

CA

Breast Cancer Update: Encouraging Trends...Many New Questions

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Two breast cancer issues of particular interest that have arisen in the scientific literature over the past few years are discussed in this issue of *CA*: The trend in certain countries toward a reduction in breast cancer mortality,¹ and the possibility of reducing the incidence of breast cancer through chemoprevention.²

Reduction in Breast Cancer Mortality

The reduction in mortality appears to be consistent (about 1% to 2% annually) in countries with a higher incidence of breast cancer, such as the United States, Canada, and the United Kingdom, whereas in countries with a lower incidence, such as Italy, no such reduction in mortality has yet been observed, at least on the national level. Some regional reductions have been noted, such as in the Italian district of Tuscany, which may correspond to regional differences in quality of health care.

The trend toward lower mortality rates might be related to three factors: lifestyle, early diagnosis, and quality of treatment. Changes in lifestyle, such as in diet or reproductive behavior, may be partly responsible for lower death rates. The trend might also be due to variations

in disease stage at diagnosis, which, in turn, are caused by women's greater attention in recent years to changes in the breast, as well as to the widespread use of screening mammography. The third possibility is that reduced mortality is due to improved treatment, particularly increased use of systemic adjuvant therapies.

What can we do to ensure that these early successes continue? To evaluate the possible preventive effects of changes in eating habits or other etiological factors related to environment and lifestyle, we need more scientific knowledge and we need to examine the results of interventional trials that require many years before completion. This area of research, then, despite its importance, will not yield definitive answers about effective preventive measures for quite some time.

By contrast, the extension of screening programs that can significantly modify the disease-stage distribution of breast cancer can have a more immediate impact on mortality.

SCREENING MAMMOGRAPHY

Today, mammography is still the only valid screening test for breast cancer. Other imaging techniques can be used only as complementary measures because of their higher cost and limited specificity for preclinical lesions.

Over the next few years, mammographic screening will be increasingly performed using digital techniques, which afford superior and more reliable quality and facilitate computer-aided diagnosis.³

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In areas of the world that do not have sufficient numbers of expert radiologists for mammography screening and interpretation, computer-aided diagnosis can be particularly useful. Moreover, many women are denied the life-saving effect of obtaining an early diagnosis because they live in areas where screening programs are not available or because they are outside the age range for which screening is provided.

Many questions remain about the application and impact of mammographic screening, such as:

- What is the real impact of mammographic screening on premenopausal women, and which is the best protocol?
- How effective is mammographic screening for women who are at high risk for breast cancer due to family history?
- What is the impact of mammographic screening in open health services, where a woman can come on her own initiative for an examination at a mammographic unit that is not dedicated exclusively to screening?

Unfortunately, the resources for research on breast cancer screening are limited, because it is thought that other preventive measures will be more profitable in the long term. There is a risk, therefore, that we will not be able to exploit the benefit of early diagnosis to its fullest potential.

IMPROVED TREATMENT FOR BREAST CANCER

The third factor that could be contributing to a reduction in mortality in countries with a high incidence of breast cancer is an improvement in treatment, especially in the widespread use of systemic adjuvant therapies. In this issue, Fisher reviews the use of systemic adjuvant therapy on the occasion of the 40th anniversary of the National Surgical Adjuvant Breast and Bowel Project (NSABP), focusing on the treatment of patients with early-stage (node-negative) breast cancer.

Results of NSABP studies indicate that, at present, all patients with negative lymph nodes can benefit from adjuvant chemotherapy, except perhaps, those with tumors smaller than one centimeter in diameter. Women with these very small lesions certainly have a better prognosis, even without adjuvant therapy, although valid studies have not yet been conducted with this subset of patients.

The next steps in the advancement of medical therapy, therefore, are not likely to further reduce mortality, but rather will focus on more selective uses of therapy.

We have already observed that a protocol of intensive diagnostic follow-up⁴ results in earlier diagnosis of bone and intrathoracic recurrences, but without any impact on survival. These observations suggest that even the most intensive therapy of metastatic breast cancer has only limited effects on survival.

Chemoprevention for Breast Cancer

Turning to the issue of chemoprevention, the results of the NSABP P-1 trial with tamoxifen are of great interest for our future prospects. After about five years of follow-up, these researchers have shown a 49% reduction of the incidence of breast cancer in women at higher risk when assigned to treatment with tamoxifen (20 mg a day). Results of two European studies published last year—one by Veronesi et al, which looked at women who had undergone hysterectomies,⁵ and one by Powles and co-workers, which examined women with increased breast cancer risk because of family history⁶—are interesting, and puzzling, because they failed to confirm the preventive effect of tamoxifen observed in the NSABP P-1 trial.

It is not easy to explain the lack of effect of tamoxifen in the European trials. Among the various possible explanations that have been proposed,⁷ the differing characteristics of the study populations seems to us the most likely explanation.

The English study examined younger women with a higher risk of breast cancer because of family history. The Italian study examined women who had undergone hysterectomies and, in about 50% of the cases, bilateral ovariectomies. The Italian study states, interestingly enough, that a significant protective effect against breast cancer was observed among the subgroup of women who used hormone replacement therapy throughout the trial. This effect was not observed, however, in the English trial.

In conclusion, the results of the NSABP P-1 trial are very significant, raising high expectations and suggesting new research directions. Nevertheless, many important questions remain unanswered:

- Which women can benefit from tamoxifen? (Perhaps those at higher risk because of family history, although the English study seems to contradict this.)
- What is the optimal dose of tamoxifen, and how long should it be taken, keeping in mind the balance between benefits and adverse effects that cannot be ignored?⁸
- Are there other substances that could produce analogous results, perhaps with fewer adverse effects?

In any case, it is certain that today we have another powerful chemopreventive weapon with which to fight breast cancer. And there is no doubt that we are moving ever more to the left in the natural history of the disease, toward prevention. This means that we are always enlarging the pool of women affected, including women in good health. It is, therefore, ever more important to carefully evaluate the potential benefits of any preventive regimen against possible adverse effects. Ironically, negative side effects are generally more difficult to evaluate than benefits, as they are closely tied to the cultural context and the personal experience of the woman.

Cross-cultural and intercultural differences in women's attitudes toward preventive strategies have been reported.⁹ For example, in the United States,

women accept invasive procedures for breast cancer diagnosis much more readily than do European women (recall rates in women screened may vary, respectively, from 20% to 1.5%). Women in the United States also tend to believe that their risk of breast cancer is higher, compared with beliefs of European women.

Until now, health professionals, especially clinicians and epidemiologists, have been the primary decision makers in the development of breast cancer prevention policies. Nevertheless, a thorough understanding of women's perspectives is essential and should be incorporated into policy decisions that affect the lives and health of women around the world.

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