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## FOURTEENTH GADDUM MEMORIAL LECTURE

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# A current view of tamoxifen for the treatment and prevention of breast cancer

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## Introduction

Tamoxifen (ICI 46,474 Nolvadex) is a non-steroidal antioestrogen (Harper & Walpole, 1966) with antifertility properties in rats and mice (Harper & Walpole, 1967a,b). The compound was shown to have efficacy in the treatment of advanced breast cancer (Cole *et al.*, 1971; Ward, 1973), but it is the low incidence of side effects and the continuing conversation between laboratory and the clinic that has guided the strategic application of tamoxifen, for the therapy of all stages of breast cancer. Indeed, tamoxifen is now being evaluated as a preventive agent in women at risk of breast cancer (Powles *et al.*, 1989; Fisher, 1992).

In the laboratory, tamoxifen prevents the induction (Jordan, 1974; 1976) and growth (Jordan & Dowse, 1976; Jordan & Jaspan, 1976) of carcinogen-induced rat mammary tumours. However if tamoxifen is administered daily after the carcinogenic insult is delivered to rats, the induction of tumours is prevented as long as the drug is administered (Jordan, 1978; Jordan *et al.*, 1979). If therapy is stopped, tumours reappear (Jordan & Allen, 1980; Gottardis & Jordan, 1987). Tamoxifen is now considered to be both a tumoristatic and tumoricidal agent so that a strategy of long term treatment (up to 5 years or indefinitely) after mastectomy has become accepted as a reasonable therapeutic approach (Jordan, 1983; 1990).

It is not the purpose of this lecture to review the development and complex pharmacology of antioestrogens; this has been done elsewhere (Jordan, 1984; 1988; Jordan & Murphy, 1990; Lerner & Jordan, 1990), rather it is to provide an up to date evaluation of the current mode of action of antioestrogens, their applications and the problems for future treatment strategies. Most importantly I will point out areas that need to be developed to clarify toxicological issues.

## Basic molecular mechanism of action

Oestrogen action is mediated through the nuclear oestrogen receptor in oestrogen target tissues (uterus, vagina and some breast cancers) (Jensen & Jacobson, 1962; Gorski *et al.*, 1968; Welshon *et al.*, 1984). It has been known for a century that oestrogen withdrawal causes the regression of some breast cancers (Beatson, 1896; Boyd, 1900) but the measurement of oestrogen receptors in tumours to predict which will respond to endocrine ablation (Jensen *et al.*, 1971; McGuire *et al.*, 1975) revolutionized breast cancer therapy and provided a target for therapeutic intervention. Tamoxifen is a competitive inhibitor of oestrogen binding at the oestrogen receptor (Skidmore *et al.*, 1972; Jordan & Koerner, 1975; Jordan & Prestwich, 1977) and blocks oestrogen action in breast cancer cells which contain receptors.

Within the cell, both oestrogen- and antioestrogen-oestrogen receptor complexes can bind to response-enhancer elements and both cause a similar alteration in chromatin structure (Pham *et al.*, 1991) but the antioestrogen-oestrogen receptor DNA complexes are transcriptionally nonproductive (Green, 1990). The precise molecular mechanism is at present obscure, but studies in yeast transfected with mutant oestrogen receptors indicate that the antagonistic effects of antioestrogens arise from a synergistic interaction of transactivating functions (TAF) of one and two sites on the oestrogen receptor protein (Pham *et al.*, 1992) and not simply from an inactivation of TAF-2 as previously thought (Berry *et al.*, 1990).

An important aspect of recent progress in understanding antioestrogen action in breast cancer is the use of clinical specimens before and after tamoxifen therapy to confirm studies conducted in the laboratory during the past decade. Oestrogen causes an increase in the growth factors transforming growth factor (TGF) $\alpha$ that can stimulate tumour growth through an autocrine loop using the epidermal growth factor receptor (Figure 1). It is also possible that TGF $\alpha$ can aid tumour cell survival by promoting angiogenesis (Schrieber *et al.*, 1986). Tamoxifen therapy causes an up regulation of the level of oestrogen receptors (Noguchi *et al.*, 1993a) but a decrease in tumour concentrations of TGF $\alpha$ (Noguchi *et al.*, 1993b) which might be partly responsible for stopping tumour growth. However, regulation of TGF $\alpha$ might also have an important impact on tumour cell survival. Recent studies (Gagliardi & Collins, 1993) have shown that antioestrogens can inhibit angiogenesis in laboratory models; an action that could explain the sustained survival advantage (up to 10 years) observed after limited (two years) adjuvant tamoxifen therapy (Early Breast Cancer Trials Collaborative Group, 1992).

Another aspect of tumour growth control by tamoxifen is the influence on endocrine and paracrine growth regulators (Figure 2). Tamoxifen increases sex hormone binding globulin (SHBG) levels in postmenopausal patients which in turn lowers the amount of free-oestradiol that is present in the serum (Rose *et al.*, 1992). Similarly, tamoxifen reduces the circulating level of insulin-like growth factor 1 (IGF1) (Pollak *et al.*, 1992), a growth factor that is known to

stimulate the growth of breast tumour cells *in vitro*. Indeed tamoxifen reduces the production of IGF-1 in normal tissues (Huynh *et al.*, 1993) so it is possible that metastatic spread would be reduced if there was a reduction in supportive paracrine growth factor that was needed for tumour cell survival. The other piece of the tumour cell mosaic is the role played by the inhibitory growth factor TGF β (Figure 1). The peptide is made in oestrogen receptor positive breast cancer cells in response to tamoxifen (Knabbe *et al.*, 1987) but in the laboratory, TGF β will inhibit the growth of oestrogen receptor negative cells (Arteaga *et al.*, 1988). These observations lead to the view that TGF β produced in oestrogen receptor positive cells could influence the growth of adjacent oestrogen receptors negative cells. However, the recent finding that tumour stromal cells can also produce TGF β in the laboratory (Colletta *et al.*, 1990) and in response to tamoxifen therapy (Butta *et al.*, 1992) provides compelling evidence that a complex intercellular conversation occurs to regulate growth.

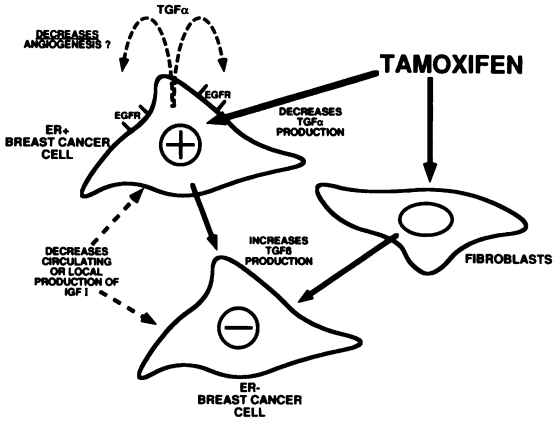


**Figure 1** The potential mode of action of tamoxifen to control the growth of oestrogen receptor positive (+) and negative (−) breast cancer cells within a tumour. Tamoxifen can decrease the production of transforming growth factor (TGF) α in oestrogen receptor-positive cells that could reduce angiogenesis and can decrease cell replication by reducing activation of epidermal growth factor receptors (EGFR). The inhibitor growth factor, TGF β, produced both oestrogen receptor-positive cells and fibroblasts, can inhibit the growth of oestrogen receptor negative cells. Insulin-like growth factor (IGF-1), a stimulatory growth factor is reduced by tamoxifen therapy.

Although the oestrogen receptor mediated mechanism might be the most important in the breast tumour, the fact that tamoxifen can provide significant survival advantages in breast cancer patients with oestrogen receptor-poor tumours (Early Breast Cancer Trials Collaborative Group, 1992) has raised the possibility that all postmenopausal women with a diagnosis of breast cancer should receive tamoxifen maintenance (Jordan, 1993). The multiple mechanisms of action of tamoxifen (Figures 1 and 2) that can potentially control tumour growth provides compelling evidence to support the clinical view that all menopausal patients can benefit from tamoxifen.

## Pharmacology of tamoxifen

Tamoxifen displays an interesting spectrum of agonist and antagonist actions in different tissues and in different species. This pharmacology has been reviewed (Furr & Jordan, 1984; Jordan, 1984; Jordan & Murphy, 1990) but several recent

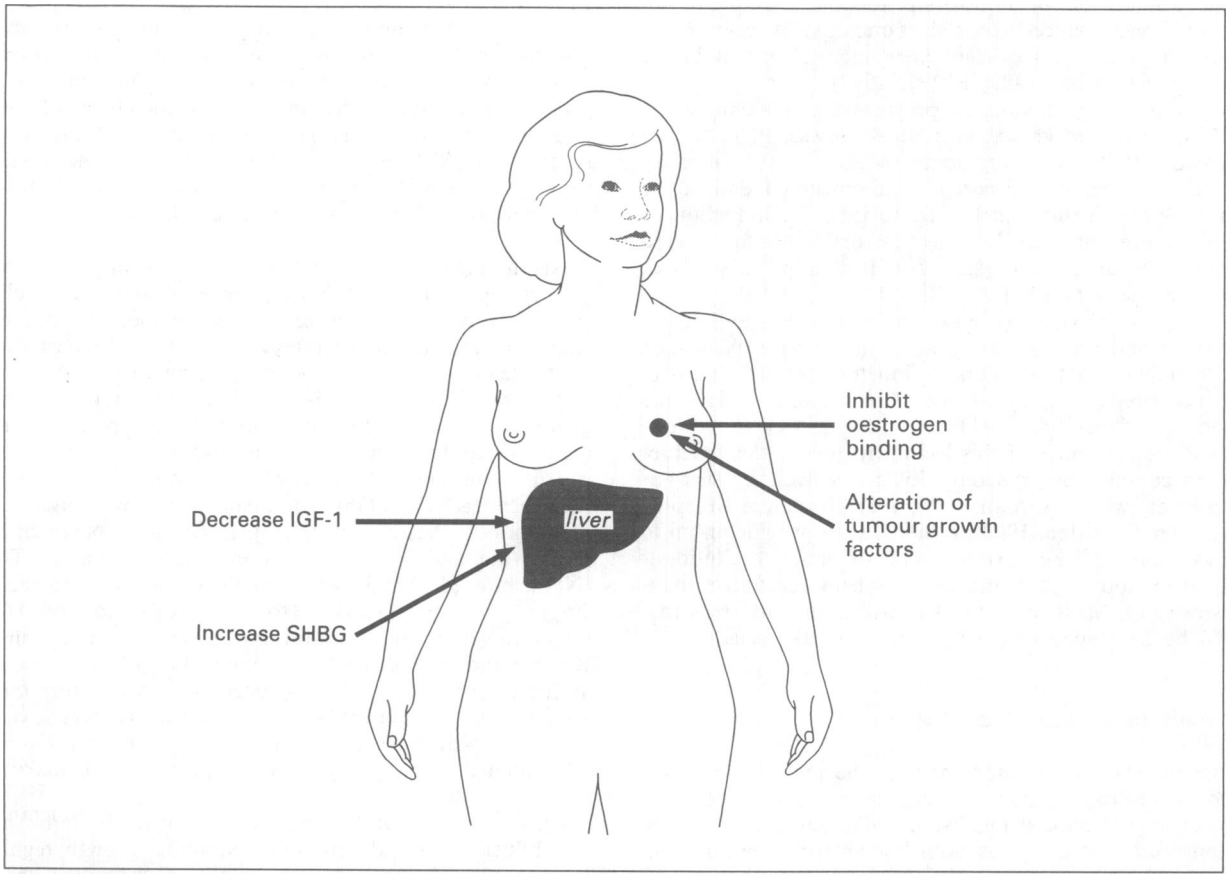


**Figure 2** An overview of the actions of tamoxifen in controlling breast cancer growth. Tamoxifen will inhibit oestrogen binding to tumour oestrogen receptors and alter the regulation of growth factors in the tumour (see Figure 1). The circulating level of insulin-like growth factor (IGF-1) is reduced and in postmenopausal patients, tamoxifen increases the circulating level of sex hormone binding globulin (SHBG). As a result, the level of free versus SHBG bound oestradiol is reduced in the tamoxifen-treated patient.

laboratory findings have implications for the clinical applications of tamoxifen. The wide acceptance of tamoxifen as a breast cancer therapy coupled with its potential as a preventive in normal women has re-focused attention on laboratory studies that could have long term consequences for patients.

In short term laboratory assays, tamoxifen is usually classified as an oestrogen in the mouse, and partial antagonist in rats and man. At present there is no adequate explanation for the species differences in pharmacology. Numerous studies have been completed to determine whether different metabolites are present in different species (Lyman & Jordan, 1985; Langan-Fahey *et al.*, 1990; Robinson *et al.*, 1991). However, the studies have only demonstrated increased production of 4-hydroxytamoxifen in the mouse (Robinson *et al.*, 1991). This metabolite has high binding affinity for the oestrogen receptor (Jordan *et al.*, 1977) but does not display exceptional oestrogenicity in mouse assays (Jordan *et al.*, 1978). In fact the view that tamoxifen is an oestrogen in the mouse might be an over simplification, because the sustained administration of tamoxifen to ovariectomized mice results in the uterus becoming refractory to oestrogen administration (Jordan *et al.*, 1990). It appears that the uterus initially responds to tamoxifen as an oestrogen but the longer tamoxifen administration is continued, uterine weight decreases back to untreated values.

The pharmacology of tamoxifen is extremely complex and appears not only to be species- but also tissue- and duration of administration-specific. This pharmacology has yet to be resolved; nevertheless, the necessity of determining the mechanism of actions of tamoxifen in various tissues to explain its agonist and antagonist actions is becoming essential. Obviously the safety of a medicine is of paramount importance so laboratory test systems are established to discover any potential toxicities that might have important consequences for the deployment of a drug. Unfortunately it may become difficult to determine what is a clinically relevant toxicological result from the laboratory in the light of extensive clinical experience.

A current concern is the potential of tamoxifen to produce liver tumours because the laboratory and clinical information is divergent. Tamoxifen has 4.5 million women years of experience and by and large the toxicology monitoring has revealed few serious side effects. At present there are no reports of increases in the incidence of hepatocellular carcinoma at the 10 mg tamoxifen twice daily dose, although two cases of hepatocellular carcinoma have been noted with the use of 20 mg tamoxifen twice daily. In contrast, tamoxifen is known to form DNA adducts in the rat liver and to cause rat liver tumours (Dragan *et al.*, 1991; Han & Liehr, 1992; White *et al.*, 1992; Williams *et al.*, 1993). These data in the laboratory cannot be ignored because they represent important information about the pharmacology of tamoxifen. Indeed the research effect must be intensified in the laboratory to determine the mechanism for the carcinogenic effect of tamoxifen. It may be found that the phenomenon is species-specific and does not occur to a significant extent in man. However the comparative study will yield valuable comparative toxicities and an insight into the mechanism of toxicity. One explanation for the carcinogenic action of tamoxifen in the rat liver may be as an oestrogenic tumour promoter. It is known that oestradiol and synthetic oestrogens are powerful promoters of rat liver carcinogenesis but the administration of contraceptive oestrogens and oestrogen replacement therapy in patients has not demonstrated an increased incidence of liver tumours that restricts clinical usage.

Overall the toxicology of tamoxifen has proved to be a controversial issue and the adverse publicity has become extremely troublesome for the hundreds of thousands of women who benefit from the drug. Fortunately the benefit of tamoxifen as an anticancer agent can be quantitated and has been the subject of a recent overview analysis of controlled clinical trials.

## An overview of adjuvant tamoxifen therapy

The effectiveness of adjuvant tamoxifen in both node positive (tumour spread to lymph nodes) and node negative breast cancer has recently been established in an overview analysis (Early Breast Cancer Trials Collaborative Group, 1992). The review included 30,000 women in randomized trials of tamoxifen. Highly significant reductions in the annual rates of recurrence and death are produced (25% for recurrence and 17% for mortality) and tamoxifen reduced the risk of developing a contralateral breast cancer by 39%. Most interestingly, the differences in survival produced by two years of tamoxifen therapy was larger at 10 years than at 5 years. However, as was predicted by the laboratory data (Jordan, 1983), the duration of adjuvant therapy was important for controlling recurrence and improving mortality. Women who received only one year of tamoxifen had a worse prognosis than those receiving more than two years of tamoxifen. Node negative women had a similar benefit from tamoxifen monotherapy whether they were above or below the age of 50. In contrast, the node positive women had more benefit from tamoxifen containing regimens if they were postmenopausal and less benefit if they were premenopausal. This, in part, could be because the node positive breast cancer patients also received combination chemotherapy which is known to cause ovarian ablation (Rose & Davis, 1977). It is therefore possible that the benefit to be gained from this form of 'endocrine therapy' i.e. chemical *oophorectory*, is optimal and tamoxifen can add little further benefit. It is perhaps pertinent to point out that the overview analysis found that ovarian ablation below the age of 50 decreases mortality (25%) to a similar extent as polychemotherapy (16%).

Finally, there has been much controversy about the role of the oestrogen receptor in predicting response to tamoxifen therapy. In the United States tamoxifen is approved as an adjuvant therapy for all postmenopausal patients with node positive disease but an increased level of oestrogen receptor might improve the chances of a beneficial response. The overview analysis found that oestrogen receptor-poor postmenopausal patients ($<10$ fmol mg$^{-1}$ cytosol protein) had a 16% reduction in annual odds of recurrence. The situation improves if the oestrogen receptor is $>10$ fmol mg$^{-1}$ cytosol protein; the reduction in the annual odds of recurrence is 36% for women over 50 years of age.

These statistical studies have established the worth of adjuvant tamoxifen to aid survival and placed a valuable therapeutic agent in the hands of the medical community. This success has resulted in an extension of adjuvant tamoxifen therapy and a careful evaluation of the potential side effects of long term adjunct tamoxifen therapy.

## Long term tamoxifen therapy

During the 1970's, several clinical trials organizations decided to select a conservative course of one year of adjuvant therapy. This decision was, however, based upon a number of reasonable concerns. Patients with advanced disease usually respond to tamoxifen for one year and it was expected that oestrogen receptor negative disease would be encouraged to grow prematurely during adjuvant therapy. If this occurred, then the physician would have already used a valuable palliative drug and would have only combination chemotherapy to slow the relentless growth of recurrent disease. The argument produced an intuitive reluctance to use long term tamoxifen therapy because it would lead to premature drug resistance: longer might not be better.

Finally, there were sincere concerns about the side effects of adjuvant therapy and the ethical issues of treating node negative patients who might never have recurrent disease. Few women in the mid 1970's had received extended therapy with tamoxifen, so that long-term side effects were largely

unknown. The majority of tamoxifen-treated patients had received only about two years of treatment for advanced disease before drug resistance occurred. Potential side effects of thrombosis, osteoporosis, and so on were only of secondary importance. The use of tamoxifen in the disease-free patients would change that perspective.

The first evaluation of long-term tamoxifen therapy in node positive breast cancer patients was initiated in 1977 at the University of Wisconsin Comprehensive Cancer Center. This pilot study was to determine whether patients could tolerate five years of adjuvant tamoxifen therapy and whether changes in the metabolism of the drug would occur during long-term treatment. No unusual side effects of tamoxifen were noted, and blood levels of tamoxifen and its metabolites N-desmethyltamoxifen and metabolite Y remained stable throughout the five years of treatment (Tormey & Jordan, 1984; Tormey *et al.*, 1987). Although this study was not a randomized trial, those patients who are receiving long-term tamoxifen therapy continue to make excellent progress and many patients have been taking the drug for more than 15 years. We have recently reported (Langan-Fahey *et al.*, 1990) that tamoxifen does not produce metabolic tolerance during 10 years of administration.

The clinical data from the pilot study in Wisconsin and the DMBA rat mammary carcinoma data (Jordan, 1983) were used to support randomized Eastern Cooperative Oncology Group trials EST 4181 and 5181. An early analysis of both EST 4181 (Falkson *et al.*, 1990) and EST 5181 (Tormey *et al.*, 1992) which compares short term with long term tamoxifen (both with combination chemotherapy) has demonstrated an increase in disease-free survival with long-term tamoxifen therapy. In fact, the five year tamoxifen arm has now gone through a second randomization either to stop the tamoxifen or to continue the antioestrogen indefinitely.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted a registration study of two years of combination chemotherapy plus tamoxifen and compared the result with the same regimen but with an additional year of tamoxifen (Fisher *et al.*, 1987). Overall, the NSABP investigators conclude that three years of tamoxifen is superior to two years of tamoxifen. Most importantly, there is now a belief that tamoxifen alone may be optimal adjuvant therapy for postmenopausal patients. However, this point is controversial as tamoxifen is clearly effective in postmenopausal but such high numbers are needed to discern any small additional advantages in survival by adding chemotherapy. Be that as it may, even if modest differences are detected in survival, or even disease-free survival, this apparent advantage does not take into account the decrease in the quality of life experienced by the recipient of combination chemotherapy. The NSABP has demonstrated a survival advantage for patients receiving an adriamycin containing regimen with tamoxifen compared with tamoxifen alone (Fisher *et al.*, 1990). In contrast, a report from Italy has demonstrated that the addition of combination chemotherapy to long term tamoxifen (5 years) therapy does not seem to improve significantly the clear cut effectiveness of tamoxifen alone to prevent occurrence in oestrogen receptor and node positive disease (Boccardo *et al.*, 1990).

Although the two year adjuvant tamoxifen study that was conducted by the Nolvadex Adjuvant Trials Organization (NATO) was the first to demonstrate a survival advantage for women with tamoxifen alone (Nolvadex Adjuvant Trial Organization, 1985) current clinical trials are all evaluating a longer duration of therapy. The Scottish trial has evaluated five years of tamoxifen versus treatment and has demonstrated a survival advantage for patients who take 10 mg b.i.d. tamoxifen (Breast Cancer Trials Committee, 1987). The Scottish trial is particularly interesting because it addresses the question of whether to administer tamoxifen early as an adjuvant or save the drug until recurrence. This comparison was possible because most patients (92%) in the control arm received tamoxifen at recurrence. Early concerns that long-term adjuvant tamoxifen would result in premature drug reistance are unjustified as the patients have a survival advantage on the adjuvant tamoxifen arm.

Finally the NSABP landmark study B14 to evaluate adjuvant tamoxifen therapy in oestrogen receptor positive, node negative patients (Fisher *et al.*, 1989) has demonstrated advantages for both pre- and postmenopausal patients. The patients were initially randomized to placebo or tamoxifen (10 mg bi.d.) for five years but now the tamoxifen treatment arm is being randomized either to stop tamoxifen or to continue for another five years.

All of the long term tamoxifen clinical trials have led to a general trend for extended tamoxifen therapy in general practice. This broad use of tamoxifen in women who are either disease free or indeed may never have a recurrence has mandated the re-evaluation of the toxicology and side effects of therapy.

## Additional benefits of tamoxifen therapy

In the mid 1980's, concerns were raised about the wisdom of treating women chronically with an antioestrogen. Oestrogen is beneficial to women to maintain bone density and to maintain a favourable lipid profile and protect against coronary heart disease. However tamoxifen exhibits numerous oestrogen-like effects in postmenopausal women (Furr & Jordan, 1984). It was believed that these partial agonist actions of tamoxifen could translate into beneficial effects to maintain bone density and to prevent coronary heart disease. At present there are several encouraging studies that indicate the possible merit of long term tamoxifen therapy.

Tamoxifen does not cause any reduction in bone density (Love *et al.*, 1988; Fentiman *et al.*, 1989; Powles *et al.*, 1990; Kalef-Ezra *et al.*, 1992) and in two clinical trials postmenopausal patients receiving tamoxifen experienced a beneficial effect on bone density compared to patients receiving no endocrine treatment (Love *et al.*, 1992a; Turken *et al.*, 1989). However, no comparisons have been made between the ability of tamoxifen or exogenous oestrogens to maintain bone in postmenopausal women. Nevertheless, since women with breast cancer are a group of patients that is uniformly ineligible for postmenopausal oestrogen replacement therapy, any bone preserving effect produced by tamoxifen is an added benefit to its antitumour actions.

Furthermore patients treated with tamoxifen also experience significant reductions in total serum cholesterol, low-density lipoprotein cholesterol and apolipoprotein B levels (Powles *et al.*, 1989; Love *et al.*, 1990; 1991a). The other interesting observation is that the high density lipoprotein cholesterol either increases or is unchanged but total serum cholesterol is reduced relative to baseline i.e. if the patient has a higher than normal baseline cholesterol there is a greater percentage decrease than a patient with a low baseline cholesterol value (Love *et al.*, 1991a). These effects of lipids are usually associated with reductions in the risk of cardiovascular disease and in one study, a significant reduction in the incidence of fatal myocardial infarction was observed in the tamoxifen-treated group compared to controls (McDonald & Stewart, 1991).

Overall, the oestrogenic activity of tamoxifen could produce a profound effect to support physiological functions in women and help to prevent the development of osteoporosis and coronary heart disease. However the oestrogenicity may also cause deleterious side effects that must be carefully monitored in patients.

## Side effects related to the ostrogenicity of tamoxifen

There are several anecdotal reports (Nevasaari *et al.*, 1978; Hendrick & Subraminian, 1980; Lipton *et al.*, 1984) of

thromboembolic events occurring in association with tamoxifen therapy. However, detailed studies documenting statistically significant increases in thromboembolic disorders during long term tamoxifen monotherapy are lacking. Venous and arterial thombosis does occur more frequently in patients receiving chemotherapy and tamoxifen (Saphner *et al.*, 1991), so it might be prudent to monitor this parameter. Tamoxifen has been associated with decreased levels of antithrombin III (Jordan *et al.*, 1987; Love *et al.*, 1992b) but these are not clinically significant reductions, except possibly in the case of a patient with a previous history of a clotting disorder. It is however important to point out that tamoxifen alters the blood transport of the coumarin type anticoagulants (Ritchie & Grant, 1984; Tenni *et al.*, 1989) so special care must be taken to ensure the appropriate types and levels of medication.

Considerable interest is currently focused on the risks of developing endometrial carcinoma during long-term tamoxifen therapy. However, the relationship between tamoxifen and endometrial carcinoma remains controversial. Interestingly, though, tamoxifen has been used as a treatment for endometrial carcinoma (Broens *et al.*, 1980; Swenerton, 1980; Bonte *et al.*, 1981). The antioestrogenic action of tamoxifen dominates in this pharmacological application. However, recent evidence from both the laboratory and clinic indicate that tamoxifen can act as a growth promoter for occult endometrial carcinoma. In the athymic mouse model, oestrogen receptor-positive human endometrial carcinoma will grow in response to tamoxifen (Satyaswaroop *et al.*, 1984). Indeed in animals co-transplanted with human endometrial tumours and breast tumours, tamoxifen will prevent the oestrogen stimulated growth of the breast tumours but enhance the growth of the endometrial tumours (Gottardis *et al.*, 1988). This observation heightened awareness about the possibility that tamoxifen could encourage the development of endometrial carcinoma during breast cancer therapy.

Tamoxifen has now been implicated in the development of endometrial tumours in patients. In one study, with accrual of over 1 800 postmenopausal women who received either tamoxifen or placebo after primary surgery for breast cancer, 13 patients in the tamoxifen-treated group compared to two in the placebo-treated group developed endometrial cancer (Fornander *et al.*, 1989). This study also showed that the incidence of endometrial cancer was correlated with the duration of tamoxifen. Women who received tamoxifen for five years were at greater risk for developing endometrial carcinoma. However, the women in the study all received tamoxifen 20 mg b.i.d. which is twice the dose normally prescribed in the United States. There are other reports of endometrial carcinoma with high dose tamoxifen treatment (Hardell, 1988; Atlante *et al.*, 1990; Magriples *et al.*, 1993) but interest is currently focused on the epidemiology of endometrial cancer at the standard dose regimen of 20 mg daily. In a study conducted by the Southwest Oncology Group, four of the 641 patients treated for one year with tamoxifen developed endometrial cancer, compared to no cases of endometrial cancer in the 325 patients treated with adjuvant chemotherapy (Sunderland & Osborne, 1991). Similarly in a study by Anderson and colleagues (1991) of one year of adjuvant tamoxifen there was a trend toward an increased risk of developing endometrial carcinoma. Unfortunately in neither report was any clinical information given. However, in a recent review of the published information (Nayfield *et al.*, 1991) (Table 1), the incidence data only translates to an extra four women per thousand who take tamoxifen who will develop endometrial carcinoma. In fact the difference becomes insignificant if high dose tamoxifen-treated patients are excluded. It has been suggested (Gusberg, 1990) that careful patient monitoring, using serial endometrial biopsies, may be an appropriate screening technique. Unfortunately, this approach may not be acceptable to patients. Careful patient monitoring and endometrial biopsies *when* the patient experiences unexplained spotting or bleeding may be the most appropriate. Surgical intervention may then become necessary.

The strategy of targeting individuals on tamoxifen who experience symptoms rather than screening the whole treatment population may have merit by analogy with oestrogen based hormone replacement therapy in postmenopausal women. Horowitz & Feinstein (1986) argue that the observed increase in endometrial carcinoma attributed to oestrogens (and presumably we can also suggest tamoxifen) may be due to increased detection of lesions that would otherwise remain as silent tumours. They support this conjecture by reporting that the incidence of 'silent' endometrial cancers diagnosed at autopsy is roughly three times the incidence in the living population. It is possible that the partial agonist action of tamoxifen could act on silent tumours and any resultant abnormal bleeding would bring about an increased detection rate. Indeed this may be beneficial to the patient. The probability of surviving five years after a diagnosis of endometrial carcinoma is 0.89 for previous oestrogen users but only 0.53 for non-users (Schwartzbaum *et al.*, 1987). One interpretation of these data is that oestrogen promotes the early detection of occult tumours by causing abnormal bleeding before the development of metastases. Early detection may be the best strategy for the patient rather than the slow growth of silent disease.

It is also important for the gynaecologiest to appreciate that tamoxifen has been associated with endometriosis, endocervical and endometrial polyps (Ford *et al.*, 1988; Neven *et al.*, 1989; Nuovo *et al.*, 1989; DeMuylder *et al.*, 1991; Corley *et al.*, 1992). As a result, any bleeding that occurs does not automatically mean the patient has endometrial carcinoma.

Despite concerns about the development of the endometrial carcinoma during long term tamoxifen therapy for breast cancer there is insufficient evidence to deny a woman tamoxifen treatment. The benefits far outweigh the risks and regular gynaecological examinations will provide adequate safeguards for both the physicians and the patient.

Overall the past decade has established the effectiveness of tamoxifen as a valuable therapeutic agent. The proven antitumour actions of tamoxifen and the low incidence of side effects have increased enthusiasm to evaluate the role of tamoxifen to prevent breast cancer in high risk women. The concept is a direct result of a sound laboratory rationale and broad clinical experience.

## The biological basis for prevention

During the past two decades a growing body of literature on the prevention of mammary cancer in rodents has been used to support the clinical use of tamoxifen to prevent breast. However it was Lacassagne (1936) who predicted that a therapeutic intervention could be developed that would 'prevent or antagonize the congestion of oestrogen in the breast'. Unfortunately, at that time no therapeutic agent was

**Table 1** Cumulative frequency of uterine cancers during adjuvant tamoxifen therapy

| *Trial* | *Tamoxifen-treated cancers* (n) | *Control cancers* (n) |
|---|---|---|
| Copenhagen | 2 (164) | 0 (153) |
| ECOG | 1 (91) | 1 (90) |
| NATO | 0 (564) | 0 (567) |
| NSABP | 2 (1419) | 0 (1428) |
| Scottish | 4 (661) | 2 (651) |
| Stockholm | 13 (931) | 2 (915) |
| Toronto-Edmonton | 0 (198) | 1 (202) |
| Total | 0.5% | 0.1% |

Adapted from Nayfield *et al.* (1991).

available and all his predictions were based upon the known effect of early oophorectomy in preventing the development of mammary cancer in high incidence strains of mice.

The animal studies with tamoxifen have been undertaken for two reasons. First, to establish the efficiency of tamoxifen in well-described models of carcinogenesis and second to discover whether tamoxifen would always be an inhibitor or whether the drug could exacerbate tumorigenesis. Two animal model systems have been used extensively: the carcinogen-induced rat mammary carcinoma model and mouse mammary tumour virus (MMTV) infected strains.

The mammary carcinogens DMBA (Huggins *et al.*, 1961) and NMU (Gullino *et al.*, 1975) induce tumours in young female rats. The timing of the carcinogenic insult is very important because as the animals age they become resistant to mammary carcinogens. Tumorigenesis does not occur in oophorectomized animals and the sooner oophorectomy is performed after the carcinogenic insult the more effective it is in preventing the development of tumours (Dao, 1962). The administration of tamoxifen to carcinogen-treated rats prevents the initiation of carcinogenesis and animals remain tumour-free (Jordan, 1976; Turcot-Lemay & Kelley, 1980).

The short term administration of tamoxifen at different times after the carcinogenic insult is effective in reducing the number of tumours that develop (Jordan *et al.*, 1979; Jordan & Allen, 1980; Wilson *et al.*, 1982) although most animals develop at least one tumour after therapy is stopped. In contrast, continuous therapy that is started one month after the administration of carcinogens completely inhibits the appearance of mammary tumours (Jordan, 1983; Gottardis & Jordan, 1987). Under these circumstances, tamoxifen is preventing promotion and is suppressing the appearance of occult disease.

Consideration of the use of tamoxifen in mouse models was delayed because the pharmacology of tamoxifen in the mouse was initially thought to be very different from the rat. Tamoxifen is oestrogenic in short term tests in oophorectomized (Harper & Walpole, 1967b) and immature mice (Terenius, 1971). However, the finding that long-term therapy renders the oophorectomized mouse vagina (Jordan, 1975) and athymic mouse uterus (Gottardis & Jordan, 1988) refractory to oestrogenic stimuli prompted a reconsideration of the value of tamoxifen as a preventive in mouse mammary tumour models. Tumorigenesis is ovarian-dependent in the MMTV model (Lathrop & Loeb, 1916). However, unless the animals are ovariectomized just after weaning about 50% of the animals produce tumours. In contrast the sustained administration of tamoxifen prevents mammary tumorigenesis in 90% of the animals; a result that is superior to ovariectomy (Jordan *et al.*, 1991).

Although the animal studies are encouraging, the most compelling evidence that tamoxifen can be an effective preventive comes from an analysis of adjuvant clinical trials. The incidence of contralateral breast cancer is estimated as 8/1 000 women annually (Chaudary *et al.*, 1984) and it was possible that the tumoristatic action of tamoxifen could reduce second primary breast cancers. Cuzick & Baum (1985) were the first to note that tamoxifen prevented the appearance of secondary breast cancers. A review of published clinical trials which involve nearly 5 000 women per arm, shows a one third reduction of contralateral breast cancer with tamoxifen treatment (Table 2). Similarly the overview analysis of randomized clinical trial (EBCTC 1992) with 9 000 women per group showed a rate of developing primary breast cancers in control of 2% but 1.3% in tamoxifen-treated groups. Since the timing of initiation in human breast cancer is unknown, tamoxifen will be given to target populations to suppress and hopefully reverse the promotional effects of oestrogen during carcinogenesis.

**Table 2** Comparison of contralateral breast cancer rates for tamoxifen-treated versus placebo-treated women with early-stage breast cancer

| *Clinical trial* | *Rate for tamoxifen-treated women* | *Rate for control-treated women* |
|---|---|---|
| Copenhagen | 1.8% | 2.6% |
| ECOG 1178 | 1.1% | 3.3% |
| Stockholm | 1.9% | 3.5% |
| Toronto-Edmonton | 1.5% | 1.5% |
| Scottish | 1.4% | 1.8% |
| CRC | 0.7% | 1.9% |
| NATO | 2.7% | 3.0% |
| NSABP-14 | 1.6% | 2.2% |
| Average | 1.6% | 2.4% |

Adapted from Nayfield *et al.* (1991).

## Current tamoxifen prevention trials

Unlike the laboratory models of mammary tumorigenesis where all animals develop tumours and the efficacy of tamoxifen is readily demonstrated, it is difficult to target the appropriate population of women at risk for breast cancer. Numerous risk factors have been identified (Table 3) but these have been reviewed elsewhere (Morrow, 1992; Morrow & Jordan, 1992). However, because the incidence of breast cancer is so small in the general population, it is essential to recruit women volunteers with a high risk profile to be able to evaluate the worth of tamoxifen. It is essential to design a double blind trial, but the large numbers of volunteers required and the long time period necessary to obtain a statistically significant results mandates an enormous clinical trials effort, data management, and compliance monitoring.

There are currently three clinical trials recruiting women to test the worth of tamoxifen to prevent breast cancer. The first trial was begun at the Royal Marsden Hospital in 1986 (Powles *et al.*, 1989; 1990). At present about 2 000 women are randomized to receive either tamoxifen 20 mg daily or placebo for five years. High risk women, for the purposes of this study, are defined as those with at least one first degree relative who developed breast cancer under age 40, or bilateral cancer at any age, or at least two first degree relatives with breast cancer at any age. Risk factors other than family history are not considered. The age range of study participants is from 30 to 66 with a mean age of 48 years. At 12 months an 83% compliance rate was noted for women in the tamoxifen arm which by two years had decrease to approximately 70%. This study is designed as a feasibility trial with the ultimate goal being a large scale multi-centre trial. In March 1992 the Medical Research Council (MRC) of Great Britain voted to restrict entry to the multi-centre trial to women over the age of 40 with a four fold or greater relative risk of breast cancer. The current estimate for the risk of the recruited population is 3.8. Concerns over the induction of liver tumours in rats by tamoxifen was cited by the MRC as the major reason for restricting entry into the study (Anonymous, 1992). The trial is, however, now (July, 1993) approved by the department of health and is actively recruiting 15,000 women.

**Table 3** Estimates of increase in the risks of a woman developing breast cancer if she has individual risk factors

| | *Increase in relative risk* |
|---|---|
| Mother or sister with breast cancer | 1.5–3.0 |
| Mother plus sister | 4.6 |
| Nulliparous woman | 1.4 |
| First pregnancy $>30$ | 2–5 |
| Atypical hyperplasia | 4.4 |
| Lobular carcinoma *in situ* (LCIS) | 6.9–12 |

Adapted from Morrow (1992).

A second study, again randomizing participants to treatment with tamoxifen, 20 mg daily or placebo, opened in the United States in May, 1992. This study, administered by the NSABP with National Cancer Institute funding, has an accrual goal of 16 000 women over the next two years. Those eligible for entry into the study include any woman over the age of 60, or women between the ages of 35 and 59 whose five year risk of developing breast cancer, as predicted by the Gail model (Gail *et al.*, 1989) equals that of a 60 year old woman. Any woman over age 35 with a diagnosis of lobular carcinoma *in situ* (LCIS) treated by biopsy alone is eligible for study entry. In the absence of LCIS, the risk factors for entry vary with age so that a 35 year old woman must have a relative risk of 5.07 while a 45 year old woman's relative risk must be 1.79 to be eligible for study entry. Treatment will continue for a minimum of five years.

Finally, in Italy, the Milan Cancer Institute has initiated a five year study of tamoxifen (20 mg daily) versus placebo for five years in hysterectomized women over the age of 45 years. The aim is to avoid any complications with either pregnancy or endometrial carcinoma. The group will recruit 20 000 volunteers for the study.

For the first time, the clinical trials community is in the process of evaluating a therapy to prevent breast cancer. However, the majority of women recruited to the trials will not develop breast cancer although they will experience symptoms and side effects related to the pharmacology of tamoxifen. The evaluation of the toxicology of tamoxifen in the trials is extremely important not only to determine the therapeutic value of the intervention but also to assess whether compliance can be maintained by the study population. Extra attention is being paid to acute and chronic toxicities.

**Table 4** Percentage of patients with acute adverse side effects from tamoxifen

| | |
|---|---|
| Fatigue* | 5–70% |
| Vasomotor instability (hot flushes) | 17–67% |
| Insomnia | 0–54% |
| Headache | 9–37% |
| Depression | 1–33% |
| Altered menses – (amenorrhoea, oligomenorrhoea, menstrual disorders, vaginal discharge, vaginal bleeding) | 1–31% |
| Pain (bone or musculoskeletal) | 2–30% |
| Fluid retention (oedema) | 2–25% |
| Nausea | 3–21% |
| Anorexia | 1–16% |
| Leukopaenia | 1–15% |
| Skin rash | 4–13% |
| Vomiting | 1–12% |
| Diarrhoea | 8–10% |
| Ovarian cysts | 3–5% |
| Constipation | 2–4% |
| Weight gain | 4% |
| Hypercalcaemia | 3–4% |
| Abdominal cramps | 1–3% |
| Thrombocytopaenia | 1–2% |
| Phlebitis | <1% |
| Dizziness, light-headedness | <1% |

*Shown are the range of the percentages of tamoxifen-treated patients reporting side effects (Pritchard *et al.*, 1980; Ingle *et al.*, 1981; NATO, 1983; 1985; Cummings *et al.*, 1985; Buchanan *et al.*, 1986; Love, 1988; Powles *et al.*, 1989; Fisher *et al.*, 1989; Paterson *et al.*, 1990; Love *et al.*, 1991b).

## Side effects of tamoxifen therapy

The side effects of tamoxifen are related to its differential oestrogenic and antioestrogenic properties at various target tissues. Several studies (Ingle *et al.*, 1981; Fisher *et al.*, 1989; Pritchard *et al.*, 1980; Nolvadex Adjuvant Trial Organization, 1983; 1985; Cummings *et al.*, 1985; Buchanan *et al.*, 1986; Love, 1988; Powles *et al.*, 1989; Paterson *et al.*, 1990; Love *et al.*, 1991b) have compared the incidence of side effects observed in patients treated with tamoxifen with those in an alternate therapy or given a placebo. The range of the percentage incidence of side effects during tamoxifen therapy are illustrated in Table 4. Interestingly the only adverse side effect consistently reported by patients receiving tamoxifen that was significantly greater than placebo was hot flushes. All of the other side effects occurred with a similar incidence in the placebo arm. This illustrates how important it is to have placebo controlled trials and good support services for prevention studies. Gynaecological symptoms can become troublesome and must be a focus for attention in premenopausal women recruited into prevention studies. Patients experience leukorrhoea, endometrial hyperplasia (Gal *et al.*, 1991; Neven *et al.*, 1990), polyps (Corley *et al.*, 1992) and one recent case report describes the rapid growth of a leiomyoma in a patient receiving tamoxifen (Dilts *et al.*, 1992). Although some premenopausal women become amenorrhoeic during tamoxifen therapy, most continue to have normal or mildly altered menstrual cycles. These women should be considered to be at risk for pregnancy and indeed tamoxifen is known to induce ovulation in sub fertile women (Furr & Jordan, 1984). Although there are no reports of teratogenicity in response to tamoxifen, the drug should not be prescribed to the pregnant patient. The endocrinological effects of tamoxifen in pre- and postmenopausal women are summarized in Figure 3. Tamoxifen induces ovarian steroidogenesis (Groom & Griffiths, 1976; Jordan *et al.*, 1991) elevating serum oestradiol levels to as high as 2500 pg $ml^{-1}$ in premenopausal women (Manni & Pearson, 1980; Jordan *et al.*, 1991). Chronically elevated oestrogen levels normally cause decrease follicle stimulating hormone (FSH) and leutinizing hormone (LH) production. Treatment with tamoxifen might be expected to elevate gonadotropin levels by blocking negative feedback. However, FSH and LH levels remain largely unchanged which indicates that tamoxifen may act directly on the ovary to increase steroidogenesis, and the balance between its agonist and antagonist activities maintains pituitary gonadotropin secretions at normal levels in the face of elevated serum oestradiol. It is unclear whether or not hypersecretion from the ovary will result in an increased pathology, but tamoxifen has been associated with an increased incidence of fibroid ovaries and ovarian cysts (Powles *et al.*, 1989).

A recent concern is the increasing reports of ophthalmic problems. Triphenylethylenes, including tamoxifen and clomiphene can cause cataracts in rats (Furr & Jordan, 1984). The difficulty in assessing the anecdotal reports is the fact that the incidence of problems is not being assessed in large treatment or placebo groups. Case reports of retinopathy (Kaiser-Kupfer & Lippman, 1978; Kaiser-Kupfer *et al.*, 1981; Vinding & Nielsen, 1983; Griffiths, 1987; Bentley *et al.*, 1992), optic neuritis (Pubesgaard & Von Byben, 1986) and keratopathy (Kaiser-Kupfer & Lippman, 1978) have been reported in patients receiving tamoxifen. Retinopathy was initially reported in patients receiving very high doses of tamoxifen, but recent reports suggest retinopathy can also occur at the usual low dose of 20 mg/day (Griffiths, 1987; Gerner, 1989; Pavlidis *et al.*, 1992).

Two prospective studies have demonstrated no adverse ocular effects associated with low dose tamoxifen therapy (Beck & Mills, 1979; Longstaff *et al.*, 1989) whereas a recent prospective study has demonstrated reversible ocular toxicity, macular degeneration, associated with low dose tamoxifen therapy (Pavlidis *et al.*, 1992). Patients with macular degeneration are not candidates for recruitment to the NSABP prevention trial. Clearly new studies to evaluate the visual acuity and ocular changes in pre-existing tamoxifen

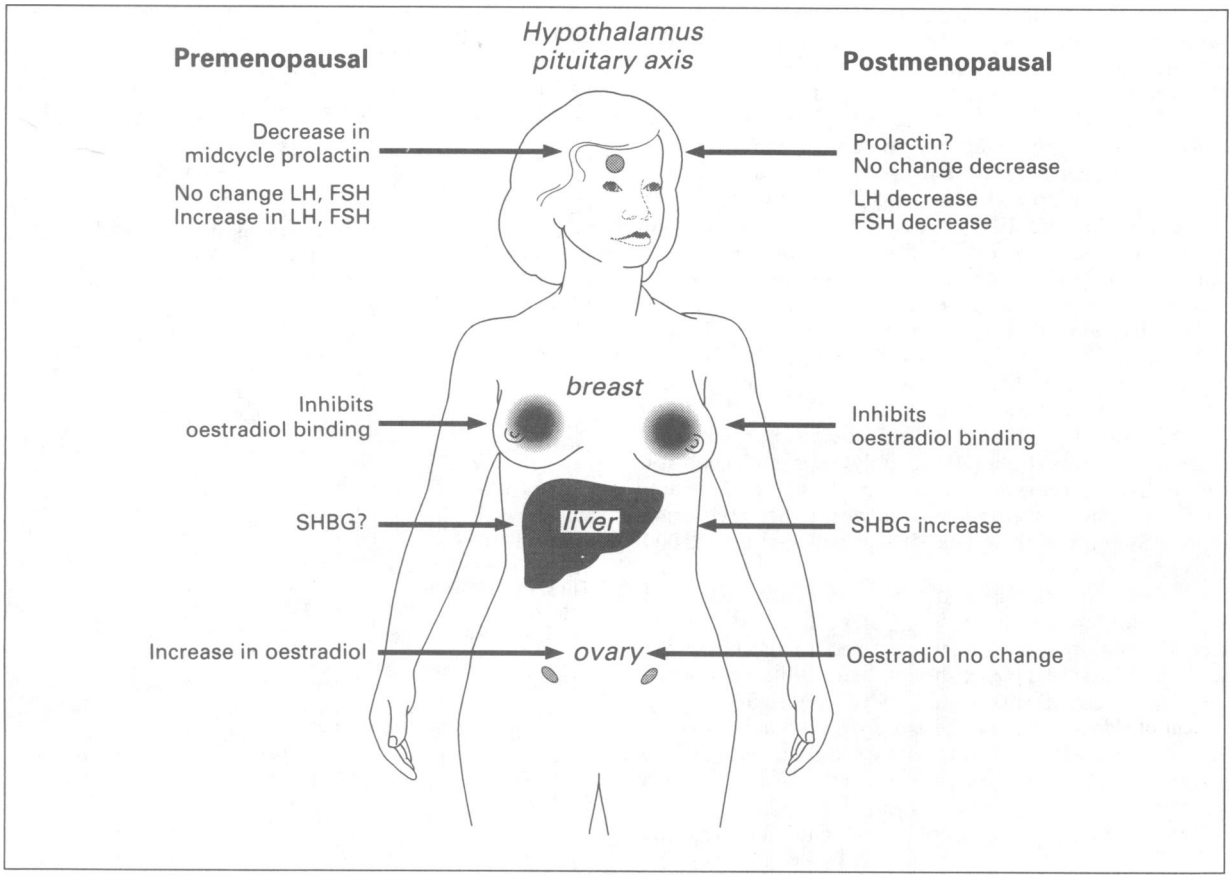


**Figure 3** The endocrine effects of tamoxifen in pre- and postmenopausal patients.

versus placebo clinical trials are essential to reassure the clinical community.

## Summary and conclusions

Tamoxifen has been found to be a safe and effective treatment for all stages of breast cancer. Long term tamoxifen therapy is associated with some rare, but potentially serious, side effects so patients should be carefully monitored. However, long term tamoxifen therapy is also associated with a number of physiological benefits over and above its tumouristatic action. These benefits include a decrease in the development of contralateral breast cancer, the maintenance of bone density in postmenopausal women and a decrease in cardiovascular disease.

The successful application of tamoxifen to treat breast cancer has increased enthusiasm to test its worth to prevent breast cancer. Although there are individual requests by patients for tamoxifen to prevent breast cancer, individual treatment is inappropriate. Tamoxifen can only be adequately evaluated as a preventive in randomized, double-blind clinical trials. These trials are in place and physicians should encourage women to participate and establish a new therapeutic option as rapidly as possible.

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