Eur J Cancer, Vol. 26, No. 6, pp. 680–684, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00
Pergamon Press plc

Prevention of Breast Cancer with Tamoxifen—an Update on the Royal Marsden Hospital Pilot Programme

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An 'anti-oestrogen' such as tamoxifen may protect prophylactically against breast cancer. At the Royal Marsden Hospital, the blind randomised feasibility study of tamoxifen 20 mg per day versus placebo in 200 healthy women has been extended into a pilot trial. A total of 435 women with a family history of breast cancer have been accrued. Compliance, acute toxicity, clotting factors, lipids and bone mass were assessed. The pilot trial has confirmed the findings of the feasibility study. Compliance was high and the frequency of side-effects was similar in both groups, except for a significant increase in hot flushes in the tamoxifen-treated women (33 vs. 17%). Bone mass and clotting factors were not affected. Tamoxifen significantly reduced serum cholesterol, low-density lipoprotein cholesterol (LDLC) and apolipoprotein B levels in post-menopausal women. In premenopausal women, the effects on lipids and lipoproteins was smaller with a significant fall in total serum cholesterol and LDLC only. The trial has approval to accrue up to 1000 women.
Eur J Cancer, Vol. 26, No. 6, pp. 680—684, 1990.

INTRODUCTION

ENDOCRINE promotion may be an important, if not essential, component for the development of clinical breast cancer from a single malignant cell. Experimental [1] and epidemiological evidence [2] indicates that oestrogens may be involved in breast cancer development, which raises the possibility that the disease could be prevented by an 'anti-oestrogenic' agent [3]. Such a 'chemopreventative' would need to be simple to administer to maintain compliance and, above all, would need to be safe.

Tamoxifen is an effective treatment for metastatic breast cancer [4] and will delay relapse and prolong survival after primary surgery [5–7]. Furthermore, it can be used to treat primary breast cancer instead of surgery [8]. In experimental tumours the drug's anti-proliferative activity is probably due to binding to the oestrogen receptor, thereby depriving the tumour of stimulation by endogenous oestrogens. The value of tamoxifen as a preventative agent depends on its acute side-effects and its possible anti-oestrogenic effects on other systems, such as bone, lipids and clotting, especially the risks of osteoporosis and cardiovascular death.

We therefore undertook a feasibility trial with tamoxifen or placebo given to 200 healthy women, aged over 40 with a family history of breast cancer, to evaluate the logistic problems of a large trial with assessment of accrual, compliance, acute toxicity and monitoring of clotting factors, lipid profile and bone mass [9]. This trial was completed in 1988 and preliminary results showed no unacceptable toxicity and a high compliance. Serum cholesterol was significantly reduced [10, 11].

This lack of anti-oestrogenic effects on normal tissues encouraged extension into a pilot trial. We have now accrued a total of over 400 healthy women into the feasability and pilot trial.

We have also analysed lipid profile. An elevation of total serum cholesterol and its main low-density lipoprotein constituent (LDLC) is associated with an increased risk of coronary heart disease (CHD) in contrast to high-density lipoprotein cholesterol (HDLC), a minor constituent of total cholesterol that is low in high-risk patients [12, 13]. The major protein constituent of LDLC, apolipoprotein B (apo B), and that of HDLC, apolipoprotein A1 (apo A1), are independent and possibly better predictors of CHD than the lipid and lipoprotein fractions [14]. Fasting and non-fasting triglyceride levels are not useful predictors of CHD [12, 15].

PATIENTS AND METHODS

Between October 1986 and March 1990, 435 healthy women were prescribed 'tamoplac' and randomised by the pharmacy to receive either tamoxifen 20 mg per day or placebo (Table 1). Women usually aged 30–69 years were eligible if they had a family history of breast cancer, with at least one first-degree relative (sister, mother, daughter) who had developed breast cancer under the age of 40 years, or bilateral breast cancer at any age, or at least two first-degree relatives with breast cancer at any age. The trial design and methods of monitoring have been described previously [9–11].

Acute toxicity and compliance were assessed and clinical examination was done every 6 months. Initially, non-fasting blood samples were taken for cholesterol and clotting factors and bone mass measurement and ovarian ultrasound were done every 6 months, now extended to annual assessment. More extensive lipid studies were done on randomly selected subset of complying women. This trial has ethical approval to continue accrual to 1000 women at the Royal Marsden Hospital.

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Table 1. Patients' characteristics

	Tamoxifen (n=217)	Placebo (n=218)
Menopausal status		
Premenopausal	108	101
Perimenopausal	9	10
Postmenopausal	94	100
Family history		
1 relative	57	56
2 relatives	90	105
> 2	63	49
No. assessable for toxicity	141	138

Lipid studies

Paired serum samples were obtained before and 6 months after treatment started in 60 randomly selected women. There were 14 fasting and 18 non-fasting premenopausal women and 12 fasting and 16 non-fasting postmenopausal women.

Total cholesterol was measured initially every 6 months and then every year by a fully enzymatic cholesterol oxidase-aminophenazone method; triglycerides (TG) by a fully enzymatic glycerol phosphate oxidase-aminophenazone method (Boehringer Mannheim Diagnostica); HDLC phosphotungstate/magnesium precipitation [16]; and apo AI and apo B by immunoturbidimetry with antisera and standards (Atlantic Antibodies, Incstar, Reading and Immuno Ltd, Sevenoaks). Standards were calibrated against CDC-IUIS-WHO apo AI and apo B reference material. LDLC was calculated by the formula of Friedwald *et al.* [17]. All samples, with the exception of HDLC in the non-fasting subjects, were assayed in duplicate.

Coagulation factors

Antithrombin 3 (AT3) and fibrinogen were measured before and every 6 months after the start of treatment. AT3 was measured with a Boehringer Mannheim kit 759376. Fibrinogen was measured with the Boehringer Mannheim kit 524484.

Table 2. Acute toxicity

	Tamoxifen (n=141)		Placebo (n=138)	
	Mild/mod/severe	Total	Mild/mod/severe	Total
Nausea	12/2/3	17 (12%)	8/ 3/1	12 (9%)
Vomiting	1/0/1	2 (1%)	3/ 1/0	4 (3%)
Hot flushes*	13/25/9	47 (33%)	8/11/5	24 (17%)
Headaches	12/5/5	22 (16%)	10/ 8/3	21 (15%)
Weight gain	3/3/1	7 (5%)	5/ 3/0	8 (6%)
Vaginal discharge	4/4/0	8 (6%)	0/ 0/0	0
Menstrual changes	6/4/0	10 (7%)	4/ 3/1	8 (6%)
Amenorrhoea	—	10	—	9
Fluid retention	2/0/0	2 (1%)	0/ 0/0	0 (0%)
Depression	1/2/0	3 (2%)	1/ 1/0	2 (1%)

*$P < 0.05$ Mann–Whitney test for trend. Mod = moderate.

Bone density

Radial bone mineral density was measured by single-photon absorption through the forearm with a bone densitometer (ND110, Nuclear Data Inc) before and every 6 months after the start of treatment and expressed as age-corrected bone mineral content as a percentage of the estimated normal measurement.

Statistics

Normal probability plots of each pretreatment lipid and lipoprotein revealed no evidence of non-normality. Pretreatment and on-treatment values were compared with the paired t-test for each treatment, for menopausal status and fasting status, and for pooled fasting and non-fasting samples where appropriate.

The chi-squared test and Mann–Whitney test for trend were used to assess differences in pretreatment characteristics and side effects.

RESULTS

Acute toxicity and compliance were assessed in 279 women who had been in the trial at least 6 months. Generally there was no difference in symptoms attributed to the medication between tamoxifen and placebo (Table 2), apart from a significant increase in hot flushes. A mild non-infected vaginal discharge occurred in 8 (6%) women on tamoxifen but there was no difference in the regularity of the periods or amenorrhoea (at least three missed periods in women who had regular periods for at least 6 months before medication). The low toxicity profile was reflected in the high compliance (Fig. 1).

Sequential measurement of age-corrected bone mineral content of the forearm showed no evidence of accelerated bone mineral loss for women on tamoxifen compared with placebo (Fig. 2). Analysis of post-menopausal women also showed no significant difference (Fig. 3). There was no significant difference in changes in fibrinogen and AT3 levels, nor in the fibrinogen/AT3 ratio (Fig. 4).

The changes in total non-fasting cholesterol randomly estimated in attendances by 355 of 463 (81%) tamoxifen women and 368 of 461 (80%) placebo women, were expressed as percentage change from pretreatment levels and are shown in Fig. 5. There

Fig. 1. Compliance expressed as % of number of women randomised to —— = tamoxifen and - - - - = placebo.

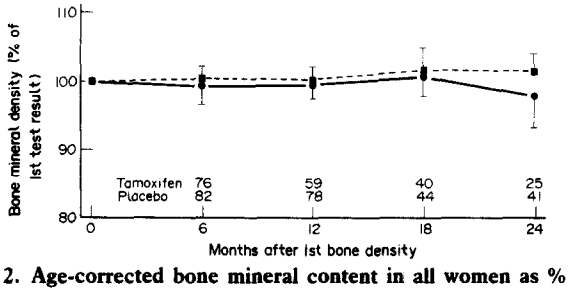

Fig. 2. Age-corrected bone mineral content in all women as % of estimated normal measurement. ●—● = tamoxifen and ■- - -■ = placebo (95% CI).

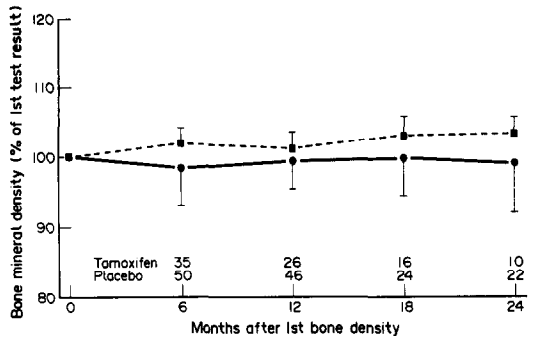

Fig. 3. Age-corrected bone mineral content in post-menopausal women shown as % of estimated normal measurement. ●—● = tamoxifen and ■- - -■ = placebo.

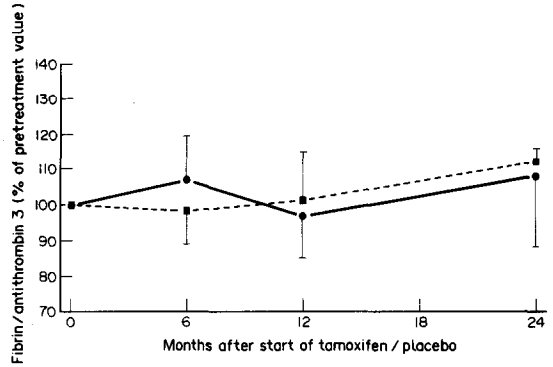

Fig. 4. Change in fibrinogen/antithrombin 3 ratio as % of pretreatment value. ●—● = tamoxifen and ■- - -■ = placebo.

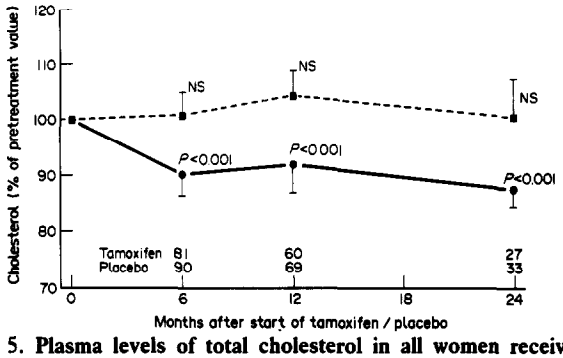

Fig. 5. Plasma levels of total cholesterol in all women receiving tamoxifen (●—●) or placebo (■- - -■). Number of women with measurement at each time point is shown (paired *t*-test at each time interval).

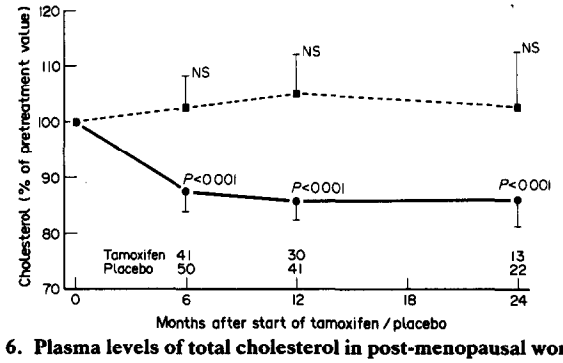

Fig. 6. Plasma levels of total cholesterol in post-menopausal women receiving tamoxifen (●—●) or placebo (■- - -■). Number of women with measurement at each time point is shown (paired *t*-test at each time interval).

was a significant 12% fall in serum cholesterol ($P < 0.001$) for women on tamoxifen compared with no effect for women on placebo, which has been maintained up to 24 months after the start of medication. This fall in cholesterol was larger 18% ($P < 0.001$) for post-menopausal women (Fig. 6).

To establish the lipid profile related to this fall in total non-fasting cholesterol, detailed analyses of lipid and lipoproteins were done in 60 women (Tables 3 and 4). Lipid and lipoprotein analyses were separated into fasting and non-fasting groups and the results pooled for those analyses that are not significantly affected by fasting status (cholesterol and apo AI and apo B) [18, 19]. There was a significant mean fall in total cholesterol (0.85 mmol/l, $P < 0.005$) in post-menopausal women and a smaller but still significant fall in premenopausal women on tamoxifen (0.44 mmol/l $P < 0.05$).

15 of the post-menopausal women had a pretreatment total cholesterol level over 6.5 mmol/l, a group which has been shown to have an increased risk of CHD in both sexes [12, 13]. The

*Table 3. Mean (95% CI) changes in lipid and lipoprotein levels in premenopausal women**

	Non-fasting		Fasting		Total	
	Tamoxifen (n=9)	Placebo (n=9)	Tamoxifen (n=6)	Placebo (n=8)	Tamoxifen (n=15)	Placebo (n=17)
Total cholesterol (mmol/l)	−0.46	−0.31	−0.54	0.34	−0.44‡	−0.01
(4–6.5)†	(0.53)	(0.42)	(0.63)	(0.45)	(0.38)	(0.29)
HDLC (mmol/l)	0.01	0.01	0.17	0.27†	‖	‖
(1–2)	(0.1)	(0.14)	(0.25)	(0.34)		
LDLC (mmol/l)	−0.55	−0.07	−0.71§	−0.17	‖	‖
(1.7–4.6)	(1.04)	(0.43)	(0.45)	(0.38)		
Apo AI (mg/dl)	6.6	−9.6	8.8	11.3	9.87	2.24
(85–165)	(9.7)	(9.4)	(19.6)	(10.9)	(10.76)	(8.86)
Apo B (mg/dl)	−6.4	−11.9	−9.4	0.08	−7.6	−6.3
(86–114)	(14.1)	(13.6)	(9.2)	(14.0)	(9.0)	(9.6)
Triglyceride (mmol/l)	0.20	0.04	0.10	0.21	‖	‖
(0.1–2.2)	(0.5)	(0.19)	(0.16)	(0.25)		

*The 95% CI is the mean ± the value in parentheses.
†Normal range.
‡$P < 0.05$ and §$P < 0.01$.
‖Not applicable because fasting and non-fasting values were significantly different and cannot be pooled.

Table 4. Mean (95% CI) changes in lipid and lipoprotein levels in post-menopausal women

	Non-fasting		Fasting		Total	
	Tamoxifen (n=7)	Placebo (n=9)	Tamoxifen (n=7)	Placebo (n=5)	Tamoxifen (n=14)	Placebo (n=14)
Cholesterol (mmol/l) (4–6.5)	−0.94* (0.71)	−0.13 (0.54)	−0.86 (0.91)	−0.05 (0.74)	−0.85‡ (0.48)	−0.10 (0.38)
HDLC (mmol/l) (1–2)	−0.12 (0.2)	0.00 (0.21)	0.08 (0.13)	0.01 (0.3)	§	§
LDLC (mmol/l) (1.7–4.6)	−0.98* (0.93)	−0.45 (0.71)	−0.91† (0.59)	−0.17 (0.72)	§	§
Apo AI (mg/dl) (85–165)	−2.9 (22.2)	−4.0 (10.6)	−7.8 (35.5)	0.3 (19.4)	−4.17 (20.7)	−2.51 (10.4)
Apo B (mg/dl) (86–114)	−14.8† (22.4)	−6.3 (12.5)	−16.9* (9.6)	14.5 (26.5)	−15.9‡ (5.8)	1.2 (13.0)
Triglyceride (mmol/l) (0.1–2.2)	0.33* (0.18)	0.12 (0.27)	0.33 (0.31)	0.23 (0.24)	§	§

*$P < 0.05$, †$P < 0.01$ and ‡$P < 0.005$.
§Not applicable because fasting and non-fasting values are significantly different and cannot be pooled.

mean drop of cholesterol in women on tamoxifen in this group was 1.91 mmol/l ($P < 0.001$) compared with a non-significant fall of 0.18 mmol/l in women on placebo.

Premenopausal women on tamoxifen showed a reduction in fasting LDLC (0.71 mmol/l, $P < 0.01$) but no significant changes in apo AI, apo B, fasting HDLC and triglycerides. Post-menopausal women on tamoxifen had a reduction in apo B (15.9 mg/dl, $P < 0.005$) and fasting LDLC (0.98 mmol/l, $P < 0.05$) and fasting triglyceride (0.33 mmol/l, $P < 0.05$) but no significant changes in fasting HDLC or apo AI.

DISCUSSION

The extension of this programme from the feasibility trial to the pilot trial with a total of over 400 women confirmed the initial indications [10] that accrual and compliance are sufficient to mount a large trial for prevention of breast cancer.

Side-effects with tamoxifen were about the same as with placebo, apart from menopausal hot flushes (33% vs. 17%). These symptoms were only severe in 6% of women on tamoxifen compared with 4% of controls and could be satisfactorily controlled with hormone replacement therapy if required. There was no evidence of increased bone loss or change in clotting factors to indicate that any anti-oestrogenic actions of tamoxifen had an adverse effect on bone or the risk of thromboembolism.

Tamoxifen significantly reduced serum cholesterol, fasting LDLC and apo B levels in post-menopausal women, especially in those women with an initially elevated level. In premenopausal women the effect on total cholesterol and fasting LDLC was smaller and there was no significant effect on other lipid and lipoprotein fractions.

A previous study [20] in women who were randomised to 40 mg per day of tamoxifen or no treatment after primary breast cancer surgery indicated similar changes in fasting cholesterol and lipoprotein profiles. Our study, on essentially normal women treated with a lower dose of tamoxifen and assessed for a longer time on treatment, confirms and extends these results. In contrast, a more recent study [21] in women with advanced breast cancer treated with tamoxifen 30 mg per day showed no significant change in total cholesterol and a significantly elevated HLDC. These women had active malignant disease which may have influenced the results.

As far as lipid risk factor status is concerned, our results indicate that tamoxifen may have a beneficial effect on lipid and lipoprotein profile. In men several prospective trials have shown that lowering total cholesterol by dietary or drug intervention reduces the risk of CHD [22] but there are no such data for women [13]. There is indirect evidence that post-menopausal oestrogen use significantly reduces the risk of CHD, but this is thought to act by increasing HDLC rather than decreasing total or LDLC [23]. There is, as yet, no direct evidence that altering apolipoprotein levels changes CHD risk.

These changes in lipid and lipoprotein profile suggest that tamoxifen has an oestrogenic rather than anti-oestrogenic action on protein synthesis in the liver [24]. Whether these changes offer protection against cardiovascular disease remain to be seen. However, it is encouraging that there was a reduction in non-cancer deaths in two large adjuvant tamoxifen trials [6, 7].

These oestrogenic effects, particularly on the liver and endometrium, raise the possibility of an increased risk of cancer in these sites. In one large trial, tamoxifen 40 mg per day given for more than 2 years was associated with a significant increase in uterine carcinoma [25] but this was not seen at the lower dose of 20 mg per day [26]. As yet there has been no indication of an increase in cancers at other sites in adjuvant tamoxifen trials and there is evidence of a reduction in contralateral breast cancer [27]. An unknown risk of cancer in other sites has to be weighed against the potential benefits on lipid profile and incidence of breast cancers [28].

These results, especially the low toxicity profile, high compliance, and lack of untoward effects on bone mass, clotting, and lipid profile have encouraged us to continue accrual to 1000 women. We also propose that this trial should be extended to other breast centres with similar higher risk women.

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Acknowledgements—We thank our data coordination team, Alwynne Tidy, Clare Jacobs and Gill Murrells for management of this trial.

Eur J Cancer, Vol. 26, No. 6, pp. 684–690, 1990.
Printed in Great Britain

0277-5379/90$3.00 + 0.00

Case-control Study of Risk Factors for Cervical Intraepithelial Neoplasia in Young Women

J. Cuzick, A. Singer, B.L. De Stavola and J. Chomet

A case-control study of 497 women under age 40 diagnosed with cervical intraepithelial neoplasia (CIN) and 833 controls was done in the London area between 1984 and 1988 to examine whether known risk factors for invasive cervical cancer produced similar risks for CIN of different grades in young women. Cases of CIN III had a risk profile similar to that seen for invasive disease whereas CIN I cases were similar to the controls in all risk factors examined except a history of genital warts. Cases of CIN II were intermediate between the two. Among several indicators of sexual and reproductive behaviour, age at first childbirth and a history of multiple sexual partners were the strongest risk factors for CIN II and CIN III. Smoking had a strong and independent effect on the risk of CIN II and CIN III, but had only a limited effect for CIN I. Use of oral contraceptives was widespread in cases and controls, but length of use of oral contraceptives was not found to be a risk factor. A small protective effect of barrier contraception was observed.
Eur J Cancer, Vol. 26, No. 6, pp. 684—690, 1990.

INTRODUCTION

SEXUAL and reproductive factors are well established features of risk for invasive cervical cancer [1–5]. Cigarette smoking is also a well documented, albeit less well understood, factor [6–10], while the risk associated with oral contraceptive usage remains controversial [11–15]. Less is known about the relation of these factors to different grades of cervical intraepithelial neoplasia (CIN), especially the mild lesion CIN I [3, 11, 16–19]. The frequency of both invasive cancer and CIN is rising rapidly in young British women [20, 21] and, to see which factors are most related, we have done a case-control study of CIN in women under the age of 40.

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SUBJECTS AND METHODS

Subjects

We studied 497 cases of CIN and 833 controls between 1984 and 1988. The mean age of the cases was 28 (range 18–39). Cases