Ductal Carcinoma In Situ of the Breast: a New Model

Daniel F. Hayes*

Several therapeutic options are available for patients with breast cancer. These include “local” therapies, such as surgery and radiation therapy, and “systemic” therapies, such as chemotherapy and hormone therapy. Unfortunately, few, if any, patients with detectable, metastatic disease are cured with currently available treatment options (1). Therefore, at least in 1997, our best chance to cure patients with breast cancer is to find and treat it early or to prevent it altogether.

The strategy of early diagnosis and treatment may be contributing to the decreasing risk of dying from breast cancer in the Western world (2). Screening mammography permits early detection of breast cancer (3). Randomized studies have demonstrated that early local treatment for screened patients reduces mortality by 20%-30% over a 10-year period compared with women who are followed without screening (4). Early systemic therapy also saves lives (5). Regardless of the risk of subsequent recurrence for a patient with newly diagnosed, nonmetastatic breast cancer, adjuvant systemic therapy of some sort decreases the odds of distant recurrence and death by 20%-30% over a 10-15-year period.

These observations raise the question: What is early breast cancer? Many investigators have proposed a model in which breast epithelial cells, like other solid tumors of epithelial origin, appear to proceed through a spectrum of biologic states from normal to frankly metastatic (6). According to this model, a series of random yet important chronologic events occurs in which epithelial cells escape normal growth control, develop the ability to invade the basement membrane, survive in the surrounding interstitial tissue of normal breast, migrate to other tissues, and multiply. Clinically, when carcinoma cells are confined to the basement membrane, they are designated in situ. Those cells that escape the basement membrane gain the designation of invasive or infiltrating carcinomas. Those that travel to other sites of the body are known as micrometastases, and if they grow in other tissues, they become detectable metastases. Ultimately, it is this process that causes the morbidity and mortality of breast cancer: the uncontrolled growth of malignant ductal breast cells in other tissues at the expense of the normal function of the host tissue. However, as the old saying goes, “All dogs are animals, but not all animals are dogs.” Presumably, all detectable metastases arise from the preceding state(s), but not all cells in the preceding state progress to detectable metastases.

Multiple clinical implications arise from this model. If breast cancer really does represent a stepwise progressive process, the following assumptions and corollaries might be made:

1) In an individual patient, breast cancer is not a “disease” (which by definition causes morbidity and mortality) unless it produces symptomatic lesions or death. The corollary from this concept is that most patients with newly diagnosed breast cancer (in situ cancer, invasive cancer, and micrometastases) have what might actually be considered a “condition” that places the patient at higher risk to develop the true disease in a manner that most clinicians now consider atypical hyperplasia.

2) All treatments for patients with breast cancer who do not have detectable, symptomatic lesions are “prophylactic.” In other words, the treatments are directed toward preventing future morbidity and mortality.

3) Except for those patients with symptomatic lesions, a subset of all patients receiving these prophylactic treatments do not need them, because in these subsets, the condition will not progress to the next step (e.g., ductal carcinoma in situ [DCIS] to invasive cancer, invasive cancer to micrometastases, micrometastases to detectable metastases).

In this context, additional clinical observations need to be addressed. The incidence of DCIS is increasing, presumably because of widespread application of mammographic screening (7). Importantly, nearly (99%) of all patients with DCIS can be cured by removal of the entire breast (a mastectomy) (8). Enigmatically, a series of studies has demonstrated that patients with invasive breast cancer treated with combined-modality breast-conserving therapy (BCT) have equal distant recurrence-free and overall survival rates when compared with women who had mastectomies (9).

More recently, studies have been performed to determine if patients with DCIS can also be safely treated with BCT. Results of these studies suggest that patients who only have an excision are more likely to have an in-breast recurrence than those who have excision and radiotherapy to the remaining breast (10). However, patients treated with either excision alone or excision plus radiotherapy have breast recurrence rates that may exceed 5% after 10 or more years of follow-up (10-12). This rate, of course, exceeds that seen in patients initially treated with mastectomy, since the latter have little or no breast tissue remaining in which to recur. It is gratifying that most of the patients who have breast recurrences after BCT can apparently be cured by a subsequent mastectomy. However, it is possible that these low but definite breast recurrence rates may be associated with occasional distant metastases that would not have occurred had the patient initially had a mastectomy. Therefore, one can only assume that initial mastectomy will prevent distant metastases and death in a few, but very few, more patients than will BCT. It must be emphasized, though, that 95% or more of the patients with DCIS are cured no matter how they are treated: by excision only, excision plus radiotherapy, or mastectomy.

*Correspondence to: Daniel F. Hayes, M.D., Breast Program, Lombardi Cancer Center, Georgetown University Medical Center, 3970 Reservoir Rd., N.W., Washington, DC 20007.

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appropriately, treatment for patients with breast cancer is shifting to the left on the spectrum model, directed toward even earlier lesions. Indeed, observations within the randomized adjuvant trials have suggested that one of the systemic therapies, tamoxifen, may prevent new, primary breast cancers (5). This observation has led to four separate large randomized trials of chemoprevention, in which women at high-risk or with in situ breast cancers are randomly assigned to receive tamoxifen or placebo (13).

Thus, we are left with the following conundrum (11). Nearly all of the patients with the "condition" of DCIS can be cured by a particularly distasteful prophylactic treatment (mastectomy), but many of them (perhaps as high as 90%-95%) do not need it. BCT without radiation will "cure" nearly, but not quite, as many patients. BCT with radiation therapy will "cure" more than BCT without radiation therapy. Tamoxifen may further decrease the risk of breast recurrence after BCT and therefore might cure even more patients. However, each of these incremental additional cure rates is gained at some expense: unsatisfactory cosmetics, side effects of radiation therapy and tamoxifen, increased monetary cost, and perhaps long-term toxic effects such as second malignancies. Ironically, it is at this stage that we are most likely to help those patients who need help, since treatment of DCIS will prevent an ultimately incurable and lethal disease: detectable distant metastases. However, to do so, we must either overtreat all patients to benefit a few or we must undertreat a few patients to their great detriment.

There is more "good news/bad news" that can be drawn from the "spectrum" model. The good news is obvious: most, if not all, patients with DCIS can be cured. The bad news is more subtle: clinical trials involving this condition are enormously expensive for the same reason. End points (such as distant recurrence and death) are infrequent and slow to occur. For example, in a study performed by the National Surgical Adjuvant Bowel and Breast Project (B24), patients with DCIS were all treated by wide excision and radiation therapy and were then randomly assigned to 5 years of tamoxifen treatment or to observation. To achieve appropriate power, this trial required accrual of more than 1800 patients from 1991 through 1994. It is estimated that the first report of results from this trial will not be available for some time. Furthermore, in spite of its size, this study is only powered to address issues of breast recurrence. Definitive observations regarding distant recurrence and mortality would have required a substantially higher number of patients.

At this expense, we are obligated to ensure that the next study of DCIS be an absolute blockbuster. But, how do we determine the next question? One way, of course, is to simply ask a question of mundane but practical importance, for which preclinical modeling is not helpful. However, an alternative means of choosing an exciting intervention for investigation would be to use laboratory-based model systems to bring novel ideas or hypotheses to the clinic.

Until now, no model has existed to study early states in the presumed breast cancer spectrum. Indeed, few reliable laboratory models have existed for any form of breast cancer (14,15). Primary human breast cancer tissues, and even those from nodular metastatic lesions, have been notoriously difficult to establish and maintain in culture. Most of the immortal, cultured breast cancer cell lines used in laboratory research have been established from effusion-based metastatic cell clones. Even when these cell lines form tumors in xenografted murine hosts, their architecture and biologic behavior do not truly reflect the heterogeneity that characterizes early clinical breast cancer. Likewise, the behavior of carcinogen-induced murine mammary tumors (e.g., those induced with 7,12-dimethylbenz[a]anthracene [DMBA]) has always been suspect, since most human breast cancers are not clearly induced by a single carcinogen (16). Transgenic mice have been produced that have a genetic tendency toward the development of mammary tumors as a result of placing various oncogenes downstream of mammary-specific promoters (14). However, as with effusion-based cultured human cell lines and DMBA-induced murine breast cancers, the manipulations required to produce these animals, and the odd characteristics of the resulting tumors, make extrapolations from these experiments to the clinic difficult.

In this issue of the Journal, Holland et al. (17) report the successful implantation in nude mice of architecturally intact DCIS taken directly from patients. Remarkably, in nearly 85% of cases, DCIS survival was observed for nearly 3 months, with appropriate light microscopy architecture reflecting the original histopathology.

There are as many unanswered as answered questions from this investigation. How long will these implants survive if left intact in the nude mice (as opposed to killing the mouse for tumor retrieval)? If left intact, will some (or all) of these lesions progress to invasive cancer? Why was survival for those lesions that already contained invasive cancer at the time of implantation compromised when compared with DCIS? Will those grafts that did survive go on to develop or display metastatic potential? Does the nude mouse host adversely affect this model in regards to the clinical situation?

Regardless, their findings are an exciting step toward our understanding of the steps required to progress from one stage of malignant transformation to the next, and this paper opens an exciting era, ripe for technologic exploitation. Can this model be used to more rapidly determine what histopathologic or, more importantly, what biologic features predict which DCIS lesions are likely to progress and which are silent? Can this model be used to insert various genes of interest (transforming or tumor suppressive) to determine their effects on early, noninvasive cancer?

The authors have made a first step toward asking some of these questions by investigating the most obvious markers (histopathology, estrogen receptor, and cellular proliferation) and the influence of exogenous estrogen. Again, more questions: Is the effect of exogenous estrogens in this model similar to what one sees in the clinic? Can the model be used to test the effects of novel chemopreventive agents that might then be more rapidly moved to the clinic?

Yes, there are many questions, but they are all good ones. This study may well be seen as a landmark in preclinical studies of breast cancer, providing us for the first time with the opportunity to gain insight into the early stages of the spectrum of transformation of normal breast cells to frank malignancy. Ultimately, demonstration of clinical utility of novel therapies requires clinical investigations. However, these may be performed substantially more efficiently applying results obtained from this...
model. The authors are to be congratulated for this exciting work. As a former mentor of mine would say after a particularly interesting laboratory meeting: “Let’s go!”

References

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