Epidemiological, experimental and clinical data strongly support the possibility that breast cancer can be prevented by using anti-estrogenic interventions in healthy women. Four trials involving over 25,000 women have so far been reported using tamoxifen 20 mg/day or placebo in healthy women to chemoprevent breast cancer, and several trials utilizing raloxifene or aromatase inhibitors are underway. Interim analyses of the Royal Marsden tamoxifen trial and the Italian national trial showed no effect on the early incidence of breast cancer. The NSABP-P1 showed a 49% reduction in early incidence of breast cancer. This was associated with a reduction in osteoporotic fractures but increases in the risks of endometrial cancer, cataract and thromboembolism. The IBIS trial showed a 32% reduction with a two-fold increase in endometrial cancer and in thromboembolic events. Mortality rates of breast cancer in women receiving tamoxifen prophylactically should be monitored and further follow-up of these trials is needed to determine whether tamoxifen provides an overall health benefit or increase specific or overall survival of breast cancer. High-risk women should not be advised to take anti-estrogens outside of a clinical trial setting.

Key words: breast cancer, prophylactic endocrine treatment, chemoprevention

Introduction

Breast cancer is the most frequent malignancy among women in Western countries, and the disease still continues to show a steady increase. It affects about one in eight or one in nine North American women and one in 13 European women. Mortality remains high despite advances in surgical techniques, screening mammography and adjuvant chemotherapy and hormonal therapy. The most consistently documented hormonally-related risk factors for breast cancer are early age at menarche, late age at menopause and late age at first full-term pregnancy. These epidemiological data indicate that estrogen may be an important factor in the pathogenesis of breast cancer. Estrogen is required for promotion of mammary tumours in rats and mice and this process can be inhibited by anti-estrogenic intervention such as ovarian ablation of tamoxifen [1, 2].

The most readily identifiable ‘high risk’ groups consist of women with a positive family history. Many familial breast cancers are hereditary and might be associated with germ line mutations in the BRCA1 or BRCA2 gene [3, 4]. In women from families with many affected members, who carry deleterious BRCA1 and BRCA2 mutations, the lifetime risk of breast cancer is estimated to be as high as 80%, but estimates based on unselected cases of breast cancer are lower than 80% [5, 6]. Women with a positive family, who are non-BRCA1/BRCAR2 mutation carriers, might carry other mutations or have sporadic breast cancer. The involvement of endocrine promotion for cancer development in women with genetic mutation for breast cancer is currently under consideration.

Rationale for tamoxifen chemoprevention

Tamoxifen is a non-steroidal triphenylethylene derivative with both estrogenic and anti-estrogenic activities. It reduces circulating insulin-like growth factor I, it inhibits angiogenesis and induces apoptosis.

Tamoxifen has been in clinical use since 1971. In randomized trials with adjuvant tamoxifen for breast cancer it has been shown that it delays recurrence and prolongs survival in about 30% of women and will prevent the development of about 40% of contralateral breast cancer in women who have received adjuvant tamoxifen for 2 or more years [7]. This result and the good safety profile in large numbers of breast cancer patients with long follow-up, has encouraged the use of tamoxifen as a possible chemopreventive agent for breast-cancer in healthy women.

Tamoxifen chemoprevention trials

The Royal Marsden Hospital trial (interim analysis)

In this study, which started in October 1986 and completed accrual in April 1996, 2,494 women were randomized, 1,250 in...
the tamoxifen and 1233 in the placebo arm [8]. Eligibility criteria included age between 30 and 70 years, with no clinical or screening evidence of breast cancer because of family history. Each participant had at least one first-degree relative aged under 50 years with breast cancer, or one first-degree relative with bilateral breast cancer, or one affected first-degree relative of any age plus another affected first-degree or second-degree relative. Women with a history of benign breast biopsy who had a first-degree relative with breast cancer were also eligible. Women with a history of any cancer or of deep-vein thrombosis or pulmonary embolism were excluded. Postmenopausal women taking hormone-replacement therapy (HRT) were eligible without having to stop such therapy. The treatment and placebo groups were well matched for age, menopausal status, use of HRT and history of benign breast biopsy. The median follow-up was 70 months in both groups. One hundred and fifty-six participants had completed 8 years of medication; 877 had prematurely stopped either for non-toxic reasons or because of side-effects (tamoxifen 320, placebo 176, \( P < 0.0005 \)). The most frequent side-effects leading to discontinuation of tamoxifen were hot flushes, period irregularities, vaginal discharge and benign abnormalities found on transvaginal ultrasonography. There were four cases of endometrial cancer in the tamoxifen group compared with one in the placebo group.

The frequency of breast cancer in this trial was the same for women on tamoxifen or placebo (tamoxifen 34, placebo 36, relative risk: 1.06). Of these 70 cancers, eight were non-invasive ductal carcinoma in situ, four in each group.

The Italian tamoxifen prevention study

In this multicentre double-blind trial, 5408 women were randomized in two groups: 20 mg/day tamoxifen or placebo for 5 years, both orally [9]. Women aged 35–70 years who had had a total hysterectomy for reasons other than neoplasm were eligible. The study started in October 1992 and recruitment ended in July 1997. In June 1997, the trialists and data-monitoring committee decided to end recruitment because of the number of women dropping out of the study and the side-effect profile of tamoxifen.

A total of 1422 (26.3%) of 5408 randomized women dropped out of this study. Of these, 1027 dropped out voluntarily with the most common causes being side-effects (301 women) and 239 women withdrew because of some serious side-effects. Only 149 women completed 5 years.

The median duration of follow-up was 46 months. There were 82 cases of cancer recorded in the study population, 41 in the breast and 41 at other sites, with no difference for the latter in distribution between the two arms of the study. Of the breast cancer cases, 19 were among women in the tamoxifen arm, 22 among those in the placebo arm. If the hazard ratio for a reduction in breast cancer development by tamoxifen was as initially hypothesized at the outset of the study (33% reduction), simulations showed that given the current aggregation of cases between tamoxifen and placebo there would be a 22% probability of obtaining a significant hazard ratio (at 5%) after a further 5 years. There were no major differences in breast cancer characteristics between patients on placebo and those on tamoxifen for size of the tumour, peritumoral vascular invasion, axillary involvement or estrogen receptors. In a subgroup analysis, a protective effect of tamoxifen against breast cancer among women who took HRT during the study period was seen.

Fifty-six women experienced 64 vascular events during the course of this study: 18 women on placebo and 38 on tamoxifen (\( P = 0.0053 \)). There were 14 documented cerebrovascular ischemic events: five on placebo and nine on tamoxifen (\( P = 0.27 \)). Even though hypertriglyceridermia was not looked at specifically at each follow-up, 17 women in the study had hypertriglyceridermia: two on placebo and 15 on tamoxifen (\( P = 0.0013 \)).

In the extended follow-up of 81.2 months, breast cancer was diagnosed in 45 (1.7%) of 2708 controls and in 34 (1.3%) of 2700 women on tamoxifen, and the difference was not significant (\( P = 0.215 \)). Among the 79 women diagnosed with breast cancer, no deaths were reported. The use of HRT increased the risk of breast cancer, as expected in view of previous epidemiological findings, and the use of tamoxifen in women using HRT seemed to reduce the risk of breast cancer to that of non-users of HRT [10].

**NSABP breast cancer prevention trial**

This study by the National Surgical Adjuvant Breast and Bowel Project (NSABP) commenced in 1992 and included 13 388 randomized women [11]. Eligibility for the trial was based on the Gail model, which accounts for both genetic and non-genetic risk factors. Women aged 60 years or older were eligible. Determination of eligibility for women aged 35–59 years was based on a diagnosis of lobular carcinoma in situ, or a weighted composite from among the following factors, to sufficiently raise the risk to that of a 60-year-old woman: the number of first-degree relatives who have been diagnosed with breast cancer, nulliparity or age at first live birth, number of benign breast biopsies and age at menarche.

Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided, \( P < 0.00001 \)), with a cumulative incidence through 69 months of follow-up of 43.4 and 22.0 per 10 000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women aged 49 years or younger (44%), 50–59 years (51%) and 60 years or older (55%). Risk was also reduced in women with a history of lobular carcinoma in situ (56%) or atypical hyperplasia (86%) and in those with any category of a predicted 5-year risk. Tamoxifen reduced the risk of non-invasive breast cancer by 50% (two-sided, \( P < 0.002 \)). Tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69%, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Tamoxifen administration did not alter the average annual rate of ischemic heart disease; however, a reduction in hip, radius (Colles’) and spine fractures were observed. The rate of endometrial cancer increased in the tamoxifen group (risk ratio 2.53); this increased risk occurred predominantly in women aged 50 years or older. All endometrial cancers in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths occurred in this group. The rates of stroke, pulmonary embolism and deep-vein thrombosis were
elevated in the tamoxifen group; these events occurred more frequently in women aged 50 years or older.

**The International Breast Cancer Intervention Study—IBIS**

A fourth large tamoxifen preventive trial was published in 2002 [12]. A total of 7152 women aged 35–70 years entered into the trial from April 1992 until March 2001. Eligible women had risk factors for breast cancer indicating at least a two-fold relative risk for ages 45–70 years, a four-fold relative risk for ages 40–44 years, and approximately a 10-fold relative risk for ages 35–39 years. Risk factors were family history, lobular carcinoma in situ and atypical hyperplasia. Reasons for exclusion were any previous cancer, a previous deep-vein thrombosis or pulmonary embolism, current use of anticoagulants, or a life expectancy judged to be less than 10 years. Women were randomly assigned 5 years of treatment with tamoxifen 20 mg/day or matching placebo. The largest risk group was women who had two or more first-degree or second-degree relatives with breast cancer (62%). Full compliance to 5 years was estimated to be 64% in the tamoxifen group and 74% in the placebo group ($P < 0.001$). Forty per cent of women used HRT at some time during the active treatment.

With a median follow-up of 50 months, 170 breast cancers were recorded; 69 in the tamoxifen group and 101 in the placebo ($P = 0.01$), with the rate being 32% lower. Nodal status, size and grade were similar in both study groups. The reduction in risk of confirmed ER-positive invasive tumors with tamoxifen was 31%. There was no reduction in the risk of ER-negative invasive tumors. There are, as yet, insufficient data for assessment of whether protection continues after treatment has stopped.

A two-fold excess of endometrial cancer was found in the tamoxifen groups (11 versus 5, $P = 0.2$). Most of these cancers were in women who were older than 50 years at randomization. The rate of venous thromboembolic events was about 2.5 times higher in the tamoxifen group than in the placebo group ($P = 0.001$).

The death rate from all causes was significantly higher in the tamoxifen group than in the placebo group (25 versus 11, $P = 0.028$).

**Discrepancy of results**

There are several reasons for the different results reported in these chemoprevention trials. The Italian study had problems with compliance. About 26% women dropped out mainly within the first year.

Another reason for the difference between the British data, the Italian data and those of the NSABP-P1 trial could relate to the study population. The selection of women who had undergone a hysterectomy in the Italian study did produce a group with a slightly less than normal risk of breast cancer, since the group contained normal-risk women (hysterectomy without oophorectomy) and reduced-risk women (hysterectomy with bilateral oophorectomy). In the NSABP-P1, the entry criteria were based mostly on non-genetic risk factors. In the British study, the entry criteria for all ages were predominantly based on a strong family history, with an associated increased risk of inheriting a high-risk breast cancer predisposing gene such as BRCA1. Using pedigree analysis, it was estimated that about 36% of all participants and over 60% of those who have developed breast cancer are in clusters that have a greater than 80% chance of being due to a breast cancer predisposition gene [13]. Estrogen promotion may not be important in the genesis of clinical breast cancer in high-risk gene carriers. This is supported by the lack of progesterone receptors in BRCA1 and BRCA2 cancers, which indicates phenotypical hormone resistance [14]. Furthermore, most breast tumors that arise in BRCA1 mutation carriers are estrogen-receptor negative [15, 16], over-express p53 more frequently and exhibit a higher nuclear grade, whereas BRCA2 mutation-associated tumors are typically estrogen-receptor positive [17]. The critical question, whether the prophylactic use of tamoxifen reduces the incidence of invasive breast cancer in BRCA1 or BRCA2 mutation carriers, has been partially answered, given the sample size, in the study of 19 breast cancer cases recruited in the NSABP-P1 study that inherited BRCA1 or BRCA2 mutations [18]. Tamoxifen reduced breast cancer incidence among healthy BRCA2 carriers by 62%, similar to the reduction in incidence of ER-positive breast cancer among all women in the BCPT. In contrast, tamoxifen use did not reduce the incidence in healthy women with inherited BRCA1 mutation. Further insight was provided by a study showing an inverse relationship between tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 mutation carriers [19]. In addition, bilateral prophylactic oophorectomy was associated with a reduced breast cancer risk in women who carry a BRCA1 mutation [20]. So this question could be best addressed by a prospective randomized trial involving a sufficient number of such women.

A second reason for the difference between the NSABP-P1 and the results of the British study could relate to the duration of follow-up. The average follow-up for NSABP-P1 was only 3.5 years compared with the median of nearly 6 years. The relatively early frequency data in the NSABP trial largely reflected treatment of occult primary cancers, rather than prevention by blocking estrogen known promotion of the transformed cell into an active cancer. It is not known whether early endocrine treatment of occult cancers would prevent the long-term appearance of these cancers and therefore confer clinical benefit, especially after cessation of treatment. Animal data indicate that tumor development could return after the end of treatment.

A third problem is the duration of tamoxifen treatment. In the B-14 adjuvant trial of the NSABP, almost twice as many distant recurrences and deaths occurred in those who took tamoxifen for 10 years as in those who stopped after 5 years [21]. In the British study, a proportion of patients received tamoxifen for a median of 8 years. Another issue that we know little about is the interaction of tamoxifen with other treatments, including HRT, given concurrently or in sequence (Table 1).

**Rationale for raloxifene chemoprevention**

Raloxifene, which is a selective estrogen receptor modulator (SERM), FDA-approved for halting bone loss, was evaluated
in a multicenter randomized blinded, placebo-controlled trial with a primary end point being the reduction of risk fracture from osteoporosis [22]. A total of 7705 postmenopausal women were randomized and with a median follow-up of 40 months, a significant reduction in breast cancer was seen (13 versus 27 cases; RR 0.24, $P < 0.001$). The risk of invasive estrogen receptor-positive breast cancer by 90% (RR 0.1). Moreover, the risk of endometrial cancer was not increased (RR 0.8).

NSABP initiated the STAR trial, which will compare tamoxifen and raloxifene 60 mg/day in 22 000 postmenopausal women.

### Rationale for aromatase inhibitors chemoprevention

Aromatase inhibitors are a class of compounds that inhibit the synthesis of estrogen from androgens in postmenopausal women. Several trials have confirmed their superiority over progestins for the treatment of advanced breast cancer in postmenopausal women for whom tamoxifen fails [23, 24]. So far, three trials have been completed in the adjuvant setting [25–27]. In 2002, the results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, which compared the established adjuvant treatment, tamoxifen, with anastrozole, a selective third-generation non-steroidal aromatase inhibitor, alone and in combination with tamoxifen as adjuvant treatment for postmenopausal women with early operable breast cancer, were published [25]. A total of 9366 women were enrolled between July 1996 and March 2000. Median follow-up was 33.3 months. Disease-free survival was significantly longer for patients on anastrozole alone than those who received either tamoxifen alone (hazard ratio 0.83, $P = 0.013$) or the combination (hazard ratio 0.81, $P = 0.006$).

The disease-free survival estimates of 3 years were 89.4%, 87.4% and 87.2% on anastrozole, tamoxifen and the combination, respectively. Compared with tamoxifen, anastrozole was associated with a 58% reduction in the incidence of contralateral cancer. If this trend persists, anastrozole has the potential to prevent (or delay) up to 80% of hormone-receptor positive cancers.

In comparison with tamoxifen alone, anastrozole was associated with significant reductions in hot flushes, vaginal discharge, vaginal bleeding, ischemic cerebrovascular events ($P = 0.0006$), venous thromboembolic events ($P = 0.006$), deep-vein thromboses ($P = 0.018$) and endometrial cancer ($P = 0.03$). By contrast, musculoskeletal disorders and fractures ($P = 0.003$) were significantly more common with anastrozole than with tamoxifen.

As a consequence, anastrozole is to be incorporated in the design of the second International Breast Cancer Intervention Study (IBIS-II) prevention trial. A total of 10 000 high-risk postmenopausal women, aged 40–70 years, will be randomized in a three-arm trial, for 5 years treatment with two tablets/ day (double dummy mg). The three arms are double placebo, tamoxifen 20 mg plus anastrozole placebo, or anastrozole 1 mg plus tamoxifen placebo. Supplementary studies for bone density and bone biomarkers (target 900 women) and cognitive fraction are also under way. A parallel IBIS-II DCIS arm has been also initiated, which will be a two-arm trial (no placebo arm) and has a target of 4000 women aged 40–70 years who have had ductal carcinoma in situ diagnosed within the previous 6 months.

A total of 4742 patients were enrolled in the IES study, which was a double-blind randomized trial to test whether, after 2–3 years of tamoxifen therapy, switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the 5 years of treatment [26]; 2362 were randomly assigned to switch to exemestane and 2380 to continue to receive tamoxifen. After a median follow-up of 30.6 months, a 32% reduction in the risk of recurrence was reported in the exemestane group corresponding to an absolute benefit in terms

### Table 1. Tamoxifen chemoprevention trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>No. of patients</th>
<th>Eligibility criteria</th>
<th>Percentage on HRT (%)</th>
<th>Prior hysterectomy</th>
<th>Percentage with one first-degree relative (%)</th>
<th>Percentage with two first-degree relatives (%)</th>
<th>No. of cancers</th>
<th>Medial follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden [8]</td>
<td>2496</td>
<td>Women 30–70 years + family history of BC</td>
<td>15.5</td>
<td>NG</td>
<td>54.7</td>
<td>17.2</td>
<td>34 versus 36, $P = 0.8$</td>
<td>70</td>
</tr>
<tr>
<td>Italian [9, 10]</td>
<td>5408</td>
<td>Women 35–70 years + total hysterectomy</td>
<td>13.9</td>
<td>98.3</td>
<td>12.4</td>
<td>2.3</td>
<td>19 versus 22, $P = 0.6$</td>
<td>46</td>
</tr>
<tr>
<td>NSABP [11]</td>
<td>13888</td>
<td>Women ≥60 years Women 35–59 years + LCIS or + 5-year predicted risk of BC of ≥1.66%</td>
<td>0</td>
<td>37</td>
<td>56.8</td>
<td>19.4</td>
<td>124 versus 244, $P &lt; 0.00001$</td>
<td>81.2</td>
</tr>
<tr>
<td>IBIS [12]</td>
<td>7000</td>
<td>Women 35–70 years + two to 10-fold relative risk</td>
<td>39.8</td>
<td>35.2</td>
<td>48.1* (16.5)</td>
<td>61.8*</td>
<td>68 versus 101, $P = 0.013$</td>
<td>69</td>
</tr>
</tbody>
</table>

BC, breast cancer; HRT, hormone replacement therapy; NG, no information was provided.

*First-degree relative $<50$; †first-degree relative with bilateral breast cancer; ‡two or more first-degree or second-degree relatives with breast cancer.

*$$P < 0.001$$; †$$P = 0.8$$; ‡$$P = 0.6$$; §§$$P = 0.2$$; $P = 0.03$$; $P = 0.006$.
of disease-free survival of 4.7%. Contralateral breast cancer occurred in 20 patients in the tamoxifen group and nine in the exemestane group ($P = 0.04$). The hazard ratio was 0.44.

Thromboembolic events and gynecologic symptoms were recorded more frequently in the tamoxifen group ($P = 0.007$ and $P < 0.001$, respectively). Exemestane was associated with a higher incidence of arthralgia and diarrhea ($P < 0.001$). Fractions were reported more frequently in the exemestane group, although the difference was not statistically significant ($P = 0.08$). A number of pilot trials with aromatase inhibitors in healthy women have been initiated. Eligibility criteria of these studies include a history of pre-invasive breast cancers, elevated serum estrogen levels in postmenopausal women, and increased density on screening mammography. NCIC-CTG (MAP 1) is comparing letrozole to placebo, (MAP 2) exemestane to placebo and (MAP 3) exemestane, with or without celecoxib, to placebo. Finally, the Italian Consortium of Hereditary Breast Ovarian Cancer developed the Apre S study, a multicenter, double-blind, randomized placebo controlled phase III study evaluating the chemopreventive effect of exemestane in unaffected postmenopausal BRCA1/2 mutation carriers [28].

**Discussion**

There are still several major questions to answer including:

1. What is the duration of the effect? Might cancer only by delayed by tamoxifen and then appear shortly after stopping treatment?
2. What is the influence on mortality? It is unclear whether cancer occurring in women receiving tamoxifen will be more resistant to treatment. If tamoxifen only delays the appearance of cancer, this may have a major influence on the eventual outcome.
3. Will women of very high risk possessing a mutation in one of the breast cancer genes BRCA1 or BRCA2 benefit more or less than other women?
4. Is there any interaction with HRT?

An attempt to answer these questions was made by the American Society of Clinical Oncology Work Group on Breast Cancer Risk Reduction Strategies [29]. They conducted an evidence-based technology assessment to determine whether tamoxifen, raloxifene and aromatase inhibitors as breast cancer risk-reduction use are appropriate for broad-based conventional use in clinical practice. They concluded that tamoxifen 20 mg/day for up to 5 years may be offered to women with a defined 5-year projected risk of breast cancer of $\geq 1.66\%$. Consideration of tamoxifen use is appropriate if the primary goal of therapy is to lower the risk of breast cancer rather than focus on other health-related issues (CHD, BMD). There is currently insufficient evidence to determine whether tamoxifen provides overall health benefit or increases specific or overall survival of breast cancer. Risk/benefit models suggest that the greatest clinical benefit with least side-effects is derived from use of tamoxifen in younger (premenopausal) women (who are less likely to have thromboembolic sequelae and uterine cancer), women without a uterus and women at higher breast cancer risk.

In all circumstances, tamoxifen use should be discussed as part of an informed decision-consideration of risks, benefits and alternatives.

It is premature to recommend raloxifene use to lower the risk of developing breast cancer outside of a clinical trial setting. On the basis of available information, use of raloxifene should currently be reserved for its approved indication to prevent bone loss in postmenopausal women. There are no current published data on raloxifene in premenopausal women. The use of any aromatase inhibitor to lower breast cancer risk is also not recommended outside of a clinical trial setting.

At the present time, the effect of using tamoxifen with other medications (such as HRT) or using tamoxifen and raloxifene or aromatase inhibitors in combination or sequentially has not been studied. Probable limitations of these recommendations are that women in the placebo arm of the NSABP trial had lower mortality rates and lower rates of stroke and pulmonary embolism than the general population. Estimated incidence rates are taken from US epidemiological studies and may not be applicable in other populations. In addition, the frequency of deaths in the women in the Italian trial was considerably lower than expected according to the Italian national age-specific mortality rates. Deaths from vascular disease were also lower than the numbers expected. Undoubtedly the population of women who volunteered to participate in this trial was self-selected and healthy in many aspects. Currently these is an FDA-approved indication for tamoxifen to ‘reduce the incidence of breast cancer in women of a high risk’ group. Finally, an overview of the outcome in breast cancer prevention trials was published a year later [30]. Data from the IBIS-1, NSABP-1 and MORE trials were based on published material, whereas those from the Royal Marsden (February 2001) and Italian studies update published reports. Relevant data on contralateral breast tumors and side-effects were included from an overview of an adjuvant trial of tamoxifen versus control. The tamoxifen prevention trials showed a 38% reduction in breast cancer incidence ($P < 0.0001$). There was no effect for ER-negative breast cancers ($P = 0.21$), but ER-positive cancers decreased by 48% ($P < 0.0001$). Rates of endometrial cancer and venous thromboembolic events were increased ($P = 0.0005$ and $P < 0.0001$, respectively). Overall there was no effect on breast cancer mortality.

In conclusion, there is substantial evidence that tamoxifen can reduce the risk of ER-positive breast cancer. The incidence of ER-negative breast cancer is not affected. Newer agents such as raloxifene and the aromatase inhibitors need to be evaluated. High-risk women should not be advised to take anti-estrogens outside of a clinical trial, as longer follow-up of completed trials is needed to assess further the effect of tamoxifen use on breast cancer mortality and other long-term risks and benefits of such treatment. The overview meta-analysis in 2005 is awaited with interest.

**References**


