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Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women

Contents

Section: ARTICLES Summary

Background Tamoxifen is a candidate chemopreventive agent in breast cancer, although the drug may be associated with the development of endometrial cancer. Therefore we did a trial in hysterectomised women of tamoxifen as a chemopreventive.

Methods In October, 1992, we started a double-blind placebo-controlled, randomised trial of tamoxifen in women (mainly in Italy) who did not have breast cancer and who had had a hysterectomy. Women were randomised to receive tamoxifen 20 mg per day or placebo, both orally for 5 years. The original plan was to follow the intervention phase by 5 years' follow-up. In June, 1997, the trialists and the data-monitoring committee decided to end recruitment primarily because of the number of women dropping out of the study. Recruitment ended on July 11, 1997, and the study will continue as planned. The primary endpoints are the occurrence of and deaths from breast cancer. This preliminary interim analysis is based on intention-to-treat.

Findings 5408 women were randomised; participating women have a median follow-up of 46 months for major endpoints. 41 cases of breast cancer occurred so far; there have been no deaths from breast cancer. There is no difference in breast-cancer frequency between the placebo (22 cases) and tamoxifen (19) arms. There is a statistically significant reduction of breast cancer among women receiving tamoxifen who also used hormone-replacement therapy during the trial: among 390 women on such therapy and allocated to placebo, we found eight cases of breast cancer compared with one case among 362 women allocated to tamoxifen. Compared with the placebo group, there was a significantly increased risk of vascular events and hypertriglyceridaemia among women on tamoxifen.

Interpretation Although this preliminary analysis has low power, in this cohort of women at low-to-normal risk of breast cancer, the postulated protective effects of tamoxifen are not yet apparent. Women using hormone-replacement therapy appear to have benefited from use of tamoxifen. There were no deaths from breast cancer recorded in women in the study. It is essential to continue follow-up to quantify the long-term risks and benefits of tamoxifen therapy.

Introduction

The idea of interfering with the initiation and promotion of breast cancer by means of pharmaceutical compounds (chemoprevention) arose about a decade ago. There are many experimental and epidemiological data to support the

use of tamoxifen as a chemopreventive. This drug has both oestrogenic and antioestrogenic properties.[1, 2] These properties, including reduction of circulating insulin-like growth factor 1, inhibition of angiogenesis, and induction of apoptosis, help explain the otherwise unexpected response to tamoxifen seen in oestrogen-receptor-negative, postmenopausal women.[3] Women with breast cancer have a 2-3-fold increased risk of contralateral breast cancer. In the randomised trials with adjuvant tamoxifen of breast cancer, the incidence of contralateral breast cancer decreased by around one-third.[3-10] This result, and the good safety profile in cancer patients based on large numbers of women with long follow-up, put tamoxifen among the front runners for evaluation as a chemopreventive in breast cancer.

However, side-effects of tamoxifen include an increased occurrence of endometrial cancer.[8, 9]. In view of this potential adverse event, we undertook a randomised trial in women who had had a hysterectomy. Such women have a reduced risk of breast cancer when there has been an associated bilateral oophorectomy.[10]

Participants and methods

Participants and inclusion and exclusion criteria

The Italian Tamoxifen Prevention Study includes healthy women aged 35-70 who had had a total hysterectomy for reasons other than neoplasm. Women were recruited via national advertising and also from direct contact with gynaecologists throughout Italy (with a minority of cases recruited from abroad). Women with severe concurrent illness or history of cardiac disease were excluded from randomisation. Endometriosis and suspected or certain previous deep-vein thrombosis were also exclusion criteria. The study started in October, 1992, and recruitment ended in July, 1997.

In June, 1997, the trialists and the data-monitoring committee decided to end recruitment because of the number of women dropping out of the study and the side-effect profile of tamoxifen (see below). Recruitment ended on July 11, 1997, and treatment and follow-up will continue as planned.

The initial plan was to have a 5-year accrual, 5 years of intervention, and another 5 years of follow-up.[11] The follow-up during treatment included a minimum of twice-yearly clinical visits to monitor side-effects and compliance.

Mammography was done annually. When women entered the follow-up phase of this study, either through completion of the course of treatment or drop-out from treatment, they continued to be followed up annually. Information about major endpoints, such as death, serious adverse events, or cancer diagnosis, was continuously collected and passed to the data centre.

The decision to recruit only hysterectomised women was based on the consideration that tamoxifen could produce an additional risk of endometrial cancer.[8, 9] Selection of hysterectomised women did produce a group at slightly less than normal risk of breast cancer, since the group contained normal-risk women (hysterectomy without oophorectomy) and reduced-risk women (hysterectomy with bilateral oophorectomy before menopause).[12] For a short period, the study was open to women who had had a subtotal hysterectomy: 91 cases (1.7%) were included with this characteristic. Such cases were subsequently excluded from the protocol (December, 1996); treatment was stopped for those already entered and these women are in the follow-up.

Study design and treatment

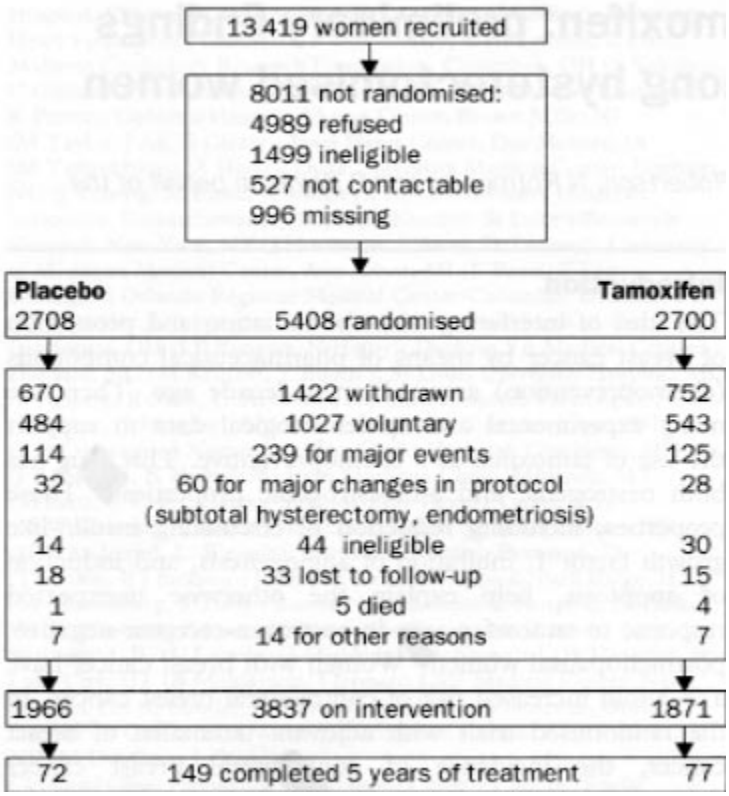

Figure 1: Trial profile

The study was randomised, double blind, multicentre, and controlled with placebo (figure 1). Eligible women who had given written informed consent to participate were randomised in two groups: 20 mg per day tamoxifen or placebo for 5 years, both orally. We intend to follow up all cases for an additional 5 years after the end of treatment. The initial sample-size calculation assumed a reduction of one-third in breast-cancer risk as shown by the data on the incidence of new contralateral breast cancer in patients treated with tamoxifen as an adjuvant.[11] Participants were stratified by centre to take into account differences in study population according to environmental, social, and demographic factors. Each participating centre obtained local ethics committee approval.

An identification number was assigned to each woman at her first contact. Because not all these women participated, these numbers could not be used to label the containers for the study compound. A five-digit code was assigned to each container. The link between the woman's identification number and that of the compound container was established during allocation.

The allocation process was centralised at the data centre at the Division of Epidemiology and Biostatistics at the European Institute of Oncology to ensure protection of the data and to avoid the same drug container being allocated twice within or between centres. Randomisation was by telephone call (occasionally fax) to the centre.

Tamoxifen was supplied directly by Zeneca in bottles containing tablets with 20 mg active ingredient. The preparation was visually identical to that of placebo, which was produced by the same company. The bottles of drug and placebo were numbered progressively and, given that the study is double blind, neither the doctors involved with the study nor the women participating knew which type of preparation was administered. The treatment to which a patient had been allocated was made known to clinicians only in the case of proven need (on the authority of the expert medical committee).

The primary endpoints are reduction in the frequency and the mortality rate for histologically confirmed breast

cancer. All other incident cancers are verified and all causes of death are recorded. Secondary endpoints include the eventual changes that the drug could cause in cardiovascular variables, psychological assessment of the participants' life-style, and assessment of cognitive capacity and its relation to Alzheimer's disease.

When women entered the follow-up phase of this study, either through completion of the course of treatment or drop-out from treatment, they continued to be followed up annually. Information about major endpoints, such as death, serious adverse events, or cancer diagnosis, was continuously collected and passed to the data centre.

Statistical analysis

Data were stored on a database and all analyses were done with SAS. We used the logrank test to compare the frequency of events between groups on an intention-to-treat basis. A simulation analysis was done to assess the possible effects of reporting the results before the time specified in the protocol. The simulations were based on the observed rate of breast cancer and recruitment pattern in the study. The time on study was taken as the minimum of the time to breast cancer and the time from randomisation to the end of the study with a case occurring only if the cancer occurred before the end of study. The time to breast cancer was simulated from an exponential distribution. The randomisation time was simulated according to the observed distribution. The hazard ratios and logrank tests were calculated under two conditions: the first corresponding to an end of study at March 31, 1998, and the second corresponding to a planned end of the study in 5 years' time. The inferences from the two situations were compared with 1000 simulations for a variety of hazard ratios between 0.5 and 1.0. Simulations were carried out for an intention-to-treat analysis and for an intention-to-treat analysis omitting all participants with less than 12 months on treatment.

Results

The study involves 55 participating centres, of which 51 were in Italy, three in South America (Brazil two, Argentina one), and one in Greece. Most patients (5230,96.7%) were recruited in Italian centres.

5408 women were randomised (figure 1), with a median age of 51 years (table 1). 3837 women are still on treatment. The overall median time on study intervention is 30.5 months. 1422 women dropped out of the study, and 149 have completed 5 years of treatment. For deaths, cancer diagnosis, and major events the median duration of follow-up is 46 months.

From the 5378 women with complete data, 5287 (98.3%) had had a total hysterectomy; 1412 (26.3%) had conservation of the ovaries, 2595 (48.3%) had a bilateral oophorectomy, 998 (18.6%) had a unilateral oophorectomy, and for 282 (5.2%) there was no information available.

- 483 women (9.0%) had an aunt with breast cancer, 418 (7.8%) had a mother with breast cancer, 242 (4.5%) had a sister with breast cancer, 139 (2.6%) had a grandmother with breast cancer, and six (0.1%) had a daughter with breast cancer. In total, 976 women (18.2%) had at least one first-degree relative or an aunt with breast cancer, 132 (2.5%) had two relatives, and 16 (0.3%) women in the study had three relatives with breast cancer.
- 1422 (26.3%) of 5408 randomised women dropped out of this study (figure 1). 1027 women dropped out of their own accord and 239 women withdrew because of some adverse event. A list of adverse events had been drawn up before the study and each event was notified to the data centre, who in turn notified the appropriate study coordinator regarding the action that needed to be taken.

Of the women who dropped out voluntarily, the most common causes were side-effects (301 women), no longer interested in the study (189), advised by their doctor (143), fear (86), unwilling to continue to take drugs (84), family problems (62), advised by a relative (33), an effect of distance (32), and 97 for other reasons. Most drop-outs occurred within the first year after randomisation (754,321,209,113,and 25 in years 1-5, respectively).

There were 15 deaths (nine in the placebo arm and six in the tamoxifen arm) in the study participants, five during active treatment and ten during follow-up. Four deaths were from gastrointestinal cancer, two from brain cancer, two from road-traffic accidents, and one each from cancer of the peritoneum, viral pneumonia, liver cirrhosis, cerebrovascular haemorrhage, stroke, violence and "died in sleep". No deaths from breast cancer were observed in

the entire study group.

Breast-cancer cases

There were 82 cases of cancer recorded in the study population, 41 in the breast and 41 at other sites (with no difference for the latter in distribution between the two arms of the study). Of the breast-cancer cases, 19 were among women in the tamoxifen arm and 22 among those in the placebo arm (figure 2, not significant). Simulation showed an estimated probability of 0.22 (SE 0.04) of reporting a significant difference (at 5%) between the two arms after a further 5 years' follow-up given the observed situation at present if the reduction in breast-cancer risk was 33%.

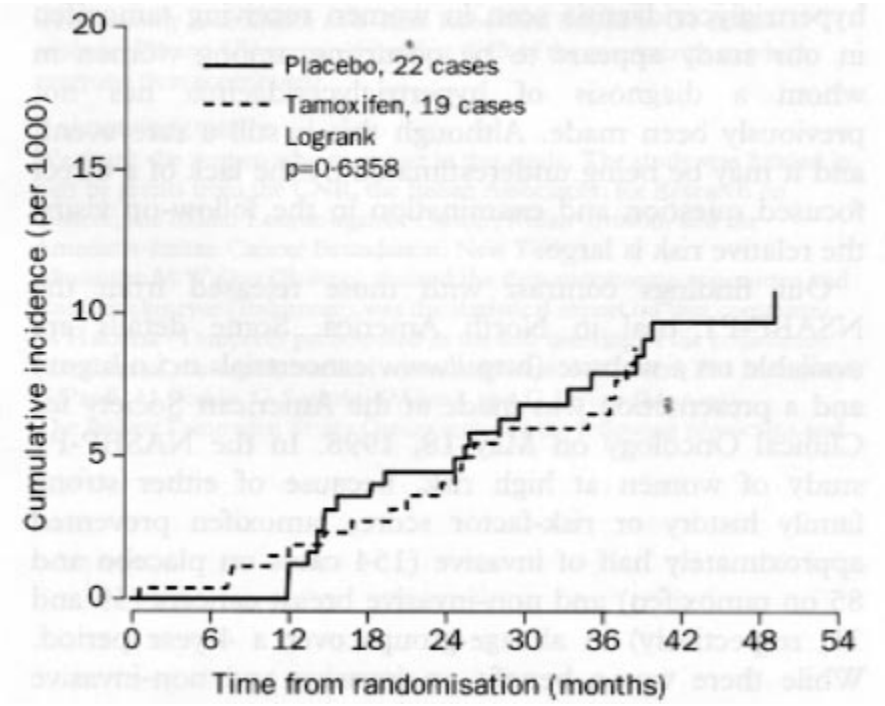

Figure 2: Breast-cancer occurrence in tamoxifen and placebo arms of trial

33 cases of breast cancer occurred during treatment (14 in patients on tamoxifen and 19 in patients on placebo), and eight occurred after withdrawal from treatment (five tamoxifen, three placebo). Among the women who followed assigned treatment for at least 1 year there were 19 breast-cancer cases in the placebo group and 11 in the tamoxifen group (p=0.16). Simulation showed for these women an estimated probability of 0.87 (SE 0.02) of reporting a significant difference (at 5%) between the two arms after a further 5 years' follow-up given the observed situation at present if the reduction in breast-cancer risk was 33%.

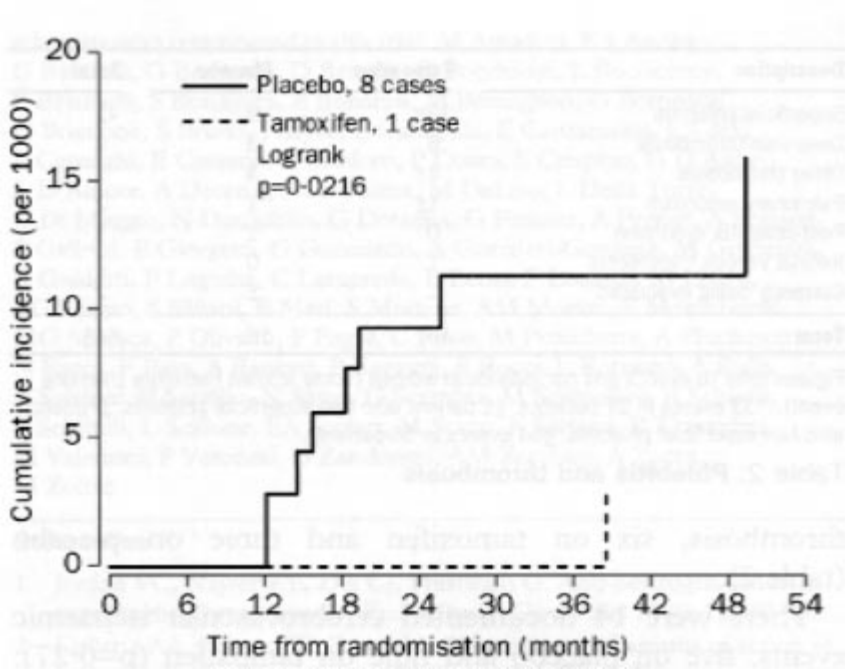

Figure 3: Breast-cancer occurrence in women using tamoxifen+HRT or placebo+HRT at baseline and throughout the trial

Of the 41 cases of breast cancer observed, 30 had never used hormone-replacement therapy, of whom 17 were on tamoxifen and 13 on placebo (p=0.44, logrank test). Nine women who developed breast cancer had used hormone-replacement therapy at baseline and throughout the trial: eight cases occurred in women on placebo (out of 390 women) and one on tamoxifen (out of 362 women, figure 3). The hazard ratio was 0.13 (95% CI 0.02-1.02). (Two women with breast cancer had used hormone-replacement therapy at some time during the trial, one in each arm.) There was no difference in the effects of tamoxifen between women who were less than 50 years when randomised (p=0.72) and women who were older than 50 years when randomised (p=0.77). There was also no difference in the frequency of oestrogen-receptor-positive breast cancers between the tamoxifen (ten cases) and placebo (eight) groups. Progesterone-receptor-positive cases were more frequent (not significant) in breast carcinomas occurring in women on placebo (ten cases) than on tamoxifen (six). Among women with at least one first-degree relative or aunt with breast cancer, there were ten cases of breast cancer among women allocated placebo and six in women allocated tamoxifen (p=0.25).

There were no major differences in breast-cancer characteristics between patients on placebo and those on tamoxifen for size and grading of the tumour, peritumoral vascular invasion, or axillary involvement. 11 of the 41 breast cancers were discovered at mammographic examination and were not palpable; the other 29 were detected by mammography and physical examination. One case was palpable and not visible at mammographic examination. There were four in-situ carcinomas. When possible, mammograms of breast cancer were retrospectively re-examined by an independent radiologist at Padua University, who detected signs of already existing carcinoma at the baseline mammography in four cases (two tamoxifen, two placebo).

Vascular events

56 women experienced 64 events of thrombophlebitis, phlebothrombosis, or embolus (or a combination) during the course of this study: 18 women on placebo and 38 on tamoxifen (p=0.0053). 42 events were superficial phlebitis, with nine women having a diagnosis of deep-vein thrombosis, six on tamoxifen and three on placebo (table 2).

There were 14 documented cerebrovascular ischaemic events: five on placebo and nine on tamoxifen (p=0.27). All five confirmed strokes occurred in the tamoxifen arm. Based on the incidence of stroke in Italy, it was estimated that

the number of strokes seen in this study was less than that to be expected in a group of women of this age. (After the "freezing" of the data set, there was a further stroke and one transient ischaemic attack, both in women on placebo).

Hypertriglyceridaemia was not looked for specifically at each follow-up visit, and the study relies on self-reports from patients and physicians and subsequent confirmation from laboratory findings. 17 women in the study had hypertriglyceridaemia: two on placebo and 15 on tamoxifen (p=0.0013). This information almost certainly underestimates the occurrence of hypertriglyceridaemia in women in the study.

Discussion

The principal investigators were concerned about the large numbers of women withdrawing from the study, the unexpected finding with hypertriglyceridaemia, the findings about vascular events, and the number of well women complaining about the side-effects of tamoxifen. In agreement with the data-monitoring committee, we ended recruitment in June, 1997. The study investigators were informed during the 6-monthly meeting (held on July 11, 1997), of the decision to end recruitment to the trial forthwith. Treatment and follow-up continues as planned. We anticipate taking part in a pooled analysis with other international trials of similar design.

A medical committee, composed of independent experts mainly from Milan University, concluded that the frequency of deaths in the women in this trial was considerably lower than expected according to the Italian national age-specific mortality rates. Deaths from vascular disease were also lower than the numbers expected from Italian national rates. Although undoubtedly the population of women who volunteered to participate in this trial is self-selected and healthy in many respects, these comparisons provide reassurance about serious adverse effects of tamoxifen.

Since we accrued hysterectomised women, we established a cohort with a risk of breast cancer less than that among women with the same age distribution in the general population. Overall, there is to date no difference between the groups in terms of breast-cancer development in the short follow-up period of this study (46 months), nor any difference when the results are examined by age at randomisation. These observations, however, are tentative and require confirmation in subsequent follow-up. There was no difference among the cases in the two arms for family history, stage of the disease, and other histological and biological characteristics, except for a lower rate of progesterone-receptor positivity in cases in tamoxifen-treated women.

If the hazard ratio for a reduction in breast-cancer development by tamoxifen was as initially hypothesised at the outset of the study (33% reduction), simulations showed that given the current aggregation of cases between tamoxifen and placebo, there would be a 22% probability of obtaining a significant hazard ratio should the study proceed to the per-protocol analyses. Thus, although we realise that the power of this study at present is low (with ? =0.05, the power is 0.34), it is possible that the finding will be overturned by continued follow-up. This will be especially true among those women who stay on treatment for more than 1 year.

In a subgroup analysis that was not part of the original protocol, we saw a protective effect of tamoxifen against breast cancer among women who took hormone-replacement therapy throughout the study period. The protocol initially allowed women to be included in the study only if they did not plan to use hormone-replacement therapy for long periods: it was not possible to deny a woman the use of hormone-replacement therapy if her physician prescribed it for menopausal symptoms. We amended the protocol to allow all women to be enrolled whether or not they used hormone-replacement therapy. Such therapy is usually delivered by patch in Italy, which is different from the oral route used elsewhere. The recent overview of epidemiological studies of hormone-replacement therapy concluded that there was a small, although statistically significant, increase in breast-cancer risk among women who were using or who had just stopped using hormone-replacement therapy.[13] For this reason our finding is of potential impact for users of hormone-replacement therapy and should be further investigated, both within our cohort of women and in other study settings.

The effects of oestrogen-replacement therapy on lipid metabolism have been widely studied.[14] Oestrogens have the potential to harm women with underlying hypertriglyceridaemia,[15] and tamoxifen can greatly increase triglyceride levels.[16, 17] This is thought to be a rare event since reports from clinical trials generally demonstrate only modest increases in serum triglycerides.[18, 19] The excess of hypertriglyceridaemia seen in women receiving tamoxifen in our study appears to be occurring among women in whom a diagnosis of hypertriglyceridaemia has not previously been made. Although this is still a rare event, and it may be being underestimated by the lack of a direct

focused question and examination in the follow-up visits, the relative risk is large.

Our findings contrast with those released from the NSABP-P1 trial in North America. Some details are available on a website (http://mv.ezproxy.com.ezproxy.libraries.wright.edu:2048) and a presentation was made at the American Society for Clinical Oncology on May 18, 1998. In the NASBP-P1 study of women at high risk, because of either strong family history or risk-factor score, tamoxifen prevented approximately half of invasive (154 cases on placebo and 85 on tamoxifen) and non-invasive breast cancers (59 and 31, respectively) in all age-groups over a 4-year period. While there was a benefit on invasive and non-invasive breast cancer and fractures (71 on placebo and 47 on tamoxifen), there was an increased risk of endometrial cancer (14 and 33) and vascular events (70 and 99). In our trial, there was a non-significant advantage of tamoxifen over placebo in women with at least one first-degree relative with breast cancer (ten cases on placebo and six on tamoxifen), although this was not a preplanned subgroup analysis.

An impact on breast-cancer mortality is crucial. The NSABP-14 trial showed a significant advantage to women who received tamoxifen for 5 years in the adjuvant setting. Women on tamoxifen were then randomised to either a further 5 years of tamoxifen or placebo. Through 4 years after the reassignment of tamoxifen-treated patients to continued therapy or placebo, advantages in disease-free survival (92 vs 86%, p=0.003) and distant-disease-free survival (96 vs 90%, p=0.01) were found for those who discontinued tamoxifen.[20] Survival was 96% for those who discontinued tamoxifen compared with 94% for those who continued the drug (p=0.08). These data could be interpreted as being compatible with the hypothesis that long-term tamoxifen therapy is associated with a more aggressive form of breast-cancer recurrence. It is essential to monitor the mortality rate from breast cancer among women receiving tamoxifen prophylactically. Otherwise there is a risk that well women may be prescribed tamoxifen when experience of long-term effects is lacking in such a population.

In conclusion, tamoxifen was not significantly protective against breast cancer in women at normal or slightly reduced risk of the disease, at least in the duration of our follow-up. Women using hormone-replacement therapy benefited from tamoxifen administration: these preliminary findings require further investigations of the impact of antioestrogens on users of such therapy. Whether the action is limited to women receiving hormone-replacement therapy transdermally or is present also in women using oral treatment should also be investigated. It is notable that no deaths from breast cancer have yet been observed in the entire cohort and a much longer follow-up will be needed to quantify the impact of tamoxifen use on breast-cancer mortality and other long-term risks and benefits of tamoxifen therapy.

Contributors

Umberto Veronesi, Alberto Costa, Cesare Maltoni, and Peter Boyle were involved in the creation and design of the study. UV and CM were the principal investigators. PB was head of the data centre. Patrick Maisonneuve designed and ran the data base and did most of the statistical analysis. Nicole Rotmensz was the principal data manager. Virgilio Sacchini was the study coordinator and Chris Robertson helped in the statistical analysis. PB and UV prepared the first draft of the manuscript to which everyone then contributed.

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Table 1: Age distribution of women in trial

Age range (years)	Number of women	Percentage of total
35-39	103	1.9%
40-44	512	9.5%
45-49	1439	26.6%
50-54	1656	30.6%
55-59	1067	19.7%
60-64	470	8.7%
65-69	151	2.8%
70	10	0.2%

Table 2: Phlebitis and thrombosis

Description	Tamoxifen	Placebo	Total
Superficial phlebitis	33*	9	42
Deep-vein thrombosis	6	3	9
Other thrombosis	4+	3	7
Pulmonary embolism	1~	1	2
Post-phlebitis syndrome	0	1	1
Retinal venous thrombosis	1	0	1
Currently being evaluated	1	1	2
Total	46	18	64@

Figures refer to events and not individuall women (some women had more than one event). *33 events in 27 patients. +1 patient also had superficial phlebitis. ~Patient also had superficial phlebitis. @64 events in 56 patients.

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