Tamoxifen and Cardiac Risk Factors in Healthy Women

Suggestion of an Anti-inflammatory Effect

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Abstract—Tamoxifen reduces the incidence of breast cancer in women at risk for that disease. Because heart disease is the leading cause of death in women and because tamoxifen is also associated with venous thrombosis, an improved understanding of the association of tamoxifen with cardiovascular disease risk factors is required. In 111 healthy women at a single center, who were participating in a randomized double-blind breast cancer prevention trial, the 6-month effects of oral tamoxifen (20 mg/d) compared with placebo on factors related to inflammation, hemostasis, and lipids were studied. Tamoxifen was associated with reductions of 26% in median C-reactive protein, 22% in median fibrinogen, and 9% in cholesterol (all $P<0.01$ compared with placebo). There were no differences in treatment effects on factor VII coagulant activity, fragment 1-2, and triglycerides. In secondary analyses, the effect of tamoxifen on C-reactive protein was larger in postmenopausal women and in women with higher waist-to-hip ratios. The effect on fibrinogen was larger in women with higher baseline cholesterol. Tamoxifen demonstrated effects on inflammatory markers that were consistent with reduced cardiovascular risk. These findings are in contrast to recent reports of increased C-reactive protein associated with postmenopausal estrogen. The potential for beneficial cardiovascular effects of tamoxifen in healthy women is suggested. **(*Arterioscler Thromb Vasc Biol*. 2001;21:255-261.)**

Key Words: tamoxifen ■ blood coagulation ■ inflammation ■ risk factors ■ cardiovascular disease

In the National Surgical Adjuvant Breast and Bowel Project P-1 trial, tamoxifen, an estrogen receptor modulator, reduced the incidence of breast cancer in healthy women at higher than average risk.[1] Similar to postmenopausal hormone therapy, tamoxifen was predicted to reduce cardiovascular risk on the basis of its lipid-lowering properties.[2–6] Indeed, 3 trials of breast cancer patients have reported 15% to 60% reductions in cardiac death in women treated with tamoxifen.[7–9] In the P-1 trial, myocardial infarction rates comparing tamoxifen and placebo did not differ.[1] However, that study was not designed to detect relevant differences in cardiovascular outcomes, and the study population was at low cardiac risk.

The translation of favorable lipid effects to cardiac risk reduction by hormones was questioned with the publication of results from the Heart and Estrogen/progestin Replacement Study (HERS), which showed no reduction in the 5-year risk of coronary events in women with coronary artery disease randomly assigned to estrogen plus progestin versus placebo.[10] In a secondary analysis, hormone therapy increased the risk of coronary events in the first year of treatment, and there was a trend to a reduced risk with hormones over time. Preliminary results from an observational study have confirmed this finding.[11]

The effects of postmenopausal hormones on inflammation and hemostasis have been proposed to explain adverse, null, or beneficial effects of these agents on cardiac risk.[12,13] Higher concentrations of inflammation markers, particularly C-reactive protein and fibrinogen, have become established as vascular disease risk markers in several studies.[14–17] Trial data have indicated that postmenopausal hormones increase C-reactive protein concentrations.[18,19] In seeming paradox, hormones have also been reported to prevent the age-related rise in fibrinogen.[20] Other studies have reported higher factor VII coagulant (VIIc) activity and prothrombin activation fragment 1-2 with hormone therapy,[21] findings with uncertain cardiovascular implications.[22,23]

In light of recommendations that tamoxifen be considered to reduce the incidence of breast cancer in healthy women and because coronary heart disease is more common than breast cancer, an improved understanding of the effect of tamoxifen on the risk of coronary disease is needed. Given the lack of conclusive data on cardiac outcomes with tamoxifen therapy,[9] an assessment of nonclinical outcomes, such as the effects on

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inflammation and hemostasis, is warranted. Hence, we studied the effects of tamoxifen on these factors at a single P-1 clinical site. Secondary objectives were (1) to confirm prior findings of tamoxifen effects on lipids and (2) to determine whether observed effects differed in subgroups defined by menopausal status and baseline cardiac risk factors. Specific hypotheses were that the effects of tamoxifen would be in a direction consistent with reduced cardiovascular risk and that the effects would be greater in those at higher baseline cardiovascular risk.

Methods

Study Design and Subjects

The P-1 trial was a multicenter randomized, double-blind, placebo-controlled clinical trial of tamoxifen (20 mg/d) in the primary prevention of breast cancer. The design and main results have been published.[1] Women without previous breast cancer were eligible if they were aged ≥60 years or 35 to 59 years with a 5-year risk of breast cancer of at least 1.66%. Other eligibility criteria included life expectancy of at least 10 years, no hormone use for at least 3 months, accessibility for follow-up, and no pregnancy or planned pregnancy. Participants at the University of Vermont were included in this substudy, and they provided informed consent with institutionally approved procedures.

Procedures

The baseline examination included the administration of questionnaires to obtain self-reported information regarding smoking status (never, former, or current) and history of diabetes, hypertension, prior hormone use, and hyperlipidemia. Measurements of body mass index (weight/height^2) and waist-to-hip ratio were completed by use of standard methods.

At the baseline and 6-month follow-up visits, blood was drawn with minimal stasis into evacuated tubes containing either EDTA, sodium citrate, or 4.5 mmol/L EDTA plus protease inhibitors (0.15 KIU/L aprotinin and 20 μmol/L D-Phe-Pro-Arg-chloromethyl ketone, Haematologic Technologies, Inc). Blood was placed on ice and processed within 30 minutes by centrifugation at 4°C and 3000*g* for 10 minutes. Plasma was divided into aliquots and stored at −70°C until the end of the trial, when assays were run with each participant's serial samples included within the same run. Clinic and laboratory personnel were not aware of the randomized treatment assignment. Total cholesterol and triglyceride levels were measured by enzymatic methods. Fibrinogen and factor VIIc were measured by standard clotting assays with respective coefficients of variation of 4% to 6% and 8%. Prothrombin fragment 1-2, a marker of thrombin generation, was measured by using a kit (Behring) with a coefficient of variation of 9.0%. C-reactive protein was measured by high-sensitivity immunoassay with a coefficient of variation of 7.7%.[24]

Statistical Analysis

Release 6.09 of the main frame version of SAS was used for analysis. For the blood analytes, measures of central tendency were calculated as the mean±SE or as the median and interquartile range, depending on the observed distributions. Formal tests of the distributions of all variables being assessed were performed. Comparisons by treatment group of baseline values of the analytes and of change in analyte values noted from the baseline to 6-month visit were made by the *t* test or the Kruskal-Wallis test, depending on the distribution of the variable being assessed. Distributions of fibrinogen, C-reactive protein, fragment 1-2, and triglycerides were nonnormal and were assessed by the Kruskal-Wallis test. In addition to the assessment of differences by treatment group in change in the analyte levels, the Kruskal-Wallis test was used to determine whether there were differences in change in analyte levels within treatment groups by approximate tertiles of baseline cholesterol, body mass index, and waist-to-hip ratio and by dichotomized categories of menopausal status and smoking status.

TABLE 1. Baseline Characteristics by Treatment Assignment

Baseline Characteristic	Treatment Assignment: Placebo (n=54)	Treatment Assignment: Tamoxifen (n=46)
Age, y	57.6±1.4	58.2±1.4
Postmenopausal, n (%)	40 (74%)	33 (72%)
White, n (%)	54 (100%)	46 (100%)
Hysterectomy, n (%)	22 (41%)	17 (37%)
Oophorectomy, n (%)	14 (26%)	13 (28%)
Prior estrogen use,* n (%)	22 (41%)	17 (37%)
Body mass index	27.5±0.7	28.7±1.0
Waist-to-hip ratio	0.79±0.01	0.77±0.1
Hypertension, n (%)	19 (35%)	11 (24%)
Diabetes, n (%)	1 (2%)	2 (4%)
Hyperlipidemia, n (%)	7 (13%)	4 (9%)
Smoking status (never/current), n (%)	30 (56%)/6 (11%)	23 (50%)/3 (7%)
≥2 cardiac risk factors,† n (%)	8 (15%)	5 (11%)

Values are mean±SE or number (percentage). For comparison of treatment groups, $P>0.05$ for all factors.

*Estrogen replacement therapy or hormone replacement therapy.

†≥2 from among current smoking, diabetes, hypertension, and hyperlipidemia.

Results

There were 111 women randomized (60 to placebo and 51 to tamoxifen); all were white. Of these, 100 women had results available from the baseline and 6-month visit for at least 1 of the measured analytes (54 women assigned to placebo and 46 assigned to tamoxifen). No participant withdrew from the study. Depending on the analyte, the number of samples included in the analyses varied slightly because of insufficient sample available or problems with blood collection or preparation. Baseline characteristics of the 11 women with missing laboratory data for these reasons did not differ from those without missing data (data not shown). On the basis of pill counts at the 6-month visit, the average proportion of pills taken was 99% among women on placebo and 98% among women on tamoxifen.

As shown in Table 1, the baseline characteristics comparing the 2 treatment groups were similar. The mean age was 57.6 years in those assigned to placebo and 58.2 years in those assigned to tamoxifen. The majority of participants were postmenopausal, and a minority had cardiovascular risk factors. There were only 13 women with ≥2 risk factors (8 assigned to placebo and 5 assigned to tamoxifen). Baseline C-reactive protein was significantly higher among postmenopausal women (median C-reactive protein 1.50 versus 0.60 mg/L, $P=0.003$).

Changes in the study measures after 6 months are shown in Table 2. Baseline values of each analyte did not differ significantly by treatment assignment. In the placebo group, the median fibrinogen concentration increased from 2.93 to 3.02 g/L. The median C-reactive protein did not change. In contrast, tamoxifen was associated with a decline in fibrinogen, with a median decline of 0.64 g/L (interquartile range of the distribution of decline −0.91 to −0.21). This represented a 22% median reduction ($P<0.001$ compared with placebo). Tamoxifen was associated with a 0.30 mg/L median decline

TABLE 2. Comparison of Study Markers at Baseline and 6 Months of Follow-Up by Treatment Assignment

		Baseline				6 Months				Change From Baseline				
Analyte	n	Mean	SE	Median	IQR	Mean	SE	Median	IQR	Mean	SE	Median	IQR	P*
Fibrinogen, g/L														
Placebo	51	3.00	0.09	2.93	2.64–3.26	3.12	0.12	3.02	2.65–3.48	0.12	0.07	−0.02	−0.18–0.32	
Tamoxifen	46	2.93	0.11	2.91	2.55–3.30	2.42	0.08	2.31	2.05–2.76	−0.50	0.09	−0.64	−0.91–−0.21	<0.001
C-reactive protein, mg/L														
Placebo	53	2.11	0.43	1.40	0.70–2.10	2.77	0.56	1.40	0.70–2.50	0.66	0.43	0	−0.20–0.40	
Tamoxifen	44	2.84	0.77	1.15	0.60–2.55	2.04	0.63	0.80	0.35–1.90	−0.80	0.22	−0.30	−1.15–−0.05	<0.001
Factor VIIc, %														
Placebo	51	131	3	131	114–145	125	4	123	113–137	−6	3	−5	−15–3	
Tamoxifen	46	130	4	129	113–142	130	4	124	114–144	−1	2	−1	−12–9	0.15
Fragment 1–2, nmol/L														
Placebo	53	1.62	0.07	1.44	1.27–1.84	1.52	0.07	1.44	1.23–1.66	−0.10	0.07	−0.08	−0.30–0.14	
Tamoxifen	45	1.49	0.08	1.39	1.11–1.75	1.56	0.09	1.48	1.02–1.80	0.06	0.07	0.10	−0.20–0.29	0.08

IQR indicates interquartile range.
*Comparison of change over time between the 2 treatment groups.

in C-reactive protein (interquartile range of the distribution of decline −1.15 to −0.05). This represented a 26% median reduction (absolute values 1.15 to 0.80 mg/L, $P<0.001$ compared with placebo). To study any potential imbalance between the groups in acute illnesses that might raise C-reactive protein or fibrinogen concentrations at the time of phlebotomy, we excluded C-reactive protein or fibrinogen values for either time point that were above the 95th percentile of the distribution of baseline values. Relative to placebo, tamoxifen still significantly lowered the concentrations of these factors. With available data for C-reactive protein and fibrinogen in 41 placebo-assigned and 28 tamoxifen-assigned participants followed for 24 months, relationships persisted ($P<0.05$ for both, data not shown).

There were no effects of tamoxifen on factor VIIc and fragment 1-2 (Table 2). Mean factor VIIc declined slightly in the placebo group and was unchanged in the tamoxifen group, whereas the median fragment 1-2 declined slightly with placebo and rose slightly with tamoxifen. For both of these coagulation markers, differences comparing tamoxifen and placebo were not statistically significant. Inferences from the data did not change with exclusion of the top 5% of the baseline distribution of each factor.

Associations of treatment assignment with lipid factors are shown in Table 3. Among placebo-assigned participants, the mean cholesterol change was −0.11 mmol/L (−4 mg/dL), a 2.2% reduction over 6 months. Tamoxifen was associated with a mean decline of 0.42 mmol/L (16 mg/dL), representing a 9% reduction ($P=0.009$ comparing tamoxifen with placebo). There was no difference between tamoxifen and placebo for triglyceride change, with values tending to increase in both groups.

Because there is diurnal variation in hemostasis factors and acute dietary influences on hemostasis and lipid factors, we used 2 methods to analyze for an effect of the time of day of phlebotomy on the results for all analytes. First, statistical

TABLE 3. Comparison of Lipid Concentrations at Baseline and 6 Months of Follow-Up by Treatment Assignment

	Baseline				6 Months				Change From Baseline				
Analyte	Mean	SE	Median	IQR	Mean	SE	Median	IQR	Mean	SE	Median	IQR	P*
Cholesterol													
Placebo (n=47)													
mmol/L	4.94	0.13	4.90	4.25–5.91	4.83	0.13	4.66	4.20–5.46	−0.11	0.06	−0.10	−0.39–0.23	
mg/dL	191	5	189	164–228	186	5	180	3.83–4.56	−4	2	−4	−15–9	
Tamoxifen (n=42)													
mmol/L	4.68	0.14	4.56	4.12–5.23	4.26	0.09	4.17	3.83–4.56	−0.42	0.09	−0.36	−0.88–−0.03	0.009
mg/dL	181	5	176	159–202	165	4	161	148–176	−16	3	−14	−34–−1	
Triglycerides													
Placebo (n=47)													
mmol/L	1.72	0.12	1.66	1.13–2.07	2.01	0.16	1.82	1.22–2.41	0.29	0.10	0.20	−0.12–0.55	
mg/dL	152	9	147	100–183	178	14	161	108–213	26	9	18	−11–49	
Tamoxifen (n=42)													
mmol/L	1.52	0.11	1.36	1.20–1.66	1.94	0.18	1.60	1.16–2.33	0.43	0.10	0.29	−0.06–0.75	0.24
mg/dL	134	9	120	106–147	172	16	142	102–206	38	9	26	−5–66	

*Comparison of change over time between the 2 treatment groups.

TABLE 4. Median Change From Baseline to 6 Months in C-Reactive Protein and Fibrinogen by Treatment Group and Categories of Selected Baseline Characteristics

Category of Baseline Factor	Change in C-Reactive Protein, mg/L		Change in Fibrinogen, g/L	
	Placebo	Tamoxifen	Placebo	Tamoxifen
Cholesterol, mmol/L				
≤4.40	0	−0.10	0.13	−0.21
4.41–5.15	0.10	−0.20	−0.02	−0.79
≥5.16	0.05	−0.70	−0.09	−0.79
*P**	0.99	0.07	0.19	<0.001
Menopausal status				
Premenopausal	0	−0.1	0.16	−0.22
Postmenopausal	0.1	−0.4	0.03	−0.75
P	0.97	0.01	0.24	0.06
Smoking status				
Never	0	−0.3	0	−0.68
Former or current	0.1	−0.3	−0.05	−0.49
P	0.44	0.93	0.68	0.36

*Significance level for comparison of 6-month change in the analyte among categories of baseline risk factors.

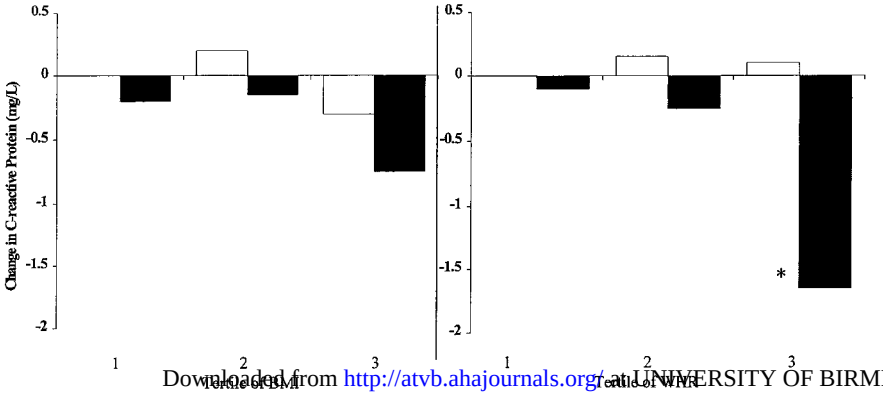
adjustment for morning compared with afternoon phlebotomy did not alter any of the associations of treatment assignment with changes in the blood variables over time. Second, restricting the analyses to 63 women having their pretreatment and their 6-month phlebotomy in the morning did not alter the interpretation of the findings (data not shown).

To study differences in the effects of treatment on fibrinogen and C-reactive protein by baseline factors, analyses were repeated after stratification by factors of interest. Results are shown in Table 4 and the Figure. Among women on placebo, changes in C-reactive protein or fibrinogen did not differ significantly within categories of any of these baseline factors. As shown in the Figure, the effect of tamoxifen on C-reactive protein was influenced by baseline waist-to-hip ratio. Among women taking tamoxifen and in the top waist-to-hip ratio tertile (>0.80), C-reactive protein declined by 1.65 mg/L compared with 0.10 mg/L in the lowest tertile ($P=0.01$ for differences in drug effect by waist-to-hip ratio tertile). Results were similar but not statistically significantly different when categories of baseline body mass index were compared. Menopausal status also appeared to influence changes in C-reactive protein with tamoxifen treatment. Reduction in C-reactive protein was 0.10 mg/L in premenopausal women and 0.40 mg/L in postmenopausal women ($P=0.01$ for comparison of drug effect by menopausal status). Baseline cholesterol tertile influenced the effect of tamoxifen on fibrinogen and perhaps also on C-reactive protein, although the latter was not statistically significant. In those assigned to tamoxifen who had a baseline cholesterol level in the second or third tertile (values >4.40 mmol/L, or >170 mg/dL), fibrinogen declined by 0.79 g/L compared with 0.21 g/L for those with baseline cholesterol in the first tertile ($P<0.001$). There were no treatment effect differences associated with baseline smoking status.

Discussion

Randomized assignment to tamoxifen, compared with placebo, was associated with reductions in fibrinogen, C-reactive protein, and total cholesterol over 6 months of follow-up. There were no effects of tamoxifen on factor VIIc or prothrombin fragment 1-2. Other findings included greater effects of tamoxifen on C-reactive protein in postmenopausal women and in women with higher baseline waist-to-hip ratios. The effect on fibrinogen may be greater in women with higher cholesterol.

If the concentrations of fibrinogen and C-reactive protein represent underlying pathophysiology that is causally related to myocardial infarction, the extent of the effect that we observed might have clinical relevance. For reference, in a prospective study among healthy women who subsequently had coronary heart disease compared with those who did not, respective baseline fibrinogen values (measured in the same laboratory as in the present study) were 3.33 and 3.19 g/L,[23] a difference that is much less than what we observed for the effect of tamoxifen. It is not known whether lowering fibrinogen or C-reactive protein concentrations reduces cardiovascular risk, but 2 clinical trials linking inflammation markers with the pharmacological effects of drugs suggest potential clinical relevance. In these studies, men with the highest C-reactive protein who were randomly assigned to either aspirin for primary prevention or pravastatin for secondary prevention of myocardial infarction (both compared with placebo) had a greater benefit of therapy compared with men with lower C-reactive protein concentrations.[16,25] Furthermore, recent reports suggest that low-dose aspirin and pravastatin have anti-inflammatory effects, as assessed by C-reactive protein and cytokine measurements.[26,27] For example, in the pravastatin trial, which consisted of patients



Average 6-month change in C-reactive protein by treatment group and categories of baseline body size. Solid bars indicate tamoxifen, and open bars indicate placebo. Tertile cut points for body mass index (BMI) are ≤24.5, 24.6 to 29.0, and ≥29.1. Tertile cut points for waist-to-hip ratio (WHR) are ≤0.74, 0.75 to 0.80, and ≥0.81. *$P=0.01$. The *P* value for difference in C-reactive protein change by BMI was 0.16.

TABLE 5. Comparative Effects of Conjugated Estrogens, Raloxifene, and Tamoxifen on C-Reactive Protein and Fibrinogen

	C-Reactive Protein, mg/L			Fibrinogen, g/L		
Drug, daily dose	Before	After	*P*	Before	After	*P*
CEE (0.625 mg)+MPA (2.5 mg)	1.03	1.93	0.0001	2.83	2.84	<0.001
Raloxifene (60 mg)	1.19	1.16	>0.05	3.34	2.92	<0.001
Raloxifene (120 mg)	1.13	1.09	>0.05	3.42	2.96	<0.001
Tamoxifen (20 mg)	1.15	0.80	<0.001	2.91	2.31	<0.001

Data are from randomized trials comparing effects of hormone therapies with placebo, in which laboratory assays were performed in a single laboratory.[18,20,30,31] Effects of different oral estrogen regimens (with or without progestin) were similar.[18,20] CEE indicates conjugated equine estrogens; MPA, medroxyprogesterone acetate. *P* values are for comparison of treatment with placebo. For CEE+MPA effect on fibrinogen, data were derived from Reference 20, Tables 1 and 2. In that study, there was no influence of CEE+MPA on fibrinogen compared with an age-related increase in the placebo group.

with average cholesterol levels, pravastatin reduced C-reactive protein by 17.4%, a value less than that observed in the present study for tamoxifen. These studies raise a hypothesis that drugs may influence cardiovascular risk through inflammation-related mechanisms.

An association of factor VIIc with vascular disease risk has been debated,[22,23,28] and even though fragment 1-2 is higher in women than in men,[29] we are aware of no study to date that has assessed prothrombin fragment 1-2 as a cardiac risk factor in healthy women or men. If confirmed, a lack effect of tamoxifen on factor VIIc and fragment 1-2 would suggest more favorable effects from tamoxifen than from postmenopausal estrogen therapy, which increases the levels of these factors.[12,20,21] Any clinical significance of these differences is uncertain at this time.

The findings in the present study related to inflammation markers differ from recent findings on postmenopausal hormones and raloxifene, another estrogen receptor modulator. Table 5 shows the comparative effects of conjugated estrogens,[18,20] raloxifene,[30,31] and tamoxifen on C-reactive protein and fibrinogen with the use of data from clinical trials in which blood was analyzed in the same laboratory. Although postmenopausal hormones prevent the age-related rise in fibrinogen,[20] they also raise C-reactive protein.[18,19] It has been suggested that a proinflammatory effect of hormone replacement therapy might relate to an increased risk of myocardial infarction shortly after beginning therapy.[18] Raloxifene reduced fibrinogen and cholesterol in 1 study[30] but did not influence C-reactive protein.[31] Differences in the effects of tamoxifen, raloxifene, and estrogen on inflammation markers may prove to have clinical implications for the use of these agents in women at increased cardiovascular risk.

Our findings confirm and strengthen the interpretation of prior reports of lower fibrinogen and cholesterol with tamoxifen[2–6,32] and its analogue droloxifene[33] and provide new information concerning C-reactive protein. When the population of women eligible for tamoxifen for the prevention of breast cancer is considered, relevant features of the present study compared with prior studies are as follows: exclusion of women with cancer,[2,32] prohibition of postmenopausal hormone use concurrent with study medication,[4,6] sufficient power,[4,34] and a double-blind control group.[34]

We observed differences in some biochemical effects of tamoxifen among subgroups of participants defined by meno-pausal status, body size, and cholesterol. Although these subgroup findings require cautious interpretation, hypothetical mechanisms may be discussed. The difference we observed in baseline C-reactive protein concentration by menopausal status may partly explain the effect modification observed by that factor. Central obesity is a known correlate of C-reactive protein,[35,36] and adipocytes are a rich source of interleukin-6, a positive regulatory cytokine for C-reactive protein.[37] We previously reported that C-reactive protein was highest among obese postmenopausal women taking estrogen compared with thin users or nonusers and obese nonusers.[13] Given a hypothesis that adipocyte regulation is involved in these hormone-induced changes in C-reactive protein (together with the present finding), a hypothesis may be made that tamoxifen has "antiestrogenic" effects on adipocyte cytokine production. Finally, a difference in fibrinogen lowering by tamoxifen based on baseline cholesterol may relate to the known positive association of fibrinogen and cholesterol levels,[38] inasmuch as cholesterol is also reduced by tamoxifen.

The major strength of the present study was the randomized, double-blind, placebo-controlled design. Randomization minimized the possibility of confounding by unmeasured variables. High adherence improved confidence that true drug effects were being evaluated. An important limitation was the lack of generalizability, inasmuch as the study population consisted of white women who were at low baseline cardiovascular risk. It is possible that women at risk for breast cancer might differ from other women in these biomarker responses. As in other studies, the present study could not assess relationships of the observed biochemical changes with clinical outcomes such as myocardial infarction. We had insufficient blood volume to determine the effects of tamoxifen on lipid subfractions, but other studies have provided information in this regard.[2–4,6] For practical purposes, phlebotomy for the present study was not always performed in the morning with the subjects in a fasting state. Even though we adjusted for this, diurnal variation was not controlled and may have influenced our results for fragment 1-2,[39] biasing findings toward the null hypothesis. High within-person variability and traumatic venipuncture artifact for fragment 1-2 also might bias to the null; however, we have reported this analyte as relatively stable within individuals,[40] and carefully collected blood samples have minimized the influence of trau-

matic venipuncture on values for fragment 1-2 in the present study and elsewhere.[29] Finally, results of subgroup analyses should be interpreted cautiously because of the relatively small number of participants.

In conclusion, compared with placebo, tamoxifen treatment was associated with 6-month declines of total cholesterol, fibrinogen, and C-reactive protein, all recognized cardiovascular risk factors. These findings support a hypothesis of the cardiac benefits of tamoxifen,[9] in addition to its benefit in lowering the incidence of breast cancer.[1] It is important to note that although the epidemiological evidence relating C-reactive protein and fibrinogen to vascular disease risk is compelling, a cause-effect relationship is not proven. A tamoxifen-lowering effect on these factors might relate either to altered production or degradation, and any clinical consequence of this is unknown. Large clinical trials would be needed to confirm a benefit of tamoxifen-associated changes in lipid, coagulation, and inflammation profiles on vascular outcomes.

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