Evolution of Knowledge Related to Breast Cancer Heterogeneity: A 25-Year Retrospective

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This Commentary will put into perspective two of our articles that appeared in the Journal of Clinical Oncology in 1983 that contributed to the evolution of knowledge related to breast cancer heterogeneity.1,2 We will consider those articles within a broader context that includes some of our other contributions to that aspect of breast cancer biology.

Until about 1960, physicians paid little attention to the proposition that breast cancers might be heterogeneous. Although pathologic examination clearly indicated tumor heterogeneity, they considered the varied outcomes of patients following surgery to be the principal indicators of that phenomenon. Anecdotal information, however, began to indicate that older patients fared better than younger patients, large tumors led to a poorer prognosis than did small tumors, and women with positive axillary nodes did worse than those with negative nodes.

During the late 1960s, we began to conduct clinical investigations that were aimed at defining predictors of outcome more precisely. Those studies eventually led to a greater awareness of the significance of tumor heterogeneity. In 1970, we were the first to report findings that we obtained from more than 2,000 breast cancer patients in several randomized trials that demonstrated that a greater incidence of treatment failure was associated with tumors that presented with increasing numbers of positive axillary nodes. Our data demonstrated the propriety of grouping women according to how many of their axillary lymph nodes were tumor positive, that is, one to three or four or more.3,4 That categorization subsequently became universally accepted and continues to be an important prognostic factor. Other pathobiologic factors have been found to be more effective in determining therapy.

During the late 1960s, tumor size also began to be viewed as a marker of breast cancer heterogeneity. Neoplastic surgery was based on the concept that the time of a tumor’s existence, as measured by size, determined surgical success5 and that the earlier the operation (ie, the smaller the tumor), the better the chance for a cure. In an effort to determine the validity of that concept, we obtained information that led us to conclude that size did not necessarily relate to either “earliness” or “lateness” of a tumor and that outcome was related to tumor and/or host factors.6 Our findings eventually led us to formulate a hypothesis that was alternative to the one on which Halstedian radical cancer surgery was based.

The results of clinical trials conducted to evaluate that hypothesis ultimately led to the acceptance of breast-conserving surgery in the mid-1980s.7

Another issue that was debated during the late 1960s related to the general belief that tumor location influenced prognosis. At that time, the presence of an inner quadrant or subareolar lesion evoked pessimism because it had been demonstrated that such tumors metastasized to internal mammary lymph nodes. As a consequence, not only was the prognosis apt to be worse, but more extensive radical surgery was also required.8 Information that we reported in 19699 from more than 1,000 patients failed to demonstrate that primary tumor location influenced prognosis. On the contrary, our findings showed that it was the biologic nature of a breast cancer, rather than its location, that was more important for making such a determination. Thus, there was no justification for anticipating that a surgical approach based on tumor location would be more rewarding than would any other approach. Those findings played a significant role in the elimination of radical internal mammary lymph-node dissection for the treatment of breast cancer.

While our investigations were in progress, others were establishing the foundation from which the modern era of steroid hormone action would arise. With the discovery of estrogen receptors (ER) and their identification in mammary tumor cells,10 the determination of the presence of ER in breast cancers began to achieve clinical importance. It was anticipated that two categories of tumors would be identified: those with ER (which could subsequently benefit from endocrine therapy) and those without ER (which would not). It was also believed that ER status could serve as a prognostic indicator and that women whose tumors contained ER would fare better than those whose tumors did not. Those findings, and the 1962 discovery of the drug tamoxifen, whose antiestrogenic properties had already been proven in animal investigations,11 were to have a profound effect on future research related to both the therapy and the prevention of breast cancer.

Although several studies were conducted with tamoxifen in a few patients with metastatic disease during the 1970s,12-14 ER determination had not been carried out in any of those trials. With the increased use of tamoxifen for the management of advanced breast cancer, the need for more information about tumor ER...
became evident. Because there was no commonly agreed-on methodology for determining ER, measurements were unreliable. Although the qualitative estimation of ER as to whether a tumor was ER positive or ER negative was more accurate, quantitative levels were less reliable. Nonetheless, because some benefit from tamoxifen was being observed, there was justification for evaluating tamoxifen and hormone receptors in women with “earlier” disease.

Because of our previous involvement with breast cancer clinical trials, we were prepared to conduct such a study. In September 1972, we had initiated the first large randomized trial to evaluate the worth of prolonged chemotherapy (l-phenylalanine mustard) administered postoperatively to axillary node-positive women with operable breast cancer. Our 1975 report was the first to demonstrate a benefit from postoperative chemotherapy. Consequently, there was a strong rationale for us to determine whether tamoxifen, when given with chemotherapy, would enhance the benefit obtained with chemotherapy alone.

Consequently, in January 1977, we began enrolling women on the first randomized trial conducted with that aim. In that study, both tumor ER and progesterone receptor (PR) values were required for all patients. To ensure the validity of the correlation between receptor values and clinical response, a program of quality control for receptor determination was established. Our second article was prompted by the need for more information about the distribution of tumor ER or PR. Consequently, in that article, we examined the distribution of each receptor according to three characteristics: age, PR within a defined ER range, and concordance of tumor ER and PR levels. In addition, we ascertained the link between receptor level and number of axillary nodes. We also presented a series of seminal findings, the most important of which was the first confirmation of the biologic hypothesis that ER and PR could predict response to tamoxifen when administered with chemotherapy. Because that information had been derived from a randomized trial, it was the first that could be viewed as being unbiased.

Using statistical models that controlled for other known prognostic factors, we were the first to conclusively demonstrate that therapeutic response was related to hormone receptor level. Moreover, when we measured ER and PR simultaneously, the response to tamoxifen therapy was more directly related to the level of PR in a tumor than to that of ER (i.e., although both ER and PR levels were independently prognostic of outcome, the latter was a better predictor of response to tamoxifen).

When quantitative levels of ER and PR were examined, these were found to be positively associated with each other. Age correlated positively with quantitative levels of ER and PR, such that more younger patients had tumors that were qualitatively negative for ER and PR. In younger women whose tumors were qualitatively receptor positive, with $\geq 10$ fmol/mg cytosol protein, quantitative levels were much lower than those in older women. Aside from demonstrating the beneficial effect from tamoxifen in certain subsets of patients and the lack of benefit in others, the data that we obtained were the first to emphasize the importance of knowing quantitative ER and PR tumor content.

When all known prognostic factors were controlled for, multivariate analyses did not negate the apparent age or PR-treatment interactions. Although ER level was found to exert a strong prognostic effect, when the PR-treatment effect was controlled for, the ER-treatment effect was negligible. Thus, effectiveness of treatment with tamoxifen and chemotherapy appeared to be more dependent on the PR of tumors. Those analyses provided evidence for a heterogeneity of patient response to tamoxifen and chemotherapy that was both age- and PR-dependent. Unfortunately, despite our findings related to PR, the use of that marker has been largely neglected in clinical practice until recently, when it was employed in studies comparing the benefits of tamoxifen with those of anastrozole, a drug that interferes with estrogen production, and in studies related to tamoxifen resistance.

After the appearance of our two articles in the JCO, we continued to investigate the relationship between hormone receptors and breast cancer heterogeneity. In late 1983, we provided the first information to indicate the value of both ER and PR for estimating the outcome of axillary node-positive breast cancer patients who had received postoperative adjuvant chemotherapy without tamoxifen. Having previously noted that ER status strongly correlated with pathologic markers of tumor differentiation such as nuclear grade (NG) and histologic grade, we related those markers to the outcome of node-positive patients who had received adjuvant chemotherapy either alone or with tamoxifen. Our findings showed that, when related to ER, PR, or NG, disease-free survival and survival were almost identical in each of the treatment groups. We also noted that, when used in combination with either or both receptors, NG was a better predictor of outcome than was either receptor alone and that the use of an increasing number of prognostic markers was associated with a more favorable outcome in both groups.

Although we had provided information about the prognostic significance of hormone receptors in node-positive patients, it was not until the late 1980s that we began reporting findings from patients with negative nodes. Between 1989 and 2004, we published reports of findings from three randomized trials involving almost 4,000 women with negative nodes and ER-negative tumors. The findings from those trials demonstrated that outcomes were similar in all age groups of women who received chemotherapy. However, when the chemotherapy patients were compared with those who had received placebo, the benefit from chemotherapy decreased with increasing age. This circumstance was the result of a better outcome associated with advancing age in the women who received placebo rather than the consequence of a poorer outcome resulting from chemotherapy. The results from one of those trials demonstrated no benefit from tamoxifen in women with node-negative, ER-negative tumors and settled the issue in that regard.

Between 1989 and 2004, we also published reports from two randomized trials involving 5,000 women with node-negative, ER-positive breast cancers. The findings from those studies after long-term follow-up have particular relevance to our 1983 JCO.
articles in that they illustrate the changes that have occurred in the clinical management of breast cancer as a consequence of information obtained about breast cancer heterogeneity. For example, the results from one of those articles demonstrated that age and menopausal status are not synonymous in that they have different clinical and biologic connotations. As a consequence, we considered which of the two might be more precise for estimating the benefits from the use of adjuvant chemotherapy and tamoxifen. When we estimated recurrence rates using age at surgery as a continuous variable, it was evident that age was preferable. In addition to relating patient outcome to age and menopausal status, our 2004 results confirmed our 1983 findings in that they showed that the quantitative concentration of tumor ER increased with age at surgery.

From the findings that we obtained during the past 25 years, which had their origins in our 1983 articles, we formulated several propositions of current clinical significance. The first of these asserts that information about the complex nature of the heterogeneity that exists both within and between breast cancers, particularly as related to therapy, needs more recognition by clinicians. It must be appreciated that a tumor is highly likely to be composed of cells having more than one histologic type—cells that, though predominantly of one nuclear grade, might also be of other grades associated with different nuclear size, pleomorphism, prominence of nucleoli, mitosis, and DNA indices. There might also be cells that are ER and/or PR positive or that have other biologic characteristics such as HER-2 that relate to tumor growth and response to therapy.

Second, we maintain that it is no longer appropriate to use age, menopausal status, tumor size, and lymph-node involvement alone to determine prognosis or to define appropriate systemic therapy. Because those indicators are imprecise surrogates of characteristics that govern tumor growth, they should be used only in conjunction with the established pathobiologic predictable factors noted above.

Third, we contend that, because the effectiveness of postoperative systemic therapy in eradicating undetected metastases is governed by the pathobiologic characteristics of metastatic tumor cells, using therapy on the basis of the nature of cells in the primary tumor is valid only if the cells in both that tumor and its metastases are concordant. Consequently, it is the heterogeneous pathobiologic characteristics of metastases that are responsible for differences in response to therapy. While host and tumor factors that influence metastases have been the target of investigation for more than 50 years, there is justification for expediting investigation into that aspect of tumor biology.

Finally, we wish to emphasize that because of profound tumor and host heterogeneity, using overall results from one particular study to make therapeutic decisions for a specific patient is tenuous. Such heterogeneity must be taken into consideration when new treatment strategies are planned and when the results from one study are compared with those from another.

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REFERENCES


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