Breast Cancer Heterogeneity: A Mixture of At Least Two Main Types?

William F. Anderson, Rayna Matsuno

Breast cancers are clinically heterogeneous (1). However, breast cancer etiologic heterogeneity is not so well established. Traditionally, breast cancer has been viewed as one biologic entity with common etiology (2). Much like the adenoma-to-carcinoma sequence for colorectal cancer (3–6), breast cancers supposedly result from stochastic molecular changes over long periods. Stepwise molecular alterations are mirrored by histologic progression from normal breast epithelium to atypical hyperplasias to carcinoma in situ to invasive breast cancer (7,8).

Emerging data demonstrate that the stratification of tumors by gene expression profiles (10–14) and other techniques (15–17) divides breast cancer into a mixture of at least two main types, with five subtypes, according to hormone receptor expression (negative or positive) and/or epithelial cellular origin (basal or luminal). The hormone receptor-negative (basal) group has three subtypes—one with HER2 overexpression, one “normal-like,” and one basal subtype with positive epidermal growth factor receptor (EGFR), absent progesterone receptor (PR), and absent HER2 expression (i.e., the so-called triple-negative subtype). The hormone receptor-positive group has two subtypes—luminal A and luminal B. Human ER-negative and basal tumors are parenthetically associated with the rare medullary carcinomas and mutations in the BRCA1 gene (18–22).

In this issue of the Journal, Asselin-Labat et al. examined expression profiles in normal mouse mammary stem cells (23). Using purification methods for the prospective and differential isolation of adult mouse mammary epithelial cells (24,25), they identified a hierarchical parent–progeny relationship between mouse mammary stem cells and their derivative colony-forming cell progeny. Mouse mammary stem cells expressed CD24+ along with relatively low levels of CD29 or CD49 and coexpressed markers with luminal features.

The authors then evaluated hormone receptor expression and other prognostic markers in the mouse mammary stem cell (or basal-like) and their derivative colony-forming progeny (or luminal) populations. Mouse mammary stem cell-enriched (basal) cells expressed EGFR but did not express ER, PR, or HER2 (consistent with the triple-negative phenotype of human breast tumors). These stem cells also expressed other hallmarks of human basal tumors, such as p63. In contrast, their derivative colony-forming cell progeny (luminal) expressed ER and PR but did not express HER2, EGFR, and p63. Oophorectomy of 8-week-old virgin mice had no effect on the mouse mammary stem cell (basal) population but suppressed their derivative colony-forming cell progeny (luminal).

These findings in mice support a cancer stem cell (or tumor-initiating cell) and/or mixture model for the human breast (or breast cancer) (26–29). In this hierarchical (or stem cell) model, the normal human breast evolves from stem cells of the terminal duct lobular unit (30), a two-cell anatomic complex composed of basal (myoepithelial) and luminal (glandular) epithelial components. After a tumor-initiating or gatekeeper event (31), tumor progression and promotion result in breast cancers with either 1) basal cellular differentiation and negative hormone receptor...
expression or 2) luminal cellular differentiation and positive hormone receptor expression.

Consistent with a stem cell and/or mixture breast cancer model, epidemiologic data show that the classically recognized inflection point in age-specific breast cancer rates at menopause [Clemmesen’s Hook (32)] reflects the confluence of two different rate curves, according to estrogen receptor expression (33). Unlike most epithelial tumors, which have linear age-specific rates on a log–log scale (34,35), rates for ER-negative tumors increase rapidly until age 50 years and then flatten or fall (Fig. 1, A). Rates for ER-positive tumors increase rapidly until age 50 years then continue to rise at a slower pace. Rates for ER-negative tumors show a bimodal breast cancer population with, predominant early-onset mode or peak frequency near age 50 years (Fig. 1, B). ER-positive rates are associated with a mostly late-onset cancer population and mode near age 70 years. Similar bimodal incidence patterns are observed for tumor size (large versus small), lymph node status (positive versus negative), grade (high versus low), and PR status (negative versus positive) with modal ages of 50 and 70 years (36).

The apparent differences in age incidence patterns suggest, somewhat paradoxically, that premenopausal hormonal exposures have greater impact on ER-negative than on ER-positive tumors (33,37,38). The timing of hormonal exposures as well as the distinction between tumor initiation and promotion or progression may partly explain this dual age-related effect (33,39). For example, premenopausal tamoxifen and oophorectomy appear to reduce hereditary and somatic breast cancers across all levels of risk, whereas postmenopausal tamoxifen prevents ER-positive but not ER-negative disease (40–44). Furthermore, hormone-dependent carcinogenesis might theoretically initiate an ER-negative progenitor with the subsequent capacity for hormone-independent promotion or progression, whereas hormone-independent genetic alterations and/or exposures could initiate an ER-positive cancer that was hormone dependent for tumor promotion or progression. A critical review of 31 publications, indeed, found differential effects for reproductive risk factors by ER expression (45). Analysis of data from a case–control study in Poland has strengthened support for this view (46). Differential associations for reproductive hormonal exposures according to hormone receptor status also have been observed in the Nurses’ Health Study (47) and Women’s Health Initiative (48).

Moreover, ER-negative and ER-positive breast cancers are differentially linked to screening mammography (49–52), with ER-negative tumors less likely than ER-positive cancers to be screen-detected. ER concentration tends to be inversely associated with HER2 overexpression (53,54). ER-negative and ER-positive tumors respond differently to chemoprevention and to systemic hormonal and/or chemotherapy (43,55–58). An increasing amount of data also demonstrate distinct clinical and molecular portraits for ER expression as tumors progress from early to late stages (59,60). Indeed, the hazard function for breast cancer death reveals two different prognostic patterns for ER-negative and ER-positive breast cancers (Fig. 1, C) (36,61).

In conclusion, the mouse model system of Asselin-Labat et al. appears to support a large body of emerging—as well as established molecular, epidemiologic, and clinical—evidence that is consistent with a stem cell or mixture breast cancer model, resulting in at least two main breast cancer types according to epithelial cellular origin and/or hormone responsiveness. Clinicians, in fact, have long suspected two main breast cancer types (62–67), which are mixed within the general population. The first breast cancer is early onset with peak incidence near age 50 years and hormone
dependent (39,68). The second breast cancer is late onset with peak incidence near age 70 years and largely hormone independent. These data provide opportunity for reflection and change. At a minimum, breast cancer can no longer be viewed as one biologic entity. The concept of a stem cell or mixture model could form the basis for revised conceptual frameworks. For if breast cancer overall consists of a mixture of at least two main types, we need a stratified rather than a unified approach for breast cancer research, prevention, and treatment. For example, breast cancer research must consider subgroup as well as main effects. Breast cancer prevention must focus on tumor-initiating or gatekeeper events. Breast cancer therapy must target the undifferentiated, self-renewing, and cancer-initiating stem cell population.

REFERENCES


**Note**

Supported in part by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.