Reviews/Analyses

Tamoxifen therapy in breast cancer control worldwide

R.R. Love¹ & V. Koroltchouk²

In most developed and many developing countries, breast cancer is the most frequent cancer and the leading cause of cancer death among women. At least 50% of all breast cancer patients worldwide would survive longer, however, if public awareness about and early detection of the condition were increased and greater use were made of efficient treatment of proven value. With early-stage, localized breast cancer, local treatment combined with adjuvant hormonal therapy with tamoxifen, a synthetic estrogen, could save the lives of 6 women out of 100 compared with local treatment alone. Tamoxifen has anti-estrogenic effects not only on breast cancer cells but also on liver metabolism and bone, with concomitant decreases in risk factors for chronic skeletal and vascular system diseases. Long-term tamoxifen treatment causes major adverse clinical effects in <5% of women; menopausal and vaso-motor symptoms occur in the majority of treated women, but their severity lessens over time. Tamoxifen is being considered as a standard therapy and is included in the WHO list of essential drugs for the treatment of breast cancer patients in both developing and developed countries. For the control of breast cancer more successfully worldwide, one challenge is to make tamoxifen therapy available to greater numbers of women.

Breast cancer is an increasing global health problem for which a hormonal treatment — tamoxifen — can, in part, provide a solution. The present article briefly reviews the dimensions of the worldwide breast cancer problem and the available data that support the case for the more widespread application of tamoxifen treatment. Finally the challenges in achieving this goal and the new broad research agenda to be addressed are identified.

Breast cancer worldwide

In 1980 breast cancer was the commonest cancer among women worldwide, with an estimated 572 100 cases, representing 18% of all cancers that affected women (1). Current estimates are that 750 000 new cases will be diagnosed in 1993 (2), and towards the end of this century over 1 million new cases of breast cancer will be diagnosed annually (3). At present, more than 40% of all breast cancers are found in developing countries, but the incidence pattern in such countries is progressively approaching that of developed countries and it is predicted that it will be more than 50% by the year 2000 (4).

More than two-thirds of breast cancers occur among women over 50 years of age, and the incidence has been increasing, particularly among post-menopausal women in developed countries. With the aging of populations, the increase in the proportion of elderly women in all countries will lead to a corresponding increase in the number of breast cancer cases. Mortality from breast cancer also appears to be increasing, although not in all developed countries (5). The mortality rates in some Western countries remain about a third of incidence rates. In Western countries, with the highest incidences at age 40 years, approximately one woman in 1000 develops breast cancer each year, while at age 60 years this rate has increased to one woman in 500. At these incidence levels, 3.3% of healthy 40-year-old women will develop breast cancer before they reach 60 years of age (6).

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Dimensions of the challenges of breast cancer control

What strategies are there available or are in the process of being developed for the control of breast cancer that can be applied worldwide? There are three basic approaches: primary prevention; early diagnosis and screening; and treatment. Primary prevention may have the greatest potential for the control of breast cancer, but is not applicable at present — other than dietary modification, which will probably require to be introduced in adolescence or early in adult life to be fully effective. Although few of the causative factors are easily manipulable, two have recently been receiving more attention and are worthy of comment. First, data are available that implicate active and passive cigarette smoking in the development of breast cancer (7, 8). These are of particular concern because of the high and increasing prevalence of smoking in developing countries and provide another cogent reason for directing more vigorous attention to the proliferation of tobacco consumption. Second, more data are becoming available which suggest that long-duration lactation is significantly protective against breast cancer (9). This information should be more widely used in public health programmes worldwide. With these exceptions, practical interventions to prevent breast cancer are not currently available.

Approximately half of all breast cancer patients are diagnosed only after the disease has reached an advanced stage, and most of them will not be cured. In its advanced stages, breast cancer is currently a disease for which palliative therapy is the most practical approach. The reasons for the refractoriness of metastatic breast cancer to significantly life-prolonging treatment are multiple: the evolution of the disease over several years, which has preceded this state, results in the development of increasingly malignant clones of tumour cells; the heterogeneity of the disease, whose recognition and implications have yet to be well defined and understood prevents optimal individual, specific treatment; and most importantly, the absence of adequately effective “curative” therapies distinguishes breast cancer from other malignancies for which remarkably effective drugs have been identified empirically. While our understanding of the biology of breast cancer has grown considerably in recent years, and our abilities to apply the currently available techniques of drug dose density, bone marrow transplantation, and biological response modifiers have increased, practical life-prolonging therapies for populations have yet to be identified.

The greatest decrease in breast cancer mortality is likely to result from treating the disease at an earlier stage. In the USA the 5-year relative survival rate for localized breast cancer is approximately 90%; in Russia it is 77%, while the total 5-year survival rates for all stages in these two countries are 75% and 55%, respectively (10, 11). At the National Cancer Institute, Cairo, the 5-year survival rates were found to be 80%, 52%, 42% and 14% for stage I, II, III and IV, respectively (12, 27). These differences are a function of public awareness of the value to breast cancer patients of early detection and appropriate early treatment.

In the absence of public education programmes, and also because of a lack of available resources for either detection or therapy, current statistics show that in developing countries 30% to 80% or more of all breast cancer patients will not be diagnosed until the disease has reached an advanced stage; the large majority will be incurable. Under these conditions, early detection must be the primary means of improving the situation for some time to come.

WHO promotes strategies designed to provide patients in all areas of the world with community access to basic facilities for appropriate diagnosis and treatment of breast cancer. The lives of at least 50% of breast cancer patients could be significantly prolonged through the appropriate use of currently available methods of diagnosis and treatment. In developed, particularly Western, countries screening mammography has been the most discussed downstaging strategy. Recent data confirm, however, that mammography is of no benefit to premenopausal women (13) and suggest that when combined with careful breast examination, mammography is only of modest benefit to women aged 50–59 years (14). Therefore, at present, the most practical population approach should include breast self-examination, physical examination by health care workers, mammography, or a combination of these, depending on the extent of the breast cancer problem, local resources, and the cultural situation (4).

The evidence that mortality from breast cancer can be further reduced through the use of systemic therapies as an adjuvant to surgery or radiotherapy is substantial. A comprehensive meta-analysis of the results from all the randomized trials of adjuvant therapies suggests that use of polychemotherapy for premenopausal women with breast cancer reduces the annual risk of recurrence by 29% and of mortality by 16% (15). Benefits of a similar magnitude result from surgical or radiation oophorectomy in premenopausal women, although this conclusion is based on much smaller numbers of treated women with heterogeneous stages of cancers, and probably should be regarded as hypothesis-generating rather than conclusive evidence for this adjuvant strategy (16).
At the population level, the relevance and application of the polychemotherapy data are somewhat uncertain. First, despite the convincing evidence of benefit from individual trials and the meta-analysis, the evidence for benefits to populations where adjuvant polychemotherapy has been widely applied is weak. Second, the practice of adjuvant polychemotherapy is highly specialized and expensive and hence its use in developing countries is impractical. In most instances, cancer chemotherapy requires some access to laboratory facilities to monitor white blood cell and platelet counts. Also, the quality of life of some patients will be compromised by adjuvant polychemotherapy (17). Finally, the vast majority of the clinical trials of such therapy have involved exclusively Western women, usually from higher socioeconomic and Caucasian groups, and the relevance of the findings for poorer women from other ethnic groups is unclear. In contrast, as discussed below, the adjuvant tamoxifen may have more widespread application.

The current public health challenges of breast cancer control, apart from the more widespread application of tamoxifen adjuvant therapy, are therefore to encourage patients to present for diagnosis and treatment at an earlier stage of the disease since this offers the most effective approach for a reduction in breast cancer mortality.

Tamoxifen as an adjuvant treatment

Evidence for efficacy

The case for more widespread use of adjuvant tamoxifen therapy rests on the quality of the evidence for its efficacy, particularly in reducing breast cancer mortality. This case is extraordinarily strong because of the 40 individual, randomized clinical trials of tamoxifen that have reported consistently on its favourable effects, together with the findings of a rigorous meta-analysis of these trials that has confirmed their conclusions (16). Here, it is appropriate to refer to the meta-analysis results because they are hypothesis-supporting (and not hypothesis-generating), since the individual trials on which they are based also overwhelmingly draw the same conclusions. In addition, the overview data provide quantitative and qualitative perspectives that are critical for making judgements about the more widespread applicability of tamoxifen.

Fig. 1 summarizes the essential results obtained with short-term (usually, a maximum of 2 years) adjuvant tamoxifen therapy. Although modest, the findings indicate that relative to controls, approximately four and six additional women per 100 will be alive 5 years and 10 years, respectively, after this treatment. The proportions of additional women who survive but suffer a recurrence are 8% and 6.5%, respectively, 5 years and 10 years later. Thus, viewed on a population basis, tamoxifen treatment can prolong and save the lives of many women with early-stage breast cancer. Of interest also, is whether further studies on subsets of treated women will provide clarifying information that defines more precisely the most appropriate target groups for this treatment to achieve the greatest benefits.

Table 1 provides a summary of some of the important results obtained with tamoxifen. In the trials the same dose appeared to be used and so the lowest widely used dose (20 mg daily) can be taken as standard. The data on the duration of the therapy are incomplete; the majority of trials used treatment periods of 2 years. It is remarkable that despite an apparent cytostatic mechanism of action, tamoxifen produces a persistent benefit many years after cessation of therapy, and that the mortality differences between the treated and untreated groups of women differed by 5–10 years. The overview data suggest that a greater benefit derives from a longer duration of treatment, but at present 2 years must be considered a reasonable standard. While the absolute benefits are greater for women who have axillary node metastases and who have tumours with positive or higher measurable levels of estrogen receptors, women with no axillary metastases and low or absent levels of estrogen receptors in their tumours also derive significant benefits from tamoxifen treatment.

The effects of adjuvant tamoxifen therapy were qualitatively similar for women who are premeno-
remains expensive Asian, tamoxifen treatment breast cancer. caused confounding 798 although level, population explanations possible therapy is according tion there on reduction R.R. Love Axillary women, greater, women, or c Adapted b Dose of Tumour estrogen receptor protein year <1 30 mg/day 20 mg/day >2 21 (3) 18 (3) Positive Negative Poor Positive 16 (6) 22 (3) 16 (6) 23 (4) Table 1: Mortality benefits of adjuvant tamoxifen according to dose, duration of treatment, nodal status, and primary tumour estrogen receptor categories

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% reduction in annual odds of death from any cause for women aged ≥50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen versus no tamoxifen</td>
<td>20 (2)c</td>
</tr>
<tr>
<td><strong>Dose of tamoxifen</strong></td>
<td></td>
</tr>
<tr>
<td>20 mg/day versus none</td>
<td>21 (3)</td>
</tr>
<tr>
<td>30 mg/day versus none</td>
<td>18 (3)</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td></td>
</tr>
<tr>
<td>≤1 year versus none</td>
<td>13 (4)</td>
</tr>
<tr>
<td>&gt;2 years versus none</td>
<td>23 (6)</td>
</tr>
<tr>
<td><strong>Axillary nodal status</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Positive</td>
<td>22 (3)</td>
</tr>
<tr>
<td><strong>Tumour estrogen receptor protein</strong></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Positive</td>
<td>23 (4)</td>
</tr>
</tbody>
</table>

- Adapted from Table 3, ref. 14.
- Absolute benefits: If 100 node-positive women have a persistent reduction in the annual odds of death of 15% — 6 additional women will be alive after 10 years; if 30%—12 additional women will be alive after 10 years.
- Figures in parentheses are standard deviations.

pausal or postmenopausal, under or over 50 years of age. In general, younger women appear to benefit less from adjuvant tamoxifen (compare Table I and Fig. 1) and in considering strategies for populations based on available data, a case can be made for including other adjuvant therapeutic approaches, such as surgical oophorectomy, although for this there are far fewer data currently available. For older women, among whom the incidence of breast cancer is greater, the benefits of adjuvant tamoxifen are quantitatively and qualitatively similar.

Are the available data for tamoxifen different from those for polychemotherapy in premenopausal women in terms of the case they present for application to populations?

It must be stated, in reply, that clear evidence of the benefits to populations from adjuvant tamoxifen therapy is not available at present. If it is accepted that the prevalence of adjuvant tamoxifen use in some Western countries is high, there are several possible explanations for the lack of benefits at the population level, but most of them arise because of confounding caused by an increasing incidence of breast cancer. Tamoxifen therapy is a daily oral treatment and is thus not difficult to administer, but remains expensive in some Western countries. Finally, although some of the subjects in the trials were Asian, tamoxifen must be considered to be significantly underevaluated in developing countries and among non-Western ethnic groups.

With a strong case for a reduction in mortality and an increase in disease-free survival resulting from the use of adjuvant tamoxifen, a more comprehensive review of its biological effects, other benefits, toxicities, and symptomatic sequelae associated with its use is important to place in better context the argument for its more widespread use.

**Biology of tamoxifen and non-breast cancer effects**

Tamoxifen is a synthetic estrogen with estrogen agonist and antagonist properties (18). The drug was originally developed as an oral contraceptive, but proved to be ineffective; subsequently, it was found serendipitously to be effective in palliating metastatic breast cancer in some women. Over the last 20 years it has been used for this purpose, but also increasingly for adjuvant therapy.

The pharmacology of tamoxifen is complex. The maximum concentration in blood occurs 4–7 hours after oral administration, and a steady-state after 4 weeks. The total time required for all detectable serological evidence of tamoxifen and its metabolites to disappear from blood is 6–8 weeks. The teratogenicity of tamoxifen is not known; this is of importance for premenopausal women who become pregnant while taking the drug, since even if tamoxifen 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 the faeces. In premenopausal women, decreases in gonadotropin levels occur with tamoxifen therapy; levels of estrogens, progesterone, and prolactin do not change. In contrast, in premenopausal women large increases in total estrogens, estradiol, and progesterone sometimes occur.

At the cellular level tamoxifen probably acts by combining with nuclear estrogen receptor protein, arresting breast cancer cells at the G1 phase. Thus tamoxifen appears to be a cytostatic instead of a cytocidal agent. This is supported by some of the adjuvant trial data, but data for the prolonged effects of the drug suggest that the situation may be more complex. Changes in various biological growth mediators are also produced by tamoxifen: sex-hormone-binding globulin levels increase (which can result in removal of more free estrogen from the circulation); levels of transforming growth factor alpha (a growth stimulatory protein) decrease; and levels of transforming growth factor beta (a growth inhibitory protein) increase. It has been proposed that
effects in breast stromal cells mediate tamoxifen’s action in neighbouring breast cancer cells.

Tamoxifen is therefore a synthetic estrogen that 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 most important use of tamoxifen in humans has been as an adjuvant treatment. In these trials, which are discussed above, the focus has been on recurrence and survival from breast cancer. Only recently has greater attention been paid 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. Among Western women, on whom more studies have been performed, the most profound effects caused by such substances are on the cardiovascular and skeletal systems; women who survive to undergo menopause are at major risk for chronic diseases of these systems. Almost half of all women in Western societies who pass their 50th birthdays will ultimately die of cardiovascular disease; another large, difficult-to-estimate proportion will suffer from the fracture of osteoporotic bones. These chronic diseases are reflections of marked changes in risk factors that occur following menopause, with associated marked decreases in ovarian hormones. In this context, what is known about the action of tamoxifen?

The effects of tamoxifen on risk factors for cardiovascular diseases appear to be generally favourable and estrogenic. Controlled studies show decreases in the 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 who are receiving tamoxifen therapy (19) (Fig. 2). These consequences of tamoxifen treatment are clinically important, as indicated by the results of the meta-analysis of tamoxifen adjuvant studies, in which a 25% reduction in vascular deaths was found (16), and by the results of one trial that reported a major reduction in the numbers of postmenopausal women with myocardial infarction (20). While these observations are consistent with risk-factor changes, they should be regarded more as hypothesis-generating than hypothesis-confirming, and in particular their postmenopausal population base should be borne in mind. The effects of tamoxifen on bone mineral density, a major measure of risk for fracture, are also likely to be favourable. The reduction in bone mass associated with the cessation of ovarian estrogen production involves mainly the more metabolically active trabecular bones in the spine and to a lesser degree in the hips. In postmenopausal women, tamoxifen has a clear bone-density-preserving effect on the lumbar spine (Fig. 3) (14). This observation is consistent with data from animal studies which suggest that tamoxifen is an antiresorptive agent similar to estrogen and thus may be associated over time with decreased rates of bone fracture.
Other significant and undefined effects

Because the major sources of data about the effects of tamoxifen have been adjuvant trials, which were designed to evaluate cancer endpoints, our understanding about the consequences of this therapy is incomplete. These trials and the findings of the meta-analysis discussed above will, nevertheless, continue to be a major source of data. While the long list of incompletely defined effects shown 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 for postmenopausal women, and probably also in premenopausal women (Table 1 and Fig. 1). The meta-analysis determined that the vast majority of deaths were from breast cancer; thus, while there may be morbidity caused by tamoxifen treatment that has not yet been fully identified, as well as possible long-term mortality effects, over a 5–10-year period after diagnosis of breast cancer the deaths from cancer and from all causes reduced. As discussed above for the major chronic diseases of Western women aged over 50 years, tamoxifen appears, if anything, to be protective.

The breadth of data that have generated the possible (hypothetical) effects shown in Table 2 will not be reviewed here, but the reasons for the particular entries are commented on below. A useful review of this topic has been carried out by Nayfield et al. (22).

The reported hormonal effects on uterine tissues, the liver, and most recently, on the colorectum can promote tumour growth. There are very limited data at present to corroborate that these effects are a significant if at all a real concern. The growth-factor-altering effects of tamoxifen may protect against haematopoietic malignancies. Depression occurs with tamoxifen, but its frequency is poorly described. Thrombophlebitis appears to occur at excess rates of 1 per 800 women-treatment years; risk factors for this complication have not been fully characterized. Although some good quality lipid, fibrinogen, and platelet data are available for postmenopausal women, data on lipoprotein, blood pressure, and glucose levels are needed since minor changes in these parameters could be critical for determining the risk for cardiovascular disease and are probably controllable. Whether the prevalence of various ocular conditions is occasionally increased by tamoxifen therapy is unknown, but some data indicate that this should be more carefully studied (23). Since estrogen therapy is associated with increased rates of cholelithiasis, and tamoxifen has similar effects on lipids and lipoproteins, the incidence of cholelithiasis among women who are receiving tamoxifen should be evaluated. The effects of hormones such as tamoxifen on the immune system are of increasing interest; in one Swedish study, hospitalization rates for immune system disorders were lower among tamoxifen-treated women. Bone mineral density changes at sites other than the lumbar spine also need to be assessed.

Since tamoxifen is metabolized in the liver and binds to different body tissues and proteins, its possible interaction with other drugs warrants evaluation.

Finally, tamoxifen is not a curative adjuvant therapy. Many women experience recurrences of breast cancer (metastatic disease), while taking tamoxifen. The mechanisms of this tamoxifen resistance and the optimal management of these patients are only beginning to receive attention (24). It is, however, notable that the incidence of second primary, i.e., contralateral, breast cancer is significantly lower for women receiving tamoxifen treatment; the meta-analysis reported above found a 39% reduction in the incidence of this event (16).

There are additional effects of particular concern for younger premenopausal women, in the main because fewer women in this category have participated in the adjuvant trials of the drug. Of greatest importance is whether in younger women, the direct and indirect hormonal effects of tamoxifen may be carcinogenic to the breast and ovaries. Available data

Table 2: Effects of tamoxifen therapy that are incompletely defined

<table>
<thead>
<tr>
<th>In women of all ages</th>
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<tbody>
<tr>
<td>Uterine endometrium: carcinogenic</td>
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<tr>
<td>Uterine myometrium: carcinogenic</td>
</tr>
<tr>
<td>Liver: carcinogenic</td>
</tr>
<tr>
<td>Colorectum: carcinogenic</td>
</tr>
<tr>
<td>Haematopoietic system: carcinogenic/protective</td>
</tr>
<tr>
<td>Central nervous system: mood-altering</td>
</tr>
<tr>
<td>Coagulation: thrombophlebitis</td>
</tr>
<tr>
<td>Cardiovascular: lipoprotein, blood pressure, glucose levels</td>
</tr>
<tr>
<td>Eye: macular, retinal, lens effects</td>
</tr>
<tr>
<td>Hepatobiliary: cholelithiasis</td>
</tr>
<tr>
<td>Immune system: functional effects</td>
</tr>
<tr>
<td>Drug interactions</td>
</tr>
<tr>
<td>Skeletal: bone mineral density changes at all sites</td>
</tr>
<tr>
<td>Breast cancer: treatment of recurrence</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>In premenopausal women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary: carcinogenic</td>
</tr>
<tr>
<td>Breast: carcinogenic</td>
</tr>
<tr>
<td>Hormonal: patterns, levels and frequency of changes</td>
</tr>
<tr>
<td>Cardiovascular: lipid, fibrinogen, platelet changes</td>
</tr>
<tr>
<td>Gynaecological: symptomatic, infectious</td>
</tr>
<tr>
<td>Vasomotor: symptomatic</td>
</tr>
<tr>
<td>Pregnancy: teratogenic, contraception</td>
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</tbody>
</table>
indicate that tamoxifen markedly increases the levels of estrogens in some women at frequencies that have not yet been completely determined, and one trial has reported that this is associated with an increase in contralateral breast cancer (18). Epithelial ovarian cancer is affected by factors that influence ovulation or epithelial disruption, which tamoxifen causes. Specific cardiovascular effects have not been evaluated in premenopausal women, and the gynaecological effects of tamoxifen are poorly described. The details of and risk factors for the vasomotor symptoms produced by tamoxifen are also poorly described. Finally, how to achieve optimal contraception with tamoxifen and its risks of teratogenesis are not known, but are important issues for premenopausal women.

The above matters deserve particular research attention and monitoring, with the more widespread use of adjuvant tamoxifen being justified by the significant mortality benefits, particularly for postmenopausal women. Because it is likely that most of the serious consequences resulting from use of tamoxifen are rare, any associations will only be observed through population monitoring.

**Contraindications**

In practical terms, there are few women, particularly postmenopausal women, who have histories that should prevent them from taking tamoxifen. Table 3 summarizes the suggested absolute and relative contraindications. While certainty about retinal macular changes following tamoxifen therapy is lacking, they are a possible side-effect and their seriousness warrants particular prudence (23). The other absolute contraindications are based on concerns about hormonal carcinogenesis, teratogenesis, and inefficacy of tamoxifen therapy for breast cancer.

**Table 3: Contraindications to adjuvant tamoxifen**

<table>
<thead>
<tr>
<th>Absolute</th>
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<tbody>
<tr>
<td>Retinal macular oedema or degeneration</td>
</tr>
<tr>
<td>History of benign or malignant liver tumour secondary to oral contraceptives</td>
</tr>
<tr>
<td>Pregnancy</td>
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<tr>
<td>Other hormonal therapy (estrogens, oral contraceptives)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of thrombophlebitis, particularly hormone-related</td>
</tr>
<tr>
<td>History of depression, particularly hormone-related</td>
</tr>
<tr>
<td>Cataract</td>
</tr>
<tr>
<td>Drugs: chlorpromazine, chloroquine, thiouridine, amiodarone and other antiarrhythmics</td>
</tr>
<tr>
<td>Severe vasomotor symptoms</td>
</tr>
<tr>
<td>Polycystic ovaries</td>
</tr>
</tbody>
</table>

The relative contraindications for tamoxifen therapy shown in Table 3 are conditions that may be important risk factors for major complications. The drugs listed in Table 3 can exhibit retinal toxicity and could act synergistically with tamoxifen to produce ocular conditions. Tamoxifen invariably increases the number and intensity of vasomotor symptoms, and up to a third of postmenopausal women receiving the drug may develop annoying gynaecological symptoms (26). For some women who experience such symptoms before beginning tamoxifen therapy and who are prescribed estrogen therapy because of their breast cancer, the resultant intensification of these symptoms may be intolerable.

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

By the year 2000 if 1 million women per annum are diagnosed to have breast cancer, the large majority at the earlier stages of the disease, available data suggest that the deaths of 60 000 of them could be averted by adjuvant tamoxifen treatment and that many thousands more will face a recurrence of breast cancer, and death from the condition will be delayed. Most breast cancer therapy can be administered at the community level and does not require the services of highly specialized doctors. Tamoxifen treatment can be given by surgeons, radiotherapists, or family doctors. Two-thirds of breast cancers occur among women aged more than 50 years, and this group is best served by the use of adjuvant tamoxifen, which is easily administered by medical personnel with minimal training and experience, and causes few side-effects. Tamoxifen can be taken for long periods without monitoring or frequent follow-ups. For most developing countries, where an ideal medical infrastructure will not be available for some decades to come, tamoxifen should receive priority as a breast cancer treatment alternative; it can save medical resources as well as lives.

Laboratories that are not equipped to compete in the search for a cancer cure could instead carry out research on ways to deliver simpler therapies with minimal requirements and costs, in order to provide as much coverage as possible for breast cancer patients in both developed and developing countries. Such target-oriented research is needed to identify the optimal methods for delivering chemotherapeutic drugs and tamoxifen. It is unrealistic to expect tamoxifen compliance in symptom-free women in many developing countries; therefore, a depot form of the drug, should be sought. Currently, the cost of a daily dose of oral tamoxifen is still too high for
most developing countries; however, it should be possible to decrease the price by increasing its use and by producing generic versions.

The major challenges to increasing tamoxifen use are summarized in Table 4. Clinical research is needed to address four issues to help define those public health efforts that are likely to be the most beneficial. While the postulated benefits of the therapy are based on a 2-year course of tamoxifen, some data suggest that treatment for a longer period provides greater benefits. As further data on the precise benefits associated with different durations of treatment become available, a cost–benefit curve can be drawn to facilitate definition of a rational public health approach. At present, insufficient data on premenopausal women are available to support use of adjuvant tamoxifen as a priority therapy for this group. It is important to investigate the benefits of tamoxifen treatment in developing countries, where breast cancer affects younger women more, especially those aged 40–50 years. In developing countries, where pill-taking would present problems, a large clinical trial of a depot form of tamoxifen should be evaluated as part of a comprehensive breast cancer programme in which delay in presenting for diagnosis is studied and a careful assessment of medical resource use is undertaken. Because health care financial resources are severely limited in developing countries, agreements with major pharmaceutical companies must be made to provide large amounts of tamoxifen at less than current Western prices. In addition, in individual countries precise quantification of the population-wide benefits to be gained will enable use of tamoxifen therapy to be placed rationally in the list of priorities developed under comprehensive national cancer control plans to provide optimal care and improve the quality of life for breast cancer patients and to ensure that scarce resources are directed towards providing the maximum benefit. Finally, since the benefits of adjuvant tamoxifen are likely to be lower for stage-III or regionally advanced breast cancer, which is often the most commonly presented form in developing countries, programmes should make greater educational efforts or increase the frequency of breast examinations to downstage the disease at diagnosis, as well as make tamoxifen more readily available.

### Table 4: Major challenges to increasing adjuvant tamoxifen use for women with breast cancer worldwide

**Clinical Research**
- Definition of optimal duration of treatment
- Increased definition of known adverse effects and their incidence
- Further data on breast cancer benefits in premenopausal women
- Data on breast cancer benefits in non-Western populations

**Applications**
- Decreasing the cost of treatment
- Development of injectable depot treatment
- Quantitation of benefits for use in national cancer control planning
- Public health strategies that combine down-staging and adjuvant tamoxifen

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**Résumé**

**La place du tamoxifène dans la lutte mondiale contre le cancer du sein**

Le cancer du sein est un problème de santé mondial de plus en plus préoccupant auquel un traitement hormonal (par le tamoxifène) peut apporter une solution partielle. Cette forme de cancer est la plus fréquente chez les femmes et l’on prévoit un million de cas nouveaux par an en l’an 2000. Actuellement, il n’existe pas de moyens pratiques de prévention, mais le tabagisme pourrait jouer un rôle plus important qu’on ne le pensait jusqu’ici dans le développement de ce cancer, tandis que l’allaitement prolongé semble avoir un effet protecteur notable. Il est important de diagnostiquer le cancer du sein à un stade aussi précoce que possible pour limiter la mortalité et la morbidité.

De nombreux essais cliniques randomisés et une méta-analyse portant sur 40 essais et 30 000 femmes ont montré qu’un traitement par le tamoxifène, venant en complément des mesures locales et régionales, présentait des avantages significatifs. Ce traitement améliorerait le taux de survie à dix ans d’environ 6 pour 100 et dans de nombreux cas, la récidive serait retardée. La plupart des données relatives au tamoxifène concernent les femmes ménopausées; avant la ménopause, les avantages sont moins nets. Qualitativement toutefois, on ne peut définir aucun groupe de femmes pour lesquelles le tamoxifène ne présenterait aucun intérêt.

Le tamoxifène a des effets estrogéniques et anti-estrogéniques. Heureusement, ses effets sur les facteurs de risque de maladie cardio-vasculaire et d’ostéoporose chez les femmes ménopausées semblent favorables. Les concentrations de cholestérol total et de cholestérol LDL sont abaissées, tandis que la densité osseuse se maintient. Ces effets donnent à penser que le tamoxifène pourra diminuer le risque de maladies cardio-vasculaires et de fractures consécutives à l’ostéoporose, principales causes de mortalité et de morbidity chez les femmes âgées dans les pays.
développés. Bien que le tamoxifène ait des conséquences globalement bénéfiques sur la mortalité, certains de ses effets n'ont pas encore été parfaitement caractérisés. L'absence de données détaillées sur ses effets avant la ménopause est particulièrement préoccupante. Le traitement par le tamoxifène n'est contre-indiqué que dans de rares cas: œdème maculaire ou dégénérescence de la rétine, autre traitement hormonal et grossesse. Les résultats des essais cliniques constituent des arguments solides en faveur de la généralisation de l'emploi du tamoxifène comme adjuvant, mais les recherches se poursuivent pour établir la durée optimale du traitement, reconnaître ses effets indésirables et évaluer ses avantages avant la ménopause et pour les populations non occidentales. Pour mettre le tamoxifène à la disposition des populations et se rapprocher du but recherché, qui est de réduire de 60 000 le nombre mondial de décès annuels dus au cancer du sein, il faudrait lancer des programmes de santé publique pour étudier la possibilité d'administrer le produit sous forme d'injections retard, quantifier soigneusement les avantages de ce type d'intervention pour la population et favoriser un diagnostic aussi précoce que possible. Les essais cliniques pourraient être l'occasion de faire participer activement les agents de santé à la définition des nouvelles stratégies visant à rendre le traitement par le tamoxifène accessible à davantage de femmes atteintes d'un cancer du sein.

References