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Papers

Long Term Effects of Tamoxifen

Biological Effects of Tamoxifen Working Party

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A total of 153 breast cancer patients who participated in two trials of adjuvant tamoxifen and who had not recurred were recruited into a study of the long term effects of tamoxifen. There were 60 controls (no tamoxifen), 73 ex-users (mostly for 2 years) and 20 current users (median treatment duration 72 months) and the median follow-up time was 7 years. A wide ranging study of lipids, hormones, bone density and haemostasis was undertaken. When compared with controls, current users had lower cholesterol levels (especially low density cholesterol), and increased triglyceride levels. Thyroid hormones were higher and sex hormone binding globulin was almost doubled. Bone density was non-significantly higher, clotting times were slightly shorter and fibrinogen and antithrombin III levels were reduced. However few of these changes persisted in ex-users, suggesting that most of the biological effects of treatment are reversible on cessation of treatment. This is reassuring for potentially negative side-effects, but also indicates that potentially positive 'side-effects' such as cholesterol lowering only occur while on active treatment.
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INTRODUCTION

THE EFFICACY of tamoxifen in preventing recurrence and death from breast cancer in the adjuvant setting has now been firmly established [1]. Its low side-effect profile and indications from animal studies that it is more effective when used early in the natural history and for long periods [2, 3] has led to the suggestion that it may have a role to play in preventing breast cancer [4]. The first indication of such an action in humans was reported by Cuzick and Baum [5] where a substantial reduction in new contralateral breast tumours was reported in women taking tamoxifen to prevent the recurrence of an early breast cancer. This observation has now been confirmed by many other groups and overall a one-third reduction in tumours has been found [1, 6].

These observations have led to the use of tamoxifen for longer periods in the adjuvant setting and also to plans for using it as a chemopreventive agent in women who do not have breast cancer, but who are at some increased risk of developing it. This expansion of its use calls for further studies of potential side effects, particularly those which may not become apparent for some time after use.

Side effects in the short term have been minimal [7, 8] and metabolic studies of patients who are still taking tamoxifen are also encouraging. In particular it has been found that women taking tamoxifen experience a 10–20% drop in LDL-cholesterol [9–15] while HDL-cholesterol appears either unchanged or slightly increased, suggesting that tamoxifen may have a beneficial effect on heart disease mortality. Short term studies of bone mineral content have also suggested that tamoxifen does not accelerate osteopenia [8, 15, 16] and may actually help to slow down its inevitable occurrence leading to osteoporosis in postmenopausal women. Concern about thromboembolic problems and levels of steroid sex hormones have also been investigated in patients still receiving tamoxifen [15, 17, 18].

Less information is available on possible effects of tamoxifen several years after treatment had been started, and to examine this we have undertaken an in-depth study using women who many years ago took part in a randomised trial in which one arm received tamoxifen for 2 years as adjuvant therapy. Only women who have not had a recurrence were studied and women in the no treatment arm of the trial have been used as controls.

PATIENTS AND METHODS

Patients

A total of 153 women were recruited from the Nolvadex Adjuvant Trial Organisation (NATO) and Cancer Research Campaign (CRC) Adjuvant Tamoxifen trials, which entered patients between 1977 and 1985. The median follow-up time was 7 years. All of them had been randomised to receive tamoxifen or not for 2 years. After 2 years a small number elected to continue receiving tamoxifen for a further period, most of whom were still receiving the drug at the time of this study. The women were divided into three groups; controls, ex-users of tamoxifen and current users. There were 60 controls, 73 ex-users and 20 current users of tamoxifen. For the ex-users the duration of treatment was 24 months in 83% of the women.

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The median time that the ex-users had been off tamoxifen was 58 months (interquartile range 47–74 months). Those currently on tamoxifen had taken the drug for a median of 72 months (interquartile range 67–90 months).

Methods

153 women previously entered into either the NATO [19] or CRC Adjuvant Breast Trial [20] and living in the Home Counties (approx. 50 mile radius around London), attended King's College Hospital (KCH) on a single occasion between November 1988 and March 1991. Following the initial diagnosis of breast cancer these women had been entered into either of the two mentioned trials and randomised to receive tamoxifen (20 mg/day) or no tamoxifen, the control group. All women studied were well, with no evidence of any recurrent disease.

All women were seen in the morning after having fasted overnight. Upon arrival at KCH Nuclear Medicine Department, a 30 ml venous blood sample was taken, a medical history questionnaire was completed and measurements of bone density, height, weight and blood pressure were made. The women were asked to provide a 20 ml early morning urine specimen for the measurement of creatinine, hydroxyproline and urinary calcium. The results of the urine assays will be reported elsewhere.

20 ml of the blood sample was separated within 2 h, divided into 1 ml aliquots, and then frozen at −20°C. 10 ml of whole fresh blood was dispatched immediately to the KCH Thrombosis Research Institute for the coagulation screen tests. The remaining samples were stored and batches were sent to the other research teams for their studies to examine the effects of tamoxifen on lipids, hormones and bone density. All samples were analysed without knowledge of the treatment group or results from the other parts of the study.

Lipids

Triglyceride levels, total cholesterol, HDL- and LDL-cholesterol, apolipoprotein A1 and B were measured. Total cholesterol and triglyceride were measured using routine enzymatic techniques on an Olympus AU 5022 multichannel analyser. HDL-cholesterol was measured similarly in serum following selective precipitation of apo B containing lipoproteins with dextran sulphate-magnesium chloride [21]. LDL-cholesterol was calculated from these measurements by the Friedwald formula [22]. Apolipoproteins A1 and B were measured by Beckman rate nephelometric technique on a Beckman Array Immunochemistry System.

Hormones

Total oestradiol (E_2), testosterone (T), prolactin (HPR), dehydroepiandrosterone (DHEA), sex hormone binding globulin (SHBG), triiodothyronine (T_3) and thyroxine (T_4) were measured in serum.

Oestradiol was measured in diethyl ether extracts of serum by radioimmunoassay (RIA) using Clinical Sciences antiserum (INCSTAR Ltd., Wokingham, Berks). Testosterone was similarly extracted from serum and measured using STRIA kits (Dept of Chemical Pathology, St Thomas' Hospital Medical School, London). DHEA was measured by 'Coat a Count' kits (DPL, Abingdon Business Park, Abingdon, Oxon). Prolactin, T_3 and T_4 in serum were assayed using NETRIA kits (North East Thames Region Immunoassay Unit, St Bartholomews Hospital, London). SHBG was measured using the Farmos IRMA kit supplied by Pharmacia (GB) Ltd, (Milton Keynes, Bucks).

Table 1. Study group divided according to tamoxifen use and menopausal status

	Ex-users	Controls	Current users	Total
Premenopausal	11	6	1	18
Postmenopausal	55	47	14	116
Unclassified	7	7	5	19
Total	73	60	20	153

Bone density

Measurements were not available for the first 21 patients. In the remaining 132 patients, bone mineral content and density were measured in the lumbar spine (L2–L4) and in the neck of the femur (trochanter) using Dual Energy X-ray Absorptiometry, NORLAND XR-26. Only the data on density are presented here.

Haemostasis

A detailed screen was performed on fresh blood samples from the 153 women. Five women with a previous deep vein thrombosis (DVT) were excluded, as was another woman where the date of a DVT was unknown. Kaolin cephalin clotting time (KCCT), thrombin time (TT) and prothrombin time (PT) were determined as well as levels of fribinogen, plasminogen, fast α_2-antiplasmin, antithrombin III and protein C antigen. Euglobulin clot lysis time was measured in the first 100 women, but for the last 53 women in the study this measurement was replaced by the tissue plasminogen activator activity (t-PA) and plasminogen activator inhibitor activity (PAI) assays. However there are not enough of these measurements for analysis once stratified by menopausal status and tamoxifen use.

Values were standardised by comparison with a citrated normal human plasma pool (NHP) taken from 32 healthy blood donors, aged 25–55 years. This standard was included in every run and results are given in terms of a ratio to this standard.

Blood for these tests was drawn into a citrated anticoagulant buffer (9 parts blood to 1 part 0.1 mol/l sodium citrate). Plasma samples were used fresh for the preparation of euglobulin fractions, or aliquotted and frozen at −70°C until analysis.

The global clotting times, KCCT, TT, PT and fibrinogen were measured on an Automated Coagulation Laboratory (ACL 300R), using kits from IL (Warrington, UK); (IL-Test APTT, IL-Test TT, IL-Test PT-Fibrinogen HS). The activities of plasminogen, ATiii and fast α_2-antiplasmin were also assayed on the ACL 300R, again using IL kits; (IL-Test Plasminogen, IL-Test Antithrombin III and IL-Test Fast α_2-Antiplasmin), with an IL calibration plasma used as the normal control. The euglobulin clot lysis time (ECLT), using euglobulin fractions, was measured by the method of Marsh [23]. Protein C antigen levels were measured using enzyme-immunoassay kits from Diagnostica Stago, France (asserachrom Protein C).

The results of the global clotting times are expressed as a ratio of patient value:normal human pooled plasma (control) value.

Statistical methods

Median values for the groups are shown in Tables 1–5 and the Wilcoxon two-sample test is used for comparing groups. A more complete representation of the data is given graphically,

Table 2. Lipids. Median values by tamoxifen use and menopausal status

	Ex-users	Controls	Current users
Premenopausal	(n = 11)	(n = 6)	(n = 1)
Triglycerides (mmol/l)	0.85	0.92	2.60
Total cholesterol (mmol/l)	5.33	5.58	3.95
HDL-cholesterol (mmol/l)	1.21	1.17	0.67
LDL-cholesterol (mmol/l)	3.70	3.62	2.09
Apolipoprotein A1 (g/l)	2.00	1.70	1.50
Apolipoprotein B (g/l)	0.80	0.70	0.80
Postmenopausal	(n = 55)	(n = 47)	(n = 14)
Triglycerides (mmol/l)	1.31*	1.12	1.33*
Total cholesterol (mmol/l)	7.00	6.63	5.81*
HDL-cholesterol (mmol/l)	1.13*	1.29	1.11*
LDL-cholesterol (mmol/l)	5.20	4.82	3.75*
Apolipoprotein A1 (g/l)	1.90	1.95	2.15
Apolipoprotein B (g/l)	1.15	1.00	1.00

*$0.01 < P < 0.05$.

where all values are normalised to the median of the control group. All significance levels are two-sided.

RESULTS

Women were first divided into two groups by menopausal status. Women who had had a hysterectomy were classified as postmenopausal if they were over 55 years of age or had had both ovaries removed, unless their oestrogen levels were found to be very high, in which case they were excluded (4 cases). All the other women who had had a hysterectomy were also excluded (15 cases). Table 1 shows the number of women in each tamoxifen treatment group. Only one premenopausal woman was still taking tamoxifen at the time of the study and this category has been omitted from the statistical analyses, but is recorded in the tables. No differences between the treatment groups could be found with regard to age, height, weight, Quetelet's index (QI), smoking history, use of oral contraceptives or hormone replacement therapy.

Table 3. Hormones. Median values by tamoxifen use and menopausal status

	Ex-users	Controls	Current users
Premenopausal	(n = 11)	(n = 6)	(n = 1)
SHBG (nmol/l)	88	83	136
Prolactin (mIU/l)	230	202	202
Total oestradiol (pmol/l)	262	294	204
Testosterone (nmol/l)	1.83	2.20	2.59
DHEA (nmol/l)	6.40	7.70	8.40
T_3 (nmol/l)	1.78	1.60	2.63
T_4 (nmol/l)	93.7	93.3	142.1
Postmenopausal	(n = 55)	(n = 47)	(n = 14)
SHBG (nmol/l)	62	55	105‡
Prolactin (mIU/l)	140	129	100
Total oestradiol (pmol/l)	30	32	30
Testosterone (nmol/l)	2.13	2.04	2.21
DHEA (nmol/l)	5.50	5.10	6.55
T_3 (nmol/l)	1.81	1.81	2.15†
T_4 (nmol/l)	96.9	97.6	126.9†

*$0.01 < P \leq 0.05$; †$0.001 < P \leq 0.01$; ‡$P \leq 0.001$.

Table 4. Bone density. Median values by tamoxifen use and menopausal status

	Ex-users	Controls	Current users
Premenopausal	(n = 8)	(n = 6)	(n = 1)
BMD spine (g/cm^2)	1.02	1.08	1.14
BMD trochanter (g/cm^2)	0.73	0.79	0.81
Postmenopausal	(n = 43)	(n = 44)	(n = 14)
BMD spine (g/cm^2)	0.92	0.97	1.08
BMD trochanter (g/cm^2)	0.75	0.75	0.81

Lipids

The results of the lipid study are shown in Table 2 and Figs 1 and 2. No significant differences were found between controls and ex-tamoxifen users except for an increased level of triglycerides in the postmenopausal group ($P = 0.02$) and a marginally decreased level of HDL-cholesterol ($P = 0.05$). Similar differences were seen in current users. Triglyceride levels were slightly lower and HDL-cholesterol levels slightly higher for ex-users in the premenopausal group. In the postmenopausal group, total cholesterol levels were 12% lower for current users. This was mostly due to a 22% lower level of LDL-cholesterol ($P = 0.02$) but HDL-cholesterol levels were also 14% lower ($P = 0.04$). Triglyceride levels were also 19% higher in current users ($P = 0.03$).

Hormones

There are marked differences between pre and postmenopausal levels of all the hormones measured except for testoster-

Table 5. Haemostasis. Median values by tamoxifen use and menopausal status, where appropriate

	Ex-users	Controls	Current users
	(n = 68)	(n = 60)	(n = 19)
KCCT (standard = 1.00)	1.00*	1.07	0.95*
Thrombin time (standard = 1.00)	1.00	1.01	1.08
Prothrombin time (standard = 1.00)	0.90	0.91	0.87
Fibrinogen (mg/ml)	3.46	3.60	2.82‡
Plasminogen (% NHP)	107	110	126*
Fast α_2-antiplasmin (% NHP)	100	100	90
Antithrombin III (% NHP)	106	104	100†
ECLT (mins)	395	420	310
Protein C antigen (% NHP)			
Premenopausal	90 (n = 11)	101 (n = 6)	—
Postmenopausal	123 (n = 53)	118 (n = 48)	103 (n = 13)

*$0.01 < P \leq 0.05$; †$0.001 < P \leq 0.01$; ‡$P \leq 0.001$.

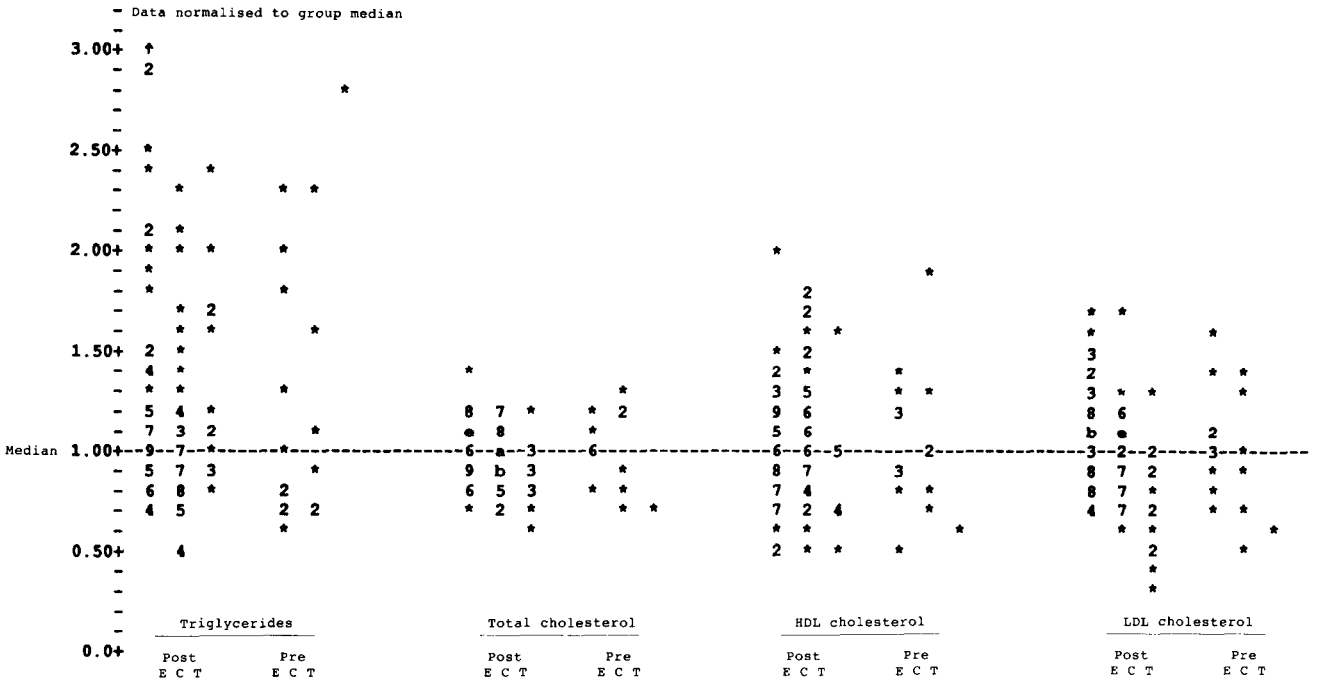

Fig. 1. Normalised lipid levels by tamoxifen use and menopausal status. a, $n = 10$; b, $n = 11$; c, $n = 12$; d, $n = 13$; e, $n = 14$. E = ex-users of tamoxifen, C = controls, T = current users of tamoxifen.

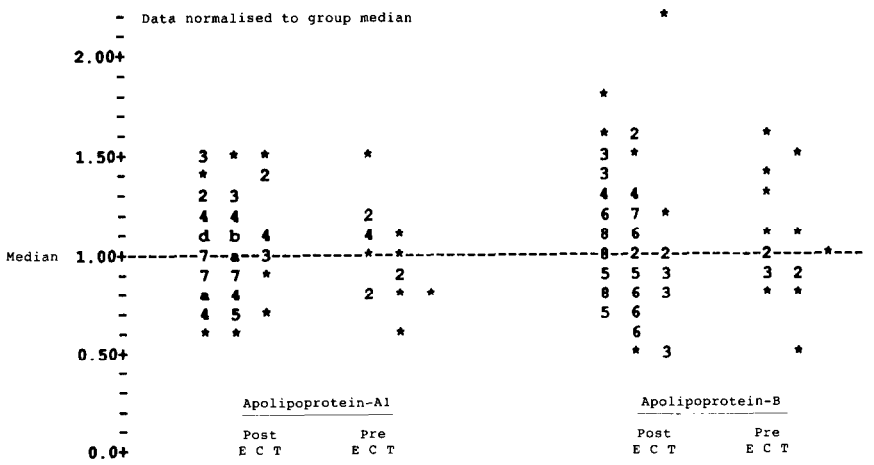

Fig. 2. Normalised lipoprotein levels by tamoxifen use and menopausal status. Symbols as in Fig. 1.

one and T_3. All the hormone analyses have been stratified by menopausal status. The data are shown in Table 3 and Figs 3 and 4. No significant differences were found between controls and ex-users. However large differences were observed between current users and controls. In particular for postmenopausal women SHBG levels were 91% higher ($P < 0.001$), T_3 levels were 19% higher ($P = 0.02$) and T_4 levels were 30% higher ($P = 0.008$), but total oestradiol levels were similar. Prolactin levels were 22% lower but this was not significant due to the high biological variability between women. The results in the one premenopausal current user were similar.

Bone density

The results for bone density are shown in Table 4 and Fig. 5. As expected bone density is generally lower in the postmenopausal women. Also, the densities are slightly higher in current users but, overall, the results by treatment group are similar and no differences are significant.

Haemostasis

The results of the coagulation and fibrinolysis screen are shown in Table 5 and Figs 6 and 7. With the exception of protein-C antigen, no differences between pre and postmenopausal women could be found and so they have been combined, including those previously unclassified for menopausal status. No significant differences were found between controls and ex-users except for a marginally shorter kaolin cephalin clotting time ($P = 0.03$). Some differences between current users and controls were apparent. Kaolin cephalin clotting times were marginally shorter, fibrinogen and fast alpha-2 antiplasmin levels were lower, ($P = 0.03$, $P = 0.0001$ and $P = 0.009$, respectively), and plasminogen levels were higher ($P = 0.02$).

DISCUSSION

Several biological effects of tamoxifen have been observed while women are taking the drug. They include large increases in SHBG levels [7, 10, 18, 24, 25], substantial reductions in

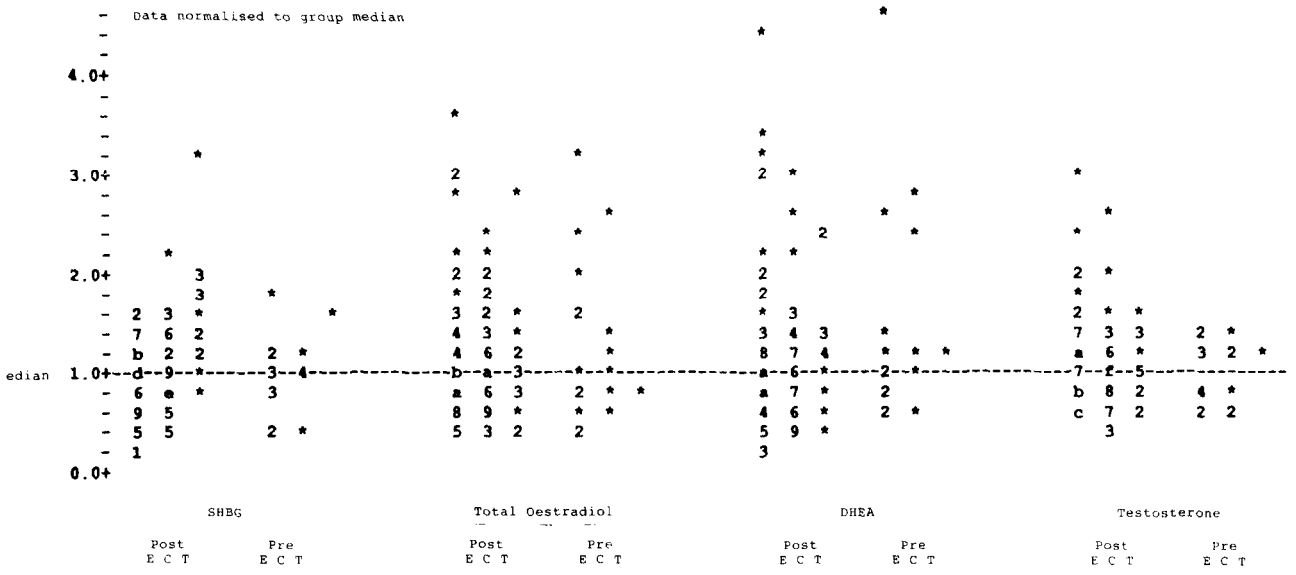

Fig. 3. Normalised hormone levels by tamoxifen use and menopausal status. Symbols as in Fig. 1. f, $n = 15$.

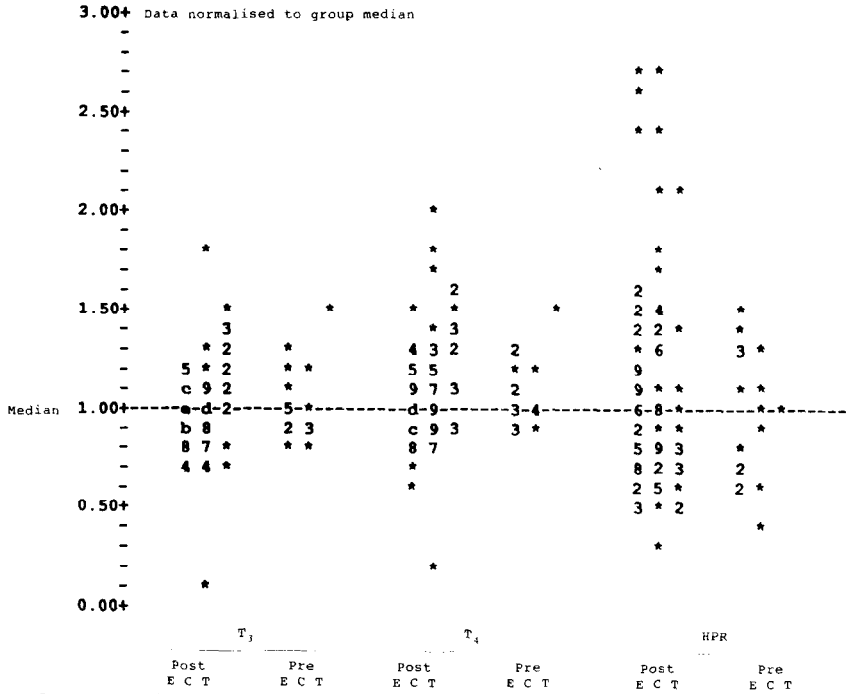

Fig. 4. Normalised hormone levels by tamoxifen use and menopausal status. Symbols as in Fig. 1.

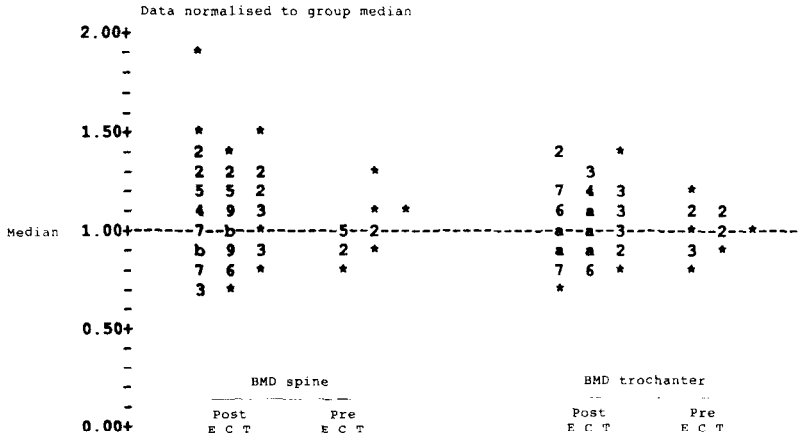

Fig. 5. Normalised bone mineral density by tamoxifen use and menopausal status. Symbols as in Fig. 1.

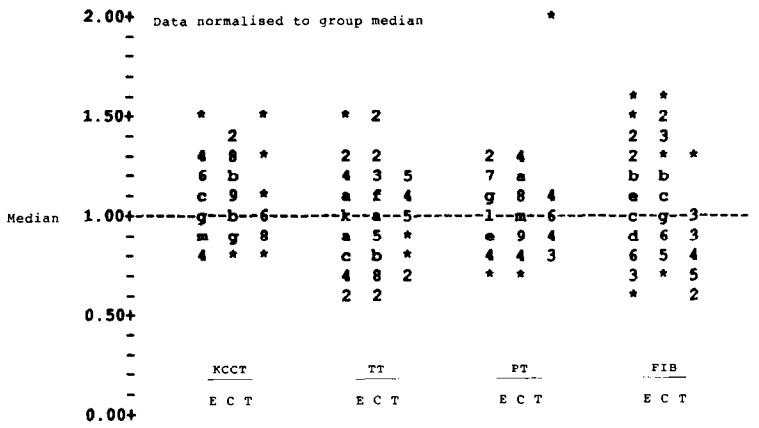

Fig. 6. Normalised haemostasis values by tamoxifen use. a–m, n = 10–22. E, C, T as in Fig. 1. KCCT = Kaolin cephalin clotting time, TT = thrombin time, PT = prothrombin time and FIB = fibrinogen.

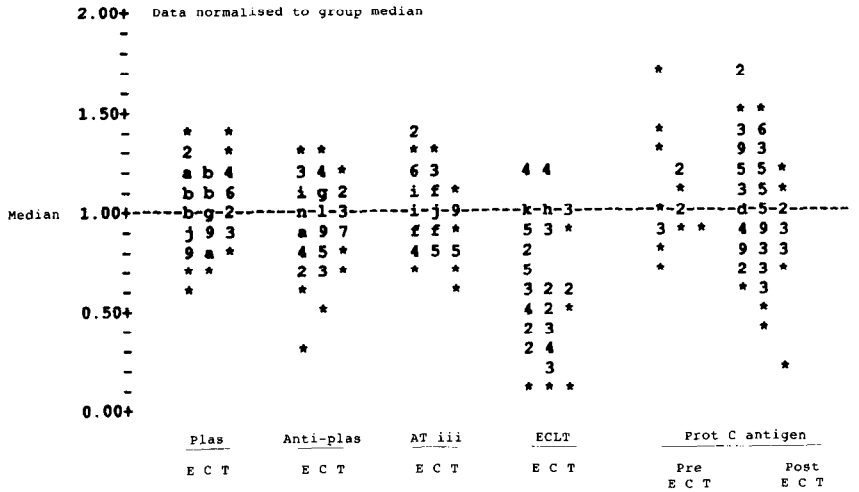

Fig. 7. Normalised haemostasis values by tamoxifen use. a–n, n = 10–23. Symbols as in Fig. 6.

LDL-cholesterol with small increases or no change in HDL-cholesterol [9–15], small increases in triglycerides [9, 10,14], decreases in antithrombin III levels [17] and increases in thyroid hormones [26]. We have also observed significant changes in these variables, and additionally, significant differences in other factors affecting haemostasis. However these differences do not appear to be retained in ex-users, with the possible exception of a slightly shorter kaolin cephalin clotting time, a higher level of triglycerides in postmenopausal women and a slightly lower level of HDL-cholesterol. These differences could well be due to chance, particularly the observations regarding HDL-cholesterol since it has not been seen in several other studies of current users.

Overall these results are reassuring with regard to potentially negative side-effects of tamoxifen but also indicate that potentially positive effects, such as the lowering of LDL-cholesterol levels, only occur while on active treatment. However, because of the chronic nature of the atherosclerotic process, any resulting benefits of cholesterol lowering on heart disease may persist well beyond the period of active treatment.

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Chemotherapy Induced Amenorrhoea in a Randomised Trial of Adjuvant Chemotherapy Duration in Breast Cancer

Leonard M. Reyno, Mark N. Levine, Peter Skingley, Andrew Arnold and H. Abu Zahra

We have previously reported the results of a clinical trial in patients with stage II breast cancer which compared a 12 week chemohormonal regimen with a 36 week chemotherapy regimen. Both pre and post menopausal women were entered. The 12 week regimen was inferior both in terms of disease-free survival and overall survival. The effect of chemotherapy on menstrual function was prospectively documented in 95 of 114 premenopausal women at 3 of the 4 participating centres. 67 of the 95 women (70.5%) developed permanent amenorrhoea. There was a statistically significant difference in the rate of induced amenorrhea between the 12 week and the 36 week groups; 23/42 vs. 44/53, respectively ($P = 0.003$). Recurrence and mortality rates were lower in the patients who became amenorrheic; 38% vs. 57% ($P = 0.03$) and 18% vs. 32% ($P = 0.17$), respectively. Similar trends were observed within treatment groups. The effect of induced amenorrhoea on outcome was seen predominantly in patients under 40 years old. These results suggest that the induction of ovarian failure is a potential mechanism for the observed effect of adjuvant chemotherapy in these patients. The difference in the ovarian failure rates between groups may be a possible explanation for the inferiority of the 12 week regimen.
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INTRODUCTION

WHILE POSTOPERATIVE adjuvant chemotherapy is standard practice for premenopausal patients with axillary node positive breast cancer, it is not known with certainty the mechanism by which such therapy prolongs remission and survival. Recent results of the Breast Cancer Trialists' Overview have demonstrated that ovarian ablation improves both relapse free survival and overall survival in women under the age of 50 [1]. It has been postulated that at least part of the benefit of cytotoxic therapy is derived from chemotherapy induced ovarian ablation [1–3]. No trial however has been designed in such a way and collected adequate data to answer this question directly.

We have previously reported the results of a clinical trial in stage II breast cancer which compared a 12 week adjuvant chemohormonal regimen which included tamoxifen with a standard 36 week chemotherapy regimen [4]. The 12 week regimen was inferior both in terms of disease-free survival and overall survival. The effect of chemotherapy on the patients' menstrual function was prospectively documented along with a questionnaire assessing quality of life [5]. We now report the ovarian