ciated with an increased risk of breast cancer. Dietary behavior plays a critical role in the earlier and earlier onset of menarche in U.S. girls. Postponement of the normative menarchal age would do as much as any other available intervention to lower future rates of breast cancer. Research is needed to determine what menarchal age optimizes lifelong health and what diet-exercise behavior would make this age a social norm. To give our great-granddaughters and their great-granddaughters even better chances of avoiding breast cancer, we should also seriously consider the viability of social and health policies to encourage young women to bear children in their late teens and early twenties and provide the necessary support for young mothers to complete their education and establish their homes and careers.

An intermediate preventive approach that would not require a change in social patterns involves hormonal manipulation by drugs. The objective of this approach is to limit and regulate circulating levels of reproductive hormones by pharmaceutical control of ovarian function from puberty to menopause except for intervals set aside for planned pregnancies. This approach is based on the observation that breast cancer risk seems to be associated with the total number of ovulatory cycles in a woman's reproductive years. It would be an expensive intervention to apply, however, and few countries could afford lifetime drugs and medical supervision for large numbers of women.

Given the likelihood of lifetime benefits from low-fat diets, the results of the WHI and related research hopefully will tell us that cancer, as well as heart disease, can be prevented in future generations of women in at least some countries by implementation of informed national agricultural and social policies.

The Development of Biological Therapies for Breast Cancer

Marc E. Lippman

Invasive breast cancer is overwhelmingly the most common serious malignancy of women, affecting approximately one woman in nine. Not only has the true age-corrected incidence of the disease increased over the past 50 years but, with the continued aging of the population, the prevalency of the disease will continue to increase as well. Although enormous progress has been made in detection and treatment of localized (nonmetastatic) disease, there has been relatively modest progress in the treatment of advanced disease—indeed, more than 40,000 women will die this year as a result of metastatic breast cancer. New therapeutic approaches are clearly needed. Here I briefly summarize the various options available for more effective treatment of metastatic breast cancer and then consider in some detail new therapies that are based on an improved understanding of the biology of the disease.

There are four approaches that may lead to more effective treatment of metastatic breast cancer. First, better use of existing chemotherapeutic agents is likely to help. Autologous bone marrow transplantation and the use of cytokines that stimulate the bone marrow may allow administration of substantially increased dosages of cytotoxic drugs. Improved response rates may also be achieved through the use of agents that attack drug resistance mechanisms or agents that potentiate the activity of antimetabolites such as 5-fluorouracil. Second, continued development of naturally occurring cytotoxic agents such as taxol may also help. Third, immunological approaches such as adoptive immunotherapy (the administration of immune cells with antitumor activity) or the development of tumor vaccines may prove useful. Fourth—and the subject of this perspective—better therapies may be developed through rationally designed biological agents that attack specific proteins responsible for the malignant properties of cancer cells.

Although it is widely accepted that cancer cells arise as a result of a series of genetic insults that activate or inactivate specific genes, the gene products responsible for the malignant phenotype remain largely unknown. In general, this phenotype is characterized by the ability to (i) grow unrestrictedly, (ii) invade across basement membranes, (iii) metastasize to distant sites, and (iv) adapt rapidly at the genome level to environmental changes, a feature most commonly manifested as the acquisition of drug resistance. The proteins responsible for the expression of these lethal properties are likely to be good candidates for therapeutic attack.

Some insight into the most appropriate protein targets for breast cancer therapy may emerge from a consideration of the prognostic variables and response variables shown to be of value in clinical practice. Prognostic variables are measurements (on patients or on their tumors) that predict whether a patient will be cured of her cancer or undergo a recurrence after local therapy. Response variables are measurements that predict whether a therapy will work (or has worked). It seems reasonable to assume that the more perfectly a prognostic or response variable is associated with a particular disease outcome, the more likely it is to contribute directly to disease pathogenesis. That is, more closely linked variables are more likely to be causative than associative and therefore better targets for biological therapy.

The traditional prognostic variables for breast cancer include TNM status (tumor size, nodal status, and the presence and site of metastasis) as well as nuclear and histologic grading. In fact, pathologic breast cancer staging (the combination of specific T, N, and M characteristics into discrete groupings) still provides one of the most reliable methods of predicting disease outcome. Measurement of estrogen and progesterone receptors is another source of prognostic information for breast cancer. When these proteins were initially introduced into the clinic over 20 years ago, they were used as response variables (predictors of the likelihood of response to endocrine therapy), but shortly thereafter they were shown to also provide prognostic information. Patients whose tumors express these hormone receptors have a better overall survival rate independent of whether they receive endocrine therapy. Conversely, S-phase analysis, a cytometric method that allows direct measurement of tumor cell growth rates, was initially introduced into the clinic as a prognostic variable but is now recognized as a response variable. Patients with more rapidly growing tumors (a higher percentage of cells in S-phase) are more likely to respond to specific forms of cytotoxic chemotherapy. The problem with these variables, however, is that they do not suggest themselves as therapeutic targets in their own right. What are needed are specific proteins whose expression directly contributes to the malignant process.

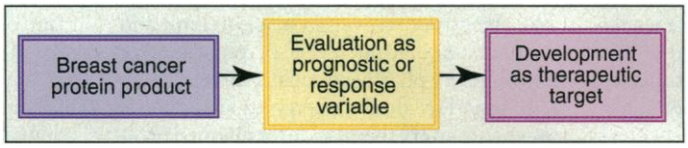
Over the past 5 years, a number of proteins have been shown to participate in the aberrant growth of breast cancer cells. These proteins include several families of cell surface growth factor receptors and their cognate ligands [the epidermal growth factor (EGF) receptor superfamily, the insulin-like growth factor (IGF-1) family, and the fibroblast growth factor (FGF) family]. Other proteins potentially involved in the invasive or metastatic phenotype have also been

The author is at the Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, DC 20007.

identified in breast cancer cells and tumors. Among these are p53 (a transcriptional regulator with tumor suppressor properties); nm23 (a putative metastasis suppressor); proteins involved in digestion of the basement membrane, including the collagenases, cathepsins, and plasminogen activators as well as their cognate inhibitors; and proteins involved in stromal-epithelial interaction, including several associated with angiogenesis. All of these proteins have been shown to have some prognostic power, although to date there has not been a multivariate analysis of significant size and scope to rank them in importance. Even if such analyses were successful, there are other justifications for individual measurements of these proteins. For example, as already illustrated for estrogen and progesterone receptor determinations, independent of prognostic significance, these proteins may be important as response variables.

The erbB2 protein is a transmembrane receptor (a member of the EGF receptor superfamily) whose extracellular domain is shed by many cancer cells. Measurement of this protein fragment in blood or urine is currently under evaluation as a response variable for monitoring the efficacy of chemotherapy. Similarly, recent determinations of basic FGF concentration in blood, urine, and cerebrospinal fluid suggest that this protein is detectable in patients with active metastatic breast cancer and that changes in its concentration may correlate with response to therapy.

A tight association between a specific protein and disease prognosis or therapeutic outcome increases the likelihood that a therapy disrupting the expression or function of that protein will have anticancer activity. Although none of the proteins shown to provide prognostic information for breast cancer has yielded a successful clinical therapy thus far, a gratifying number of examples are in final stages of preclinical testing or are even further along in development. Monoclonal antibodies to erbB2, for example, are now in early clinical trials. Preclinical studies indicate that treatment with such antibodies can sensitize certain tumors to cytotoxic agents such as platinum. Antibodies to erbB2 have also been coupled to a variety of toxins and have shown anticancer activity against human breast cancers growing in nude mice. Similarly, monoclonal antibodies to the EGF receptor are in clinical trials. Preclinical studies indicate that these antibodies display antitumor activity both on their own and in a synergistic manner with classical cytotoxic agents.



Identifying targets for biological therapies. Breast cancer proteins that reliably predict disease outcome or therapeutic response are likely to contribute to disease pathogenesis and, therefore, represent good candidate targets for biological therapies.

The development of an angiogenic response is mandatory for malignant progression of all epithelial tumors, including breast cancer. Recent experiments indicate that biochemical quantification of capillaries at the primary tumor site can accurately predict metastatic spread. Other work suggests that heparin-binding growth factors such as the FGF family and pleiotrophins are likely to be important in promoting tumor angiogenesis. Antibodies to FGF have been coupled to toxins and have shown potent anticancer activity toward human breast cancers growing in nude mice. Clinical trials with these antiangiogenic molecules are likely to begin soon. Agents that bind tightly to heparin-binding growth factors and sequester these factors outside the cell, such as suramin and pentosan polysulfate, have already entered clinical trials, and some anticancer activity has been reported. Similarly, the angiogenesis inhibitor AGM1470, a derivative of a naturally occurring fungal product that substantially inhibits endothelial cell growth, has also entered clinical trial.

Like most other cancer therapies, biological therapies will undoubtedly have undesirable toxicities because the proteins they target may not be unique to malignant cells. Nonetheless, these therapies appear sufficiently promising to warrant thorough clinical investigation.