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- 1 Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. *Diabetes Care* 1978;1:168-88.
- 2 Chase HP, Jackson WE, Hoops SL, Cockerman RS, Archer PG, O'Brien D. Glucose control and the renal and retinal complications of insulin-dependent diabetes. *JAMA* 1989;261:1155-60.
- 3 Krolewski AS, Warram JH, Christlieb AR, Busick EJ, Khan CR. The changing natural history of nephropathy in type 1 diabetes. *Am J Med* 1985;78:785-94.
- 4 Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
- 5 Viberti GC, Pickup JC, Jarrett RJ, Keen H. Effect of control of blood glucose on urinary excretion of albumin and β_2 -microglobulin in insulin-dependent diabetes. *N Engl J Med* 1979;300:638-41.
- 6 Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. *N Engl J Med* 1985;311:365-72.
- 7 Feldt-Rasmussen B, Mathiesen ER, Deckert T. Effects of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. *Lancet* 1986;ii:1300-4.
- 8 Bending JJ, Viberti GC, Watkins PJ, Keen H. Intermittent clinical proteinuria and renal function in diabetes: evolution and the effect of glycaemic control. *BMJ* 1986;292:83-6.
- 9 Microalbuminuria Collaborative Study Group, UK. Microalbuminuria in type 1 (insulin-dependent) diabetic patients: prevalence and clinical characteristics. *Diabetes Care* 1992;4:495-501.
- 10 Microalbuminuria Collaborative Study Group, United Kingdom. Risk factors

for development of microalbuminuria in insulin dependent diabetic patients: a cohort study. *BMJ* 1993;306:1235-9.

- 11 Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate measurement in man by the single injection method using ^{51}Cr -EDTA. *Clin Sci* 1969;39:169-80.
- 12 Fawdry RM, Gruenewald SM, Collins LT, Roberts AJ. Comparative assessment of techniques for estimation of glomerular filtration rate with $^{99\text{m}}\text{Tc}$ -DTPA. *Eur J Nucl Med* 1985;11:7-12.
- 13 Jarrett RJ, Keen H, Grabauskas V. The WHO multinational study of vascular disease in diabetes; general description. *Diabetes Care* 1979;2:175-86.
- 14 Wiseman MJ, Saunders AJ, Keen H, Viberti GC. Effect of blood glucose control on increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *N Engl J Med* 1985;312:617-22.
- 15 Yip JWC, Mattock BM, Morocutti A, Sethi M, Trevisan R, Viberti GC. Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. *Lancet* 1993;342:883-7.
- 16 Feldt-Rasmussen B, Mathiesen ER, Jensen T, Lauritzen T, Deckert T. Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. *Diabetologia* 1991;34:164-70.
- 17 Viberti GC, Mogensen CE, Groop LC, Pauls JF for the European Microalbuminuria Captopril Study Group. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. *JAMA* 1994;271:275-9.
- 18 Dahl-Jorgensen K, Bjørø F, Kierulf P, Sandvik L, Bangstad HJ, Hanssen KF. Long-term glycaemic control and kidney function in insulin-dependent diabetes mellitus. *Kidney Int* 1992;41:920-3.
- 19 Beck Nielsen H, Olesen T, Mogensen CE, Richelsen B, Olsen HW, Ehlers N, et al. Effect of near normoglycaemia for 5 years on progression of early diabetic retinopathy and renal involvement. *Diabetes Res* 1990;15:185-90.
- 20 Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;329:304-9.
- 21 Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the diabetes control and complications trial. *Kidney Int* 1995;42:1703-20.
- 22 Earle K, Viberti GC. Familial, hemodynamic and metabolic factors in the predisposition to diabetic kidney disease. *Kidney Int* 1994;45:434-7.
- 23 Walker JD, Close CF, Jones SL, Rafferty M, Keen H, Viberti GC, et al. Glomerular structure in type 1 (insulin dependent) diabetic patients with normo- and microalbuminuria. *Kidney Int* 1992;41:241-8.
- 24 Parving HH, Hammon E, Skjøtt P, Edsberg P, Bahnsen M, Lauritzen M, et al. Prevalence of microalbuminuria, retinopathy and neuropathy in patients with insulin-dependent diabetes. *BMJ* 1988;296:156-60.
- 25 Hanssen KF, Dahl-Jorgensen K, Lauritzen T, Feldt-Rasmussen B, Bruchmann-Hansen O, Deckert T. Diabetic control and microvascular complications: the near-normoglycaemia experience. *Diabetologia* 1986;29:677-84.

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Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomised trial

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Abstract

Objective—To determine any cardiac or vascular morbidity associated with long term treatment with tamoxifen given after mastectomy for primary breast cancer.

Design—Cohort study using linkage between database of a randomised trial and statistics of Scottish hospital inpatients to identify episodes of cardiac and vascular morbidity.

Setting—NHS hospitals in Scotland.

Subjects—1312 women who had undergone mastectomy for breast cancer and who were randomised either to a treatment group to receive adjuvant tamoxifen or to a control group to be given tamoxifen only on first relapse of disease. Maximum duration of tamoxifen treatment was 14 years. Total woman years of follow up were 9943.

Main outcome measures—Randomised and observational comparisons of risk (expressed as hazard ratios) of myocardial infarction, other cardiac event, cerebrovascular disease, or thromboembolic event according to treatment allocated and between non-users, former users, and current users of tamoxifen.

Results—Use of tamoxifen was associated with lower rates of myocardial infarction. Hazard ratio for women in control group was 1.92 (95% con-

fidence interval 0.99 to 3.73) compared with women allocated to adjuvant treatment. The association was stronger for current use: hazard ratio for non-users was 3.49 (1.52 to 8.03) compared with current users. Current users of tamoxifen, however, had higher rates of thromboembolic events: hazard ratio for non-users was 0.40 (0.18 to 0.90) compared with current users.

Conclusions—Our results provide further evidence that tamoxifen reduces the risk of myocardial infarction. Thromboembolic events should be carefully monitored in trials of tamoxifen, particularly those of prophylactic treatment, in which tamoxifen is given to healthy women.

Introduction

Tamoxifen, an oestrogen receptor antagonist, is widely used as an adjuvant treatment for primary cancer of the breast. The optimal duration of adjuvant treatment has not been established, and, although present indications suggest that five years of treatment is better than two years or less, it is possible that this should be life long. Several large trials of tamoxifen as a prophylactic treatment are also now under way. As these expose large numbers of healthy women to the

drug, it is essential to assess the long term effects of treatment.

We previously reported that in the Scottish adjuvant tamoxifen trial women given long term adjuvant tamoxifen treatment showed a significant decrease in the number of deaths from myocardial infarction compared with those randomised for no adjuvant treatment.¹ There was no significant difference in the incidence of other fatal vascular events between the two arms of the trial.

In order to take account of non-fatal myocardial infarctions and other forms of cardiac and vascular disease, we now report the incidence of several potentially relevant events requiring admission to hospital in both arms of the trial population. These have been ascertained by linkage between the database of the tamoxifen trial and the Scottish Health Service computerised inpatient record scheme at the Information and Statistics Division. As this scheme records the diagnosis for all acute admissions to NHS hospitals in Scotland, we have been able to identify all relevant admissions to Scottish hospitals of trial patients after their mastectomy. Admissions to mental health institutions and obstetric units are not covered by the scheme.

Patients and methods

Between 1978 and 1984, 1312 eligible women with primary operable breast cancer were entered into the Scottish adjuvant tamoxifen trial.² Of these, 242 (18%) were premenopausal, being within one year of their last menstrual period. Women in the treatment arm of the trial received tamoxifen 20 mg daily for five years after their mastectomy (or until earlier relapse); women in the control arm did not receive adjuvant tamoxifen, but this was to be given for treatment of later relapse of disease. Women in the treatment arm who were alive and still free of relapse at five years were offered further randomisation either to stop tamoxifen treatment or to continue taking it until relapse or death. Information on recurrence and death was sought annually.

No baseline data were available for factors not considered relevant to survival from breast cancer. In particular information on smoking, blood lipids, weight, and blood pressure (important factors in cardiovascular morbidity) was not collected.

In designing the present study, we decided to include all eligible women rather than just postmenopausal women as previously¹ because our intention was to examine a range of potential health related effects and the inclusion of younger women would not increase the incidence of myocardial infarction itself.

DATA LINKAGE

A computerised linkage program at Information and Statistics Division attempted to identify episodes in the computerised inpatient record scheme for all trial patients for the period from 1 January 1978 to 31 December 1992. Surname, forename, date of birth, date of mastectomy, and date of death (if appropriate) were used as matching items. A probability based score was used to measure the likelihood of two records matching. The odds of a correct match were calculated for each variable and multiplied together to give the

overall probability that the two records belonged to the same person. The threshold value was kept low to minimise the risk of true matches being rejected.

In the Scottish cancer trials office each matching pair of records was checked. For each confirmed match, the date of admission and code of cause³ (other than those related to breast cancer) were added to the existing trial database. This included dates of patients' birth, randomisation, local and systemic relapse, and death. Allocated treatment and its duration were entered for all trial subjects. From the resulting database all the above items except locoregional relapse alone were extracted for the analysis. Table I shows the causes of hospital admissions considered in this report. These categories were defined before the data were inspected. Because of the small numbers involved, deep vein thrombosis and pulmonary embolus were analysed as a single group of thromboembolic events. Most of the subjects admitted to hospital for both deep vein thrombosis and pulmonary embolism had identical dates for the two; when they differed the earlier of the two dates was taken as the date of the thromboembolic event.

STATISTICAL ANALYSIS

To avoid the possible confounding effect of systemic recurrence of breast cancer and consequent treatment, each subject was considered to be at risk for the analysed events from the date of randomisation up to, but not beyond, that of any systemic recurrence.

Statistical evaluation was by the Cox proportional hazards method using the EGRET package, with censoring at date of systemic relapse, death, or at follow up to 31 December 1992. Results are given as hazard ratios and 95% confidence intervals. A hazard ratio greater than 1 indicates a benefit from tamoxifen, which is significant if the confidence interval does not overlap unity. All analyses were adjusted for age at entry.

TABLE II—Woman years at risk in treatment and control arms of study by exposure to tamoxifen

Woman years at risk*	Treatment arm (n=661)	Control arm (n=651)
Before use of tamoxifen†	224	3982
While using tamoxifen	3750	431
After stopping tamoxifen use	1457	99
Total	5431	4512

*Time from entry to trial to end of follow up period or to first systemic relapse.

†This is "never used tamoxifen" category.

The primary analysis investigated the main effect of treatment allocated by randomisation. As this did not take account of stopping treatment in the treatment arm or giving tamoxifen for locoregional relapse in controls (table II), additional analyses were carried out with time dependent covariates to examine risk according to actual tamoxifen use. Specifically, two factors were introduced: firstly, for comparison of women who never used tamoxifen with those who ever used it, women took the value 1 (never) until they were prescribed tamoxifen, after which the value changed to 2 (ever). The second factor, for current use of tamoxifen, had the value 2 at times of prescribed tamoxifen treatment (current user) and 1 at other times (not a current user). The values of these factors were known at all times for women in the trial. A third factor, the results of which are not reported in detail, took three values (never, current user, former user) defined in a similar way. Since the number of events available for analysis was small, the potential for checking the model's assumptions was limited. Details of the complexity of time dependent covariate analysis have been described elsewhere.⁴

TABLE I—Causes of hospital admissions included in study and numbers of cases analysed and of cases rejected because of presence of systemic cancer

International Classification of Diseases, Ninth Revision ³		No of cases	
Description	Code	Analysed	Excluded
Myocardial infarction	410	37	9
Cerebrovascular disease	430-437	45	7
Pulmonary embolism or phlebitis and thrombophlebitis	4151, 451	25	10
Other ischaemic heart diseases	411-414	42	10

Results

Subjects in the two arms of the study were well matched for age and menstrual status. The mean age in the treatment arm was 58.6 years (range 30-79) while that in the control arm was 59.1 years (27-79). In the treatment arm 18.5% of women were premenopausal, and 18.4% were premenopausal in the control arm.²

HOSPITAL ADMISSIONS

The incidence of hospital admission for myocardial infarction (fatal and non-fatal) was lower in the treatment arm of the study than in the control arm, and this difference was of borderline significance (table III, fig 1). There was also an apparent reduction in the incidence of other ischaemic cardiac episodes in the treatment arm, but this did not reach significance. There was a slight increase in the number of hospital admissions for thromboembolic events in the treatment arm, but there were no differences in admissions for cerebrovascular events (table III, fig 1).

TABLE III—Number and rate of adverse events and hazard ratio for women in control arm of study compared with those in treatment arm

Event	No of events (crude rate/1000 years at risk)		Hazard ratio (95% confidence interval)	P value
	Treatment arm (n=661)	Control arm (n=651)		
Myocardial infarction	14 (2.6)	23 (5.1)	1.92 (0.99 to 3.73)	0.051
Cerebrovascular disease	25 (4.6)	20 (4.4)	0.96 (0.53 to 1.73)	0.89
Thromboembolic event*	15 (2.8)	10 (2.2)	0.76 (0.34 to 1.70)	0.50
Other ischaemic heart disease	18 (3.3)	24 (5.3)	1.56 (0.85 to 2.87)	0.15

*Deep vein thrombosis or pulmonary embolism.

FIG 1—Survival curves for women randomised to adjuvant tamoxifen treatment or to control for the four study end points

TABLE IV—Number and rate of adverse events and hazard ratio for women who never used tamoxifen compared with those who ever used it

Event	No of events (crude rate/1000 years at risk)		Hazard ratio (95% confidence interval)	P value
	Ever used tamoxifen	Never used tamoxifen		
Myocardial infarction	15 (2.6)	22 (5.2)	2.03 (1.05 to 3.92)	0.033
Cerebrovascular disease	28 (4.9)	17 (4.0)	0.87 (0.47 to 1.59)	0.65
Thromboembolic event*	17 (3.0)	8 (1.9)	0.61 (0.26 to 1.42)	0.24
Other ischaemic heart disease	20 (3.5)	22 (5.2)	1.55 (0.84 to 2.84)	0.16

*Deep vein thrombosis or pulmonary embolism.

TABLE V—Number and rate of adverse events and hazard ratio for women who were not current users of tamoxifen compared with current users

Event	No of events (crude rate/1000 years at risk)		Hazard ratio (95% confidence interval)	P value
	Current users	Not current user*		
Myocardial infarction	7 (1.7)	30 (5.2)	3.49 (1.52 to 8.03)	0.001
Cerebrovascular disease	15 (3.6)	30 (5.2)	1.31 (0.69 to 2.46)	0.40
Thromboembolic event†	15 (3.6)	10 (1.9)	0.40 (0.18 to 0.90)	0.025
Other ischaemic heart disease	12 (2.9)	30 (5.2)	1.73 (0.87 to 3.43)	0.10

*Never used tamoxifen or former user.

†Deep vein thrombosis or pulmonary embolism.

FIG 2—Numbers of women by category of tamoxifen use and time since randomisation

TAMOXIFEN USE

The patterns of tamoxifen use were complex (fig 2). In the event of a relapse of disease women in the treatment arm stopped taking tamoxifen whereas women in the control arm started taking tamoxifen. In addition a secondary randomisation altered the duration of tamoxifen use in the treatment arm.

When actual tamoxifen use was taken into account, the effect on risk of myocardial infarction was increased for the comparison of those who had ever used tamoxifen with those who had never used it (hazard ratio 2.03 (95% confidence interval 1.05 to 3.92)) (table IV) and for the comparison of current users with not current users (hazard ratio 3.49 (1.52 to 8.03)) (table V). Further analysis, comparing all three categories of tamoxifen use, showed that patients who had never received tamoxifen had a risk of hospitalisation for myocardial infarction (hazard ratio 3.36 (1.43 to 7.88) compared with current users) similar to that of former users (4.10 (1.39 to 12.13)).

THROMBOEMBOLIC EVENTS

Hospital admissions for the thromboembolic events of deep vein thrombosis and pulmonary embolus were increased in tamoxifen users, but this reached significance only for comparison of current users with not current users (table V).

The 15 current users who had a thromboembolic event ranged in age from 42 to 78 years (median 67) and had been receiving tamoxifen for between one and 134 months (median 62). Four of the women had been premenopausal at the time of starting tamoxifen treatment and had taken tamoxifen for 11, 38, 62, and 97 months.

Checking hospital discharge data for the six months before the thromboembolic event revealed that eight of the 25 cases had had inpatient surgery during this time. The time between surgery and the thromboembolic event was between three and seven weeks. Six of the eight patients were current users of tamoxifen, and two were in the control group. A ninth patient, a former user, had metastatic colon cancer. The results of reanalysis with these nine cases excluded showed no increased risk for women randomised to tamoxifen treatment and a smaller effect, with loss of statistical significance, in the comparison of current users with not current users.

Discussion

The primary comparison of the effects of allocated tamoxifen treatment (table III, fig 1) has greatest reliability because the equivalence of the groups on unmeasured baseline factors should be ensured by randomisation, but the effect of tamoxifen may be diluted by failure to take account of subsequent changes in its use. The analyses using time dependent covariates take account of this factor but, being observational in nature, are less reliable. We do not know that the women being compared in these analyses have equal distributions of risk factors and we acknow-

Key messages

- Increasing use of tamoxifen as adjuvant treatment for breast cancer and its use as a prophylactic in clinical trials highlight the need to determine the consequences of long term treatment
- In this study the database for the Scottish adjuvant tamoxifen trial was matched with records of inpatients in Scottish hospitals
- Tamoxifen treatment resulted in significant reduction in incidence of hospital admission for myocardial infarction
- There was some evidence that tamoxifen increased risk of pulmonary embolism
- The benefits of tamoxifen treatment for breast cancer outweigh any adverse effects, but healthy women in clinical trials should be monitored for thromboembolic events

ledge that the absence of information on smoking and blood pressure is a limitation, but we have no reason to suppose that these are associated with the decision to change treatment. The main reason for the change of status of women remaining in the analysis was locoregional relapse of disease which occurred more often in women in the control arm.² Treatment other than tamoxifen could possibly increase the risk of cardiovascular morbidity, and the observational comparisons may therefore underestimate the benefit for myocardial infarction but could overemphasise the risk of deep vein thrombosis and pulmonary embolism.

CARDIOVASCULAR AND CEREBROVASCULAR MORBIDITY

Our results indicate a protective effect of tamoxifen against hospital admission for acute myocardial infarction. This protection was greatest in current users and so may be lost when tamoxifen treatment is stopped. This is consistent with our previous report of fatal episodes. Our findings are also in keeping with reports that concentrations of plasma cholesterol and its low density lipoprotein fraction are lower in current tamoxifen users than in former and non-users.⁵⁻⁸ These factors are known to be related to coronary artery disease in men.⁹

A study of cardiovascular morbidity in 2365 patients in the Swedish trial of adjuvant tamoxifen reported a significant reduction of all cardiac disease in patients receiving tamoxifen,¹⁰ but there was no apparent decrease in either the myocardial infarction or ischaemic heart disease subgroup. As well as showing a reduction in myocardial infarction, our data suggest that ischaemic heart disease may have been reduced in the tamoxifen users. We found little association of tamoxifen use with cerebrovascular events (cerebral haemorrhage and cerebral thrombosis). Analysis of all cerebrovascular events in the Swedish data (similar to our cerebrovascular disease category) also failed to show an effect (Rutqvist, personal communication).

THROMBOEMBOLIC EVENTS

The Swedish workers failed to find a difference in the incidence of "thromboembolic disease" between patients receiving adjuvant tamoxifen and controls. They included cerebral thrombosis in this category. In our separate analysis of the effect of tamoxifen on the specific thromboembolic events of deep vein thrombosis and pulmonary embolism, the patients taking tamoxifen seemed to be at greater risk, but this was significant only in the analysis by current use (table V).

Our finding clarifies the effect of tamoxifen described in a retrospective review of venous and arterial thromboembolic complications in seven consecutive trials of adjuvant treatment for breast cancer conducted by the Eastern Cooperative Oncology Group.¹¹ This indicated a substantially greater number

of events in premenopausal patients receiving chemotherapy and tamoxifen than in those receiving chemotherapy alone. It has been suggested that a decrease in levels of antithrombin III in women treated with tamoxifen may be one factor contributing to hypercoagulability.¹²

Unlike in the above review, we censored for systemic relapse in our analysis, reducing the likelihood that the observed increase in thromboembolic events was related to breast cancer. Nine thromboembolic events occurred in patients who might be considered to have been at increased risk due to recent surgery or similar factors, but the time gap of 3-7 weeks between the two events decreases the likelihood of a direct relation. We could not identify all those who had had additional surgery without experiencing a thromboembolic event.

The numbers of subjects in our study are small, and the results concerning deep vein thrombosis and pulmonary embolism (our thromboembolic disease) should be interpreted with caution. However, they indicate that the incidence of thromboembolic events within tamoxifen prevention trials should be carefully monitored and that women entering these trials must be informed of this potential risk.

CONCLUSION

It is important to appreciate that our results do not cast doubt on the evidence that adjuvant tamoxifen is beneficial to women with breast cancer. In addition, our results and those which we have previously reported concerning fatal myocardial infarction¹ demonstrate an additional benefit for users of tamoxifen which is greater than any possible harmful thromboembolic effects.

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- 1 McDonald CC, Stewart HJ, for the Scottish Breast Cancer Committee. Fatal myocardial infarction in the Scottish adjuvant tamoxifen trial. *BMJ* 1991;303:435-7.
- 2 Scottish Breast Cancer Trials Committee. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish trial. *Lancet* 1987;ii:171-5.
- 3 *International classification of diseases, ninth revision* Geneva: World Health Organisation, 1978.
- 4 Altman DG, de Stavola BL. Practical problems in fitting a proportional hazards model to data with updated measurements of the covariates. *Stat Med* 1994;13:301-41.
- 5 Dewar JA, Horobin JM, Preece PE, Tavendale R, Tunstall-Pedoe H, Wood RAB. Long term effects of tamoxifen on blood lipid values in breast cancer. *BMJ* 1992;305:225-6.
- 6 Cuzick J, Allen D, Baum M, Barrett J, Clark G, Kakkar V, et al. Long term effects of tamoxifen. *Eur J Cancer* 1993;29A:15-21.
- 7 Bruning PF, Bonfrer JMG, Hart AAM, de Jong-Bakker M, Linders D, van Loon J, et al. Tamoxifen, serum lipoproteins and cardiovascular risk. *Br J Cancer* 1988;58:497-9.
- 8 Love RR, Newcomb PA, Wiebe DA, Surawicz TS, Jordan VC, Carbone PP, et al. Effects of tamoxifen therapy in postmenopausal patients with node-negative breast cancer. *J Natl Cancer Inst* 1990;16:1327-32.
- 9 The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988;148:36-9.
- 10 Rutqvist LE, 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. *J Natl Cancer Inst* 1993;85:1398-406.
- 11 Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis for patients who received adjuvant therapy for breast cancer. *J Clin Oncol* 1991;9:286-94.
- 12 Jordan VC, Fritz NF, Tormey DC. Long-term adjuvant therapy with tamoxifen: effects on sex hormone binding globulin and antithrombin III. *Cancer Res* 1987;47:4517-9.

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