EDITORIAL

New Perspective on Cancer of the Contralateral Breast: A Marker for Assessing Tamoxifen as a Preventive Agent

Bernard Fisher, Carol Redmond

For most of this century, when a woman has had a primary breast cancer, issues have been raised regarding her opposite (contralateral) breast. One major and persistent consideration relates to how frequently a contralateral breast cancer might be expected to occur. Vigorous debate questions whether a woman's risk for such an event might be considered great enough to justify a prophylactic mastectomy or, at least in some circumstances (e.g., when the primary tumor is a lobular invasive cancer), whether a random biopsy of the contralateral breast should routinely be done. Deliberations have also taken place regarding how to distinguish between a metastatic lesion and a second primary tumor in the contralateral breast; whether the prognosis of a patient who has had a breast cancer is altered when a new primary tumor appears in the opposite breast; whether the first and second primary tumors were synchronous in origin but metachronous in expression or whether they were metachronous from their inception; and whether radiation therapy after removal of a primary tumor by mastectomy or lumpectomy increases the incidence of contralateral breast cancer.

Most of these issues have been either fairly well resolved or supplanted by more important ones. The contralateral breast of a woman with breast cancer has recently taken on new significance: It has assumed importance as a marker for assessing the worth of a putative breast cancer preventive agent. Because a patient with breast cancer is at increased risk for developing a primary tumor in the opposite breast, an agent that can decrease the incidence of second primary cancers deserves consideration for evaluation in a trial to test the hypothesis that the agent can prevent breast cancer in a "normal" woman at increased risk for such an event. This strategy is analogous to selecting for testing, in the adjuvant therapy setting, agents that have demonstrated efficacy in the treatment of systemic disease.

While several agents (e.g., a low-fat diet or retinoids) merit evaluation in breast cancer prevention, one particularly worthy of appraisal is the drug tamoxifen. Trials indicating the worth of this anti-estrogen in the treatment of patients with clinically detectable breast cancers are among the more successful efforts of the past decade in breast cancer management. Numerous studies have demonstrated the benefit of tamoxifen, first in reducing tumor recurrence and in prolonging survival when the drug has been used either as a single agent or in combination with chemotherapy for the treatment of advanced breast cancer and second as postoperative adjuvant therapy in stage I or II disease (*1-5*). Moreover, extensive information indicates that tamoxifen can be administered with good compliance and minimal toxicity during extended therapy, requisites as important as an agent's proven efficacy—especially when considering its use as a breast cancer preventive agent in normal women.

Various findings in the extensive body of literature about tamoxifen—its pharmacokinetics, metabolism, and antitumor effects in experimental animals and in humans—provide support for evaluating its worth as a breast cancer preventive agent. Animal studies indicate that tamoxifen impairs tumor initiation (*6*). When mice were treated with tamoxifen, carcinogen-induced mammary tumors did not appear. Investigations using a variety of models have evaluated the effect of tamoxifen on tumor promotion and have provided evidence that tamoxifen given after a carcinogen, but before the appearance of a tumor, prevents the occurrence of a palpable tumor as long as tamoxifen administration is maintained (*6,7*). Thus, if modern concepts of carcinogenesis as they relate to the process of initiation and promotion are applicable to human breast cancer, there seems to be sufficient cause for considering tamoxifen a possible preventive agent.

The overall findings from the Stockholm adjuvant tamoxifen trial, reported by Rutqvist et al. (*8*), in this issue of the Journal are particularly important. They supply additional information to the existing literature indicating that tamoxifen administration reduces the incidence of contralateral breast cancer, thus strengthening the justification for testing the drug in a large prevention trial. In the Stockholm trial, tamoxifen (40 mg/day for 2 years or 5 years) was given to node-negative and node-positive postmenopausal women. After a median follow-up of 7 years, 47 untreated and 29 tamoxifen-treated patients developed a second cancer ($P = .03$).

These findings are comparable with those obtained from the National Surgical Adjuvant Breast and Bowel Project B-14 study (*5*). In that trial, involving 2892 women with negative nodes and estrogen receptor-positive tumors, patients were randomly assigned to receive tamoxifen (20 mg/day) or placebo for

Received August 8, 1991; accepted August 8, 1991.

Supported by Public Health Service grants CA-12027, CA-37377, and CA-39086 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by grant R-13 from the American Cancer Society.

B. Fisher, National Surgical Adjuvant Breast and Bowel Project, University of Pittsburgh Medical School, Pittsburgh, Pa.

C. Redmond, National Surgical Adjuvant Breast and Bowel Project and Department of Biostatistics, University of Pittsburgh.

Reprint requests to: National Surgical Adjuvant Breast and Bowel Project Headquarters, Room 914, Scaife Hall, 3550 Terrace St., Pittsburgh, PA 15261.

at least 5 years. A recent update of findings (National Surgical Adjuvant Breast and Bowel Project: unpublished data) revealed that, after an average follow-up of 53 months, 55 second cancers were found in the contralateral breasts of the placebo-treated patients and 28 in the tamoxifen-treated patients ($P = .001$). Most important, a reduction in the incidence of second cancers was observed in women younger than 50, as well as in those 50 or older.

The Stockholm trial findings also coincide with observations from the British Cancer Research Campaign breast trial (*9*) and a Scottish study (*3*). In the British Cancer Research Campaign study, women younger than 75 years with stage I or II breast cancers were randomly assigned to one of four treatment groups (a 2 × 2 factorial design) to test the worth of tamoxifen (20 mg/day for 2 years) and cyclophosphamide therapy. After a median follow-up of 3 years, 4 months, seven contralateral cancers occurred in the tamoxifen-treated group and 18 in the control group ($P = .02$). The Scottish trial enrolled premenopausal and postmenopausal women less than 80 years old, with negative nodes, and postmenopausal node-positive women, all of whom received tamoxifen, 20 mg/day for 5 years (either from the time of surgery or at the time of first relapse). At the present time there is a clinical, but not statistically significant, reduction in contralateral breast cancer (Stewart HJ, Scottish Trials Office, Edinburgh: personal communication).

Thus, the results from the Stockholm, National Surgical Adjuvant Breast and Bowel Project, British Cancer Research Campaign, and Scottish trials indicate that, despite differences in study design, patient and tumor characteristics of the populations followed, and amount and duration of therapy, tamoxifen given for at least 2 years reduces the incidence of contralateral breast cancer. This finding supports testing that drug in a randomized trial to determine its efficacy as a breast cancer preventive agent in normal women at increased risk for the disease.

While the overall findings from the Stockholm trial are significant, the multiple observations obtained from extensive subset analyses might be viewed as hypothesis generating. Many of the findings, conclusions, and speculations in the report of the trial were derived from relatively few patients with contralateral cancers. Consequently, although they demand attention, it is our opinion that results from further investigations are necessary before their worth can be more completely ascertained. In that context, several of the findings in the Stockholm report, which are relevant to the conduct of a prevention trial, are noteworthy. Of particular significance is the finding regarding the duration of tamoxifen administration. Since the results of the Stockholm trial show no difference in the incidence of contralateral cancers whether the drug was given for 2 or 5 years (there were seven second cancers in each instance, the cumulative incidence rates were similar, and risk reduction continued after cessation of treatment), the authors of the report concluded that the administration of tamoxifen for only 2 years in a prevention trial might be adequate. They argued that administration for this length of time would be cost-effective and would result in fewer side effects and better compliance. While the merit of such a conclusion may ultimately be proven, we have reservations about it for several reasons.

Aside from the complex trial design, which makes it difficult to ascertain the comparability of the patients in the two groups and the relatively few events upon which the claims are based, results from at least one other study seem to contradict the Stockholm trial findings. Whereas the early results from the British Cancer Research Campaign trial (*9*) demonstrated a benefit from 2 years of tamoxifen therapy, a more recent update (*10*) indicated that, after a median follow-up of 7.8 years, the original benefits had not been completely sustained. There were 25 contralateral cancers in the control group and 22 in the tamoxifen-treated group ($P = .58$), and the reduction in contralateral cancers was evident only in postmenopausal patients (16 versus 8, respectively; $P = .08$).

Two studies, which employed tamoxifen for less than 2 years, failed to demonstrate a reduction in the incidence of contralateral breast cancers. In a recently reported Danish study (*11*), tamoxifen (30 mg/day) was given for only 48 weeks to postmenopausal women at high risk for metastases; after a median follow-up of nearly 8 years, there was no reduction in the occurrence of contralateral breast cancers. Similarly, in the Christie (Manchester) trial (*12*), where tamoxifen was given (20 mg/day) for only 1 year, there was no reduction in the incidence of second cancers after 10 years.

For the above reasons, it is our opinion that, in a prevention trial involving women at increased risk for breast cancer, 2 years of tamoxifen therapy is likely to be inadequate to achieve a prolonged reduction in the incidence of breast cancers. In a first-generation prevention trial, it seems more appropriate to use a dose and duration of therapy that have more convincingly demonstrated a reduction in the incidence of contralateral breast cancer than has the 2-year regimen reported in the Stockholm trial. Should a benefit be obtained with the longer tamoxifen therapy, subsequent generations of prevention trials can evaluate a variety of manipulations related to dose reduction and duration of therapy. In addition, the use of combinations of preventive agents can be tested. It is important that the first trial be a true test of tamoxifen so that, if no prevention of cancer is observed, it can be assumed that the finding was obtained using a sufficient amount of the drug—rather than because the drug dose was too low and therefore the trial was, in effect, no contest. In addition, a shorter duration of therapy may not only reduce or negate benefits related to cancer treatment but may also be less effective in reducing the incidence of cardiovascular disease and in inhibiting the progression of osteoporosis, both of which are important components of a breast cancer prevention study.

Another aspect of the Stockholm report that deserves further investigation is related to the estrogen receptor status of contralateral breast cancers in tamoxifen-treated patients. Data from the Stockholm study led the investigators to consider that women who receive tamoxifen are more likely to have contralateral tumors that are estrogen receptor negative. In our view, and in the opinion of Rutqvist et al. (*8*) as well, the number of contralateral cancers (seven in the control group versus three in the tamoxifen-treated group) is too limited for firm conclusions, and more information is needed to support the Stockholm findings. Certainly, information about the receptor content of tumors, which might be obtained in a tamoxifen trial, will be

of considerable biological importance and should lend support to or refute the Stockholm findings.

Results from the Stockholm trial indicating that incidence of contralateral breast cancers decreased only in patients at high risk for the development of metastatic disease are difficult to explain. The authors provide assurance that these results were unrelated to a greater preponderance of recurrent disease in the contralateral breast of high-risk patients. The findings were attributed to chance variation associated with subset analysis. Whatever the reason, the observations are not concordant with those from the National Surgical Adjuvant Breast and Bowel Project B-14 trial (*5*) involving patients considered at low risk for metastatic disease. Those low-risk patients, with negative nodes and estrogen receptor-positive tumors, perhaps more closely resemble subjects in a prevention trial than they do patients with more advanced disease.

We support the conclusion of Rutqvist et al. (*8*) that there is ample reason to initiate a controlled trial to test the value of tamoxifen as a preventive agent in healthy women at increased risk for developing breast cancer. British and other American investigators concur with that idea. In a few months, the National Surgical Adjuvant Breast and Bowel Project will implement a randomized trial in the United States and Canada to evaluate the efficacy of tamoxifen in inhibiting the occurrence of primary breast cancer, cardiovascular disease, and osteoporosis. Women who are cancer free but who have a clearly defined increased lifetime risk for breast cancer will be eligible for the trial.

Several concerns remain regarding the conduct of such a trial. It must be emphasized that the endorsement of a trial to evaluate the worth of tamoxifen as a breast cancer prevention agent does not provide the physician with an imprimatur to administer tamoxifen to women who do not have the disease, regardless of their degree of risk for developing it. Unfortunately, agents are all too often administered before their efficacy has been proven, merely because they are being tested in a trial. This practice is to be condemned. Clinical trials such as the breast cancer prevention trial are conducted to evaluate the worth of a therapy prior to its uncontrolled use on the population as a whole. While there is ample reason to carry out such a trial, its mere conduct does not, a priori, prove the efficacy of the agent being tested. Should an appropriate trial find the agent to be of no value, countless women would be spared taking, for years, an inappropriate therapy. This approach (conducting a randomized trial) for clinical problem solving represents the application of the scientific method and should not be replaced by therapeutic decision making based on political, biased, or populist considerations.

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