treatment, and surveillance of breast cancer. This article will include predictive, prognostic, and current ASCO recommendations for breast cancer markers. Additionally, emerging biomarkers will be explored. Many of these may show great promise in the quest to personalize care for patients with breast cancer.

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An estimated 207,090 new cases of invasive breast cancer are estimated to have occurred in women in the United States during 2010 (American Cancer Society [ACS], 2010). Unfortunately, approximately 39,840 women in the United States are estimated to have died from breast cancer in 2010. From 1999 to 2006, breast cancer incidence rates in the United States decreased by about 2% per year. One theory postulates this decrease was partially due to the reduced use of hormone replacement therapy (HRT) by women after the results of the Women's Health Initiative were published in 2002. These results suggested a connection between HRT and increased breast cancer risk. Additionally, this decrease is thought to be the result of treatment advances, earlier detection through screening, and increased awareness (Breastcancer.org, 2010).

Recommendations for prevention and screening include yearly mammograms beginning at the age of 40 for most women and a clinical breast exam about every 3 years for women in their 20s and 30s and every year for women over 40. For women who are at high risk for familial breast cancer, the ACS recommends magnetic resonance imaging

(MRI) in addition to mammogram (ACS, 2010).

Serum tumor markers may play an important role in patient management; however, the role of serum markers is less well established in breast cancer. Lack of sensitivity for early-stage disease, combined with a lack of specificity, precludes the use of all existing serum markers for the early diagnosis of breast cancer (Duffy, 2006). For example, CA 15-3 concentrations are found in approximately 10% of patients with stage I disease, 20% with stage II disease, 40% with stage III disease, and 75% with stage IV disease ("Clinical Practice Guidelines," 1996). The ideal tumor marker should meet several criteria (Table 1).

Established Biomarkers in Breast Cancer

SERUM TUMOR MARKERS

Tumor markers are proteins that may be elevated in the presence of cancer. These substances can be found in the blood, urine, or tissues. However, tumor marker levels are not altered in all people with cancer, especially if the cancer is in an early stage (National Cancer Institute [NCI], 2010a). Additionally, tumor markers are present in low concentrations in the serum of patients without cancer (Kiang, Greenberg, & Kennedy, 1990). The European Group on Tumor Markers identified members of the MUC-1 family of mucin glycoproteins (CA 15-3, CA 27-29, and CEA) as the best serum markers for breast cancer, but they could not recommend these proteins for diagnosis due to low sensitivity (Molina et al., 2005). Increased concentrations of CA 15-3 can be found in approximately 5% of apparently healthy individuals and in certain benign diseases, especially liver disease.

Table 1. Tumor Marker Criteria

- Be evidence based and validated in studies that include long-term follow-up
- Provide prognostic and predictive information along a continuum
- Help guide therapy and have a place in relevant guidelines
- Be easily performed on readily attainable specimens
- Provide timely information
- Be reasonably priced

Note. Adapted from "Incorporating Genomic Classifiers in Clinical Pathways for Early Breast Cancer," by F. Smith, 2009, Copyright Elsevier (2009).

Jesneck et al. (2009) looked at 97 women undergoing image-guided biopsy to diagnose a primary breast lesion or women undergoing routine screening mammography with no evidence of breast abnormalities. The study looked at the feasibility of using serum proteins (tumor markers) as a diagnostic tool. There were 98 serum proteins measured in the blood by enzyme-linked immunosorbent assay (ELISA) Luminex platform. These biomarkers were selected based on the known literature reports about their association with breast cancer. The results demonstrated that the serum biomarkers for breast cancer are not sensitive or specific enough for breast cancer screening. The study concluded that better biomarkers may be identified with new protein assay technology and larger data sets in the future. Additionally, a protein's subtle diagnostic ability may be enhanced by the assimilation of other medical information, such as gene expression and medical imaging.

Nolen et al. (2008) studied women with locally advanced breast cancer (N = 44) receiving liposomal doxorubicin and paclitaxel in combination with hyperthermia in the neoadjuvant setting. Serum samples were collected prior to each cycle of treatment. These samples were assessed by Luminex assay for 55 serum biomarkers, including cancer antigens, growth/angiogenic factors, apoptosis-related molecules, metastasis-related molecules, adhesion molecules, adipokines, cytokines, chemokines, hormones, and other proteins. The biomarker levels were compared retrospectively with clinical and pathologic treatment responses. Univariate analysis of the data identified several groups of biomarkers that differed significantly among treatment outcome groups early in the course of neoadjuvant chemotherapy. Multivariate statistical analysis revealed multibiomarker panels that could differentiate between treatment response groups with high sensitivity. The study demonstrated that serum biomarker profiles may offer some predictive power concerning treatment response and outcome in the neoadjuvant setting.

The National Comprehensive Cancer Network (NCCN), along with the American Society of Clinical Oncology (ASCO), does not recommend the routine use of any serum tumor markers (such as CA 15-3 or CA 27.29) for diagnosis, monitoring of response, or surveillance in breast cancer patients. For

monitoring patients with metastatic disease during active therapy, CA 27.29 and CA 15-3 can be used in conjunction with diagnostic imaging, history, and physical examination. In the absence of readily measurable disease, an increasing CA 15-3 or CA 27.29 may be used to indicate treatment failure (Harris et al., 2007; Table 2).

HORMONE RECEPTORS

Assessment of the presence of estrogen receptors (ERs) and/or progesterone receptors (PRs) is currently a component of routine evaluation of breast cancer specimens. Estrogen receptors, first analyzed in breast cancer in the late 1950s, were the first molecular markers evaluated for prognosis and therapy response for breast cancer. Estrogen receptor status has been shown to have significant predictive value for tumor response to hormone therapy in metastatic disease as well as for adjuvant therapy after local excision (Kelley, 2010; Harris et al., 2007). The role of PR status in predicting tumor response to therapy is still unclear, although it has shown promise. There is an indication that a double-positive (ER+/PR+) tumor responds better to hormonal therapy than single- positive (ER+/PR- or ER-/PR+) tumors (Dowsett et al., 2008; Grann et al., 2005).

The standard approach to breast cancer diagnostics via hormone receptor analysis is immunohistochemical staining (IHC), which involves the use of antibodies and enzymes, such as horseradish peroxidase, to stain tissue sections for the tumor antigens of interest (Zoon et al., 2009). This evaluation method can be performed on either frozen or formalin-fixed paraffin-embedded (FFPE) tissue, as well as on small

Table 2. Selected American Society of Clinical Oncology 2007 Guideline Recommendations

Specific marker	2007 Recommendation
CA 15-3 and CA 27.29 as markers for breast cancer screening, diagnostic, or staging tests	Present data are insufficient to recommend for screening, diagnosis, and staging.
CA 15-3 and CA 27.29 to detect recurrence after primary breast cancer therapy	Present data do not support the use of CA 15-3 and CA 27.29 for monitoring for recurrence after primary breast cancer therapy.
CA15-3 and CA 27.29 to contribute to decisions regarding therapy for metastatic breast cancer	For monitoring patients with metastatic disease during active therapy, CA 15-3 and CA 27.29 can be used in conjunction with diagnostic imaging, history and physical exam. Present data are insufficient to recommend use of CA 15-3 and CA 27.29 alone for monitoring response to treatment. However, in the absence of readily measureable disease an increasing CA 15-3 or CA 27.29 may be used to indicate treatment failure.
CEA to contribute to decisions regarding therapy for metastatic breast cancer	For monitoring patients with metastatic disease during active therapy. CEA can be used in conjunction with diagnostic imaging, history and physical exam. Not recommended alone as a marker for response to treatment.
HER2 evaluation in breast cancer	HER2 expression and/or amplification should be evaluated in every primary invasive breast cancer either at the time of diagnosis or at the time of recurrence primarily to guide selection of patients who will benefit from trastuzumab therapy in the adjuvant or metastatic setting.
uPA and PAI-1 as a marker for breast cancer	uPA/PAI-1 may be used for the determination of prognosis in patients with newly diagnosed, node negative breast cancer. The specimen should be a minimum of 300 mg of fresh or frozen tissue.
Circulating tumor cell (CTC) assays as markers for breast cancer	The measurement of CTCs should not be used to make the diagnosis of breast cancer or to influence any treatment decisions in patients with breast cancer. The recently FDA-approved test for CTC (CellSearch Assay) in patients with metastatic breast cancer cannot be recommended until further validation is completed.

Note. Based on information from "American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer," by L. Harris et al., 2007, *Journal of Clinical Oncology*, *25,* pp. 5287–5312. Adapted with permission from American Society of Clinical Oncology.

amounts of tissue acquired in procedures such as core biopsies. Immunohistochemical staining also has the advantage of not only determining the percentage of positive nuclei, but also the intensity of staining in individual nuclei (Zoon et al., 2009).

ASCO and the College of American Pathologists recommend that ER/PR status be determined on all newly diagnosed invasive and recurrent breast cancers (Hammond et al., 2010). Predictive markers such as ER/PR expression can change during the course of disease. Reassessment of these markers at the time of progression may benefit treatment decisions (Amir et al., 2010). However, metastatic tissue may be difficult to obtain for analysis. A potential noninvasive method using peripheral blood may have some promise in the future. Aktas et al. (2009) reevaluated and compared the ER/PR expression by circulating tumor cells (CTCs) with the primary tumor of 166 women. Results demonstrated primary tumors and CTCs displayed a concordant ER and PR status in only 34% and 61% of cases. Most of the CTCs were ER/PR negative despite the presence of an ER/PR-positive primary tumor. The predictive value of hormone receptor status expression profile of CTCs for palliative endocrine therapy has to be prospectively evaluated.

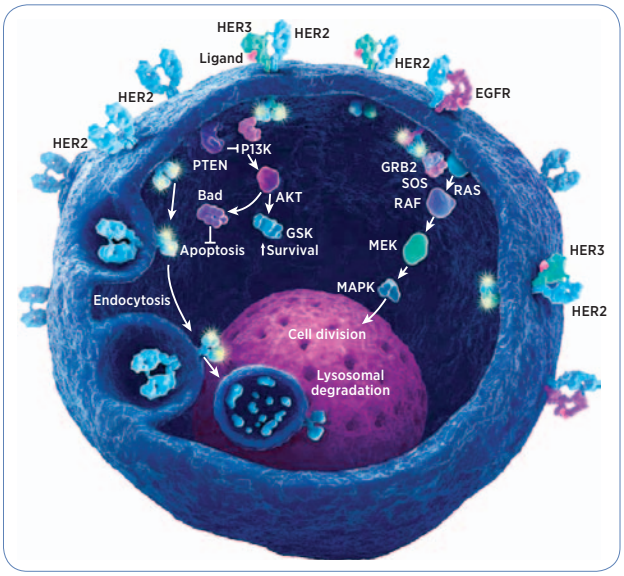

Figure 1. Illustration of human epidermal growth factor receptor (HER) pathways, which play a critical role in cancer biology. Dysregulation of HER-mediated signaling pathways results in the growth and spread of cancer cells. The HER family consists of four structurally related receptors: HER1 (EGFR), HER2, HER3, and HER4. HER family receptors are activated by ligand-induced dimerization, or receptor pairing. Dimerization is a critical step in HER family–mediated signaling, and HER receptors are able to homodimerize or heterodimerize with other HER family members, allowing for multiple receptor combinations. The formation of dimers leads to intracellular phosphorylation that provides docking sites for a variety of molecules. These molecules then relay signals to different downstream cascades, including the MAPK proliferation pathway and the PI3K/Akt prosurvival pathway-2 pathways frequently overactivated in cancer. Inappropriate signaling may occur as a result of receptor overexpression or dysregulation of receptor activation, which may lead to increased/uncontrolled cell proliferation, resistance to apoptosis, enhanced cancer cell motility, and angiogenesis. Courtesy of Genentech.

HER2/HERmark

The human epidermal growth factor receptor 2 (HER2, HER2/*neu*, c-erbB-2) is a transmembrane protein tyrosine kinase receptor that is important in initiating signal transduction pathways in normal and abnormal cells (Figure 1). HER2, which is overexpressed or amplified in approximately 15% to 30% of human breast tumors, is also a biomarker of poor prognosis. HER2 testing is recommended for all newly diagnosed breast cancer patients for the selection of those that may benefit from treatment with the humanized monoclonal antibody trastuzumab (Herceptin; Larson et al., 2010; Harris et al., 2007). Current methods of testing for HER2 are IHC and/or fluorescence in situ hybridization. As with ER/PR expression, HER2 is reported as a percentage of stained vs. unstained tumor cells.

One of the challenges with the current testing of HER2 is a lack of standardization in the use and interpretation of assays (Jacobs, Gown, Yazihi, Barnes, & Schnitt, 2000). In an attempt to improve the current methods of HER2 analysis, Monogram Biosciences recently released the HERmark breast cancer assay. This assay measures HER2 total protein (H2T) and functional HER2 homodimer (H2D) levels on the cell surface of FFPE breast cancer tissue. H2T expression demonstrates a sensitivity that is approximately 7 to 10 times greater than conventional immunohistochemistry. The HERmark assay is a quantitative assay that sensitively and reproducibly measures continuous H2T and H2D protein expression levels and therefore may have the potential to stratify patients more accurately with respect to response to HER2-targeted therapies than current methods, which rely on semiquantitative protein

measurements or on indirect assessments of gene amplification. The HERmark measurement reports whether a patient is HER2 negative, positive, or equivocal based on quantified HER2 protein levels expressed as numeric values (Larson et al., 2010).

Recent studies indicate that HERmark is an accurate method for identifying breast cancer patients who are likely to benefit from HER2-directed therapy. However, as a prognosticator of disease progression, studies suggest that measurements of the activated form of HER2 may be more useful than measurement of total HER2 expression. Thus, despite HERmark's potential use as a predictive indicator of patients' response to anti-HER2 therapy, additional studies are required to confirm these preliminary findings and to investigate whether HER2 activation measurement is a superior prognosticator of clinical outcomes (Zoon et al., 2009).

BRCA1/BRCA2

Genetic mutations can increase a woman's lifetime risk of developing breast cancer. Breast cancer susceptibility gene 1 (*BRCA1*) and breast cancer susceptibility gene 2 (*BRCA2*) are human genes that belong to a class of genes known as tumor suppressors. Mutations of these genes have been linked to hereditary breast and ovarian cancer (NCI, 2010a). Specific mutations of the *BRCA1* and *BRCA2* genes are highest in families with a history of multiple cases of breast cancer, cases of both breast and ovarian cancer, one or more family members with two primary cancers, and the Ashkenazi Jewish community (Fitzgerald et al., 1996). A woman who has inherited a harmful mutation in *BRCA1* or *BRCA2* is about five times more likely to develop breast cancer than a woman who does not have such a mutation (NCI, 2010a). Overall, it has been estimated that inherited *BRCA1* and *BRCA2* mutations account for 5% to 10% of breast cancers among white women in the United States (Campeau, Foulkes, & Tischkowitz, 2008).

Genetic testing for *BRCA1* and *BRCA2* mutations has been established throughout North America and much of Europe. Testing is offered to women who have a 10% or greater risk for being positive for a *BRCA1* mutation (Young et al., 2009). Mutations in several other genes, including *TP53*, *PTEN*, *STK11/LKB1*, *CDH1*, *CHEK2*, *ATM*, *MLH1*, and *MSH2*, have been associated with hereditary breast and/or ovarian tumors (NCI, 2010b; Campeau et al., 2008; Walsh et al., 2006). However, the majority of hereditary breast cancers can be accounted for by inherited mutations in *BRCA1* and *BRCA2* (Lynch, Silva, Snyder, & Lynch, 2008).

Several options are available for patients who are found to have a positive mutation. These include surveillance, prophylactic mastectomy and salpingo-oophorectomy, risk avoidance, and chemoprevention (NCI, 2010a). A large Dutch study of women at increased risk for hereditary breast cancer found that MRI was superior to mammography in early detection of tumors in women either harboring mutations in the *BRCA* genes or at high risk for cancer because of family history. The study did not look at MRI as a standard screening technique for all women, but rather only those considered at risk (Rijnsburger et al., 2010).

GENE PROFILES

Onco*type* DX is a 21-gene breast cancer assay that provides an individualized prediction of chemotherapy benefit and 10-year distant recurrence to inform adjuvant treatment decisions in certain women with early-stage breast cancer (www.genomichealth.com). Both ASCO and NCCN have included the Onco*type* DX assay in their guidelines as an option to predict whether certain patients will benefit from chemotherapy.

Dowsett et al. (2010) looked at whether recurrence score (RS) provided independent information on risk of distant recurrence (DR) in the tamoxifen and anastrozole arms of the Arimidex, Tamoxifen, Alone or in Combination Trial. There were 1,231 evaluable patients (N0: n = 872; N+: n = 306; node status unknown: n = 53); 72, 74, and 6 DRs occurred in N0, N+, and node status unknown patients, respectively. Recurrence score was significantly associated with time to DR in multivariate analyses ($p < .001$ for N0 and $p = .002$ for N+). The study confirmed the performance of RS in postmenopausal HR+ patients treated with tamoxifen in a large contemporary population and showed that RS is an independent predictor of DR in N0 and N+, HR+ patients treated with anastrozole, adding value to estimates with standard clinicopathologic features.

Several studies have demonstrated that the Onco*type* DX RS has significantly impacted adjuvant chemotherapy decisions, perhaps sparing women unpleasant side effects and significant toxicities (Partin, et al., 2010; Smith, 2010).

MAMMAPRINT

MammaPrint (Agendia, 2010) is an in vitro diag-

nostic multivariate index assay. It analyzes 70 critical genes that comprise a definitive gene expression signature and stratifies patients into two distinct groups: low or high risk of distant recurrence. MammaPrint can be performed on core needle biopsies or tissue taken from a surgical specimen. It is important to obtain the fresh, unfixed tissue sample within 60 minutes of surgical removal (www.agendia.com). Both MammaPrint and Onco*type* DX provide individualized metastatic risk assessment, scratching the surface of personalized treatment.

UROKINASE PLASMINOGEN ACTIVATOR

The urokinase-type plasminogen activator (uPA) and its main inhibitor PAI-1 play key roles in tumor-associated processes such as degradation of the extracellular matrix, tissue remodeling, cell adhesion, and migration. Elevated expression of both molecules is known to correlate with negative outcomes in node-negative breast cancer. To date, these molecules are the only prognostic markers to have reached the highest level of evidence (LOE I) in multicenter clinical trials for prognosis of node-negative breast cancer (Malinowsky et al., 2010). Current ASCO guidelines recommend the validated invasion markers uPA/PAI-1 for routine risk assessment in N0 breast cancer (Harris et al., 2007; Table 2).

Biomarkers on the Horizon

Ki67

Ki67 is a nuclear nonhistone protein. Ki stands for the University of Kiel (the researchers' location), and 67 refers to the number of the clone on the 96-well plate. It is a marker of proliferation and was first identified in the 1980s using a mouse monoclonal antibody against a nuclear antigen from a Hodgkin lymphoma cell line (Gerdes, Schwab, Lemke, & Stein, 1983, as cited in Weigel & Dowsett, 2010). Ki67 is expressed during the G^1, S, and G^2 phases of the cell cycle with a peak during mitosis and an absence during G^0 (Lopez et al., 1991).

The correlation of Ki67 and other biomarkers in invasive breast cancer has been studied extensively. The relationship with ER has been predominantly described as an inverse correlation with lower proliferative activity in ER+ tumors (Haerslev, Jacobsen, & Zedeler, 1996, as cited in Weigel & Dowsett, 2010). There are hints of a correlation with HER2 as well, but this is not completely defined (Nicholson et al., 1993). The most recently published analysis of 15,790 cases from 43 studies reported an association of Ki67 positivity with shorter overall survival.

In early as well as locally advanced breast cancer, baseline Ki67 has been found to predict for response to chemotherapy (Chang et al., 2000; Faneyte et al., 2003). Jones et al. (2009) found that post-neoadjuvant chemotherapy measurement of Ki67 is a strong predictor for recurrence-free and overall survival. However, a high pretreatment score is associated with a good chance to achieve a pathologic complete remission (pCR), and this is a predictor of long-term outcome in these patients.

In the IMPACT (Immediate Preoperative Anastrozole Tamoxifen or Combined with Tamoxifen) trial neoadjuvant anastrozole was compared with tamoxifen and the combination. In this trial the change in proliferation rates after 2 weeks of treatment as measured by Ki67 was significantly greater for anastrozole than for tamoxifen or the combination, suggesting that Ki67 might be a better marker for long-term outcome than clinical response. Likewise, long-term follow-up of the IMPACT trial showed that the absolute level of Ki67 suppression after 2 weeks of neoadjuvant endocrine therapy significantly correlated with long-term disease-free survival outcome, and more so than baseline pretreatment Ki67 (Dowsett et al., 2005).

The aim of the POETIC (PeriOperative Endocrine Treatment for Individualizing Care) trial is to determine whether the measurement of Ki67 after 2 weeks of presurgical treatment with an aromatase inhibitor is sufficiently more predictive than in the absence of treatment to merit introducing this to routine clinical practice. If POETIC proves successful, it would allow a new and rapid 2-week assessment of whether a particular form of treatment will be effective in the long term for an individual patient (Smith, 2007). A positive result may have implications for change in practice (Weigel & Dowsett, 2010). However, Ki67 staining is still not recommended as a predictive/prognostic marker for routine use (Stuart-Harris, et al., 2008).

CIRCULATING TUMOR CELLS

There is currently a major effort to identify biomarkers that can be obtained with minimally invasive methods and persist beyond surgery (Weigel & Dowsett, 2010). The existence of CTCs in the blood of cancer patients was first reported in 1869, but only in the past decade has molecular methodology made it possible to detect them reproducibly (Smith et al.,

1991). The development and optimization of new technologies to identify and characterize such cells, and the establishment of the association of their presence with potentially clinical significance, are highly relevant (Sieuwerts et al., 2009).

The CellSearch System is the first diagnostic test to automate the detection and enumeration of CTCs, and is the standard in a new class of diagnostic tools. The presence and number of CTCs in the blood provides valuable information to physicians for developing individual management programs for patients with metastatic breast cancer. The system's sensitivity, specificity, and reproducibility allow for more rapid observation of CTCs as early as the first cycle of treatment, helping to evaluate disease progression sooner. The CellSearch System was originally cleared by the FDA in January 2004 as a diagnostic tool for identifying and counting CTCs in a blood sample to predict progression-free survival (PFS) and overall survival in patients with metastatic breast cancer (*Medical News Today*, 2008).

A high CTC count at diagnosis of metastatic breast cancer is described as being a significant negative prognostic factor. If the number of CTCs does not decrease, patients are likely to progress under chemotherapy (Cristofanilli et al., 2004). Cristofanilli and colleagues (2005) looked at patients with measureable metastatic breast cancer who had five or more CTCs found in 7.5 mL of whole blood. Blood was drawn before the start of treatment and monthly for up to 6 months. CTCs were isolated and enumerated using immunomagnetics. A total of 177 patients were enrolled onto a prospective study. Of these 177 patients, 83 were entering first-line treatment, and these patients were the focus of the analysis. Forty-three patients (52%) had ≥ five CTCs at baseline.

Median PFS was 7.2 months (95% confidence interval, 4.9 to 9.4 months); median OS was > 18 months. Patients with ≥ 5 CTCs at baseline and at first follow-up (4 weeks) had a worse prognosis than patients with < 5 CTCs (baseline: median PFS, 4.9 vs. 9.5 months, respectively; log-rank, p = .0014; median OS, 14.2 vs. > 18 months, respectively; log-rank, p = .0048; first follow-up: median PFS, 2.1 vs. 8.9 months, respectively; log-rank, p = .0070; median OS, 11.1 vs. > 18 months, respectively; log-rank, p = .0029). Circulating tumor cells before and after the initiation of therapy were strong, independent prognostic factors. The study concluded that the detection of CTCs before initiation of first-line therapy in patients with metastatic breast cancer is highly predictive of PFS and OS. This technology can aid in appropriate patient stratification and design of tailored treatments (Cristofanilli et al., 2005).

MICROARRAY ANALYSIS

The first microRNA was discovered in *C. elegans* in 1993 while screening for genes involved in developmental timing (Lee, Feinbaum, & Ambros, 1993). One of the genes discovered in screening did not encode a protein, but rather a small 22-nucleotide RNA. By 2001, more than 100 of these small regulatory RNAs, later named microRNAs or miRNAs, were identified in various species, including humans (Lagos-Quintana, Rauhut, Lendeckel, & Tuschl, 2001; Lau, Lim, Weinstein, & Bartel, 2001; Lee & Ambros, 2001, as cited in Zoon et al., 2009). MicroRNA deregulation in breast cancer was first demonstrated by Iorio et al. in 2005 (cited in Zoon et al., 2009). Since that first study there has been a surge of data accumulated on the expression of various microRNAs and their roles in breast cancer.

Today, global gene expression analysis based on microarray technology has facilitated a new molecu-

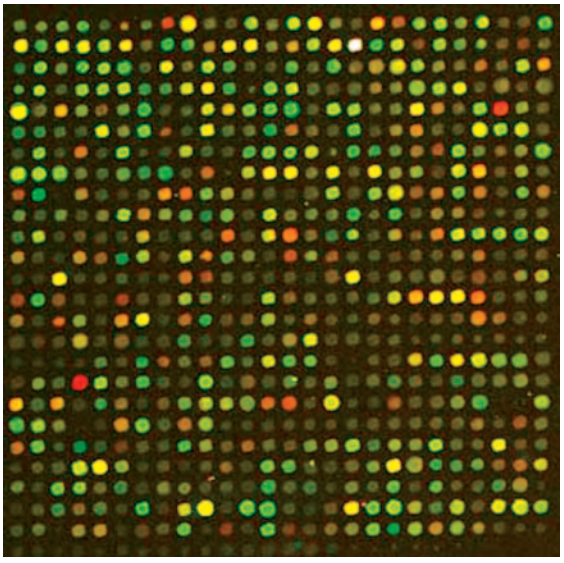

Figure 2. Illustration of DNA microarray technology. DNA microarray technology is frequently used to monitor changes in gene expression for thousands of genes simultaneously. When a gene is expressed in a cell, it generates messenger RNA (mRNA). Overexpressed genes generate more mRNA than underexpressed genes. This can be detected on the microarray. Image used with permission from www.wormbook.org (Reinke, 2006).

Table 3. Selected Future Biomarkers in Breast Cancer

Biomarker	Function	Clinical use
Cyclin D	Regulator of cell cycle progression	Overexpression has been linked to development of endocrine resistance in breast cancer
PTEN	Tumor suppressor	Mutations resulting in loss of PTEN are relevant in breast cancer; may antagonize tumorigenesis and sensitize breast cancers to trastuzumab
Proteomics	Potential ability to predict effectiveness of treatment	Better screening and treatment options
IGF-1R	Plays major role in cancer cell proliferation, survival, and resistance to anticancer therapies	Identify subgroups of triple-negative breast cancer tumors with specific targets

Note. PTEN = phosphatase and tensin homolog; IGF-1R = insulin-like growth factor-1 receptor. Based on information from Alao (2007), Pandolfi (2004), NCI (2010c), Carlson (2010).

lar taxonomy for classification of cancer (Figure 2). In particular, for diagnosis of breast cancer, several gene signatures have been reported that allow stratification of patients. Such gene signatures, however, have not yet entered clinical practice, which suggests the need for even better and more accurate molecular tumor markers, for example, ones based on miRNA profiles (www.exiqon.com). Continued research into this field is ongoing and may hold some promise as predictive and prognostic markers.

Conclusions

Breast cancer is not a uniform cancer entity, but consists of several unique subtypes with different molecular profiles, biological behavior, and risk profiles. This poses a challenge for the clinical management of this heterogeneous disease (Weigel & Dowsett, 2010). The shift toward an earlier diagnosis of breast cancer due to improved imaging methods and screening programs highlights the need for new factors and combinations of biomarkers to quantify the residual risk of patients and to indicate the potential value of additional treatment strategies (Weigel & Dowsett, 2010).

There is no doubt that the use of molecular markers to inform the diagnosis, prognosis, and treatment decisions of patients with cancer is an increasing commitment (Li, 2010). Prognostic and predictive markers are highly relevant in therapeutic decision-making in order to individualize treatment. Cancer researchers are exploring numerous molecular and biological markers in hopes of developing better screening and treatment options (NCI, 2010c; Table 3). Advances in genomics, proteomics, and molecular pathology have generated many candidate biomarkers with potential clinical value. Their use for cancer staging and personalization of therapy at the time of diagnosis could improve patient care and potentially change the way we manage breast cancer (Ludwig & Weinstein, 2005).

IMPLICATIONS FOR ADVANCED PRACTICE

Advanced practitioners (APs) in oncology must keep current with guidelines of standard care for breast cancer patients. While the established biomarkers in breast cancer will continue to provide essential data regarding treatment options, there are many predictive and prognostic markers currently undergoing significant testing and validation for the future. The roles and responsibilities of the AP are expanding and becoming increasingly more important in all practice settings. As APs and educators it is imperative to understand the complexity of breast cancer and its unique signature. It is through education that APs lead the charge in furthering patient understanding of this complex disease.

DISCLOSURES

The author has no conflicts of interest to disclose.

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