Current Approaches to Breast Cancer Prevention

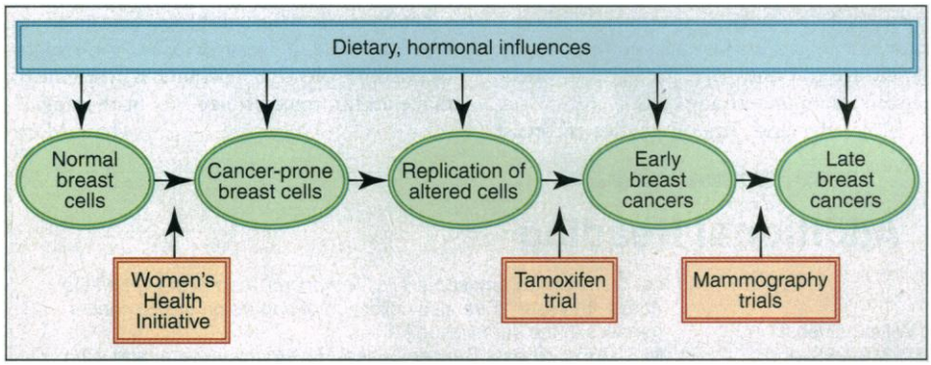
Maureen Henderson

One of the most dramatic features of breast cancer is the disparity in incidence rates between highly westernized and nonwesternized countries. Women born and raised in the United States are at least five times as likely to get breast cancer as women born and raised in Japan. But Japanese women increase their risk if they live in rapidly westernizing Japanese cities or emigrate and live in the United States. As is true with coronary heart disease, differences in diet are thought to be a major underlying factor in the different incidence rates of breast cancer, particularly among postmenopausal women.

Breast cancer is believed to take 3 to 30 years to develop. During this time there are at least three opportunities to interrupt its natural history. The first and most generalizable opportunity is to prevent or limit cancer-causing exposures that would trigger the self-perpetuating replication of damaged breast cells. The second opportunity is to reverse, or at least contain, the growth of cells that have not yet reached a diagnosable precancerous state. The third opportunity is to remove or kill recognizable precancerous or very early cancerous lesions before they cause clinical symptoms.

For the first time in history, healthy women in the United States and several other countries have the opportunity to participate in trials designed to test the success of preventive interventions targeted at each of these three stages in the natural history of breast cancer.

The Women's Health Initiative (WHI), scheduled to enroll the first of its participants in 1993, will test the hypothesis that 10 years of a diet that is very low in fat and high in fruits and vegetables will lower breast cancer incidence in postmenopausal women. The WHI will also investigate whether postmenopausal replacement hormones prevent coronary heart disease and osteoporotic fractures, and it will help to clarify the circumstances in which these hormones increase the risk of breast and endometrial cancers. The WHI will randomize about 70,000 women into the low-fat diet trial, the hormone trial, or both. The hormone trial will test the benefits of estrogen alone or in combination with progestin. Combined hormones are being prescribed more and more often because they do not increase the risk of endometrial cancer as much as estrogen alone, but their impact on coronary heart disease, osteoporosis, and breast cancer is virtually unknown. All the women in the hormone and diet trials will have an opportunity to participate in a third trial to learn the extent to which supplements of calcium and vitamin D can prevent osteoporotic fractures.



Breast cancer prevention trials. The three major prevention trials described in the text can be viewed as targeting essentially three different stages in the natural history of breast cancer. Preventive strategies that target early events in disease development will require trials of longer duration than those that target later events.

The WHI will be a long-duration trial because it intervenes at the earliest possible stage in the natural history of breast cancer; the success of the interventions will be measurable only when the natural history has been completed. Women who enter the trial will be followed for an average of 9 to 10 years.

The "Clinical Trial to Determine the Worth of Tamoxifen for Preventing Breast Cancer" will take only 5 years to complete because it intervenes much later in the natural history of the disease. This trial targets what is assumed to be an established proliferative carcinogenic process associated with a relatively high risk profile. The 16,000 women who volunteer for this trial (about one-quarter have already been recruited) will help to demonstrate whether tamoxifen prevents clinical cancers and, if so, at what personal cost.

Tamoxifen is an anti-estrogenic drug of proven benefit as an adjuvant treatment for certain breast cancer patients. The idea that tamoxifen might be useful in prevention is based on the observation that primary breast cancer patients treated with tamoxifen appear to have a lower risk of developing a new cancer in the opposite breast. The drug does cause side effects, however, and, although most are minor, a few are sufficiently serious to restrict its potential application to women at a high risk of breast cancer. The trial includes women 60 years of age and older (considered to be at high risk because of their age) and younger women judged to have reached at least the same level of risk for other reasons. In theory, all participants are at high enough risk to have ongoing, albeit invisible, carcinogenic activity somewhere in their breast cells.

The third preventive opportunity during breast cancer's natural history is to detect precancerous lesions or very early cancers and treat them before they progress further. The Canadian National Breast Cancer Screening Study is comparing the costs and benefits of annual clinical breast examination and mammography with the costs and benefits of annual clinical breast examination alone. This study includes approximately 90,000 women. Early results suggest that the study is raising some very critical questions: Should mammography be routinely used before the age of 50? What are the cost and marginal benefit of adding annual mammography, or mammography every 2, 3, or 5 years, to a good annual clinical breast examination?

A collaborative group of Chinese and U.S. investigators has recruited 360,000 Chinese women into a randomized trial to assess the impact of routine monthly breast self-examination (compared with no self-examination) on breast cancer mortality. Mammography is not generally available in China and it will be a national advantage if routine breast self-examination can be used to lower breast cancer death rates in the future.

All these trials focus on the prevention of breast cancer in postmenopausal women who are at the highest, most imminent risk of disease. Ideally, breast cancer should be prevented earlier—before the carcinogenic process begins. Diet and dietary fat metabolism are considered to be important factors in cancer prevention early in reproductive life.

Early age at menarche (first menstruation) and delayed first pregnancy are factors asso-

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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

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