

## **Tamoxifen therapy in breast cancer control worldwide.**

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**Abstract**

In 1980 breast cancer was estimated to be the most frequent major cancer in women worldwide. Incidence and mortality appear to be increasing in developed countries. Disease prevention is undefined or postulated strategies are impractical. When breast cancer progresses to metastatic stage, it is incurable and the impact of palliation on duration of life is limited. With early stage regional disease, local treatment combined with adjunctive hormonal treatment with tamoxifen can save 6 women out of 100 from death compared with local treatment alone. Tamoxifen is a synthetic estrogen with antiestrogenic effects on breast cancer cells but estrogenic effects on liver metabolism and bone with resultant decreases in risk factors for chronic diseases of the vascular system and skeleton. With long term tamoxifen treatment major clinical adverse effects occur in under 5% of women; symptomatic menopausal-vasomotor symptoms occur in a majority of treated women, but lessen over time. In controlling breast cancer more successfully worldwide one challenge is to bring tamoxifen therapy to greater numbers of women.

Breast cancer in women is a growing global health problem for which a hormonal treatment - tamoxifen - can provide part of the answer. This report briefly reviews the dimensions of the worldwide breast cancer problem, and the available data which support the case that more widespread application of tamoxifen treatment is justified. Finally the challenges in achieving this goal and the new broad research agenda to be addressed are identified.

### **Breast cancer worldwide: cases, incidence, morality and trends.**

In 1980 breast cancer was the most common major cancer in women worldwide with an estimated 572,100 cases, 18.4% of all cancers in women (1). The next most frequent cancers in women were those of the uterine cervix (15.0%) and colon/rectum (9.2%). Current estimates are that 750,000 new cases will be diagnosed in 1993 and as many as 1 million new cases annually will be recorded at the turn of the millennium. Sixty percent of these cases occur in women in developed countries (1) and two thirds or greater occur in women over 50 years of age.

While various factors contribute to changes in estimated disease specific incidence and mortality, and these are difficult to identify or adjust for if appropriate, it appears that particularly in western developed countries the incidence of breast cancer is increasing. Mortality also appears to be increasing (2) although not in all developed countries. Mortality rates in some western countries remain about one third of incidence rates. Among western women with the highest incidence rates, at age 40 approximately one woman in 1000 develops breast cancer each year, while at age 60 this rate has increased to one woman in 500. At these rates, in a group of healthy 40 year old women 3.3% will develop breast cancer before age 60 (3).

### **Dimensions of the challenges of breast cancer control.**

In the face of the increasing problems which these foregoing numbers, rates and trends portray, what strategies are available or developing which can be applied worldwide? While many

causative or risk factors for breast cancer are well defined, these data appear fragmented because they do not fit well together in complete models for disease development. While additionally, few causative factors are easily manipulable, two recently receiving more attention are worthy of comment. Some data implicate active and passive (4,5) cigarette smoking in breast cancer development. These are of particular concern because of the high and increasing prevalence of smoking in developing countries and provide another cogent reason for more vigorous attention to the tobacco epidemic. Second, more data are becoming available suggesting that long duration lactation is significantly protective against breast cancer (6). This information should be more widely used in public health programs worldwide. With these exceptions practical interventions to prevent breast cancer are not currently available.

At advanced stages, breast cancer is currently a disease for which palliation is the most practicable approach. The reasons for the refractoriness of metastatic breast cancer to significantly life-prolonging treatment are multiple: (1) The evolution of the disease over several years has preceded this state during which time increasingly malignant clones of tumor cells can develop; (2) Heterogeneity of the disease, whose recognition and implications have yet to be well defined and understood prevents optimal individual-specific treatment; (3) Most importantly, an absence of adequately effective - "curative" therapies separates breast cancer from other malignancies for which remarkably effective drugs have been identified empirically. While our knowledge of breast cancer biology has grown exponentially in recent years, and our abilities to apply currently available techniques of drug dose density, bone marrow transplantation, and biological response modifiers have increased, practical life-prolonging therapies for populations are yet to be defined.

While all cases of clinical breast cancer are diagnosed after several years in development, and thus "late," detection when the primary breast tumor is smaller is associated with a lower likelihood of regional spread of disease and lower stage, and confers a better prognosis.

Practical strategies to "downstage" disease in populations are likely to have benefit in reducing mortality. In developed, particularly western countries, screening mammography has been the most discussed downstaging strategy. Recent data confirm however that mammography is of no benefit in premenopausal women (7) and suggest that when combined with careful breast examination, mammography is of modest only benefit in women 50-59 (8). Thus at present the most practical population-benefitting approach is a low technology one: increasing the proportion of women who have regular breast examinations.

In developed countries the vast majority of women with breast cancer present with regional disease whose initial treatment is with ablative surgery or limited surgery plus radiotherapy. A major fraction of these women however are destined to develop clinically evident metastatic disease ultimately, disease present in a subclinical, micrometastatic form at the time of initial diagnosis. With the development of data from rigorous randomized controlled clinical trials, it has become clear that adjuvant, that is additional, systemic treatment at diagnosis can decrease the risks of developing metastatic disease and dying from breast cancer. A comprehensive overview analysis of these studies has shown that polychemotherapy for premenopausal women reduces the annual risks of recurrence by 29% and of mortality by 16% (9). [A 15% annual risk reduction means that 4-6 additional women in 100 will be alive after 10 years as a result of therapy.] This overview also suggests similar magnitudes of benefit from surgical or radiation oophorectomy in premenopausal women, although this conclusion is based on much smaller numbers of treated women with heterogenous stages of cancers and probably should be regarded as hypothesis-generating rather than conclusive evidence for this adjuvant strategy (10). In population terms, the relevance and application of the polychemotherapy data are somewhat uncertain. First, despite convincing evidence of benefit from individual trials and the overview analysis, the evidence for benefits to populations where adjuvant polychemotherapy has been widely applied is weak. Second, the practice of adjuvant polychemotherapy is very technical and expensive and on these grounds direct application to women in developing countries is

impractical. Finally, the vast majority of the clinical trials have been accomplished exclusively in western women usually of higher socio-economic and caucasian groups, and the relevance of these conclusions to poorer women of other ethnic groups must be considered uncertain.

In contrast to the polychemotherapy adjuvant therapy results, the adjuvant tamoxifen results may have more widespread application and the aspects of this are the focus of the remainder of this report.

In summary, the current public health challenges of breast cancer control, aside from the more widespread application of tamoxifen adjuvant therapy, are to apply limited data about tobacco and lactation to prevention and to increase the frequency of breast examinations to downstage cancers at diagnosis.

## **Tamoxifen as adjuvant treatment: evidence for efficacy.**

The case for more widespread application of adjuvant tamoxifen therapy must rest on the quality of the evidence for efficacy, particularly in reducing mortality. This case is extraordinarily strong because of the large number of individual randomized clinical trials which have been reported - 40 - or are not yet available - 4 - which have given a consistent picture of the favorable effects as well as a rigorous meta-analysis of these trials which has confirmed their conclusions (10). For purposes here it seems most reasonable to refer to the overview/meta-analysis results because in the case of adjuvant tamoxifen trials these data are hypothesis-supporting (and not hypothesis generating) because the individual trials on which they are based also overwhelmingly show the same conclusions individually. In addition, these overview data provide quantitative and qualitative perspectives which are critical to judgements about more widespread applicability.

In Figure 1 is reproduced the essential results of short term (in the majority 2 years maximum) adjuvant tamoxifen therapy. While modest, the figure results indicate that approximately 4 to and 6 additional women in 100 will be alive after 5 and 10 years consequent to this treatment. The percentages of additional women who are alive but with recurrence of disease are 8% and 6.5% at 5 and 10 years respectively. Thus when considered on a population basis, this treatment can prolong and save the lives of many women with early stage breast cancer.

The numbers discussed so far present the overall picture. Of interest is whether further data on subsets of treated women provide clarifying information which defines more precisely where to apply this treatment to achieve the greatest benefits.

Table 1 summarily addresses some of the important issues. In these trials there do not appear to be any dose differences and so the lowest dose widely used, 20 mg daily, can be regarded as standard. The data on duration are incomplete; the majority are for treatment periods of 2 years. It is remarkable that despite an apparent cytostatic mechanisms of action (see below), there is persistence of benefit seen many years after cessation of therapy, with in fact a widening of the mortality differences between treated and untreated groups of women between 5 and 10 years. The overview data suggest greater benefit with longer duration of treatment, but at present two years must be considered a reasonable standard. While absolute benefits are greater to women who have axillary node metastases and who have tumors with positive or higher measurable levels of estrogen receptors, women with no axillary metastases and low or absent levels of estrogen receptors in their tumors also derive significant benefits from treatment.

The effects of adjuvant tamoxifen in women who are premenopausal or postmenopausal, under or over 50 years of age are qualitatively similar. In general, younger women appear to benefit less from adjuvant tamoxifen (Table 1 compared to Figure 1) and in considering strategies for populations based on available data, a case can be made that other adjuvant therapeutic approaches such as surgical oophorectomy should be considered, although for this there are far fewer data presently.

For older women, for whom the incidence of breast cancer is greater, the benefits of adjuvant tamoxifen are quantitatively and qualitatively similar.

Do the available data for tamoxifen differ with respect to a broad case for application to populations, from these for polychemotherapy in premenopausal women presented earlier?

Figure 1

**Ten-year Mortality in Tamoxifen Trials: Overall Results for 30,000 Women (9).**  
(Reproduced with permission.)

Table 1

**Magnitudes of mortality benefits of adjuvant tamoxifen with different doses, duration, different nodal status, and in different primary tumor estrogen receptor categories.\***

<u>Category</u>	Reduction in % (SD) annual odds of death from any cause. 50 years**
Tamoxifen vs No Tamoxifen	20 (2)
Dose: Tamoxifen 20 mg/day versus No Tamoxifen	21 (3)
Tamoxifen 30 mg/day versus No Tamoxifen	18 (3)
Duration: Tamoxifen 4 years versus No Tamoxifen	13 (4)
Tamoxifen > 2 yrs versus No Tamoxifen	23 (6)
Nodal States: Axillary Node Negative	16 (5)
Axillary Node Positive	22 (3)
Tumor Estrogen Receptor (ER) protein: ER Poor	16 (6)
ER Positive	23 (4)

\* Abstracted from Table III Lancet 339:1-15, 1992 (10)

\*\*Absolute benefits: If 100 node positive women have persistent reduction in annual odds of death of 15%, 6 additional women, if 30%, 12 additional women, will be alive after 10 years.

It is the case that clear evidence of benefits to populations from adjuvant tamoxifen is not available. If one accepts that the prevalence of adjuvant tamoxifen use in some western countries is high, possible explanations for the absence of population benefit are several but lie chiefly in confounding of this effect by rising incidence. Tamoxifen therapy is a daily oral treatment and thus less technically complex, but costs remain high in some western countries. Finally, some of the subjects in tamoxifen trials have been Asian women, but tamoxifen also must be considered to be significantly under-evaluated in developing countries, and nonwestern ethnic groups.

With a strong case for benefits in mortality reduction and disease free survival increases from adjuvant tamoxifen, a more comprehensive review of biological effects, other benefits, toxicities, and symptomatic sequelae of tamoxifen treatment is important to further place in context the argument for more widespread use.

### **Biology and non-breast cancer effects of adjuvant tamoxifen treatment.**

Tamoxifen is a synthetic estrogen with estrogen agonist and antagonist properties (11). It was originally developed as an oral contraceptive, in which role it is ineffective, and it was then found serendipitously to be effective in palliating some women with metastatic breast cancer. Over the last 20 years the drug has been used in that setting, but also increasingly as adjuvant therapy.

The pharmacology of tamoxifen is remarkably complex. After oral administration maximal blood levels are reached in 4-7 hours, and a steady state of drug levels in the blood is achieved after 4 weeks. It takes 6-8 weeks for all serological evidence of tamoxifen and its metabolites to disappear from the blood. While the teratogenicity of tamoxifen is unknown, this is important in premenopausal women who may become pregnant while taking the drug because even if it is stopped, the fetus is likely to receive continuous exposure during the entire first trimester.

Tamoxifen is metabolized by the liver, excreted in bile and eliminated from the body in feces. In postmenopausal women, gonadotropin decreases are seen with tamoxifen therapy; estrogens, progesterone and prolactin levels do not change. In contrast in premenopausal women large increases in total estrogens, estradiol and progesterone occur in some women.

At the cellular level tamoxifen is considered to exert its effects by combining with nuclear estrogen receptor protein with resultant arrest of breast cancer cells in the G1 phase of the cell cycle. Thus tamoxifen appears to be a cytostatic instead of a cytotoxic agent. This concept is supported by some of the adjuvant trial data, but the prolonged effect data referred to earlier suggest more complex effects. Changes in various biological growth mediators are also seen with tamoxifen treatment: sex hormone binding globulin levels increase (which can remove more free estrogen from the circulation); transforming growth factor alpha levels decrease (a growth stimulatory protein); and transforming growth factor beta levels increase (a growth inhibitory protein). Effects in breast stromal cells have been suggested to mediate tamoxifen's action in neighboring breast cancer cells.

In summary, tamoxifen is a synthetic estrogen which might be expected to have direct estrogenic effects, but also has estrogen antagonist effects. In addition it causes hormonal and growth factor perturbations whose long term consequences can be expected to be profound. The largest use of tamoxifen in humans has been as adjuvant treatment. In these trials reviewed above, the focus has been on recurrence and survival from breast cancer. It is only recently that greater attention has been given to the possible non-breast organ, tissue and risk factor effects of this therapy.

Cardiovascular and skeletal effects.

Hormones exert powerful effects on several organ systems. In western women, where more studies have been done, the most profound effects are on the cardiovascular and skeletal systems. Women who survive to undergo menopause become at major risk for chronic diseases of these systems; indeed almost half of women in these societies who pass their fiftieth birthdays will ultimately die of cardiovascular disease. Another large, difficult-to-estimate fraction will suffer from skeletal fractures of osteoporotic bones. These chronic diseases are reflections of marked changes in risk factors which occur following menopause with associated marked decreases in ovarian hormones. In this context then, what is known of the actions of tamoxifen?

The effects of tamoxifen on risk factors for cardiovascular disease appear to be generally favorable and estrogenic. Controlled studies show decreases in levels of total and low density lipoprotein cholesterol, fibrinogen and platelets, and an absence of major changes in blood pressure or glucose metabolism in postmenopausal women (12) (Figure 2). That these consequences of tamoxifen treatment are clinically important is suggested by the results of the meta-analysis of tamoxifen adjuvant studies in which a 25% reduction in vascular deaths was found (10), and by analysis of one trial in which major reduction in numbers of postmenopausal women with myocardial infarction was found (13). While these observations are consistent with the risk factor changes, they should be regarded more as hypothesis-generating than hypothesis-confirming, and in particular their postmenopausal population base should be noted.

The effects of tamoxifen on bone mineral density, a major measure of risk for fracture, are also likely to be favorable. The decline in bone mass associated with the cessation of ovarian estrogen production involves mainly the more metabolically active trabecular bone found in the spine and to a lesser degree in the hips. In postmenopausal women tamoxifen clearly has a bone density-preserving effect in the lumbar spine (14) (Figure 3). This observation is consistent with animal data which suggest that tamoxifen is an antiresorptive agent like estrogen and thus may be associated over time with decreased rates of fracture.



Figure 2

**Mean fasting levels ( $\pm$  standard error) of total cholesterol over time in postmenopausal patients receiving tamoxifen or placebo (12).** (Reproduced with permission.)

Figure 3

**Change in mean ( $\pm$  standard error) lumbar spine bone mineral density in postmenopausal women receiving tamoxifen or placebo (14).** (Reproduced with permission.)

### Other significant and undefined effects.

Because the major sources of data about the effects of tamoxifen have been the adjuvant trials which were designed for cancer endpoints evaluation, a complete picture of consequences of this therapy is not yet available. These trials and the meta-analysis will nevertheless continue to provide major data. While the long list of incompletely defined effects in Table 2 should prompt caution and further evaluation and research, these uncertainties must be placed in context. With adjuvant tamoxifen treatment, recurrence of breast cancer and death are unquestionably averted in postmenopausal women, and probably in premenopausal women (Table 1 and Figure 1). In the overview analysis the vast majority of deaths were from breast cancer; thus while there may be morbidity from tamoxifen treatment as yet incompletely recognized, and possible long term mortality effects, over a 5-10 year period after diagnosis of breast, cancer death and death from all causes are averted with this treatment. As reviewed above for the major chronic diseases of western women over 50, tamoxifen appears, if anything, to be protective.

The breadth of data which have generated the possible - hypothetical effects listed in Table 2 cannot be reviewed here, but the rationales for the particular entries deserve comment. Other reviews which can be useful are referenced (15).

Hormonal effects on uterine tissues, the liver and most recently on the colorectum can be to promote tumor growth. There are very limited data at present which support the case that these are of numerically significant if at all real concern. The growth factor-altering effects of tamoxifen may protect against hematopoietic malignancies. Depression does occur with tamoxifen; its frequency is poorly described. Thrombophlebitis appears to occur at excess rates of 1/800 women treatment years; risk factors for this complication are undescribed. While some good quality lipid, fibrinogen, and platelet data are available for postmenopausal women, further lipoprotein, blood pressure and glucose data are needed because minor changes in these may be

critical to risk for cardiovascular disease and manipulable. Whether various ocular conditions are increased infrequency with tamoxifen is unknown; some data have prompted more careful study (16). Since estrogen therapy is associated with increased rates of cholelithiasis and tamoxifen has similar effects on lipid and lipoproteins, rates of cholelithiasis on tamoxifen are worthy of evaluation. The effects of hormones like tamoxifen on the immune system are of increasing interest. In one Swedish study hospitalization rates for immune disorders were lower in tamoxifen-treated women. Bone mineral density changes at other sites than the lumbar spine need assessment.

With hepatic metabolism and binding to different body tissues and proteins, possible interaction of tamoxifen with other drugs used at varying frequency in different populations warrants evaluation.

Finally, tamoxifen is not a curative adjuvant therapy. Many women develop recurrences of breast cancer - metastatic disease while taking tamoxifen. The mechanisms of this tamoxifen resistance and the optimal management of these patients are just beginning to receive attention (17). It is however notable that rates of second primary i.e. contralateral, breast cancer are significantly lower with tamoxifen treatment; the overview found a 39% reduction in these events (10).

There are additional effects of particular concern in younger premenopausal women. In the main this has been because fewer premenopausal women have been included in adjuvant trials. Of greatest concern are the possibilities that the direct and indirect hormonal effects of tamoxifen may be carcinogenic to the breast and ovary in younger women. Specifically here available data indicate that tamoxifen markedly increases estrogens in some women at frequencies incompletely described, and is associated with an increase in contralateral breast cancer in one trial (18). Epithelial ovarian cancer is a disease affected by factors that influence ovulation or

epithelial disruption which tamoxifen does in increasing this event. Specific cardiovascular effects are completely unevaluated in premenopausal women, and gynecologic effects are poorly described. The details and risk factors for vasomotor symptoms are also poorly described. Finally, how to optimally achieve contraception and the actual risks of teratogenesis are unknown and important issues for premenopausal women.

Again these uncertainties (Table 2) define issues which deserve particular research attention and monitoring with the more widespread use of adjuvant tamoxifen justified by the significant mortality benefits, particularly in postmenopausal women. Indeed because of the likely rarity of most of the serious consequences, it will only be through population monitoring that any associations will be observed.

Table 2

**Effects of tamoxifen which are incompletely defined.**

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In women of all ages

Uterine endometrium carcinogenic  
Uterine myometrium carcinogenic  
Liver carcinogenic  
Colon-rectum carcinogenic  
Hematopoietic: carcinogenic/protective  
Central nervous system: mood altering  
Coagulation: thrombophlebitis  
Cardiovascular: lipoprotein, blood pressure, glucose  
Eye: macular, retinal, lens  
Hepatobiliary: cholelithiasis  
Immune system: functional  
Drug interactions  
Skeletal: bone mineral density changes at all sites  
Breast cancer: treatment of recurrence

In premenopausal women

Ovary: carcinogenic  
Breast: carcinogenic  
Hormonal: patterns, levels and frequency of changes  
Cardiovascular: lipid, fibrinogen, platelet  
Gynecologic: symptomatic, infectious  
Vasomotor: symptomatic  
Pregnancy: teratogenic, contraception

Contraindications to adjuvant treatment with tamoxifen.

In practical terms there are few women, particularly postmenopausal women, who have histories which should prevent them from taking tamoxifen. In Table 3 are summarized the suggested absolute and relative contraindications. While certainty about retinal macular changes consequent to tamoxifen is lacking, it is a possible side effect and the seriousness of these

conditions would seem to warrant particular prudence (16). The other absolute contraindications are based on concerns regarding hormonal carcinogenesis, teratogenesis, and inefficacy of tamoxifen therapy for breast cancer respectively.

The relative contraindications identify conditions which may be major risk factors for major complications. The drugs listed can have retinal toxicity and this may be synergistic with tamoxifen in producing ocular conditions. Tamoxifen invariably increases the number and intensity of vasomotor symptoms, and in postmenopausal women possibly one third develop annoying gynecologic symptoms (19). For some women who have these symptoms before tamoxifen therapy is begun and who are proscribed estrogen therapy because of their breast cancer, the increments in these symptoms may be intolerable.

Table 3

**Contraindications to adjuvant tamoxifen.**

Absolute:	Retinal macular edema or degeneration History of benign or malignant liver tumor secondary to oral contraceptives Pregnancy Other hormonal therapy (estrogens, oral contraceptives)
Relative:	History of thrombophlebitis, particularly hormone related History of depression, particularly hormone related Cataract  Drugs: Chlorpromazine, chloroquine, thioridazine, amiodarone, other Severe vasomotor symptoms Polycystic ovaries

**Widespread use of adjuvant tamoxifen: benefits and challenges.**

In the year 2000, if one million women per year are diagnosed with breast cancer and the large majority of these cases can be diagnosed in lower stages, then available data suggest that 60,000 of these women could be saved from death by adjuvant tamoxifen treatment and many thousands more will have recurrence and death from breast cancer delayed. While this crude estimate of potential benefits from widespread application of adjuvant therapy is based on extensive clinical trial data, there are clearly major gaps in our knowledge and systems which must be addressed if such benefits are to be realized in populations.

The major challenges are summarized in Table 4. Clinical research is needed to address four issues to help define public health efforts likely to be most beneficial. While the postulated magnitude of benefit is based on a two-year course of tamoxifen, some data suggest longer treatment provides greater benefits. With further information on precise benefits with different durations of treatment as well as other "costs," a cost benefit curve can be drawn to allow approximate definition of a rational public health approach. At present the data for premenopausal women are insufficient to support adjuvant tamoxifen use as a priority effort for this subgroup. There are very few rigorous data in nonwestern populations, and various biologic data suggest that assuming similar or in fact any benefit from adjuvant tamoxifen in other populations is hazardous. The clinical research questions can be addressed simultaneously with some application questions. For example, international collaborative programs which combine clinical and applications research in developing countries can address multiple challenges. To give a specific example, in a nonwestern developing country in which pill taking presents problems, a large clinical trial of a depot preparation of tamoxifen might be evaluated as part of a comprehensive breast program in which delay in presenting for diagnosis is studied and careful assessment of medical resource use is undertaken. Clinical trials as a focus for quality improving educational programs offer a means of actively involving physicians and other health care workers in public health problem solving, as well as care giving in their own countries. Because limited health care financial resources only are available in any country, agreements with major

pharmaceutical companies must be developed to provide large amounts of drug at lower than current western prices. In addition, in individual countries precise quantitation of population-wide benefits will allow placing of this center control approach rationally in the list of priorities developed under rigorous National Cancer Central plans. Finally, since the benefits of adjuvant tamoxifen are more likely to be limited with Stage III or regionally advanced breast cancer, which is often the most common presentation of this cancer in developing countries, breast cancer programs with combine greater educational efforts or examination frequency to downstage disease at diagnosis along with greater availability of tamoxifen are likely to provide greater population benefits.

In summary, the applications challenges are those of defining appropriate cost beneficial strategies for adjuvant tamoxifen use unique to each country.

Table 4  
**Major challenges in increasing adjuvant tamoxifen use  
for women with breast cancer worldwide.**

Clinical Research:

- ï Definition of optimal duration of treatment
- ï Increased definition of known adverse effects and their incidence
- ï Further data on breast cancer benefits in premenopausal women
- ï Data on breast cancer benefits in nonwestern populations

Applications:

- ï Decreasing cost of treatment
- ï Development of injectable "depot" treatment
- ï Quantitation of benefits for use in National Cancer Control Planning
- ï Public health strategies which combine downstaging and adjuvant tamoxifen

## Summary

Breast cancer is a growing global health problem for which a hormonal treatment - tamoxifen - can provide part of the answer. Breast cancer is the most common major malignancy in women and may account for 1 million cases by the year 2000. Sixty percent of cases occur in developed countries and the incidence is increasing. Currently prevention of breast cancer is impractical, but tobacco control may play a more important role in development of this disease than has been previously appreciated, and long duration lactation appears to be significantly protective. Downstaging of disease at presentation for diagnosis is an important strategy to limit mortality and morbidity.

Tamoxifen treatment as an adjuvant to loco-regional measures, has been demonstrated in many separate randomized clinical trials and in a meta-analysis of 40 trials in 30,000 women, to have significant benefits. Ten years after diagnosis approximately 6 women out of 100 treated with

tamoxifen will be saved from death and recurrence of breast cancer will be delayed for many others. The preponderance of data available are for postmenopausal women; in premenopausal women the beneficial effects are smaller. Qualitatively there are no subgroups of women who do not appear to benefit from tamoxifen treatment; in particular, older women > 70 benefit also.

Tamoxifen has estrogenic and antiestrogenic effects. Fortunately its effects on risk factors for cardiovascular disease and osteoporosis in postmenopausal women appear to be favorable. Total and low density lipoprotein cholesterol are lowered, and bone mineral density in the lumbar spine is preserved with treatment. These effects are suggested to decrease the likelihood of cardiovascular disease and osteoporotic bone fractures which are the major causes of mortality and morbidity in older women in developed countries. While overall mortality benefits are demonstrated with tamoxifen treatment, a significant number of hypothesized or suggested mostly adverse, but some favorable effects of this hormonal treatment remain at present undefined. Greater concern lies in the absence of comprehensive data for premenopausal women. There are few rare contraindications to tamoxifen: retinal macular edema or degeneration, other hormonal treatment and pregnancy. While the clinical trials data would strongly support more widespread application of adjuvant tamoxifen treatment, clinical research is needed to address questions regarding optimal duration of treatment, occurrence of adverse side effects and breast cancer benefits in premenopausal and nonwestern populations. To bring tamoxifen to populations and move to the goal of averting possibly 60,000 premature deaths per year from breast cancer worldwide, will require public health programs which explore the use of depot injectable treatments, carefully quantify the population benefits of this intervention, and which work also to increase the prevalence of lower stage disease at diagnosis. Clinical trials are advocated as a mechanism for actively involving health care workers in definition of new strategies for bringing adjuvant tamoxifen to more women with breast cancer.



## References

1. Parker, I.M., Laara, E., Muir, C.S. Estimates of the worldwide frequency of sixteen major cancers in 1980. *Int J. Cancer* 41:184-197, 1988.
2. Stjernsw%ord, J., Stanley, K.E., Hansluwka, H., Lopez, A.D. Progress against cancer? *New Engl J Med* 315:965, 1988.
3. Love, R.R. The risk of breast cancer in American women. *JAMA*, 257(11):1470, 1987.
4. Hirayama, T. Health effects of active and passive smoking. In: *Smoking and Health* 1987. Aoki, M., Hisamian, S., Taminoga, S. Eds. Elsevier, Amsterdam 1988, pp. 75-86.
5. Palmer, J.R., Rosenberg, L., Clark E.A., et al. Breast cancer and cigarette smoking: an hypothesis. *Am J. Epidemiology* 134:1-13, 1991.
6. Luan, J.M., Yu, M.C., Ross, R.K., et al. Risk factors for breast cancer in Chinese women in Shanghai. *Cancer Res* 48:1949-1953, 1988.
7. Miller, A.B., Baines, C.J., To, T., Wall, C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *Can Med Assoc J* 147:1459-1476, 1992.
8. Miller, A.B., Baines, C.J., To, T., Wall, C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *Can Med Assoc J* 147:1477-1488, 1992.

9. Early breast cancer trialists' collaborative group, Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. *Lancet* 339:72-85, 1992.
10. Early breast cancer trialists' collaborative group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. *Lancet* 339:1-15, 1992.
11. Love, R.R. Tamoxifen therapy in primary breast cancer: biology, efficacy and side effects. *J Clin Oncology* 7:803-15, 1989.
12. Love, R.R., Wiebe, D.A., Newcomb, P.A. Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Ann Int Med* 115:860-4, 1991.
13. McDonald, C.C., Stewart, H.S. Fatal myocardial infarction in the Scottish adjuvant tamoxifen trial. *BMJ* 303:435-7, 1991.
14. Love, R.R., Mazess, R.B., Barden, H.S., et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *New Engl J Med* 326:852-6, 1992.
15. Nayfield, J.G., Karp, J.E., Ford, L.G, et al. Potential role of tamoxifen in prevention of breast cancer. *J Natl Cancer Institute* 83:1450-59, 1991.
16. Pavlidis, N.A., Petris, C., Briassoulis, E., et al. Clear evidence that long term low dose tamoxifen treatment can induce ocular toxicity. *Cancer* 69:2961-64, 1992.
17. Touchette, M. Tamoxifen resistance in breast cancer. *J NIH Res* 4:67-72, 1992.

18. Houghton, J., Riley, D., Baum, M. The NATO and CRC trials of adjuvant tamoxifen therapy. In: Long-term tamoxifen treatment for breast cancer. Ed: V.C. Jordan, University of Wisconsin Press, Madison, WI (in press).
  
19. Love, R.R., Cameron, L., Connell, B.L., Leventhal, H. Symptoms associated with tamoxifen treatment in postmenopausal women. Arch Int Med 151:1842-47, 1991.