

Chapter 2

Breast Cancer Biology and Clinical Characteristics

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Introduction

While breast cancer is often studied as a single disease, advances in our understanding of the epidemiology, biology, and molecular basis for breast cancer indicate that it is a heterogeneous disease that can be divided into several distinct subtypes. Proper classification of breast tumors into relevant subtypes is important for studying breast cancer etiology, predicting clinical course, and making decisions related to breast cancer treatment. Distinctions between subtypes of breast cancer can be made on the basis of patient characteristics or according to phenotypic or genotypic characteristics of the tumor itself, such as tumor stage, grade, histology, and genetic profile. While the motivation and methodology behind these different classification systems varies, there is great overlap between the subtypes of disease they describe. Nevertheless, the distinctions between subtypes of disease highlighted by these classifications not only translate to differences in clinical outcome, they also imply important differences in tumor etiology.

Tumor Classification Schemes

Patient Characteristics

The nature, incidence, and prognosis of breast cancer have been observed to vary according to a variety of patient characteristics. Perhaps the strongest epidemiologic distinctions can be made on the basis of patient age, menopausal status, and family history of breast cancer. Observed differences between premenopausal and postmenopausal disease and between familial and

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sporadic disease are supported by differences in underlying tumor biology which translate to distinct prognostic profiles.

Age at Diagnosis/Menopausal Status

As with most types of cancer, increasing age is the strongest risk factor for female breast cancer. Less than 2% of invasive breast cancers are diagnosed in women aged less than 35 years (Ries et al. 2007a), but incidence rates increase by a factor of almost 100 between the ages of 30 and 50 years (Pike et al. 1993). Although comparatively rare, breast cancer in young women is associated with a markedly poorer overall survival and shorter recurrence-free survival relative to disease in older women (Chung et al. 1996; Winchester et al. 1996; Maggard et al. 2003). In part, this discrepancy in survival may be attributed to the fact that breast cancer is significantly less likely to be diagnosed at an early stage in young women than in older women (Althuis et al. 2003; Maggard et al. 2003; Anderson et al. 2006). However, evidence also exists to suggest that breast tumors diagnosed in young women have a biology distinct from breast tumors diagnosed in older women (Walker et al. 1996; Anderson and Matsuno 2006; Benz 2008). Closely related to the distinction of breast cancer cases according to age, but perhaps more germane to differences in tumor biology, breast cancers are commonly distinguished according to a woman's menopausal status at the time of breast cancer diagnosis. This distinction is relevant not only because of differences in the age of premenopausal vs. postmenopausal women, but also because of the very different hormonal milieus of premenopausal vs. postmenopausal women (Verkasalo et al. 2001). Unlike postmenopausal women, premenopausal women are exposed to cycling ovarian hormones. Endogenous hormone levels in postmenopausal women are comparatively much lower, with adipose tissue serving as the primary source of endogenous estrogen (van den Brandt et al. 2000; Hankinson 2005–2006).

Premenopausal breast cancers are associated with a more aggressive tumor biology relative to breast cancer in older, postmenopausal women. Approximately 38–64% of breast cancers diagnosed in women aged <40 years have a high grade, compared to only 17–38% in women aged ≥60 years (Sidoni et al. 2003; Anderson et al. 2007a). Consistent with these differences in tumor grade, breast cancers in younger, premenopausal women are also more likely to be estrogen receptor (ER) negative (42–46% vs. 17–20% of postmenopausal cases) (Zavagno et al. 2000; Sidoni et al. 2003; Anderson et al. 2007a; Dunnwald et al. 2007), progesterone receptor (PR) negative (45–50% vs. 21–31%) (Sidoni et al. 2003; Anderson et al. 2007a; Dunnwald et al. 2007), and exhibit high Ki-67 expression (48% vs. 26%) (Sidoni et al. 2003); these differences persist even after adjusting for differences in tumor grade (Talley et al. 2002). Furthermore, tumors in premenopausal women are more likely than tumors in postmenopausal women to overexpress HER2-neu (HER2) (Sidoni et al. 2003; Hartley et al. 2006), have a basal-like molecular phenotype (Millikan et al. 2008), and overexpress p53 (Breast Cancer Linkage Consortium 1997; Sidoni et al. 2003).

Premenopausal disease is also more likely to be familial (Claus et al. 1990; Sidoni et al. 2003) and, specifically, is strongly associated with *BRCA1* mutations (John et al. 2007). These differences in tumor biology contribute to differences in disease survival: 5-year relative survival rates for women diagnosed prior to age 40 years are approximately 78–84% compared to >90% among women diagnosed at age 60 years or older (Ries et al. 2007b).

Epidemiologic studies indicate that, in addition to differences in tumor biology, risk factors for premenopausal breast cancer differ from those for postmenopausal disease (Gilliland et al. 1998; Titus-Ernstoff et al. 1998; Enger et al. 2000; van den Brandt et al. 2000; Clavel-Chapelon and the E3N-EPIC Group 2002). For example, obesity is associated with a reduced risk of premenopausal but an increased risk of postmenopausal breast cancer (Huang et al. 1997; Enger et al. 2000; van den Brandt et al. 2000; Anderson et al. 2007b), and oral contraceptive use is associated with an increased risk of premenopausal but not postmenopausal disease (Anderson et al. 2007b; Shantakumar et al. 2007). Similarly, nulliparous women have a reduced risk of breast cancer relative to parous women at a young age, but after age 40 nulliparous women have a higher risk of breast cancer compared to parous women (Pathak 2002; Anderson et al. 2007b). Taken together, these differences in disease epidemiology, prognosis, and tumor biology highlight the important distinction between premenopausal and postmenopausal breast cancers.

Family History of Breast Cancer

Approximately 15% of breast cancers arise in women with a history of the disease in first-degree relatives (i.e., mothers, sisters, or daughters) (Collaborative Group on Hormonal Factors in Breast Cancer 2001), and approximately 5–10% of breast cancers may be directly attributable to heredity (Madigan et al. 1995; Newman et al. 1998; Hemminki and Czene 2002). While the heredity of breast cancer susceptibility is not fully understood, it is assumed that the majority of familial breast cancers are attributable to a small number of high penetrance susceptibility genes. To date, two breast cancer susceptibility genes have been well described: *BRCA1* (Miki et al. 1994) and *BRCA2* (Wooster et al. 1995). Familial breast cancers in general, and *BRCA1*-associated breast cancers in particular, are characterized by an epidemiologic, phenotypic, and clinical profile that distinguishes them from sporadic breast tumors. (A detailed discussion of the relationship between family history and breast cancer risk is provided in Chapter 13.)

The phenotypic characteristics of familial tumors are similar to those of premenopausal tumors in that they tend to exhibit a more aggressive biology. Although differences in tumor stage at diagnosis are not pronounced (Eerola et al. 2001; Rennert et al. 2007), *BRCA1*-associated and *BRCA2*-associated breast cancers are characterized by a higher tumor grade relative to sporadic tumors (Marcus et al. 1996; Breast Cancer Linkage Consortium 1997; Palacios et al. 2005). With respect to other markers of tumor aggressiveness, few

distinctions have been noted between *BRCA2*-associated tumors and sporadic tumors (Lakhani et al. 2002). However, compared to sporadic tumors, *BRCA1*-associated breast tumors are more likely to be hormone receptor negative [68–90% of *BRCA1*-associated tumors are ER negative (ER–) compared to only 20–35% of sporadic tumors], HER2 negative (Lakhani et al. 2002; El-Tamer et al. 2004; Palacios et al. 2005; Rennert et al. 2007), overexpress p53 (Lakhani et al. 2002; Palacios et al. 2005), and have higher Ki-67 expression levels (Marcus et al. 1996; Palacios et al. 2005).

Tumor Characteristics

As previously suggested, observed differences in the nature and prognosis of breast cancer according to patient characteristics are largely explained by differences in tumor characteristics, and distinctions between subtypes of breast cancer may also be made on the basis of clinical and molecular tumor characteristics. Molecular and genetic studies of breast cancer provide evidence supporting the classification of breast cancer subtypes according to tumor appearance, histology, tumor marker expression, and gene expression profiles.

Clinical Characteristics

Tumor stage and tumor grade are commonly used by pathologists to describe the severity and aggressiveness of breast cancers. These two attributes are interrelated and often correlated, but are distinct in important ways. Both measures are independently informative in predicting disease course and are commonly used to guide breast cancer treatment decision-making with respect to surgical and adjuvant therapies. Similarly, the histological type of a tumor is useful in characterizing tumor biology and is increasingly being documented as a significant parameter in defining and describing disease epidemiology.

Stage

The staging of breast tumors provides a description of the extent and spread of a tumor. Specifically, tumor stage is determined by the size of the tumor, whether the lymph nodes are involved (and how many lymph nodes are involved), and whether the cancer has spread to other parts of the body. Breast tumors may be classified as stage 0–IV according to the American Joint Committee of Cancer (AJCC) staging system, with increasing stage corresponding to increasing tumor size and spread. Stage 0 breast cancer (i.e., in situ breast cancer) is characterized by an accumulation of malignant cells that have not invaded into surrounding tissue. Breast tumors designated as stage I, II, III, or IV involve some invasion of tumor cells beyond the basement membrane, and

are thus referred to as invasive tumors. Stage I breast cancer is confined to the breast tissue and has a maximum diameter of less than 2 cm while stage IV breast cancer involves distant metastases.

In general, it is presumed that most breast tumors will progress through these stages over time if left undetected. Consistent with this assumption, the epidemiologic literature suggests that risk factors for in situ disease are similar to those for invasive disease (Kerlikowske et al. 1997; Trentham-Dietz et al. 2000; Gill et al. 2006; Reinier et al. 2007), and laboratory studies indicate that patterns of genetic alterations and imbalances observed in in situ tumors are nearly identical to those observed in invasive breast cancers (Buerger et al. 1999; Hwang et al. 2004). Also consistent with progression through breast cancer stages, the distribution of tumor stage at diagnosis has shifted toward earlier stages in countries where mammographic screening has become widespread (Anderson et al. 2004; Li et al. 2005): age-adjusted incidence rates for ductal carcinoma in situ (DCIS) increased by approximately 660% between 1973 and 2000, while incidence rates for invasive breast cancer increased by only 36% over the same time period (Anderson et al. 2004). Not all early stage tumors, however, will progress to advanced stages and in situ breast cancer is thus generally considered a non-obligate precursor to invasive disease. Factors determining which in situ tumors will or will not progress to invasive disease if left untreated are largely unknown because there are few studies on the natural history of breast cancer. Follow-up studies of patients with in situ breast cancer originally misdiagnosed as benign breast disease (and thus treated only with biopsy) suggest that approximately 20–53% of patients with in situ breast cancer treated with biopsy alone will go on to develop invasive breast cancer within 3–31 years (Rosen et al. 1980; Page et al. 1982, 1995; Collins et al. 2005).

As might be inferred from the criteria used to stage breast tumors, disease prognosis is inversely associated with tumor stage in developed countries. Breast cancers diagnosed at stage 0 or stage I are very responsive to available therapies and are associated with 5-year disease-specific survival rates approaching 100% (Ernster et al. 2000; Ries et al. 2007b). Disease diagnosed at a more advanced stage is associated with a less favorable prognosis; 5-year relative survival rates are approximately 86%, 57%, and 20% when disease is diagnosed at stage II, III, and IV, respectively (Ries et al. 2007b).

The majority of breast cancer cases diagnosed in developed countries are diagnosed at an early stage. Based on US breast cancer incidence data from 1988 to 2001, approximately 16%, 40%, 34%, 6%, and 4% of breast cancers are diagnosed at stages 0–IV, respectively (Ries et al. 2007b). Given the relationship between cancer stage and access to health care and screening, stage distributions can vary substantially between countries as well as within countries by various demographic and socioeconomic factors. For example, in the United States, African-American, Hispanic white, and Native American women with breast cancer are about two times more likely to be diagnosed at an advanced stage relative to non-Hispanic white women (Li et al. 2003; Smigal et al. 2006). The distribution of stage is also shifted toward more advanced stages with

decreasing age at diagnosis (Anderson et al. 2007b; Ries et al. 2007b). Thus, tumors in younger, premenopausal women are more likely to have spread beyond the primary site at the time of diagnosis relative to breast cancers diagnosed in postmenopausal women, contributing to the previously described differences in the survival between premenopausal vs. postmenopausal breast cancer.

Differences in the distribution of tumor stage by demographic factors may be largely attributable to differences in the prevalence of breast cancer screening (Blanchard et al. 2004) and access to medical care (Bradley et al. 2002), but are also likely to reflect differences in tumor biology and, in particular, tumor aggressiveness. Specifically, tumors diagnosed at stage III or stage IV are more likely than tumors diagnosed at earlier stages to have a lobular histology (14% vs. 9%) (Li et al. 2005), to be high grade (65% vs. 39%) (Ries et al. 2007b), and to be hormone receptor negative (31% vs. 19%) (Dunnwald et al. 2007). As discussed below, these markers of tumor aggressiveness are strong predictors of disease course and are associated with differences in tumor etiology.

Grade

Tumor grade provides a description of how closely breast tumor cells resemble normal breast tissue when viewed microscopically. One commonly used measure for defining tumor grade for breast cancer is the Bloom–Richardson Scale (Bloom and Richardson 1957). Using this semi-quantitative measure, grade is defined according to three morphologic features of breast tumor cells: (1) the degree of tumor tubule formation, (2) mitotic activity, and (3) nuclear pleomorphism. Tumors are assigned a grade of 1–3 based on the combination of these three characteristics, with an assignment of grade 1 indicating a tumor composed of well-differentiated breast cells that generally appear normal and are not growing rapidly, grade 2 indicating a tumor composed of moderately differentiated breast cells, and grade 3 indicating a tumor of poorly differentiated breast cells that tend to grow and spread more aggressively. Several modifications and amendments to the original Bloom–Richardson Scale have been proposed over the years (Haybittle et al. 1982; Contesso et al. 1987; Meyer et al. 2005) but overall, tumor grade is inversely correlated with the degree of differentiation and proliferation in tumor cells. Thus, across grading scales, lower grade is indicative of slower growing cancer that is less likely to spread and higher grade is indicative of more aggressive, rapidly progressive disease.

Consistent with the slower growth rate of low-grade tumors, there is a high level of correlation between grade and stage at diagnosis: approximately 73% of invasive low-grade tumors are diagnosed as stage I disease compared to only 32% of high-grade tumors (Ries et al. 2007b). The distribution of tumor grade also varies substantially with other tumor characteristics. In particular, although the distribution of tumor grade does not appear to be significantly different between breast cancers of ductal vs. lobular histology (Li et al. 2005), tumors of high grade are more likely to be hormone receptor negative

(Dunnwald et al. 2007) and are more likely to exhibit a “triple-negative” (i.e., ER–/PR–/HER2–) (Rakha et al. 2006; Bauer et al. 2007) or basal-like (Carey et al. 2006; Yang et al. 2007) phenotype.

Tumor grade is also associated with a number of patient characteristics. Specifically, breast cancers diagnosed at an early age (Sidoni et al. 2003; Anderson et al. 2007a) or prior to menopause (Zavagno et al. 2000) tend to be of higher grade relative to breast cancers in older, postmenopausal women: <4% of low-grade but >9% of high-grade breast cancers are diagnosed in women aged <40 years (Anderson et al. 2007a). Additionally, in the United States, breast cancers diagnosed in non-Hispanic white women tend to be of lower grade, on average, than breast cancers diagnosed in women of other racial/ethnic groups (Li et al. 2003). Familial breast cancers also tend to be of higher grade relative to sporadic breast cancers (Marcus et al. 1996; Breast Cancer Linkage Consortium 1997; Lakhani et al. 2000; Palacios et al. 2005). Specifically, *BRCA1*-associated breast cancers demonstrate significantly greater pleomorphism and higher mitotic count than sporadic tumors and *BRCA2*-associated tumors are characterized by significantly lower tubule formation than sporadic tumors (Breast Cancer Linkage Consortium 1997; Lakhani et al. 2000). With respect to other epidemiologic risk factors, a number of studies have found that use of combined estrogen plus progestin menopausal hormone therapy (CHT) is more strongly associated with an increased risk of low-grade than high-grade breast cancer (Manjer et al. 2001; Garcia-Closas et al. 2006; Borgquist et al. 2007); few studies, however, have examined differences in other risk factors for low vs. high-grade breast cancer.

Tumor grade is of particular relevance with respect to the clinical course of breast cancer. Although closely correlated with stage at diagnosis, grade is a significant independent predictor of disease prognosis (Warwick et al. 2004; Rosenberg et al. 2005; Arriagada et al. 2006; Ries et al. 2007b; Soerjomataram et al. 2008) and an important predictor of response to adjuvant therapy (Pinder et al. 1998; Page et al. 2001). Among women with incident invasive breast cancer, overall 5-year relative survival rates are close to 100% for low-grade disease, but less than 80% for high-grade disease (Collaborative Group on Hormonal Factors in Breast Cancer 2001); prognosis is best for women with low-grade, early-stage disease (approximately 100%) and worst for women with high-grade, advanced-stage disease (<20% 5-year relative survival). While grade is a strong predictor of survival in the first 5 years after breast cancer diagnosis (Warwick et al. 2004; Arriagada et al. 2006; Ries et al. 2007b), there is evidence to suggest that this tumor characteristic may continue to have an impact on survival many years after diagnosis (Contesso et al. 1987; Warwick et al. 2004; Rosenberg et al. 2005).

Histology

Breast cancers are also characterized by pathologists according to tumor histology: the microscopic organization and growth pattern of cancer cells. The

two most common histological types of breast cancer are ductal and lobular carcinomas. Although the majority of breast cancers are ductal cancers, the distribution of histological types varies between in situ vs. invasive disease. With respect to in situ lesions, ductal carcinoma in situ (DCIS) constitutes 80–85% while lobular carcinoma in situ (LCIS) accounts for only about 5% of all in situ tumors (Li and Daling 2007). DCIS incidence rates have risen dramatically over the past few decades in developed countries because these tumors can be detected by mammography (Levi et al. 1997; Barchielli et al. 1999; Kricker et al. 2004; Li et al. 2005). With respect to tumor biology, DCIS is considered a precursor of invasive breast cancer (Franceschi et al. 1998; Warnberg et al. 2001a; Li et al. 2006; Soerjomataram et al. 2006). In contrast, LCIS is generally considered to be a marker of invasive breast cancer risk, rather than as a true precursor lesion. However, recent data indicate that invasive tumors diagnosed after LCIS are much more likely to be lobular than to be ductal (Li et al. 2006). LCIS is challenging to study epidemiologically because it lacks clinical signs and is typically only found incidentally on procedures performed for another reason. While it has long been thought that LCIS is not associated with any specific mammographic findings, there is evidence that calcifications are seen in 21–67% of LCIS cases (Carson et al. 1994; Crisi et al. 2003; Arpino et al. 2004a).

With respect to invasive disease, approximately 70–73% of invasive breast cancers in developed countries are invasive ductal carcinomas (IDC) and 13–16% are invasive lobular carcinomas (ILC) (Levi et al. 2003; Li et al. 2003; Verkooijen et al. 2003). The remaining ~15% of invasive cases is composed of a heterogeneous group of several histological variants, each of which accounts for no more than 2% of all invasive cases and none of which have been particularly well characterized. In order of most to least frequent (based on US cancer registry data) these rarer histological subtypes include: mucinous (2.3%), comedo (1.6%), inflammatory (1.5%), tubular (1.4%), medullary (1.2%), and papillary (0.4%) carcinomas (Li et al. 2005). Analyses using US SEER registry data indicate that there are several clinical differences across these subtypes. Compared to ductal carcinomas, mucinous, comedo, tubular, and medullary carcinomas are less likely to present at an advanced stage; mucinous, tubular, and papillary carcinomas are less likely, and comedo, medullary, and inflammatory carcinomas are more likely to be ER–/PR– and high-grade (Li et al. 2005). With respect to prognosis, data in recent years have shown that mucinous and tubular carcinomas have 31% and 52% lower risks of mortality, respectively, compared to ductal tumors (Li et al. 2003).

Several recent studies have more clearly described the distinct descriptive epidemiology and risk factor profiles of IDC vs. ILC. Incidence rates of ILC (including both pure lobular and mixed ductal–lobular tumors) were observed to increase more rapidly over the 1990s compared to incidence rates of IDC in both the United States and Switzerland. In the United States, ILC rates increased 65% from 1987 to 1999, while rates of IDC increased only 3% (Li et al. 2003). A similar incidence trend was observed in Geneva, Switzerland,

where ILC rates increased 14.4% per year between 1976 and 1999 compared to an increase of only 1.2% per year for IDC rates (Verkooijen et al. 2003). More recent data from the United States indicate that, since 1999, both IDC and ILC rates have declined at a rate of about 4% per year. The reasons for these changing incidence patterns are unclear, but it may be related to saturation of breast cancer screening in developed countries and/or to the abrupt cessation of CHT use that occurred after the Women's Health Initiative randomized trial reported that the risks of hormone therapy outweighed its benefits.

Pathologically, the growth patterns of ILC and IDC are distinct. ILC is characterized by tumors that grow as sheets or linear strands of cancer cells that are microscopically quite different from the discrete solid masses that are characteristic of IDC (Davis et al. 1979). As a result of this difference, ILC is more difficult to palpate on a clinical exam and to detect by mammography compared to IDC (Dixon et al. 1982). Despite the fact that ILC is more likely to present at an advanced stage than IDC, in recent years ILC has been associated with a 26% lower risk of mortality compared to IDC (Li et al. 2003), likely due to the fact that it is almost always hormone receptor positive (Li et al. 2005) (and thus amenable to treatment with adjuvant hormonal therapy). Consistent with the growth pattern of ILC, expression of the cell–cell adhesion molecule E-cadherin is almost universally absent in ILC, while it is almost universally present in IDC (Acs et al. 2001). For this reason, E-cadherin expression is sometimes used clinically to distinguish ILC from IDC. Recent studies have also identified numerous other molecular differences between ILC and IDC through the use of various array platforms, further suggesting that there are important differences in the origins and etiologies of these two histological types of breast cancer (Aldaz et al. 1995; Nishizaki et al. 1997; Gunther et al. 2001; Coradini et al. 2002; Korkola et al. 2003; Arpino et al. 2004b; Loo et al. 2004). As discussed in Chapter 5, the epidemiologic risk factor most consistently observed to differentially impact risk of ILC vs. IDC is CHT use, which is much more strongly related to risk of ILC than it is with risk of IDC.

Molecular/Genetic Profile

Molecular and genetic markers are also widely used to discriminate subtypes of breast cancer. The distinction of tumor subtypes on the basis of tumor marker expression, particularly the distinction between tumors that express ER (ER+) and those that do not (ER–) correlates well with previously described phenotypic classifications and has prognostic significance. Individual assays for tumor markers, including PR, HER2, p53, epidermal growth factor receptor (EGFR), and especially ER, have become common clinical practice because of their utility in selecting targeted therapies and in predicting clinical course. Specifically, breast tumors that are ER+ are most likely to benefit from hormonal therapies such as selective estrogen receptor modulators (SERMs, e.g., tamoxifen) and aromatase inhibitors, while tumors that are HER2+ are most likely to benefit from trastuzumab therapy. Recently, however, advances

in gene expression profiling technology have made it possible to evaluate a large number of tumor markers and genetic alterations in concert. While breast cancer subtypes identified through gene expression profiling reflect many previously established differences according to individual tumor markers and other tumor characteristics, these newly identified subtypes also reflect a more complex interplay of a variety of transcriptional programs. Here we consider the significance of breast cancer subtypes distinguished on the basis of ER expression status alone as well as subtypes distinguished by more refined gene expression profiles.

Estrogen Receptor (ER) Status

In normal breast tissue, estrogen is the predominant controller of cell proliferation and its activity is mediated by the estrogen receptor (ER). Although there are two forms of ER (ER α and ER β), ER α is the predominant form in breast tissue; we refer to ER α simply as ER throughout this chapter. In developed countries where tumor ER expression is routinely assessed on breast cancer patients, approximately 75% of breast tumors are ER+ (Li et al. 2003). Pronounced differences in the epidemiology and clinical profiles of ER+ and ER- breast cancers have been noted for decades (McGuire 1975; Leclercq et al. 2002) and suggest vastly different tumor etiologies. Breast cancer risk factors related to endogenous hormone exposure, such as parity and age at first live birth, are more strongly associated with risk of ER+ breast cancer, while risk factors for ER- disease are more likely to involve non-hormonal mechanisms (Potter et al. 1995; Huang et al. 2000; Ma et al. 2006; Rosenberg et al. 2006). Clinically, ER+ breast cancers are associated with a much more favorable prognosis than ER- tumors: the estimated 5-year survival probability for patients with ER+ breast cancer is approximately 90%, compared to only 77% for patients with ER- disease (Grann et al. 2003). These tumor types are also clinically distinguished by the fact that hormonal therapies (including selective estrogen receptor modulators and aromatase inhibitors) offer significant improvement in disease survival among patients with ER+, but not ER-, breast cancer (Rutqvist and Johansson 2007).

Increasing evidence suggests that ER expression is strongly correlated with a number of other tumor markers, including many that are not regulated by estrogen (Lacroix et al. 2004). ER expression is strongly correlated with PR expression, with greater than 80% of ER+ tumors also being PR+ and greater than 90% of ER- tumors being PR- (Surveillance Epidemiology and End Results Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 17 Regs Limited-Use). ER expression is also associated with genes and protein products involved in cell cycle regulation and proliferation: ER+ tumors exhibit higher expression of cyclin-dependent kinase inhibitors p21 and p27 (Reed et al. 1999; Oh et al. 2001), cyclin D1 (Reed et al. 1999; Oh et al. 2001), and apoptosis inhibitor bcl-2 (Callagy et al. 2003), while ER- tumors exhibit higher expression of p53 (Sorlie et al. 2001; Callagy et al. 2003), cyclin

E (Callagy et al. 2003), and proliferation indicator Ki-67 (Molino et al. 1997; Ruiz et al. 2006). These differences in cell biology may largely explain the pronounced phenotypic and clinical differences between ER+ and ER– tumors.

As may be gathered from the differences described above, distinctions between ER+ and ER– tumors overlap with previously described classification systems. With respect to patient characteristics, ER– tumors are more common among patients diagnosed at a young age (Anderson et al. 2006) and among patients with a genetic predisposition for breast cancer (Palacios et al. 2005). ER+ and ER– tumors also exhibit differences in the distribution of tumor grade (Callagy et al. 2003): approximately 75% of ER+ tumors are low-grade, while approximately 75% of ER– tumors are high-grade (Surveillance Epidemiology and End Results Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 17 Regs Limited-Use). With respect to histology, approximately 25% of ductal tumors are ER– while lobular tumors are almost never ER– (Korhonen et al. 2004). Additionally, while ER– tumors are most likely to exhibit patterns of gene expression associated with myoepithelial lineage, ER+ tumors are strongly associated with luminal cell lineage (Jones et al. 2004; Lacroix et al. 2004).

The relevance of ER expression as a major discriminator of breast cancer subtypes has been confirmed by gene expression profiling studies (Perou et al. 2000; Sorlie et al. 2001; van't Veer et al. 2002; van de Vijver et al. 2002; Sorlie et al. 2003; Farmer et al. 2005; Hu et al. 2006). Importantly, however, these studies also reveal a substantial amount of heterogeneity within ER+ and ER– subtypes of breast cancer.

Molecular Subtypes of Breast Cancer

Gene expression profiling technology has been used to identify and discriminate between subtypes of breast cancer (Perou et al. 2000; Sorlie et al. 2001; van't Veer et al. 2002; van de Vijver et al. 2002; Farmer et al. 2005). cDNA microarrays have been used to assay gene expression in breast tumors which allows the hundreds of genes involved in cell growth, death, and proliferation to be analyzed concurrently. Hierarchical clustering is then employed to group together those tumors with similar “molecular portraits.” Studies utilizing this approach have discovered and validated several molecular subtypes of breast cancer. While different investigators have used different sets of genes to characterize breast cancer subtypes, the gene expression profiles that have been most widely utilized and validated are those identified by the Perou and Sorlie groups (Perou et al. 2000; Sorlie et al. 2001, 2003; Fan et al. 2006; Hu et al. 2006; Sorlie et al. 2006). These groups identified five subtypes of breast cancer with distinct molecular profiles: luminal A, luminal B, HER2-overexpressing, basal-like, and normal-like (also called unclassified). Of note, ER status alone can reliably distinguish between broad groups of these subtypes as almost all luminal

A and luminal B tumors are ER+ and the vast majority of HER2-over-expressing, basal-like, and normal-like tumors are ER-. Although there is little population-based data to approximate the distribution of these subtypes, it is clear that the majority of breast cancers belong to the luminal A subtype (41–69%), and the HER2-overexpressing and normal-like phenotypes are the least common (5–10%) (Sorlie et al. 2001; Carey et al. 2006; Yang et al. 2007). Existing epidemiologic evidence also suggests that the distribution of the five subtypes varies with demographic and genetic factors: breast cancers diagnosed in premenopausal women or African-American women are more likely to be basal-like or HER2-overexpressing (Carey et al. 2006; Yang et al. 2007), and *BRCA1*-related breast cancers are almost always basal-like (Foulkes et al. 2003). Additional differences in the epidemiologies of luminal A, luminal B, HER2-overexpressing, basal-like, and normal-like tumors remain to be understood although, consistent with the previously described association between reproductive history and risk of ER+ breast cancer, hormonal factors appear most strongly associated with risk of luminal A breast cancer (Yang et al. 2007; Millikan et al. 2008; Phipps et al. 2008a, b).

The primary factors discriminating between luminal A, luminal B, HER2-overexpressing, basal-like, and normal-like subtypes of breast cancer reflect the cellular origin of these tumors within the breast: luminal A and luminal B subtypes express genes characteristic of luminal cell lineage (particularly ER), while HER2-overexpressing, basal-like, and normal-like subtypes demonstrate no such expression. Within the group of luminal-like tumors, luminal A tumors are characterized by a higher level of expression of luminal-specific genes (e.g., ER, GATA-binding protein 3 [GATA3], hepatocyte nuclear factor 3 alpha [HNF3A], X-box-binding protein 1 [XBP1]), and a lower level of expression of proliferative genes (e.g., cyclin B1, proliferation-associated antigen Ki-67) as compared to luminal B tumors (Sorlie 2004). Among the group of non-luminal tumors, HER2-overexpressing tumors are characterized by a high level of HER2 expression, while basal-like tumors exhibit the gene expression pattern most similar to that of basal epithelial cells, generally including a lack of ER, PR, and HER2 expression (the so called “triple-negative” phenotype) accompanied by expression of EGFR and/or basal cytokeratins (e.g., cytokeratin 5/6) (Nielsen et al. 2004). Normal-like tumors demonstrate strong expression of genes characteristic of adipose and other non-epithelial cells, although it remains to be seen whether this tumor subtype represents a clinically relevant group or simply poorly sampled tumor tissue (Sorlie 2004).

Existing data from gene expression-based studies, and from studies using simplified IHC-based definitions of luminal A, luminal B, HER2-overexpressing, basal-like, and normal-like tumor subtypes, indicate that the observed genotypic differences between these subtypes translate to distinctive clinical profiles (Table 2.1). Consistent with the fact that luminal A tumors are ER+, tumors of this type are most commonly low-grade and are associated with an early stage at diagnosis and favorable prognosis (Carey et al. 2006; Kim et al.

Table 2.1 Characteristics of breast cancer subtypes defined by gene expression profiles

| | Luminal A | Luminal B | HER2-overexpressing | Basal-like | Normal-like |
|--|--------------------------|---------------------------------|---------------------|--|--|
| Approximate distribution: | 55–65% | 7–12% | 6–10% | 10–15% | 5–10% |
| Tumor biology/appearance: | | | | | |
| Presumed cellular origin | Luminal epithelial | Luminal epithelial | Basoluminal | Basal epithelial | Non-epithelial |
| Predominant tumor marker expression pattern: | ER + and/or PR + , HER2- | ER + and/or PR + , HER2 + | ER-, PR-, HER2 + | ER-, PR-, HER2-, cytokeratin 5/6 + and/or EGFR + | ER-, PR-, HER2-, cytokeratin 5/6-, EGFR- |
| Stage at diagnosis: | | | | | |
| I | 44% | 39% | 28% | 24% | 48% |
| II | 47% | 54% | 53% | 62% | 39% |
| III–IV | 9% | 6% | 19% | 13% | 13% |
| Grade: | | | | | |
| Poorly differentiated | 58% | 56% | 70% | 82% | 81% |
| Mod./well-differentiated | 42% | 44% | 30% | 18% | 19% |
| Clinical characteristics: | | | | | |
| Average 5-year survival: | 75–90% | 45–90% | 20–75% | 30–80% | 50–87% |
| Targeted therapies: | Tamoxifen | Tamoxifen, possibly trastuzumab | Trastuzumab | None available | None available |

2006; Stark et al. 2007). In comparison, basal-like and HER2-overexpressing tumors are more likely to present at an advanced stage, to be of high-grade and, therefore, are associated with a markedly worse survival: the average 5-year survival among patients with luminal A disease is approximately 90%, while estimates for patients with HER2-overexpressing or basal-like breast cancer may be as low as 20–30% (Sorlie et al. 2001, 2003; Carey et al. 2006; Hu et al. 2006). Patients with luminal B disease appear to experience a slightly, but not significantly poorer prognosis than patients with luminal A tumors, but patients with tumors of either luminal subtype may be expected to benefit from targeted hormonal therapy. Although patients with HER2-overexpressing, basal-like, and normal-like breast cancers have a poorer prognosis than patients with luminal disease, it is suggested that they may respond more favorably to anthracycline-based neoadjuvant chemotherapy (Banerjee et al. 2006; Kim et al. 2006; Carey et al. 2007).

Understanding the different patterns of gene expression evident in different subtypes of breast cancer has helped to explain differences in clinical profiles. The classification of subtypes according to genetic and molecular characteristics correlates well with differences in prognosis, tumor aggressiveness, and response to available therapies. These subtypes have now been identified and validated in a number of different study populations and on a number of different platforms (Fan et al. 2006; Hu et al. 2006). The fact that these five disease subtypes reflect much of what has long been known about different aspects of disease, such as age at diagnosis and menopausal status, genetic predisposition, tumor stage and grade, histology, and individual tumor marker expression illustrates the benefit of jointly considering multiple tumor characteristics. Although technology will undoubtedly change and progress, it is certain that any attempts to classify subtypes of breast cancer in the future will need to concurrently consider a wide variety of genotypic and phenotypic factors in their characterization.

Origins of Breast Cancer Subtypes

The previously described distinctions between subtypes of breast cancer imply differences in tumor etiology. However, while the phenotypic and genotypic differences between disease subtypes have been well characterized, the biology underlying the initiation, progression, and divergence of these subtypes is not fully understood. Given the magnitude of the genomic, genetic, and epigenetic differences between subtypes of breast cancer defined by gene expression profiles and by tumor grade, it is likely that distinctions between these subtypes are fixed at tumor inception (Lacroix et al. 2004). For example, loss of genomic material in chromosome 16q is observed in approximately 65% of low-grade tumors but in less than 20% of high-grade tumors (Royslance et al. 1999); because the recovery of lost genomic material is an unlikely event in cancer

progression, this suggests that low and high-grade tumors arise through different etiologic pathways (Bergamaschi et al. 2006). Consistent with such a hypothesis, there is increasing evidence to suggest that breast cancers are relatively genetically stable throughout progression (Lacroix et al. 2004) and that tumor grade and tumor marker expression are highly concordant between in situ, invasive, and metastatic components of a breast cancer (Warnberg et al. 2001b).

In order for cancer to occur, a normal cell must accumulate several genetic and/or epigenetic changes including an activation or amplification of oncogenes, mutation or loss of tumor suppressor function, and the ability to proliferate indefinitely (Hanahan and Weinberg 2000). While the specific set of acquired alterations leading to the transformation of a normal cell could, in part, determine the makeup or subtype characterization of a cancer, the characteristics of the cell of origin itself are also thought to be relevant to subtype distinctions. The cancer stem cell model provides one framework under which the characteristics of a breast cancer are directly tied to its cellular origin (Dontu et al. 2003; Campbell and Polyak 2007; Stingl and Caldas 2007; Melchor and Benitez 2008).

Adult stem cells are tissue-specific, self-renewing cells capable of differentiating into all cell types in their tissue of origin. Given that the human breast undergoes many morphological changes throughout life, particularly during pregnancy, the existence of mammary stem cells has long been postulated (Daniel and Deome 1965; Dulbecco et al. 1982). Recent studies have been able to confirm that such cells exist in the normal adult breast (Shackleton et al. 2006) and characterize these cells in breast tumor tissue (Stingl et al. 2001; Al-Hajj et al. 2003; Shipitsin et al. 2007). The model of how these mammary stem cells generate different epithelial cell lineages is assumed to involve a hierarchy of proliferation similar to other epithelial cell systems (Villadsen 2005). Under such a system, self-renewing mammary stem cells give rise to progenitor cells which, in turn, give rise to terminally differentiated luminal and myoepithelial cells (Fig. 2.1). Unlike stem cells, progenitor cells have a finite division capacity and are more differentiated. Some progenitor cells appear to be bipotent, capable of giving rise to either luminal or myoepithelial cell lineages (Stingl et al. 2001), while others appear to be restricted to luminal lineages (Dontu et al. 2004; Stingl and Caldas 2007). The fact that tumor cells exhibit many properties of normal adult stem cells, such as self-renewal, high proliferative capacity, and longevity, has led to the hypothesis that breast tumors originate in stem cells which have undergone some genomic transformation (i.e., “cancer stem cells”). In contrast to stem and progenitor cells, the terminally differentiated cells which comprise the majority of breast tissue rarely proliferate and are continuously replaced; thus, there is some question as to whether terminally differentiated cells have adequate opportunity to accumulate the multiple genetic/epigenetic changes necessary to initiate oncogenesis.

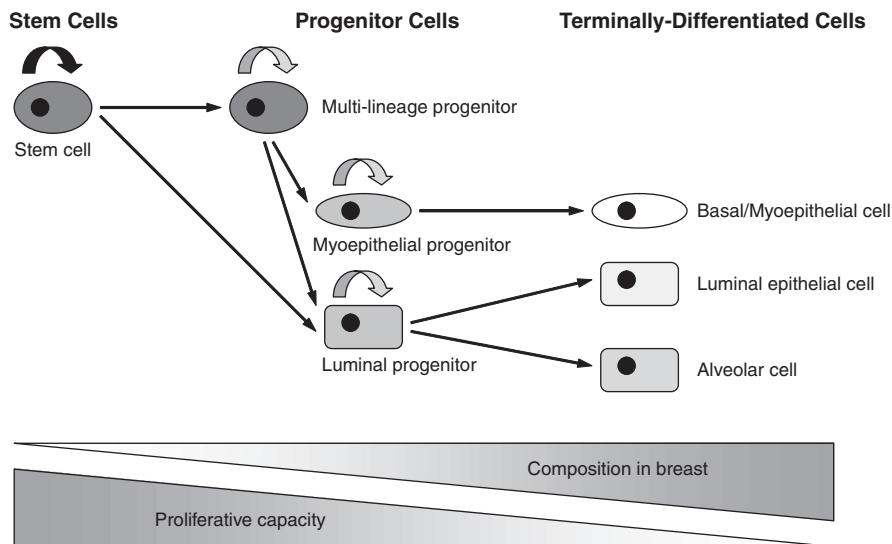


Fig. 2.1 Hierarchy of mammary epithelial cells in the normal adult breast

The tumorigenicity of mammary stem cells is supported by a landmark paper by Al-Hajj et al. (2003), who demonstrated that cells from a solid human breast tumor exhibiting a $CD44^{+}/CD24^{-/low}$ phenotype could induce breast tumors in immunocompromised mice with transfection of as few as 200 cells, and that induced tumors demonstrated an array of cell types similar to those found in the original tumor. In contrast, injecting thousands of cancer cells that came from the same human tumors but that had an alternate phenotype (i.e., not $CD44^{+}/CD24^{-/low}$) failed to induce any tumors. Further studies have confirmed the oncogenic properties of $CD44^{+}/CD24^{-/low}$ cells (Ponti et al. 2005) and have demonstrated that the gene signatures for these cells are enriched for stem cell markers (Shipitsin et al. 2007). Specifically, $CD44^{+}/CD24^{-/low}$ cells exhibit increased expression of genes involved in cell motility and genes in the TGF- β pathway and a lack of ER expression. While it is generally considered that the $CD44^{+}/CD24^{-/low}$ phenotype, in conjunction with epithelial-specific antigen (ESA) expression, characterizes cancer stem cells, these biomarkers are not highly specific (Honeth et al. 2008) and there is a great need to develop more specific cancer stem cell markers.

Under the cancer stem cell model of breast oncogenesis, cancer-inducing mutations and/or alterations in protein expression affect either mammary stem cells or progenitor cells, giving rise to cancer stem cells which are able to self-renew and differentiate into the other cells that comprise a tumor. In contrast to more traditional models of clonal evolution and multistep oncogenesis, the cancer stem cell model posits that only a small subset of cells within a breast tumor (i.e., cancer stem cells and their progenitor cells) are able to drive

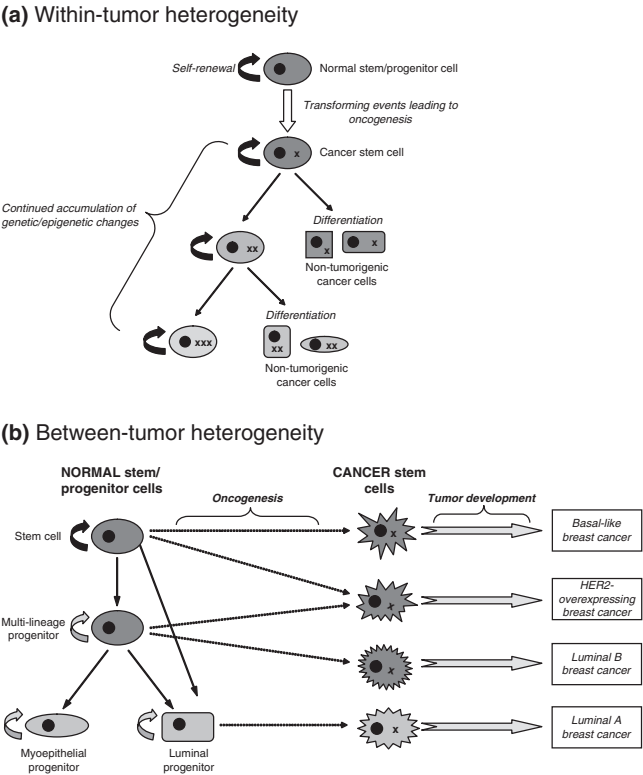


Fig. 2.2 Possible sources of heterogeneity under the cancer stem cell model

proliferation and accumulate genetic and/or epigenetic changes (Campbell and Polyak 2007; Stingl and Caldas 2007). As a result, heterogeneity within a tumor is expected to arise as the result of aberrant differentiation of cancer stem cells and the continued accumulation of genetic and epigenetic changes in cancer stem cells (Fig. 2.2a).

With respect to heterogeneity between tumors, the cancer stem cell model implies that breast tumor characteristics, including grade and tumor marker expression largely reflect the type of stem cell or progenitor cell in which the tumor arose (Fig. 2.2b). For example, basal-like breast tumors exhibit a gene expression profile similar to that of mammary stem cells (Yehiely et al. 2006) but differ from differentiated myoepithelial cells in that they do not express smooth muscle actin (Livasy et al. 2006); based on these observations, it has been suggested that basal-like tumors are derived directly from mammary stem cells (Stingl and Caldas 2007) or from ER⁻ bipotent progenitor cells (Stingl et al. 2001). Conversely, given the lack of ER expression in mammary stem cells (Asselin-Labat et al. 2006; Shipitsin et al. 2007), it has been proposed that luminal breast tumors must arise from ER⁺ luminal progenitor cells (Dontu et al. 2004). The underlying implications of this model are thus that the basic

patterns of gene expression, specific to different types of stem or progenitor cells within the breast, are largely maintained throughout the pathway leading to breast cancer and are fundamentally responsible for distinctions between subtypes of breast cancer (Korsching et al. 2002). Accordingly, differences between subtypes of breast cancer defined on the basis of biological characteristics such as grade, tumor marker expression, and/or gene expression pattern, are suggested to be fixed at tumor inception.

Conclusions

Evidence suggests that the distinction between different subtypes of breast cancer arises early in cancer development. A number of classification systems have been utilized to distinguish subtypes of breast tumors according to epidemiologic, morphologic, genetic, and molecular characteristics. While the specific subtypes identified through each of these classification systems highlight important distinctions in clinical outcome and tumor etiology, there is great overlap between tumor subtypes identified on the basis of patient characteristics and various tumor characteristics. The classification system most recently proposed from gene expression profiling studies appears to offer the most refined system of classification, and has been shown to have both epidemiologic and clinical relevance. Given the heterogeneity of breast cancer, distinguishing breast cancers into relevant subtypes is often critical when studying the disease's etiology, predicting disease prognosis, and making appropriate treatment decisions.

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