Effect of Tamoxifen on Serum Cholesterol in Japanese Women with Breast Cancer

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Background: To investigate whether tamoxifen therapy has a favorable effect on plasma lipids, serum cholesterol levels were measured in 228 Japanese women with breast cancer (116 premenopausal women and 112 postmenopausal women).
Methods: These women were treated with tamoxifen or tamoxifen + chemotherapy (tamoxifen-treated group) or were given no therapy or chemotherapy alone (control group).
Results: There was no difference between cholesterol levels before treatment and after a 2-year follow-up period in these groups, except for the postmenopausal tamoxifen-treated group. In this particular group, the mean levels of serum cholesterol after 1 and 2 years of follow-up (197 and 188 mg/dL, respectively) were 8% and 12% lower than those before treatment (215 mg/dL, $P < 0.0001$). In addition, the mean level of serum cholesterol after a 2-year follow-up period was significantly higher in the postmenopausal tamoxifen-treated group than in the postmenopausal control group (218 and 188 mg/dL, respectively, $P = 0.0066$).
Conclusions: In multiple regression models that included age, body mass index, and chemohormonal therapy, only tamoxifen treatment appeared to predict the change between cholesterol levels before treatment and after 2-year follow-up in postmenopausal women. These results suggest that tamoxifen has the potential benefit of reducing the serum cholesterol level, which may be closely related to cardiovascular risk, in Japanese postmenopausal women.

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Key words: tamoxifen, cholesterol, Japanese women, breast cancer, cardiovascular risk

INTRODUCTION

Tamoxifen is one of the standard hormonal therapies for breast cancer.[1] Meta-analyses of adjuvant trials have clearly shown that tamoxifen prolonged overall survival and extended disease-free survival in patients with primary breast cancer.[2] Recent evidence indicates that tamoxifen could increase the risk of endometrial cancer.[3,4] In contrast, it was suggested that tamoxifen could decrease serum lipids in postmenopausal women and reduce the risk of coronary artery disease.[5,6] These effects of tamoxifen remain to be determined in Japan. To investigate the influence of tamoxifen on cardiovascular risk factors, serum cholesterol levels were measured in Japanese women with breast cancer who were or were not treated with tamoxifen.

PATIENTS AND METHODS

From the opening of the National Cancer Center Hospital East in June 1992 until December 1994, 287 patients with breast cancer had been hospitalized in the division of breast surgery. Women with breast cancer who had undergone total or partial mastectomy with axillary dissection were enrolled in this study. Men with breast cancer, women with bilateral breast cancer, double primary cancer, metastatic breast cancer, and those whose disease had relapsed within 1 year during treatment, or those who had no data on serum cholesterol level before treatment were excluded from this study. After all exclusions were made, the remaining 228 patients were selected as the study population.

Patients chose to receive adjuvant chemohormonal therapy having given their informed consent after an explanation of the prognosis based on clinicopathologic factors, and survival benefits and toxicity related to adjuvant therapy. Most patients with node-positive breast cancer and node-negative high-risk breast cancer were receiving cytotoxic chemotherapy, tamoxifen, or tamoxifen + chemotherapy. Chemotherapy consisted of oral fluoropyrimidine compounds (OFP), cyclophosphamide + doxorubicin ± 5-fluorouracil (CA(F)), or cyclophosphamide + methotrexate + 5-fluorouracil (CMF). OFP was administered with tamoxifen for 2 years, and CA(F) and CMF were injected during the initial 5 to 6 months of chemohormonal therapy. Adjuvant therapy was usually started within 4 weeks of surgery. In this study, patients who had received tamoxifen 20 mg (po) daily for at least 6 months were designated as the tamoxifen-treated group, and patients given no adjuvant therapy or

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chemotherapy alone were designated as the control group. No information on smoking and drinking habits was precisely recorded. A few patients receiving lipid-lowering drugs were included in this study: 1 premenopausal and 2 postmenopausal tamoxifen-treated patients, and 2 postmenopausal patients in the control group. No patients were taking additional estrogenic compounds.

Total serum cholesterol was measured enzymatically with a test kit (Mizuho Medy, Torisu, Japan). Blood samples from tamoxifen-treated patients, who were not required to fast, were collected before treatment and after a 1- and 2-year follow-up period. Cholesterol levels of patients in the control group were measured on the same time schedule.

Patient characteristics were analyzed by the chi-square test and the 2-sample t test. Statistical significance was determined by the paired t test for differences between cholesterol levels before treatment and after a 1-year or 2-year follow-up period, and the 2-sample t test for differences between cholesterol levels in the tamoxifen-treated group and the control group. Comparisons on the change between serum cholesterol levels before treatment and after a 2-year follow-up period in premenopausal and postmenopausal women were evaluated by using multiple regression.

RESULTS

Patient characteristics are shown in Table 1. Postmenopausal women had the disease in a more advanced stage and more of them received tamoxifen. The body mass index before treatment was significantly higher in postmenopausal women than in premenopausal women. In addition, mean levels of total serum cholesterol were higher in postmenopausal than in premenopausal women before treatment (211 versus 188 mg/dL, $P < 0.0001$ for 2-sample t test).

There was no significant difference in the type of chemotherapy (OFP, CA(F), or CMF) given to premenopausal and postmenopausal women ($P = 0.363$). Thirty-one premenopausal women and 52 postmenopausal women had received tamoxifen for 2 years or longer. In the premenopausal control group, the mean level of total serum choles-

Table 1. Patient characteristics.[a]

Characteristics	Number of patients (%)		P value
	Premenopausal women	Postmenopausal women	
Total patients	116	112	
Age (y)			
Range	27–54	45–83	
Mean	44	61	
Stage[b]			
0, I	39 (34)	25 (22)	0.02[c]
IIA, IIB	70 (60)	68 (61)	
IIIA, IIIB	7 (6)	18 (16)	
Nodal metastases			
0	73 (63)	66 (59)	0.754[c]
1–9	35 (30)	39 (35)	
≥ 10	8 (7)	7 (6)	
Operation method			
Mastectomy	86 (74)	98 (88)	0.0169[c]
Quadrantectomy	30 (26)	14 (12)	
Adjuvant therapy			
No therapy	42 (36)	34 (30)	< 0.0001[c]
Chemotherapy	26 (22)	4 (4)	
Tamoxifen	5 (4)	28 (25)	
Tamoxifen + chemotherapy	43 (37)	46 (41)	
Duration of tamoxifen Treatment (y)			
< 1	1	1	0.791[c]
1 to < 2	16	21	
≤ 2	31	52	
Body mass index (kg/m^2)			
Range	17–39.6	17–30.2	0.0462[d]
Mean	22.8	23.6	

[a]Comparison of 228 premenopausal and postmenopausal Japanese women who underwent total or partial mastectomy with axillary dissection at the National Cancer Center Hospital East; [b]excluding a postmenopausal patient with unknown stage; [c]analysis of significance by the chi-square test; [d]2-sample t test was used for the difference in values between premenopausal and postmenopausal women.

terol was increased by 6% after a 1-year follow-up period, but showed no further significant change after a 2-year follow-up period (Table 2). In the premenopausal tamoxifen-treated group, no significant change in total serum cholesterol level was observed after 1 and 2 years of follow-up. However, tamoxifen treatment of postmenopausal women was associated with a significant decrease in the mean levels of total serum cholesterol of 8% and 12% after a 1- and 2-year follow-up period (215 versus 197 mg/dL, and 215 versus 188 mg/dL). In the postmenopausal control group, total serum cholesterol levels were slightly increased after 1- and 2-years of follow-up, though there was no significance. Compared with the postmenopausal control group, there was a significant decrease in the mean level of total serum cholesterol in the postmenopausal tamoxifen-treated group after a 2-year follow-up period (Table3).

Table 2. Changes in levels of serum cholesterol after tamoxifen treatment in Japanese women with breast cancer.[a]

Patient group	Pretreatment	1-year follow-up	2-year follow-up
Premenopausal women			
Control group			
No. of patients	68	68	33
TSC[b] (mg/dL)	187 ± 30	198 ± 34	193 ± 35
P value[c]		0.0003	0.162
Tamoxifen-treated group			
No. of patients	48	48	31
TSC[b] (mg/dL)	190 ± 31	186 ± 31	187 ± 31
P value[c]		0.335	0.232
Postmenopausal women			
Control group			
No. of patients	38	38	17
TSC[b] (mg/dL)	205 ± 31	208 ± 35	218 ± 37
P value[c]		0.372	0.399
Tamoxifen-treated group			
No. of patients	74	74	52
TSC[b] (mg/dL)	215 ± 33	197 ± 34	188 ± 31
P value[c]		< 0.0001	< 0.0001

[a]Comparison of the serum cholesterol levels of 228 Japanese women, aged 27–83 years, who underwent total or partial mastectomy with axillary dissection at the National Cancer Center Hospital East. Premenopausal and postmenopausal women were divided into women treated with tamoxifen with or without chemotherapy (tamoxifen-treated group), and women with no therapy or chemotherapy alone (control group); [b]levels of total serum cholesterol (TSC) are expressed as mean ± SD; [c]paired *t* test was used for differences in patients before treatment.

Table 3. Comparison of cholesterol levels after tamoxifen treatment.[a]

Characteristics	Serum cholesterol levels (mean ± SD, mg/dL)		*P* value[b]
	Control group	Tamoxifen-treated group	
Premenopausal women			
Pretreatment	187 ± 30	190 ± 31	0.565
(no. of patients)	(68)	(48)	
2-year follow-up	193 ± 35	187 ± 31	0.481
(no. of patients)	(33)	(31)	
Postmenopausal women			
Pretreatment	205 ± 31	215 ± 33	0.105
(no. of patients)	(38)	(74)	
2-year follow-up	218 ± 37	188 ± 31	0.0066
(no. of patients)	(17)	(52)	

[a]Cholesterol levels are compared in 228 Japanese women, aged 27–83 years, who underwent total or partial mastectomy with axillary dissection at the National Cancer Center Hospital East. Premenopausal and postmenopausal women were divided into women treated with tamoxifen with or without chemotherapy (tamoxifen-treated group), and women with no therapy or chemotherapy alone (control group); [b]2-sample *t* test was used for differences between the 2 groups of patients.

In multiple regression models that included age (continuous), body mass index (continuous), chemotherapy (chemotherapy/no chemotherapy), and hormonal therapy (tamoxifen/no tamoxifen), only tamoxifen appeared to predict the change between total serum cholesterol levels before treatment and after 2-year follow-up in postmenopausal women ($P = 0.0073$). No significant factors predicted the change in total serum cholesterol levels in premenopausal women.

DISCUSSION

Cardiovascular disease is one of the most life-threatening diseases in the world. Hyperlipidemia is associated with an increased risk of cardiovascular disease. The National Cholesterol Education Program showed that the desirable blood cholesterol level is under 200 mg/dL, and that the borderline-high blood cholesterol level ranges between 200 and 239 mg/dL.[7] A recent Danish prospective cohort study found that total cholesterol concentration in women was as closely related to mortality from coronary artery disease as it was in men.[8] A cohort study in Japanese women suggested a positive relationship between total cholesterol and coronary artery disease.[9] Another report indicated that the hormonal change in the menopausal status resulted in a high incidence of hyperlipidemia in Japanese women.[10] The postmenopausal women examined in this study had borderline high blood cholesterol levels, and they will require monitoring of plasma lipids and for the possibility of coronary artery disease.

Many investigators have reported the effect of tamoxifen on serum lipids in postmenopausal women. When tamoxifen had been administered to postmenopausal women for periods of 6 months and 5 years, the levels of total serum cholesterol and low-density lipoprotein cholesterol decreased by 10% to 13%, and by 10% to 22%, respectively.[5,11–14] Love et al. reported favorable changes in atherogenic lipoprotein levels and fibrinogen levels in postmenopausal women treated with tamoxifen.[5] This study showed the same tendency of reduction in total cholesterol levels by 12% in Japanese postmenopausal women receiving tamoxifen for 2 years.

The lipid-lowering effects of tamoxifen in premenopausal women and of chemohormonal therapy (tamoxifen + cytotoxic chemotherapy) have not been clearly determined. A pilot tamoxifen chemopreventive trial showed that tamoxifen reduced total cholesterol levels in premenopausal women as well as in postmenopausal women.[15] When premenopausal and postmenopausal patients with advanced breast cancer received chemohormonal therapy, the levels of total cholesterol and low-density lipoprotein cholesterol were significantly lowered.[16] In this study, total serum cholesterol levels were lowered in postmenopausal women receiving chemohormonal therapy, although tamoxifen did not influence total serum cholesterol levels in premenopausal women treated with tamoxifen or chemohormonal therapy; this is why these premenopausal women had low baseline levels of total serum cholesterol.

One of the mechanisms of the lipid-lowering effect of tamoxifen is its estrogenic effect on lipids and lipoproteins, similar to that of hormone-replacement therapy in peri- and postmenopausal women.[17] Recent studies showed that tamoxifen inhibited lipid peroxidase in rat cardiac microsomes,[18] and that tamoxifen decreased erythrocyte membrane lipids and increased erythrocyte antioxidative enzyme activity in breast cancer patients.[19] Another study showed that cholesterol synthesis was down-regulated by tamoxifen and toremifene to inhibit the conversion of Δ^8-cholesterol to lathosterol.[20] In addition, the plasma homocysteine level, a risk factor of atherosclerotic disease, is lowered in postmenopausal women treated with tamoxifen.[21] These results suggest that tamoxifen may have an indirect effect in preventing atherosclerosis.

The Scottish Cancer Trials Breast Group showed that tamoxifen reduces the risk of myocardial infarction.[6] The limitation of the present study is that there is no evidence of reduction of cardiovascular mortality by tamoxifen in Japanese women. There are few reports of population-based prospective studies about the relationship between cardiovascular risk and serum lipids in Japanese women.[9] Tamoxifen treatment, however, resulted in desirable blood cholesterol levels from borderline-high levels in postmenopausal women with breast cancer. A future study relating to tamoxifen treatment in Japan will need address the favorable and adverse effects of tamoxifen: the prevention of cardiovascular disease and osteoporosis, thromboembolic events, and the risk of endometrial cancer.

In conclusion, tamoxifen is associated with reduced total serum cholesterol levels in Japanese postmenopausal women. This effect may contribute to a favorable change in the risk of cardiovascular disease.

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