

P. Saline - bjji

FRIENDS OF THE NATIONAL INSTITUTE OF NURSING RESEARCH

August 19, 1993

VIA FACSIMILE: (202) 456-2461

Hillary Rodham Clinton
The First Lady
The White House
1600 Pennsylvania Ave., NW
Washington, DC 20500

Dear Mrs. Clinton:

As the architect of health care reform, I am writing to seek your participation in a one-time national event that impacts one of the largest segments of the health care delivery system - nursing.

As you may know, Secretary Shalala signed S.B. 1 in June, establishing the National Institute of Nursing Research, a long awaited accomplishment that signals the significant role nurses will play in improving the quality and containing the cost of health care. Nurse leaders decided there should be some forum to showcase this new Institute and the non-profit organization, *Friends of the National Institute of Nursing Research* (FNINR) was created to this end.

On November 17, 1993 nurses and health care leaders from across the United States will gather to celebration the creation of the Institute. I am writing to invite your participation in any manner possible. Events include a Congressional briefing session (9:00-11:00 am in the Capitol), a luncheon for 200 in the Caucus Room of the Russell Senate Office Building, and a VIP reception and *Nightingala* dinner at the Mayflower Hotel that evening. Your presence at any or all of the events would obviously add greatly to the program's impact. We have also invited the President to attend and hope you both could support the growing contribution of nurses, not only to the health and welfare of the Nation, but also the cost effectiveness and quality of health care.

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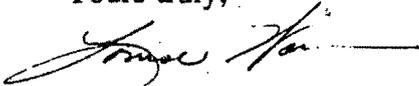
Hillary Rodham Clinton

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August 19, 1993

While this may seem short notice given the depth and breadth of your schedule, I would appreciate your every consideration. I will follow up with Patty Solis to see if you would be able and willing to attend this one-time only occasion.

Yours truly,



Louise Woerner
Chairman, Organizing Committee

LW:er

cc: Patty Solis
Scheduling Director
Office of Mrs. Clinton

OFFICE OF DOMESTIC POLICY

THE WHITE HOUSE

FROM THE OFFICE OF: **CAROL H. RASCO**
ASSISTANT TO THE PRESIDENT
FOR DOMESTIC POLICY

TO: _____

DRAFT RESPONSE FOR CHR BY: _____

PLEASE REPLY (COPY TO CHR): _____

PLEASE ADVISE BY: _____

LET'S DISCUSS: _____

FOR YOUR INFORMATION: _____

REPLY USING FORM CODE: _____

FILE: The Health Project (should be

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SCHEDULE: _____ started

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THE HEALTH PROJECT

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October 22, 1993

Ms. Carol H. Rasco
Assistant to the President
for Domestic Policy
The White House
Washington, DC 20500

Dear Ms. Rasco:

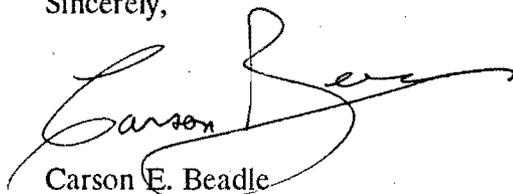
Your thoughtful letter of September 21, 1993 arrived on the eve of The Health Project's annual Board of Directors' meeting and planning session for this year's C. Everett Koop National Health Awards. As such, it had special impact and was appreciated by all in attendance. The visit later in the day by Alexis Herman, Michael Lux and Marilyn DiGiacobbe, further reinforced the Administration's interest in and support, for health promotion and disease prevention.

The Health Project has two distinguishing characteristics. First, is that honorees must demonstrate true cost savings from the improved health of its participants as a result of their health promotion/disease prevention program. Second, is that not only are worksite programs honored, but community programs are highlighted as well. This will be the first year in awarding community programs and the presentations in both categories will be made at the *Healthy Cities Conference* in San Francisco on December 8, 1993. It is Dr. Koop's plan to make the presentations as he did last year. Should you wish an appropriate person from the Administration to be in attendance, they would be most welcome.

As for worksite programs, The Health Project has been working closely with other organizations interested in spreading the adoption of these programs in companies around the nation. The goal has been to involve employers because of the role they serve as a meeting place, where peer pressure and ease of communications conspire to encourage people to utilize these programs and become healthier employees and families.

Should it be useful to you or your associates to discuss some of our findings as health care reform progresses, I would be pleased to be available as needed. Thank you again for your personal interest in The Health Project.

Sincerely,



Carson E. Beadle

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THE HEALTH PROJECT

*A Private/Public Organization That Encourages Better
Health Behavior and Informed Use of Health Care Services*

The Health Project (THP) is a private-public organization formed to bring about critical attitudinal and behavioral changes in the American health care system, so that providers and consumers employ its vast resources with increasing knowledge and understanding.

Health care has become a major concern of Americans as they struggle with complex issues such as cost and availability. However, the way we use health care services and the attention we give to our personal health is pervasive. Many organizations are working hard to develop programs that encourage better health habits and improved understanding of how to use health services more efficiently.

The mission of The Health Project (THP) is to seek out, evaluate, promote and distribute programs with demonstrated effectiveness in influencing personal health habits and the cost effective use of health care services. These programs have the objectives of (1) providing appropriate quality care, and (2) sharply reducing the alarming rate of health care inflation, by holding down unnecessary expenditures.

The project is a dedicated undertaking, capitalizing on carefully selected private and public health initiatives which have improved measurably the health status of Americans. It will store those proven programs in a repository so that corporations and community agencies may draw on them according to their needs, constantly improving and enlarging them through a widening user network centered in THP in order to improve health care outcomes throughout the country.

THP will focus on improved personal health care practices, as well as the efficient, effective and economical use of the system when it becomes necessary. Thus,

- consumers have a responsibility not to neglect or abuse their bodies and expect others to pay the costs, and that extravagant use of the system is not an inalienable right;
- providers must broaden their outlook by thinking as much in the broader, more positive terms of good health as they do in the specifics of curing sickness, assuming responsibility for educating their patients in good health care habits; while
- employers must play a leadership role in encouraging proper health care behavior and cultivating good health care purchasing practices by employees, with emphasis on good health incentives rather than scare tactics, so that those in poor health circumstances beyond their control are not discriminated against; and finally
- all parties to the health care process must recognize that improved personal health habits are not only desirable but also necessary in the prevention of the serious chronic illnesses which occur later in life; and that increasingly knowledgeable system utilization practices are essential to progressively higher health care standards.

The programs that make up the overall THP effort are not meant by any definition to distract from consideration by other groups of such hard issues as access to health care coverage, managed care, medical tort reform and insurance industry policies and practices. Instead, they will be positive, productive, well publicized action programs for optimum use of the nation's precious health care resources.

THE WHITE HOUSE

WASHINGTON

September 23, 1993

Hazel Cunningham, MPH

P6/(b)(6)

Dear Mrs. Cunningham:

File

Thank you for writing to me on the Breast Cancer Prevention Trial. I have had the enclosed response prepared by Dr. Broder of the National Cancer Institute, and I believe it along with the accompanying materials answers your questions.

Thank you for your interest in our women's health studies.

Sincerely,

Carol H. Rasco

Carol H. Rasco
Assistant to the President for
Domestic Policy

CHR:ram

BREAST CANCER PREVENTION TRIAL

The Breast Cancer Prevention Trial (BCPT) is an especially important investigation in that it may identify a practical method of preventing the development of breast cancer in a large number of women at increased risk of developing the disease. It will measure the preventive effects of tamoxifen on three major diseases in women -- breast cancer, heart disease, and osteoporosis -- and the potential risks for the development of side effects and other types of cancer. It is hoped that the BCPT will provide essential information for women and their physicians so they can make informed health care choices. The purpose of the BCPT is to increase the number of options available to women at high risk of developing breast cancer, so that they are not limited to the current options of intensive screening or prophylactic mastectomy.

The concept and program-planning activities for the BCPT were initiated and conducted in a deliberate and systematic fashion between 1984 and 1989. During the development process, the BCPT concept was carefully reviewed by and received unanimous endorsement from outside experts on three National Cancer Institute (NCI) scientific advisory bodies. The detailed protocol for this study was developed with input from medical experts and the public. Also, the U.S. Food and Drug Administration (FDA) conducted extensive reviews of the protocol and consent form, including a public hearing, before approving the use of tamoxifen in this research. Just as with estrogen replacement therapy, there is reason to expect that tamoxifen for breast cancer prevention has been introduced into clinical practice without results from a controlled randomized clinical trial. The BCPT allows the evaluation of tamoxifen for breast cancer prevention before there is a more general adoption of this practice.

Information from the trial is constantly reviewed to ensure that no participant is exposed to unnecessary health risks. When new data become available, action is taken to plan further studies, update the BCPT consent form (all revisions are sent to every enrolled participant so that she may reconsider her continued participation), and/or modify the protocol, as indicated by the results of the review. Scrutiny of new information by the BCPT Steering Committee and independently by the End Results/Safety Monitoring and Advisory Committee (ERSMAC) is also an ongoing process. ERSMAC members review all new information about tamoxifen as well as unblinded data from the trial. Based on this continuous monitoring, recommendations are made regarding protocol and consent form actions and study participation.

You question whether the trial would ever have received approval from FDA without strong data to suggest that postmenopausal women would receive protection from heart attacks as well as breast cancer. You also raise the question that a study by Drs. Trudy

Bush and Kathy Helzlsouer of Johns Hopkins University has shown that the number of heart attacks that would be prevented has been inflated.

In this context, encouraging information has recently been provided by the Stockholm Breast Cancer Study Group based on a trial of adjuvant tamoxifen therapy in early stage breast cancer patients. A copy of this report, published in the September 1, 1993, Journal of the National Cancer Institute, is enclosed.¹ The Swedish investigators observed a statistically significant 32-percent overall reduction in the risk of cardiovascular disease incidence. This benefit was observed after a 2-year period of tamoxifen therapy and was even greater when the tamoxifen treatment period lasted 5 years. The Stockholm results suggest that the observed reduction in incidence of cardiovascular events may eventually lead to a 20-percent reduction in cardiac mortality. The expectation of cardiovascular benefit is likely to be limited to women who are 60 years of age or older and consequently at high risk of cardiovascular disease. Other studies and analyses have previously suggested a decrease in cardiovascular morbidity or mortality associated with the use of adjuvant tamoxifen.^{2,3} With the availability of the newly published results from Stockholm, the evidence in favor of benefit from tamoxifen has been further strengthened.

The North American Breast Cancer Prevention Trial with tamoxifen, which is being conducted by the National Surgical Adjuvant Breast and Bowel Project, is only one of several large trials testing the worth of tamoxifen for preventing breast cancer. In the BCPT, approximately 30 percent of registrants fall into the age category associated with a reduction in cardiovascular morbidity. In the 60 and older age group, the cardiovascular benefit from tamoxifen may be as important as the breast cancer prevention potential of the medication.

¹Rutqvist, L.E., Mattsson, A. for the Stockholm Breast Cancer Study Group. "Cardiac and Thromboembolic Morbidity Among Postmenopausal Women With Early-Stage Breast Cancer in a Randomized Trial of Adjuvant Tamoxifen," Journal of the National Cancer Institute, 85:139801406, 1993.

²McDonald, C.C., and Steward, H.J. "Fatal Myocardial Infarction in the Scottish Adjuvant Tamoxifen Trial," The Scottish Breast Cancer committee. British Medical Journal 303:435-437, 1991.

³Early Breast Cancer Trialists' Collaborative Group. "Systemic Treatment of Early Breast Cancer by Hormonal, Cytotoxic, or Immune Therapy, 133 Randomized Trials Involving 31,000 Recurrences and 24,000 Deaths Among 75,000 Women," Lancet, 339:1-15, 71-85, 1992.

The results from the Stockholm Breast Cancer Study Group support the continuing effort to develop tamoxifen therapy for disease prevention. Tamoxifen prevention trials were first organized to test the main idea that tamoxifen prevents the development of breast cancer. This idea was strongly supported by the combined results from eight randomized, controlled clinical trials of adjuvant tamoxifen therapy, which showed a highly significant 35 percent reduction in new primary breast cancer in the contralateral breast. This is the only pro-active intervention known to prevent the development of new primary cancers in humans. The primary endpoint for the BCPT, and the one used for trial planning and size calculations, has always been decreased incidence of breast cancer. However, with the early evidence of cardiovascular benefits and the accumulating support from newly reported studies, it is as important as ever to follow study subjects carefully for cardiac endpoints as well.

You also express concern that postmenopausal women who are randomized to the placebo group are denied the protection from heart attacks and osteoporosis that hormone replacement therapy with estrogen would provide. Although replacement estrogen has been shown to be effective in reducing the risk of osteoporosis and possibly of cardiovascular disease, like tamoxifen, it also has been linked to an increase in endometrial cancer. There is some suggestion that it is linked to breast cancer as well. Unfortunately, estrogen replacement therapy (ERT), despite its widespread use, has never been fully evaluated in a clinical study of risks versus benefits. Scientists at the National Institutes of Health (NIH) have long recognized the importance of clarifying the risks and benefits of replacement hormones, and are supporting research to help answer questions about this issue. To that end, NIH has launched the Women's Health Initiative. One of the components of the Initiative is a randomized, placebo-controlled study of the utility of ERT to protect women against cardiovascular and skeletal morbidity.

BACKGROUND INFORMATION ON
THE BREAST CANCER PREVENTION TRIAL

The following is important information about the Breast Cancer Prevention Trial (BCPT) that addresses concerns about the administration of the drug tamoxifen to healthy women.

- o The Breast Cancer Prevention Trial is designed to differentiate between the real benefits and side effects of tamoxifen and those occurring by chance. It will provide information to estimate more reliably the true magnitude of benefit and risk in the general population -- which includes premenopausal women. It will also provide data useful for identifying those groups of women that would have the greatest net benefit from tamoxifen use.
- o The response from women concerned about breast cancer has been overwhelming. As of July 1, 1993 more than 45,000 risk assessments had been performed, identifying approximately 31,000 women eligible to participate in the BCPT based on their risk of developing breast cancer. At this time, over 8,000 women have been entered in the trial and are taking either tamoxifen or placebo. Many of the remaining eligible women are awaiting the additional screening exams and formal randomization to enter the trial. Early participation indicates that this is one of the most active research clinical trials that has ever been launched.
- o Women interested in participating in the BCPT receive a full discussion of the protocol as they are evaluated for eligibility and consider whether they want to participate. In general, this multistep process starts with an orientation session that provides introductory information and a brochure describing the BCPT. If interested in participation is sustained, the woman must sign up to receive a risk assessment and then participate in an assessment interview. A follow up appointment is used to discuss the risk assessment and to review the protocol in detail. If the woman chooses to continue, informed consent is obtained and medical examinations are completed to confirm eligibility.

- o The expectation that tamoxifen therapy is a reasonable intervention for breast cancer prevention is based on years of experience with this drug in controlled clinical trials. Clinical trial experience with tamoxifen in adjuvant therapy for breast cancer was summarized in the January 4, 1992, issue of Lancet. For 30,000 women in 40 trials, a 25-percent reduction in recurrence and a 17-percent reduction in mortality on average were observed. In addition, a 40-percent reduction in new breast cancers in the opposite breast (contralateral breast cancer) was reported. This benefit accrued to premenopausal as well as to postmenopausal patients. In the NSABP B-14 trial, there was an overall 50-percent reduction in new contralateral breast cancers. The data from this trial suggest an even greater benefit in reduction of contralateral breast cancers for premenopausal women than for postmenopausal women. In premenopausal women participating in NSABP B-14, there were no cases of endometrial cancer, and the rare case of thromboembolism responded to therapy. (A recently reported study from Sweden in the September 1, 1993 issue of the Journal of the National Cancer Institute showed no increase in thromboembolism associated with adjuvant therapy.) Other side effects were comparable in the pre- and postmenopausal groups. Consequently, it is projected that the potential risks of tamoxifen therapy in premenopausal women are fewer than those for postmenopausal women.

Another justification for including premenopausal women in the BCPT is that some are at an unusually high level of risk based on such factors as an extensive family history of breast cancer. Because many years elapse between a breast tumor's inception and its detection, a preventive intervention may be more effective if used earlier in life, especially before a tissue abnormality develops. In cases where risk is unusually high, it is unfair to deny younger women the opportunity to participate in reasonable preventive research, especially when many are at risk of undergoing such extreme procedures as bilateral prophylactic mastectomy.

- o Endometrial cancer. Data pertinent to the development of endometrial cancer occurring in the setting of long-term tamoxifen therapy have been provided by numerous studies, including NSABP b-14, using the same dose of tamoxifen as in the BCPT (20 mg per day). As stated in the consent form:

An increased risk of uterine cancer has been reported with the use of tamoxifen. Existing data from several large controlled clinical trials using 20 mg of tamoxifen show that 9 out of 3,097 women on tamoxifen developed uterine cancer (0.3 percent) versus 4 out of 3,091 women not treated with tamoxifen (0.1 percent). No deaths from uterine cancer were reported. The uterine cancers that have occurred have been at an early stage and are thought to be curable. The treatment for early stage uterine cancer usually involves a hysterectomy (surgical removal of the uterus) and may include radiation therapy.

It is important to note that this increased risk is similar to that recently reported in women on conventional hormone replacement therapy. Also noteworthy is the fact that none of the 437 premenopausal women on tamoxifen in NSABP's B-14 trial developed endometrial cancer.

Women in the trial will be required to have an annual pelvic examination. In addition, any reports of abnormal bleeding will be investigated immediately.

- o Thrombosis/embolism. Women on tamoxifen have an increased risk for developing phlebitis and blood clots. In the NSABP B-14 study, 3 of 1,414 women receiving placebo (0.2 percent) versus 18 of 1,403 women receiving tamoxifen (1.3 percent) developed deep-vein thrombosis or embolism. Two deaths occurred from complications of deep-vein thrombosis. Because of the information gained in NSABP B-14, women with a history of deep-vein thrombosis or embolism will be excluded from the BCPT.

- o Liver (hepatic) cancer. The follow up of 4,028 women who received tamoxifen for at least 2 years as participants in seven large randomized trials of adjuvant therapy for early stage breast cancer has been reported. Two patients developed liver cancers; both were participants in the Stockholm Trial, which prescribed high doses of tamoxifen (40 mg a day). (These cases were reported by Fornander et al. in Lancet in 1989.) Both cases appear to have occurred early in the course of treatment (within the first 2 years the women were in the study). To date, no liver cancers have been reported in women receiving 20 mg a day.

In the United States, clinical trials of tamoxifen in an adjuvant setting have required evaluation of liver lesions occurring during therapy (for purposes of determining whether they are a new primary liver cancer or a breast cancer that has metastasized to the liver). Liver biopsy for suspected first recurrence has been mandatory. When liver lesions have necessitated evaluation for recurrence, no primary hepatocellular cancer has been found.

- o Ocular toxicity. Pavlidis et al., writing in Cancer, June 15, 1992, reported four cases of ocular toxicity in 63 patients receiving tamoxifen at a dose of 20 mg a day for varying durations. The four patients who had taken tamoxifen for periods ranging between 10 and 85 months, had complaints of decreased visual acuity and finding of macular edema and dotlike paramacular deposits; in addition, one patient had subepithelial corneal opacities. These changes were reversible with discontinuation of medication, and acuity returned to previous levels, with slight residual visual impairment in one eye in one patient. The findings of Pavlidis et al. were inconsistent with previous reports of ocular toxicity that implied a much lower rate of occurrence. A study is being conducted to evaluate the true ocular effects of tamoxifen.

ARTICLE

Cardiac and Thromboembolic Morbidity Among Postmenopausal Women With Early-Stage Breast Cancer in a Randomized Trial of Adjuvant Tamoxifen

Lars E. Rutqvist, Anders Mattsson for the Stockholm Breast Cancer Study Group*

Background: Tamoxifen, which binds to estrogen receptors, is widely used as adjuvant therapy after surgery for early-stage breast cancer. Our previous randomized trial of adjuvant tamoxifen therapy for breast cancer showed a significant decrease of new, contralateral breast cancers in patients who received tamoxifen. Tamoxifen may also influence risk factors for cardiac and thromboembolic disease (e.g., serum cholesterol and antithrombin III). **Purpose:** The purpose of this study was to assess morbidity from cardiac and thromboembolic disease among 2365 postmenopausal patients with early-stage breast cancer in the Stockholm randomized trial of adjuvant tamoxifen (40 mg daily for 2 or 5 years) versus no adjuvant endocrine therapy. Patients were entered in the study from November 1976 through December 1988. **Methods:** In our retrospective study, the analysis of morbidity was based on data from a computerized, population-based register of hospital admissions and discharge diagnoses. Mortality data were obtained from the Swedish National Central Bureau of Statistics. In the Stockholm study, treatment with tamoxifen was initiated within 4-6 weeks of modified radical mastectomy or breast-conserving surgery including axillary lymph node dissection and postoperative radiation therapy to the breast. In that randomized trial, 755 patients at low risk of death from breast cancer received adjuvant tamoxifen only; 760 received no treatment. In addition, 628 high-risk patients were randomly assigned to receive adjuvant chemotherapy plus tamoxifen (173 patients) or postoperative radiotherapy plus tamoxifen (151) or, as a control, to receive chemotherapy (171) or postoperative radiation therapy (133), both without tamoxifen or other endocrine therapy. Median follow-up was 6 years. **Results:** Tamoxifen therapy resulted in a statistically significant reduced incidence of hospital admissions due to cardiac disease.

The relative hazard (tamoxifen for 2 or 5 years versus control) was 0.68 (95% confidence interval [CI] = 0.48-0.97; $P = .03$). In the randomized comparison of 5 versus 2 years of tamoxifen, there was a statistically significant difference favoring the longer treatment (relative hazard = 0.37; 95% CI = 0.15-0.92; $P = .03$). There was little difference between the tamoxifen and control groups in terms of admissions due to thromboembolic disease. **Conclusions:** These findings suggest that long-term adjuvant treatment with tamoxifen may result in substantial reduction of cardiac morbidity in patients with low risk of death from breast cancer as well as in women in chemopreventive studies who have high risk of developing breast cancer. **Implications:** Our results support continuation of ongoing trials of tamoxifen therapy in these two groups of subjects. [J Natl Cancer Inst 85:1398-1406, 1993]

Tamoxifen has become widely accepted as adjuvant therapy after surgery for early breast cancer. An overview of randomized trials of adjuvant therapy for early-stage (operable) breast cancer showed a statistically significant survival benefit with tamoxifen ($P < .001$) among postmenopausal patients with either lymph node-negative or lymph node-positive disease (1). The chemopreventive ability of the drug is being tested in large-scale randomized trials intended to recruit several thousand healthy women at high risk of developing breast cancer (a British trial and the National Surgical Adjuvant Breast and Bowel Project [NSABP]). Our previous randomized trial of tamoxifen

*See "Notes" section following "References."

therapy adjuvant to surgery for breast cancer showed a statistically significant decrease ($P < .05$) of new, contralateral breast cancers in patients who received tamoxifen (2). Tamoxifen has a low toxicity in comparison with that of most other drugs used in cancer therapy. The short-term side effects are few and usually mild. However, one concern with adjuvant therapy is that the drug may have adverse long-term effects such as endometrial and liver cancers (3). This concern is particularly relevant for patients with low risk of death from breast cancer and for healthy women receiving chemopreventive treatment.

The main mechanism of action of tamoxifen is a competitive binding to estrogen receptors. Tamoxifen is one of several triphenylethylene substances that can act both as estrogenic agonists and antagonists. The balance between agonism and antagonism varies between different species as well as different organ systems in one species. The anti-tumor effect in women with breast cancer has conventionally been ascribed to estrogen antagonism. Theoretically, such an effect may result in an increased morbidity and mortality due to cardiac disease; epidemiologic studies have suggested that an early menopause or castration of premenopausal women is associated with an increased cardiovascular mortality (4,5). In contrast, estrogen replacement therapy in postmenopausal women may protect them against cardiovascular disease (6).

The rationale for the current study was based on recent data indicating that tamoxifen acts mainly as an estrogenic agonist in most tissues in postmenopausal women (7). As early as 1984, Rössner and Wallgren (8) demonstrated that tamoxifen treatment resulted in changes in serum lipoproteins similar to those seen with estrogen replacement therapy. Two months after initiation of tamoxifen therapy, total serum cholesterol levels were significantly decreased, by approximately 15% ($P < .01$), mainly as a result of decreased levels of low-density lipoprotein (LDL) cholesterol. These observations suggest that long-term treatment with tamoxifen in postmenopausal women should, if anything, decrease morbidity from cardiac disease. If this hypothesis were true, an important benefit of tamoxifen in

women at high risk of developing breast cancer and in those with node-negative breast cancer, who are at low risk of death from the disease, could be prevention of death from cardiac disease, which in the long term may be more common in these groups than death due to breast cancer.

The clinical significance of the effect of tamoxifen on blood coagulation, possibly as a result of decreased levels of antithrombin III, remains controversial, since there is little information on thromboembolic disease morbidity.

The purpose of this study was to assess retrospectively the morbidity and mortality from cardiac and thromboembolic disease among 2365 postmenopausal women with early-stage breast cancer who were included in the Stockholm randomized trial of adjuvant tamoxifen therapy versus no adjuvant endocrine therapy. The analysis of morbidity was based on data collected in a computerized, population-based register of hospital admissions and corresponding discharge diagnoses covering about 95% of all hospital admissions in the Stockholm area. The significance of treatment duration could be evaluated because the study design included a randomized comparison between 2 and 5 years of tamoxifen at a dose of 40 mg/d.

Patients and Methods

Study Design

The design of the trial of adjuvant tamoxifen in early breast cancer was described previously and is summarized in Fig. 1 (9,10). In brief, after primary surgery, postmenopausal patients younger than 71 years with invasive, unilateral breast cancer were randomly assigned to receive adjuvant tamoxifen (40 mg daily) for 2 years or no adjuvant endocrine therapy. Patients with a history of cancer were not included. Treatment with tamoxifen was initiated within 4-6 weeks of surgery, which consisted of a modified radical mastectomy or breast-conserving surgery including axillary lymph node dissection. All patients treated with breast-conserving surgery were routinely given postoperative radiation therapy to the breast at a total dose of 50 Gy given in doses of 2 Gy a day 5 days a week for about 5 weeks. Patients with positive tumor margins were excluded.

During November 1976 through December 1988, 2365 patients were entered in the trial: 1188 were randomly assigned to receive tamoxifen with or without other treatment and 1177 were assigned to the control group.

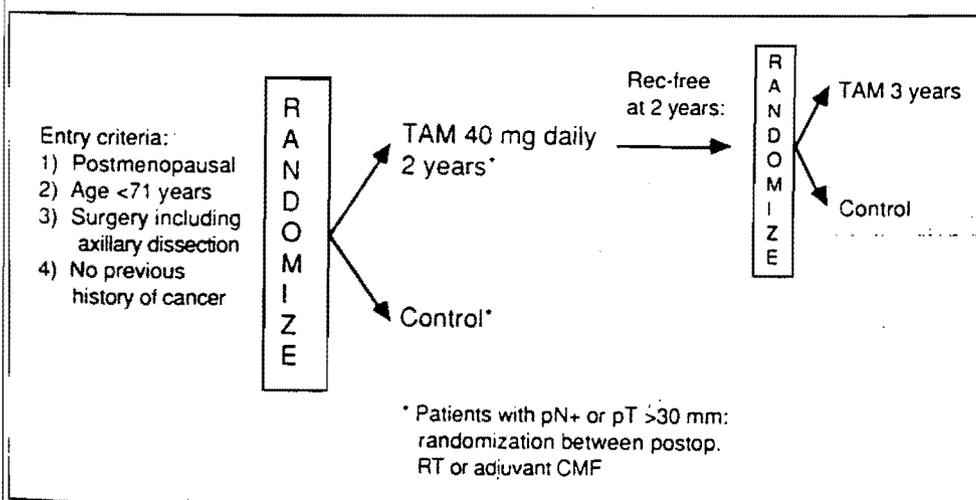


Fig. 1. Trial design. TAM = tamoxifen; Rec = recurrence; pN+ = node-positive; pT = tumor stage; postop. RT = postoperative radiation therapy; CMF = cyclophosphamide, methotrexate, and fluorouracil.

who received no tamoxifen. Informed consent was obtained according to the procedures required by the ethics committee of the Karolinska Institute. A total of 850 patients (36%) were considered to be at high risk of death from breast cancer because they had histologically verified lymph node metastases or a tumor diameter exceeding 3 cm. Of these, 628 patients were included in a concurrent randomized comparison of postoperative megavoltage radiation therapy to the chest wall and regional lymph nodes given at a total dose of 46 Gy in doses of 2 Gy a day (5 days a week for about 4½ weeks) versus adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil. These patients had been randomly assigned to receive adjuvant chemotherapy plus tamoxifen (173 patients) or postoperative radiotherapy plus tamoxifen (151 patients) or, as a control, to receive chemotherapy (171 patients) or postoperative radiation therapy (133 patients), both without tamoxifen or other endocrine therapy. Tamoxifen was administered concurrently with either radiation therapy or chemotherapy. During March 1982 through May 1985, the radiotherapy resources in the Stockholm area were restricted, so a 2:1 randomization in favor of chemotherapy was employed during that period. This randomization explains the imbalance between the number of patients allocated to the chemotherapy and radiotherapy groups (see Table 3). The randomization between tamoxifen or no adjuvant endocrine therapy, on the other hand, was balanced throughout the period of patient accrual. The remaining 222 high-risk patients were not considered to be fit for adjuvant chemotherapy, mainly because of advanced age, and were all given postoperative radiation therapy.

The design of the trial thus permits an unbiased and unconfounded evaluation of the effect of tamoxifen in 755 patients at low risk of death from breast cancer who did not receive any other type of adjuvant systemic treatment as well as among 433 high-risk patients who received tamoxifen concurrently with either adjuvant chemotherapy or postoperative radiation therapy.

Four percent of the patients in the tamoxifen group did not receive the allocated treatment (9), and 10% discontinued therapy before 2 years because of side effects such as gastrointestinal disturbances and hot flashes. About 1% of the control patients received adjuvant tamoxifen.

In 1983, a new trial was initiated: Patients who had received tamoxifen and were disease-free at 2 years were randomly assigned to stop the treatment or to continue for 3 more years, for a total treatment period of 5 years (Fig. 1). As of December 31, 1989, 447 patients were included in this trial; 225 continued treatment for 3 more years.

Recurrence-Free and Overall Survival

Recurrence-free and overall survival data from the trial were published previously (9,10). In summary, tamoxifen treatment resulted in a statistically significant prolongation of disease-free survival ($P < .01$) and a nonsignificant trend toward improved overall survival. The treatment effect was unrelated to tumor stage; i.e., the benefit with tamoxifen in terms of the proportionate reduction of breast cancer recurrences was similar among low-risk and high-risk patients. Moreover, in the high-risk patients, the treatment effect was similar among women who received tamoxifen in combination with postoperative radiation therapy and in those treated with tamoxifen plus adjuvant chemotherapy. In all subgroups, the benefit of tamoxifen was restricted to patients with estrogen receptor-positive disease. No treatment benefit in terms of either disease-free or overall survival could be demonstrated among patients with estrogen receptor-negative primary tumors.

Cardiac and Thromboembolic Morbidity

Cardiac and thromboembolic morbidity was analyzed by use of a computerized register of hospital admissions. The same technique had been used in a previous analysis of all types of intercurrent morbidity in the trial (11). That study, however, was based only on those 1846 patients accrued through September 1986, and the median follow-up was only 4.5 years. The results concerning cardiovascular disease did not reveal any statistically significant differences between the tamoxifen and control groups. The current study is a more in-depth analysis with the aim of specifically evaluating occurrence of cardiac or thromboembolic disease. Moreover, the

number of patients is larger through inclusion of all 2365 patients randomly assigned to treatment through December 1988, and the median follow-up is longer (6 years of follow-up).

The Stockholm County Council registers basic data on all county residents, including such information as date of birth, domicile, and marital status. The registration is based on an identification number that is unique to all persons living in Sweden. The information in this register is prospectively supplemented with data on hospital admissions from nearly all hospitals in the region. A few small, private hospitals and long-stay centers do not report admissions, but none of these institutions have an emergency unit and most of them have a geriatric profile. Thus, it appears that about 95% of all admissions for in-patient care in the county are included in the County Council register (12). Elderly patients with chronic diseases account for most of the unreported admissions. The register includes information about the time and duration of the patient's hospital stay as well as the main discharge diagnosis of the responsible physician. Registration and coding are done according to internationally accepted rules (13).

For this study, we matched trial patients against the register files by computerized record linkage, using their identification numbers. No attempt was made to check the concordance between the discharge diagnosis in the register and in the original clinical records because routine checks by the Stockholm County Council have revealed that discordances are uncommon, occurring in less than 1% of all admissions (Leimanis A [Stockholm County Council]; personal communication).

Cause-Specific Mortality

The officially recorded underlying causes of death were available from the Swedish National Central Bureau of Statistics.

Follow-up

Computerized data were available on hospital admissions before January 1, 1990, and on deaths before January 1, 1989. The follow-up times in the mortality analysis ranged from 0 to 12 years, with a median of 5 years. In the analysis of hospital admissions, they ranged from 1 to 13 years, with a median of 6 years. In the analysis of hospital admissions based on the comparison of 2 versus 5 years of tamoxifen, the follow-up times from rerandomization at 2 years ranged from 2 to 8 years, with a median of 5 years. Less than 1% of the patients were lost to follow-up for mortality. About 2% of the patients emigrated from Stockholm County during the observation period and were thus lost to follow-up in the analysis of hospital admissions. There were no statistically significant differences between the tamoxifen-treated study groups and the control groups in the proportion of patients lost to follow-up (data not shown).

Statistical Methods

Logrank comparisons between the group allocated to tamoxifen therapy and the control group were made for time from randomization to death or to first hospital admission due to cardiac or thromboembolic disease. In the comparison of tamoxifen treatment for 2 versus 5 years, similar comparisons were made for time from rerandomization at 2 years to death or to first hospital admission due to cardiac or thromboembolic disease. Only the main discharge diagnosis was considered. The types of disease were defined according to the codes in the Swedish version of the 8th revision of the International Classification of Diseases (13): (a) myocardial infarction, (b) ischemic heart disease other than myocardial infarction, (c) miscellaneous cardiac disease, and (d) thromboembolic disease. The rationale for analyzing only first hospital admissions was the fact that if a patient is transferred from one department to another (e.g., from an intensive care unit to a cardiology ward), that hospital stay is registered as two separate admissions, usually with the same discharge diagnosis. In all analyses of hospital admissions, patient data were censored at the date of local or distant breast cancer recurrence.

Note that in analyses of the three subgroups of cardiac diagnoses mentioned above (a, b, and c), the total number of admissions may be

greater than the total number of admissions in the overall analysis of any cardiac disease, because one patient may have a first admission for each of the subgroups of diagnoses but can, by definition, have only one first admission for any cardiac disease. For instance, if a patient is admitted for myocardial infarction and later for angina pectoris, one event is counted in analyses of myocardial infarction and one event in analyses of other ischemic heart disease. However, in the overall analysis of cardiac morbidity, only the first of these admissions is counted as an event.

Cumulative incidence rates were estimated by use of actuarial methods (14). Relative hazards were calculated according to Haybittle (15). All analyses were on the basis of "intention to treat." All patient data were analyzed according to the allocated treatment regardless of whether the patient actually received that treatment. No patient randomly assigned to treatment was excluded from analysis.

Results

Table 1 shows an analysis of first hospital admissions by allocated treatment. In the tamoxifen group, there was a statistically significant reduction in admissions due to any cardiac disease ($P = .03$). This result is illustrated graphically in Fig. 2. There appeared to be a benefit with tamoxifen during the entire period of observation. The relative hazard (tamoxifen versus control group) was below unity during all of the periods studied: During 0-2 years, it was 0.69 (95% confidence interval [CI] = 0.89-1.60); during 2-5 years, 0.50 (95% CI = 0.26-0.95); and after 5 years, 0.82 (95% CI = 0.50-1.37). However, the number of events during each period was relatively small, which explains the wide confidence intervals.

The number of first hospital admissions for myocardial infarction, other ischemic heart diseases, and miscellaneous cardiac diseases was lower for patients treated with tamoxifen, although the difference was not statistically significant for any of the three disease categories (Table 1). The observed differences in the tamoxifen group versus the control group for ischemic heart disease other than myocardial infarction were mainly due to admission of fewer patients with a discharge diagnosis of angina pectoris (seven versus 13 patients). The observed differences in the tamoxifen group versus the control group for miscellaneous cardiac diseases were mainly due to admission of fewer patients with a discharge diagnosis of atrial fibrillation (17

versus 23 patients) and congestive heart failure (seven versus nine patients).

There was no statistically significant difference between the treatment groups in terms of first admissions due to thromboembolic disease (Table 1). This result is illustrated graphically in Fig. 3.

Table 2 shows the analysis of first admissions for patients included in the randomization between 2 or 5 years of tamoxifen. There was a statistically significant decrease of admissions due to any cardiac disease in the 5-year group ($P = .03$). This result is displayed graphically in Fig. 4. The greatest benefit with tamoxifen was observed during 0-3 years after rerandomization, i.e., during the period of treatment in the 5-year group, but there appeared to be some benefit also after 3 years. During 0-3 years, the number of first admissions in the 2-year and 5-year groups was eight and one, respectively. The relative hazard for the 5-year group versus the 2-year group was 0.12 (95% CI = 0.02-0.97). After 3 years, the corresponding figures were six versus four admissions (relative hazard: 0.64; 95% CI = 0.18-2.28). The small number of events did not permit any meaningful subgrouping according to different diagnoses. However, as in the analysis presented in Table 1, there appeared to be a benefit with tamoxifen for a wide variety of cardiac diagnoses: (a) angina pectoris (no patients in the 2-year group versus three in the 5-year group), (b) atrial fibrillation (two versus five patients), and (c) congestive heart failure (no patients versus two) (data not shown).

To test the hypothesis that tamoxifen may affect the risk of thromboembolic events differently in patients who receive concurrent chemotherapy compared with those who receive tamoxifen alone, the analysis of hospital admissions due to thromboembolic disease was done according to tumor stage and allocated treatment (Table 3). The relative hazards were similar for the high-risk patients regardless of whether they had received concomitant chemotherapy or loco-regional radiation therapy.

Table 4 shows an analysis of cause-specific mortality. There were no statistically significant differences in favor of the tamoxifen group in terms of deaths due to breast cancer and cardiac disease: The relative hazards of 0.88 and 0.83,

Table 1. Number of first hospital admissions due to cardiac and thromboembolic disease according to allocated treatment*

Main discharge diagnosis	No. of first admissions by allocated adjuvant treatment		Relative hazard: TAM versus control group (95% CI)
	TAM†	Control‡	
Any cardiac disease	51	72	0.68§ (0.48-0.97)
Myocardial infarction	18	21	0.83 (0.45-1.56)
Ischemic heart disease other than myocardial infarction	14	21	0.65 (0.33-1.26)
Miscellaneous	36	46	0.75 (0.49-1.16)
Thromboembolic disease	49	45	1.06 (0.71-1.60)

*The number of first hospital admissions due to any cardiac disease is smaller than the sum of the numbers of first hospital admissions because of the three subgroups of cardiac diagnoses. This difference is due to the fact that one patient can have a first admission in each of the three subgroups but only the first of these events is counted in the overall analysis.

†TAM = adjuvant tamoxifen therapy; n = 1188 patients.

‡Control = no endocrine therapy; n = 1177 patients.

§ $P = .03$.

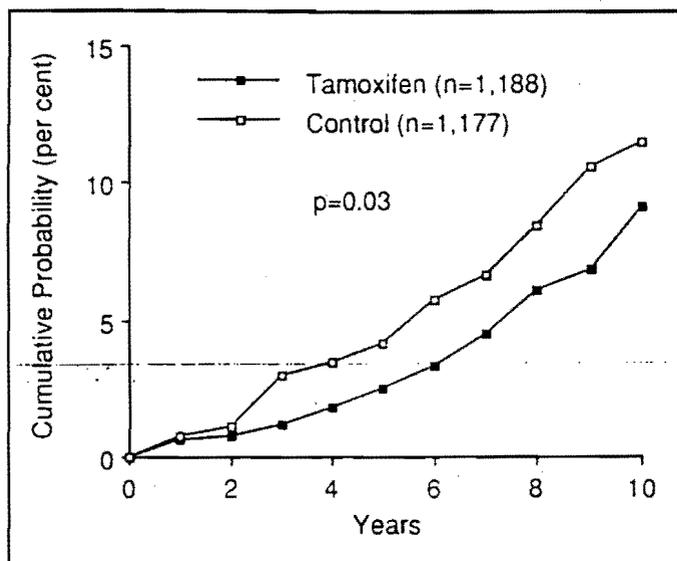


Fig. 2. Cumulative probability of first hospital admission due to any cardiac disease according to allocated treatment. The logrank *P* value is indicated.

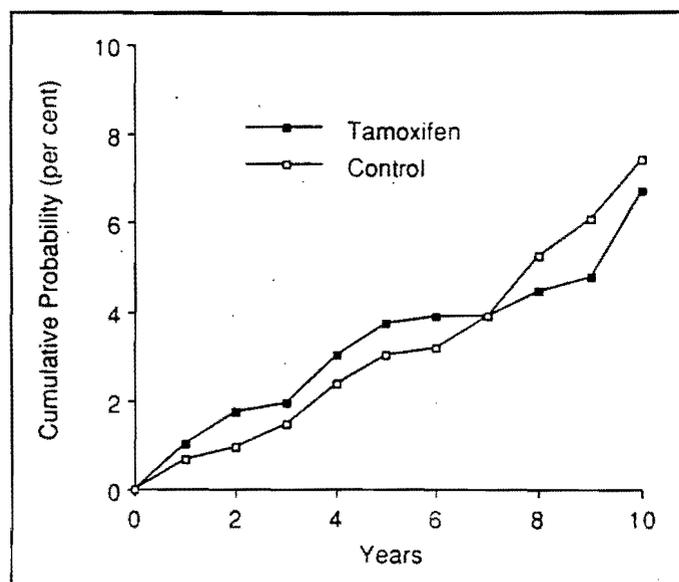


Fig. 3. Cumulative probability of first hospital admission due to thromboembolic disease according to allocated treatment.

respectively, suggested mortality reductions of 12% and 17%.

Discussion

This study was based on a computerized register of hospital admissions and officially registered causes of death. The incidence of hospital stays with a discharge diagnosis of cardiac or thromboembolic disease according to the responsible physician was used as a proxy measure of the morbidity related to such diseases. The admission register covers about 95% of all hospital stays in Stockholm County (12); only 2% of the data on patients were censored because they emigrated from the county during the period studied. Elderly patients with chronic diseases accounted for most of the unregistered admissions, so the data on more acute conditions requiring in-patient care are probably more than 95% complete. For logistical reasons, however, data on conditions that did not require hospitalization, such as superficial thrombophlebitis or less serious cardiac disease, were not included in the analysis. Because some cardiac diseases may be rapidly fatal, the patient is never admitted to the hospital. Thus, it may be more appropriate to use mortality data to determine the occurrence of such diseases. Finally, a potential source of error in analyses using discharge diagnoses and registered causes of death is, of course, that such data may not always be accurate. The diagnostic criteria for myocardial infarction may vary among hospitals and among physicians. Moreover, without the use of repeated electrocardiogram examinations, it is impossible to detect silent cases of myocardial infarction, which may account for up to 20% of all cases. In a previous analysis of the completeness of registration of cases of myocardial infarction in the admission register, it was found that the coverage was about 77% of the estimated total number of fatal and nonfatal cases in the Stockholm area (16). In a more detailed analysis based on cases in one hospital, it was found that registration errors were few (4%) and the completeness of registration of hospitalized cases was high (98%) (16).

Despite these problems, there is no reason to believe that the observed statistically significant difference in the number

Table 2. Number of first hospital admissions due to cardiac and thromboembolic disease according to allocated duration of tamoxifen therapy in the randomized comparison of 2 versus 5 years of treatment with tamoxifen

Discharge diagnosis	No. of first admissions by allocated duration of adjuvant tamoxifen therapy		Relative hazard: 5- versus 2-year group (95% CI)
	2 y*	5 y†	
Any cardiac disease‡	14	5	0.37§ (0.15-0.92)
Myocardial infarction	3	3	0.99 (0.20-4.92)
Ischemic heart disease other than myocardial infarction	5	0	0 (0-0.77)
Miscellaneous	11	2	0.24 (0.08-0.72)
Thromboembolic disease	7	6	0.85 (0.29-2.51)

*n = 222 patients.

†n = 225 patients.

‡The number of first hospital admissions due to any cardiac disease is smaller than the sum of the numbers of first hospital admissions because of the three subgroups of cardiac diagnoses. This difference is due to the fact that one patient can have a first admission in each of the three subgroups but only the first of these events is counted in the overall analysis.

§*P* = .03.

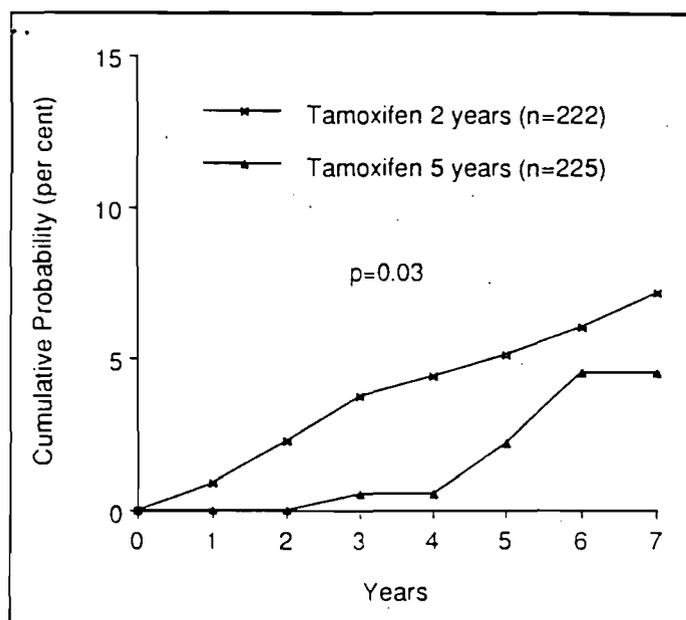


Fig. 4. Cumulative probability of first hospital admission due to any cardiac disease according to allocated duration of tamoxifen therapy among patients included in the 2-year versus 5-year comparison. The logrank *P* value is indicated.

of hospital admissions due to cardiac disease between the tamoxifen and control groups was due to bias. The treatment allocation was randomized, and any misclassification or underreporting in the admission register and the cause-of-death register was probably nondifferential. For instance, there is no reason to assume that adjuvant treatment with tamoxifen per se affected the probability that a patient would enter the hospital for a particular disease or that it affected the ability to accurately determine the underlying cause of death. By shifting the estimated relative risks toward unity, nondifferential misclassification may decrease the statistical power of a study to detect true differences, but it does not create spurious differences by shifting relative risks away from unity.

The 10-year update of the international overview of adjuvant tamoxifen studies showed a 12% decrease in deaths due to causes other than breast cancer among patients who

Table 4. Cause-specific mortality according to allocated treatment*

Underlying cause of death	No. of deaths in allocated adjuvant treatment groups		Relative hazard: TAM versus control (95% CI)
	TAM	Control	
Breast cancer	153	169	0.88 (0.70-1.09)
Other malignancies	17	16	1.02 (0.52-2.03)
Cardiac disease	12	14	0.83 (0.39-1.80)
Myocardial infarction	9	11	0.80 (0.33-1.91)
Other ischemic heart disease	1	0	—
Miscellaneous	2	3	0.65 (0.11-3.78)
Thromboembolic disease	6	7	0.83 (0.28-2.46)
Other intercurrent disease	15	13	1.13 (0.54-2.36)
Total	203	219	0.90 (0.74-1.09)

*TAM = adjuvant tamoxifen therapy; n = 1188. Control = no endocrine therapy; n = 1177.

received tamoxifen therapy (1). However, detailed data on cause-specific mortality were available only from four individual trials. In those studies, the decrease in the number of deaths unrelated to breast cancer that were associated with tamoxifen was primarily due to a 25% reduction in mortality due to vascular disease (*P* = .06).

In one of these studies, the Scottish Adjuvant Tamoxifen Trial, there was a statistically significant reduction of mortality due to myocardial infarction: 10 deaths in the tamoxifen group versus 25 deaths in the control group (*P* < .01) (17). The tamoxifen protocol schedule was 20 mg daily for 5 years. There was no decrease of any other type of cardiac mortality in the trial.

The mechanism of the putative reduction of cardiac disease with tamoxifen, as well as with estrogen replacement therapy, may be related to tamoxifen's beneficial effects on serum lipoproteins (8). However, tamoxifen may also directly affect blood vessels. Gangar et al. (18) found that transdermal estradiol decreased vascular resistance in the internal carotid arteries in postmenopausal women. De Ziegler et al. (19) made similar observations in uterine arteries. Nuclear binding of estrogens, as well as other steroid hormones, has been demonstrated in the heart and in the walls of large blood vessels (20). It is thus possible that

Table 3. Number of first hospital admissions due to thromboembolic disease according to allocated treatment, tumor stage, and, among the high-risk patients, concomitant adjuvant therapy (adjuvant chemotherapy or postoperative radiotherapy)

Tumor stage, concomitant adjuvant therapy	Adjuvant tamoxifen therapy		Control*		Relative hazard: tamoxifen group versus control group (95% CI)
	No. of patients	No. of admissions	No. of patients	No. of admissions	
High-risk†	433	19	417	20	0.89 (0.47-1.66)
Concurrent chemotherapy/radiotherapy (randomization)					
Chemotherapy	173	10	171	10	0.86 (0.35-2.11)
Radiotherapy	151	4	133	4	0.86 (0.21-3.46)
Radiotherapy (no randomization)	109	5	113	6	0.91 (0.28-2.99)
Low-risk‡	755	30	760	25	1.22 (0.72-2.07)
Total	1188	49	1177	45	1.06 (0.71-1.60)

*No endocrine therapy, except for 1% of control patients, who received adjuvant tamoxifen.

†pN+ (histo-pathologically involved axillary lymph nodes) or pT (size of primary tumor as measured on the histo-pathological specimen) >30 mm.

‡pN0 (absence of involved axillary lymph nodes) and pT (size of primary tumor as measured on the histo-pathological specimen) ≤30 mm.

estrogens may have a generalized effect on the arterial system of postmenopausal women through estrogen receptor-mediated mechanisms.

The results of our study are in agreement with the observations in the international overview and in the Scottish trial. All of these findings show a statistically significant decrease of cardiac morbidity with tamoxifen. The daily tamoxifen dose in the current trial was 40 mg, compared with 20 mg in the Scottish study. Reduced cardiac morbidity can thus obviously be obtained with either dose. Our study results suggest that tamoxifen reduced the incidence of myocardial infarction and angina pectoris as well as other diseases that can be related to myocardial ischemia, such as congestive heart failure and atrial fibrillation. The mechanism for reduction of myocardial ischemia could be the direct effect of tamoxifen on blood vessels (18-20) discussed earlier in this article. Such an effect is also consistent with the observed early benefit of tamoxifen, i.e., during the 2-5 years of treatment in our study (Fig. 2). If the main mechanism of tamoxifen were a decrease of atherogenesis, a delay in the occurrence of this benefit could be expected because atherogenesis is a relatively slow process. Whether the putative direct effect of tamoxifen on blood vessels is dose related remains an open question, since comprehensive information on cardiovascular morbidity is unavailable from most major tamoxifen studies, including the Scottish trial, and there are no randomized studies of different daily doses that have addressed this issue.

The analysis of cause-specific mortality suggested a 17% reduction of the total cardiac mortality with tamoxifen. This included a 20% reduction of deaths due to myocardial infarction. However, both figures were based on small numbers and the differences were not statistically significant (Table 4).

In the randomized comparison of 2 versus 5 years of treatment with tamoxifen, there was a statistically significant benefit in terms of cardiac morbidity with the longer treatment. This observation provides support for treatment schedules longer than 2 years and may help to explain why the results of the Scottish trial showed greater reduction in mortality due to myocardial infarction than was observed in our study. In the Scottish trial, the protocol duration of treatment in all tamoxifen-treated patients was 5 years.

However, the optimal duration of treatment with tamoxifen in terms of prevention of breast cancer recurrence and death remains controversial. Most randomized trials of adjuvant tamoxifen in early-stage breast cancer have compared study groups treated with tamoxifen for 1 or 2 years with untreated control groups. Trials permitting direct comparisons between patients treated with tamoxifen for 5 years and patients treated for 1 year suggested that the longer treatment was better in terms of recurrence-free survival (1). Also, in the international overview of adjuvant tamoxifen trials, the survival benefit in trials of more than 2 years of tamoxifen compared with no treatment appeared to be greater than that in trials of tamoxifen for 2 years or less compared with no treatment (1). However, the relevance of such indirect comparison of the effects of treatment duration may be questioned. A nonrandomized study by the NSABP

comparing 2 years of tamoxifen treatment with 3 years suggested that the longer treatment resulted in an improved recurrence-free survival rate (21). Nevertheless, no unconfounded randomized trial has yet shown a statistically significant survival benefit from prolonging the treatment beyond 2 years. Randomized trials aiming to establish the optimal treatment time are important, since long-term treatment with tamoxifen may be associated with an increased frequency of side effects such as endometrial and liver cancer.

Previously, we reported a statistically significant increase of endometrial cancer among the tamoxifen patients in the preliminary results of the current trial (3). The increase was most pronounced in the 5-year group and may have been related to the estrogenic activity of the drug. Increased risk of endometrial cancer among patients treated with tamoxifen has also been reported from adjuvant studies that have used a lower daily dose (30 mg) and a shorter treatment time (1 year) (22,23). An increase in the karyopyknotic index of vaginal epithelium in postmenopausal women, which indicates estrogenic activity, has been reported even with daily doses of 20 mg (24). A recent study suggested that the risk of endometrial hyperplasia and endometrial cancer with tamoxifen was directly related to the cumulative dose of tamoxifen; therefore, the daily dose, as well as the treatment time, may be important (25). Another argument against very long-term treatment is the observation that the growth of breast cancer cells that have acquired tamoxifen resistance may be stimulated by tamoxifen (26).

Laboratory animals develop hyperplastic liver nodules and liver cancer after long-term exposure to tamoxifen (27). The mechanism for this effect, as well as its clinical relevance, remains controversial. Liver cancer is a difficult diagnosis, since any liver tumor in a breast cancer patient is likely to be diagnosed as a metastasis from breast cancer rather than a new primary malignancy. Moreover, the rate of autopsy among breast cancer patients is often low. Since primary liver cancer is a rare disease in most developed countries, even a fairly large increase in the relative risk associated with long-term exposure to tamoxifen is unlikely to offset the benefit of the drug in the adjuvant setting. Whether this conclusion also holds true for chemopreventive treatment of healthy women at high risk of developing breast cancer remains to be established.

Our analysis showed a statistically significant reduction in cardiac morbidity for patients treated for 5 years with tamoxifen, compared with the reduction for patients treated for 2 years. Longer follow-up is necessary to establish if this benefit will be translated into a significant reduction of cardiac mortality. Most of the mortality observed so far was related to breast cancer. With longer follow-up, an increasing proportion of deaths will probably be due to cardiac disease. Among breast cancer patients, the risk of recurrence and death from their disease decreases with time after diagnosis, and the mortality pattern becomes gradually similar to that of the general population, in which the most common cause of death is cardiovascular disease, in particular ischemic heart disease.

Prophylactic treatment with tamoxifen in healthy women

at high risk of developing breast cancer is currently being tested in large-scale, randomized trials in both Europe and the United States. In this setting, the effects of the treatment on morbidity and mortality from cardiac disease may prove to be at least as important as the putative effect on the primary end point, i.e., breast cancer incidence.

The effect of tamoxifen on blood coagulation, if any, remains controversial. Some reports have claimed that tamoxifen reduces the level of antithrombin III (28), whereas other studies have failed to demonstrate such an effect (29,30). In a summary of seven consecutive Eastern Cooperative Oncology Group trials, there was a slight increase in thromboembolic events associated with tamoxifen therapy alone and a substantial increase in patients allocated to combined treatment with tamoxifen plus chemotherapy compared with untreated controls or those who received chemotherapy alone (31). In the placebo-controlled NSABP B-14 trial, there was a substantial increase in thromboembolic disease among the tamoxifen patients (32). In the current study, there was no increase in thromboembolic events among the tamoxifen patients regardless of whether tamoxifen was given alone or in combination with chemotherapy. For logistical reasons, the analysis only included events that required inpatient care; therefore, most cases of thrombophlebitis or other less serious thromboembolic events were not included.

Conclusions

In summary, there was a statistically significant reduction in cardiac morbidity associated with long-term tamoxifen. Treatment for 5 years resulted in greater reduction in mortality due to cardiac disease than treatment for 2 years, and the difference was statistically significant. There was no statistically significant increase in thromboembolic events in patients treated with tamoxifen. These observations support ongoing trials of adjuvant therapy for breast cancer patients with low risk of disease recurrence and ongoing chemopreventive studies aiming to reduce breast cancer incidence in women at high risk of developing breast cancer.

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EXCHANGE

**European Organization
for Research and
Treatment of Cancer**

**U.S. National
Cancer
Institute**

The European Organization for Research and Treatment of Cancer (EORTC) and the U.S. National Cancer Institute (NCI) are offering an exchange program to enable cancer researchers to work at NCI or EORTC-related institutions for one to three years.

General Conditions

Awardees will receive an annual subsistence allowance of \$30,000. Half of this amount will be provided by U.S. sources, the remainder by European sources.

European awardees will receive the U.S. contribution either from the NCI or from their extramural host institution. The European contribution of the exchangeship will be provided either by the scientist's home institution or by a European granting agency.

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Documentation

The following documents are required, in English, from all applicants:

- Completed application form.
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- Agreement to release the applicant from the home institution for the duration of the exchangeship.
- Assurance of intention to return to the home institution at the end of the exchangeship.
- Statement concerning the provision of 50 percent of financial support by

European sources. Non-EORTC member country candidates must continue at full salary at the home institution for the duration of the exchangeship.

- Three letters of recommendation mailed directly to the NCI Liaison Office by the recommending individuals.

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NCI Liaison Office
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PROGRAM

Type on small stationery and then include retyped the draft sent by HHS as well as fact sheet and article. I'll need to personally sign letter.

Dear Mrs. Cunningham:

Thank you for writing to me on the Breast Cancer Prevention Trial. I have had the enclosed response prepared by Dr. Broder of the National Cancer Institute and I believe it along with the accompanying materials answer your questions.

Thank you for your interest in our women's health studies.

Sincerely,

CHR