Influence of Tamoxifen on Carotid Intima-Media Thickness in Postmenopausal Women

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Background—Intima-media thickness of the common carotid artery (IMT-CCA) is an early marker of atherosclerosis. Tamoxifen is a selective estrogen-receptor modulator with estrogen-like effects on cardiovascular risk factors but as-yet unexplored effects on carotid artery structure. The goal of this study was to determine the influence of tamoxifen on IMT-CCA in menopausal women.

Methods and Results—With a predefined calculation of the sample size, 67 menopausal women with cancer who were treated with tamoxifen for ≥1 year and 37 menopausal women with cancer who were never treated with tamoxifen were enrolled. IMT-CCA, internal diameter, and pulse pressure were determined with a high-definition echotracking device and applanation tonometry in a central core laboratory that was blinded to treatment. Both groups were similar for clinical characteristics, including cardiovascular risk factors. IMT and internal diameter were significantly lower in the tamoxifen group (mean duration of treatment, 2.4±0.9 years) than in the control group (609±117 μm versus 662±147 μm, P=0.04, and 4.89±0.60 mm versus 5.12±0.58 mm, P=0.03, respectively). Pulse pressure was not influenced by the use of tamoxifen. After adjustment for age, cardiovascular risk factors, carotid pulse pressure, duration of menopause, and previous use of hormone replacement therapy, IMT remained significantly lower among tamoxifen users (P<0.00001), with an impact on IMT (−0.70 μm) equivalent to spontaneous evolution with 12 years of aging (5 μm/y).

Conclusion—The use of tamoxifen was associated with a significantly lower carotid IMT in menopausal women with cancer. Randomized trials are needed to confirm the cardioprotective effect of selective estrogen-receptor modulators in terms of prevention of atherosclerosis. (Circulation. 2002;106:2925-2929.)

Key Words: selective estrogen receptor modulators • atherosclerosis • carotid arteries • prevention • menopause

Mechanistic and clinical studies have shown favorable effects of estrogen replacement therapy (ERT) on lipid profile and pathophysiological processes involved in atherosclerosis.1 Observational studies have suggested a consistent beneficial effect with ERT for primary prevention of cardiovascular (CV) disease in postmenopausal women,2 but the results from randomized trials8–5 using predominantly daily continuous combined conjugated equine estrogen and medroxyprogesterone acetate therapy have challenged these findings. An increased interest is emerging for the evaluation of selective estrogen-receptor modulators (SERMs), agents with estrogen-like effects on bone and CV risk factors but without proliferative effects on breast tissue. Tamoxifen is a SERM with mixed estrogen agonist and antagonist properties that is currently used for the treatment of breast cancer with higher efficacy in estrogen-receptor (ER)–positive tumors.6 Tamoxifen has several favorable antiatherosclerotic properties.7–11 Data from several breast cancer trials,12–14 but not all,15 have suggested that tamoxifen may reduce cardiac events in women.

A linear association has been shown between increased intima-media thickness of the common carotid artery (IMT-CCA) and incidence of CV events, suggesting that IMT could be considered an early marker of atherosclerosis.16 The progression of IMT has been shown to be predictive of CV events.17 Although previous studies suggest that ERT and hormone replacement therapy (HRT) may lower IMT,18–21 the effects of SERMs on carotid artery structure are as yet unknown. We hypothesized that the use of tamoxifen would have estrogen-agonist effects similar to ERT on the carotid artery structure, leading to a lower IMT. The purpose of the present study was to examine the effects of tamoxifen on IMT-CCA in menopausal women with breast cancer by using a high-resolution echotracking system.

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Methods

Patients

Women with breast cancer were consecutively recruited in 2 oncology centers if they fulfilled the following criteria: (1) were menopausal, which was defined as amenorrhea ≥1 year and (2) were treated by tamoxifen (20 mg daily) for ≥1 year. The women in the control group were recruited in the same departments among menopausal women treated for breast cancer or other tumors who had never been treated with tamoxifen. The exclusion criteria for both groups included amenorrhea for <1 year and the use of ERT or HRT within 1 year before inclusion.

Using data from McGrath et al16 and by considering the higher frequency of breast cancer treated with tamoxifen because of the higher number of ER-positive tumors, 66 and 33 patients in the tamoxifen and control groups, respectively, were the minimum sample sizes needed for detection of a 9% difference in IMT-CCA in a 2-sided test (α=0.05, β=0.20). The protocol was approved by the Committee for the Protection of Human Subjects in Biomedical Research of Pitié Salpêtrière University-Hospital in Paris. Written informed consent to participate in the study was obtained from each patient.

Artery Measurements

All arterial measurements were performed in a central core laboratory that was blinded to patient treatment by a single technician (B.L.) under the supervision of a single physician (P.B.) who was certified in vascular echography and trained for echotracking.22,23 Measurements were performed in a controlled environment that was kept at 22±1°C and after 15 minutes of rest. Carotid internal diameter and IMT were measured on the right CCA and 2 cm beneath the carotid bifurcation with a 7.5-MHz pulsed ultrasound echotracking system (Wall Track System, Neurodata) by analyzing the radiofrequency signal originating from an M line perpendicular to the longitudinal and transversal axes of the artery, which was selected on the 2D B-mode image (Sigma 44 KONTRON). This system has been validated and described in detail, and the repeatability of carotid measurements has been reported previously.22,23

Mean circumferential wall stress (σθ, kPa) was calculated according to Lamé's equation as follows: \[ \sigma_\theta = \frac{\text{MBP} \times D_2}{2h}, \] where MBP is mean blood pressure, D is mean internal diameter, and h is wall thickness. Because wall thickness is influenced by variations in internal diameter, arterial mass (AM), because of its incompressibility, is an interesting parameter for evaluating arterial remodeling.22

AM was normalized to the length of the arterial segment and calculated as \[ \text{AM} = \rho L \pi (D_2 + 2\Delta MT)^2 - (D_1)^4/4, \] where \( \rho \) is arterial wall density (\( \rho = 1.06 \)) and L is the length of the arterial segment. AM was expressed as mg/cm length, as previously described and validated.23

The CCA pressure waveform was determined with applanation tonometry using a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments).23 Brachial blood pressure values (systolic, diastolic, and mean) measured with an oscillometric method (Dinamap model 845, Critikon) were the averages of 3 measurements performed during 3 successive 15-minute periods.

Statistical Analysis

Wilcoxon and Friedman tests were used for comparisons of continuous and categorical variables, respectively. A stepwise multivariate regression analysis was used to assess the possible determinants of IMT, with AM considered the dependent variable. For the latter analyses, adjustment was performed with the following variables: age, body surface area, heart rate, mean arterial pressure, smoking status, diabetes, local pulse pressure (PP), serum levels of fibrinogen, glycemia and cholesterolemia, duration of menopause, the previous use and duration of HRT, chemotherapy, and sus-clavicular radiotherapy.

Results

Patients

A total of 67 women treated with tamoxifen (mean duration of treatment, 2.4±0.9 years) and 37 women in the control group were recruited consecutively for the study. The characteristics of the study population are described in Table 1. Both groups were similar in terms of age, body mass index, heart rate, blood pressure, duration of menopause, previous use and duration of ERT and HRT, and CV risk factors, with the exception of fibrinogen, which was significantly lower among tamoxifen users.

All patients in the tamoxifen group had breast cancer; 51 of these tumors were ER-positive, 10 were unknown, and 6 were ER-negative. In the control group, 25 women had breast cancer (17 ER-negative, 6 unknown, and 2 ER-positive), and 12 women had other tumors (10 gynecological and 2 colon cancers). No difference between groups was observed regarding the previous use or type of chemotherapy (44% versus 38%, \( P=0.67 \)) and sus-clavicular radiotherapy (30% versus 43%, \( P=0.19 \)). No difference in the stage of breast cancer was observed between groups (stage I, 70% and 64%; stage II, 24% and 16%; and stage III, 6% and 20% of patients in tamoxifen and control group, respectively; \( P=0.12 \)). None of the patients had CV symptoms, documented coronary artery disease, or a previous history of stroke.

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of the Study Population</th>
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<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>White race, n (%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
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<tr>
<td>Smoking habit, n (%)</td>
</tr>
<tr>
<td>Current</td>
</tr>
<tr>
<td>Past</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Previous coronary disease, n (%)</td>
</tr>
<tr>
<td>Duration of menopause, y</td>
</tr>
<tr>
<td>Type of menopause</td>
</tr>
<tr>
<td>Surgical, n (%)</td>
</tr>
<tr>
<td>Spontaneous, n (%)</td>
</tr>
<tr>
<td>Previous HRT, n (%)</td>
</tr>
<tr>
<td>Duration of previous HRT, y</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
</tr>
<tr>
<td>Cholesterolemia, mg/dL</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
</tr>
</tbody>
</table>

Values are frequencies or mean±SD.
Comparison of carotid mean IMT and AM in tamoxifen users and controls.

Carotid Artery Parameters
Carotid mean IMT and AM in the tamoxifen and control groups are shown in the Figure. Carotid mean IMT and AM were significantly lower in the tamoxifen group than in the control group (IMT: 609±117 μm versus 662±147 μm, nonadjusted P=0.04, adjusted P<0.001; AM: 112±27 mg/cm versus 128±34 mg/cm, nonadjusted P=0.008, adjusted P<0.001, respectively; Figure).

Internal diameter was also significantly lower in the tamoxifen group compared with the control group (4.89±0.60 mm versus 5.12±0.58 mm, P=0.03). Carotid PP was not significantly influenced by the use of tamoxifen (55±17 mm Hg versus 59±17 mm Hg in tamoxifen and control groups, P=0.19).

Independent Determinants of IMT and AM
Table 2 shows the independent determinants of IMT and AM among all included women. After adjustment, IMT remained significantly lower among tamoxifen users (explaining 13% of the variance, P<10^-6) independent of the other variables that are known to influence IMT (age, body surface index, and PP). The independent influence of aging on IMT was 5.5±0.88 μm/y whereas that of tamoxifen treatment was −70±12 μm (Table 2).

Discussion
To our knowledge, no previous study has investigated the effects of a SERM on carotid IMT in menopausal women. The findings of this case-control study suggest a substantial reduction of carotid IMT with long-term tamoxifen therapy in menopausal women with no previous coronary artery disease.

SERMs
The 2 SERMs clinically available at present are tamoxifen, which is the most widely prescribed agent for adjuvant treatment of primary breast cancer, and raloxifene. Their molecular mechanisms of action are not fully understood but are modulated by their affinity for ERα and β.1,24 Tamoxifen binds with similar affinity to both ERs, whereas raloxifene has a higher affinity for ERα. The tissue distribution of ERα and β seems to differ, although the complete distribution map is not yet available. ERs are present in smooth muscle cells of coronary arteries and endothelial cells in various sites.1,24

Tamoxifen and the Usual Determinants of Carotid IMT
IMT-CCA is generally accepted as an early marker of atherosclerosis and a predictor of CV events.16,17,25 However, ultrasound imaging cannot discriminate between the intima and the media layers of the vessel wall to distinguish atherosclerosis, which is viewed as a disorder restricted to the intima,23 from true arteriosclerosis, which is the adaptive response of the media layer to changes in tensile stress. Classical CV risk factors also influence carotid IMT through aging and morphological (ie, body surface area), mechanical (ie, high blood pressure), and metabolic factors (ie, diabetes). In previous works,22,23 we showed that IMT-CCA was influenced by the pulsatile component of blood pressure (ie, PP) measured at the site of the carotid artery, rather than by its steady component (ie, mean blood pressure). In the present study, we confirmed that carotid PP, but not mean blood pressure, was a significant determinant of IMT-CCA and AM (Table 2). Interestingly, after adjustment for carotid PP, tamoxifen therapy remained a significant determinant of IMT and AM, explaining 13% and 6% of their variances, whereas the only other determinants were age and body surface area (Table 2). The impact of tamoxifen treatment on IMT (−70±12 μm after a mean treatment duration of 2.4±0.9 years) was equivalent to 12 years of aging of the arterial wall (age increases IMT 5.5±0.9 μm/y).

Effects of Tamoxifen on CV Risk Factors
The favorable impact of tamoxifen on IMT-CCA may occur through changes in biological factors. Tamoxifen has favorable effects on plasma lipid profile, lipoprotein(a), fibrinogen, and homocysteine in healthy menopausal women and in women with breast cancer.8–11 In a 2-year placebo-controlled trial, 20 mg/d tamoxifen significantly reduced serum levels of fibrinogen by 18%, total cholesterol by 12%, and LDL cholesterol by 19% in healthy menopausal women.9 Similar effects have been shown with raloxifene26 and droloxifene,27 a structural analogue of tamoxifen. Tamoxifen users in our study also had significantly lower fibrinogen levels. Although SERMs have some favorable antiatherosclerotic properties, their direct effects on the arterial wall remain unknown. Estrogen-agonist effects on the arterial wall have been observed with tamoxifen in monkeys fed an atherogenic diet.28 Both tamoxifen7 and droloxifene27 also improve endothelium-dependent flow-mediated vasodilation.

The efficacy of tamoxifen in breast cancer is higher among ER-positive tumors.6 In our study, 76% versus 8% of breast carcinomas were ER-positive in the tamoxifen and control groups. However, the overexpression of ERα and the different molecular structure of the variants in breast tumor cells seem to be specific for tumor cells and are not correlated to the normal tissue of the breast with malignant disease.29 However, it is unlikely that the overexpression of ERs in breast tumor cells could predict the amount or the molecular structure of the ERs in the arterial wall. Moreover, studies in knockout mice suggest that either ERα or ERβ is sufficient to protect against carotid vascular injury.30 However, the clinical responsiveness to treatment with ERT and HRT may be influenced by ER polymorphisms. The sequence variation in the intron-1 region of the gene encoding ERα has been associated with the magnitude of responsiveness of HDL-cholesterol levels to HRT.31 Further genotype-phenotype
pharmacological studies are needed to evaluate the relevance of this interaction.

**HRT and IMT**

Prevention of CCA wall thickening or regression of IMT-CCA has been demonstrated with interventions such as antihypertensive treatments, statins, and antiplatelet drugs. Several studies have suggested that ERT and HRT may decrease IMT-CCA in menopausal women without coronary artery disease. In a case-control study, McGrath et al observed a significantly lower IMT in women receiving HRT compared with an age-matched control group (0.67 ± 0.01 versus 0.74 ± 0.02 mm, P = 0.006). The use of HRT ≥1 year was also independently associated with a lower IMT when compared with that in never-users. Self-selection of ERT was associated with a reduced progression of IMT. The effects of 1 mg of 17β-estradiol compared with placebo were evaluated recently in a randomized 2-year trial in menopausal women with LDL ≥130 mg/dL and without previous CV disease. The average rate of IMT progression was significantly lower with estradiol compared with placebo, with a placebo-estradiol difference of 0.0053 mm/y (P = 0.046).

Whether IMT improvement with ERT, HRT, or SERM will translate into CV benefit for primary prevention remains to be proven. Initiation of oral HRT reduces the serum-soluble markers of vascular inflammation, such as intracellular adhesion molecule-1 and vascular cell adhesion molecule-1, but increases the plasma levels of liver-derived inflammatory markers, including C-reactive protein (CRP) and matrix metalloproteinase-9. These effects have raised the hypothesis of a proinflammatory effect of HRT promoting plaque destabilization, a phenomenon that may explain the early increase in CV events observed in older women in secondary prevention trials and in the Women’s Health Initiative. Because nonoral estrogen does not raise CRP, the effects with oral estrogen may also be a first-pass effect. Unlike HRT, raloxifene does not influence CRP levels. Moreover, a significant reduction of 26% in CRP was observed with tamoxifen compared with placebo in healthy women. Whether reducing CRP may result in a lower number of CV events has not yet been established. However, results with aspirin and pravastatin raise the hypothesis that part of the CV benefit may be obtained through anti-inflammatory effects. Some studies with tamoxifen in breast cancer have suggested a reduced incidence of fatal myocardial infarction and cardiac morbidity in women not selected for CV risk. In an analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, although raloxifene did not reduce the risk of CV events among the overall cohort of osteoporotic menopausal women, its use was associated with a significant 40% reduction in coronary and cerebrovascular events in the subgroup of women at high risk for CV events.

There are some shortcomings in the present study. First, the study design does not allow us to draw conclusions on a cause and effect relation. For example, other determinants of carotid IMT, such as lipoprotein(a), homocysteine, and CRP levels, were not measured, thus hampering the mechanistic explanation of the difference in IMT-CCA between tamoxifen users and the control group. Second, in nonrandomized trials, women using HRT may have healthier lifestyles and may be more carefully monitored by their physicians. Women in our study were recruited from 2 cancer departments in the same area, were followed with a similar schedule, and were managed by the same physicians. Moreover, IMT-CCA was measured in a central core laboratory that was blinded to patient treatment. Third, 12 of 37 women in the control group had tumors other than breast cancer, although no data have suggested that the type of cancer influences IMT. No difference was observed among groups regarding the use or the type of chemotherapy, the radiotherapy, and the stage of breast cancer. Finally, women with ER-positive breast cancer may be different from women with ER-negative tumors; therefore, the lower IMT in tamoxifen users may be related to the earlier greater exposure or sensitivity to endogenous estrogen. The influence of tamoxifen on IMT remained significant after adjustment for possible confounding factors, but the possibility of unknown variables that may have an impact on IMT cannot be fully ruled out.

**TABLE 2.** Stepwise Robust Regression Analysis of the Determinants of the Carotid Artery Structure

<table>
<thead>
<tr>
<th>Parameters</th>
<th>r Increment</th>
<th>β Coefficient</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 year)</td>
<td>0.19</td>
<td>55.3 ± 8.8</td>
<td>6.69</td>
<td>&lt;10−4</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.16</td>
<td>294 ± 47</td>
<td>5.07</td>
<td>&lt;10−4</td>
</tr>
<tr>
<td>Tamoxifen therapy</td>
<td>0.13</td>
<td>−70.0 ± 12.0</td>
<td>−5.75</td>
<td>&lt;10−4</td>
</tr>
<tr>
<td>Carotid pulse pressure (10 mm Hg)</td>
<td>0.02</td>
<td>7.3 ± 4.0</td>
<td>1.99</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Dependent variable: AM (mg/cm)†

<table>
<thead>
<tr>
<th>Parameters</th>
<th>r Increment</th>
<th>β Coefficient</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 year)</td>
<td>0.2</td>
<td>1.5 ± 0.02</td>
<td>8.21</td>
<td>&lt;10−5</td>
</tr>
<tr>
<td>Body surface area (kg/m²)</td>
<td>0.09</td>
<td>4.1 ± 0.9</td>
<td>5.51</td>
<td>&lt;10−5</td>
</tr>
<tr>
<td>Tamoxifen therapy</td>
<td>0.06</td>
<td>−1.185 ± 0.26</td>
<td>−4.35</td>
<td>&lt;10−4</td>
</tr>
<tr>
<td>Carotid pulse pressure (10 mm Hg)</td>
<td>0.09</td>
<td>0.45 ± 0.08</td>
<td>5.45</td>
<td>&lt;10−5</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.02</td>
<td>1.05 ± 0.42</td>
<td>2.78</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Total variance explained r² = 0.81.
†Total variance explained r² = 0.71.
Clinical Application
Given the results of clinical trials of HRT, there is an emerging interest regarding the potential for CV protective effects of SERMs. To our knowledge, this is the first study suggesting a beneficial effect of a SERM on an early marker of atherosclerosis. Results from randomized trials are needed to determine the true value of this therapy, because deleterious side effects may alter the clinical benefit. SERMs increase the risk of venous thromboembolism by a magnitude comparable to that of HRT. Unlike raloxifene, tamoxifen increases the risk of endometrial hyperplasia and could not be the ideal alternative to HRT, particularly in women with an intact uterus.

The present findings may generate hypotheses that should not be considered the final answer but may allow for further study of the impact of the therapy by funding large-scale, randomized, controlled trials. The results of the Raloxifene Use for The Heart (RUTH) trial will be particularly interesting.

Conclusions
The use of tamoxifen was associated with a significantly lower carotid IMT in postmenopausal women with cancer. Controlled trials are needed to confirm a possible cardioprotective effect of SERMs in terms of prevention of atherosclerosis.

Acknowledgments
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References
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