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Should Tamoxifen Be Used in Breast Cancer Prevention?

Rita Kramer and *Powel Brown*

Breast Center, Baylor College of Medicine & the Methodist Hospital, Houston, Texas, USA

Abstract

Breast cancer is the most commonly diagnosed cancer in women. The risk of developing breast cancer can be lowered by maintaining a healthy bodyweight and avoiding long-term use of combined estrogen and progestogen replacement after menopause. However, many women are at an increased risk of developing breast cancer secondary to age, early menarche, a family history of breast cancer or a personal history of benign breast disease. These women may now be offered tamoxifen as a chemoprevention therapy. Five years of tamoxifen treatment results in a reduction in the relative risk of developing estrogen receptor-positive breast cancer of 48%. This benefit outweighs the risk of tamoxifen-related adverse events for many healthy women. However, the benefit-risk ratio of tamoxifen chemoprevention varies for individual women. The randomized clinical trials evaluating standard-dose tamoxifen versus placebo as chemoprevention therapy are reviewed and analyzed to determine which particular women are most likely to benefit and least likely to experience a tamoxifen-related adverse event. Tamoxifen decreases the risk of breast cancer associated with aging, having a first-degree relative with disease, and a personal diagnosis of atypical ductal hyperplasia or lobular carcinoma *in situ*. Women who have had a hysterectomy and are at low risk of a thromboembolic event have a decreased risk of adverse effects associated with tamoxifen therapy. The strengths and weaknesses of the Gail model (frequently used to assess an individual's risk of developing invasive breast cancer over the next 5 years) are highlighted. A method for assessing the benefit-risk ratio for an individual woman is presented. Alternative breast cancer chemoprevention strategies are considered, including the use of aromatase inhibitors. This article discusses the pros and cons of these various preventive therapies and concludes that at this time, tamoxifen remains the gold standard for breast cancer prevention.

Breast cancer is the most commonly diagnosed cancer in US women and the leading cause of cancer death for women between the ages of 20 and 59 years. It is estimated that 217 440 new cases of breast cancer will be diagnosed in the US in 2004[1] and that 40 580 women will die of the disease. Approximately one in ten women has a mother, sister or daughter with breast cancer, and an even greater number have watched a close friend struggle with the disease.[2] Many women are highly motivated to decrease their personal risk of developing breast cancer. However, many of the risk factors are not amenable to changes in lifestyle or behaviour. Tamoxifen chemoprevention has been demonstrated

Table I. Randomised trials of tamoxifen chemoprevention

Study	Number of patients randomised (tamoxifen vs control)	Decrease in breast cancer events				
		total	invasive	DCIS	ER+	ER−
Royal Marsden[4,9]	1238 vs 1233	No	No	No	NA	NA
NSABP P-1[5]	6681 vs 6707	Yes	Yes	Yes	Yes	No
Italian Tamoxifen Prevention Study[3,10]	2700 vs 2708	No	No	No	NA	NA
IBIS-I[6]	3753 vs 3566	Yes	Yes	Yes	Yes	No
Cuzick et al.[7] meta-analysis	14 192 vs 14 214	Yes	Yes	Yes	Yes	No

DCIS = ductal carcinoma *in situ*; **ER+** = estrogen receptor-positive; **ER−** = estrogen receptor-negative; **IBIS-I** = First International Breast Cancer Intervention Study; **NA** = not applicable; **NSABP P-1** = National Surgical Adjuvant Breast & Bowel Project P-1.

to lower the increased risk of breast cancer associated with aging, a family history of the disease and a personal history of benign breast disease.

Four randomised clinical trials have analysed the impact of tamoxifen on the risk of invasive breast cancer.[3-6] A recent meta-analysis reported that 14 192 women were randomised to receive tamoxifen treatment while 14 214 received placebo.[7] Despite the fact that only two of the individual studies revealed a significant reduction in the risk of invasive breast cancer with tamoxifen therapy, the data in total, when analysed in a fixed-effect model, revealed a 38% reduction in the risk of invasive breast cancer (95% CI 28, 46; $p < 0.0001$) and all the studies were compatible with this result. The question is no longer whether or not tamoxifen is an effective chemopreventative agent. Rather, the challenge facing clinicians is to determine which women may benefit from therapy and for an individual woman weighing the risks and benefits of tamoxifen chemoprevention to determine if a net health benefit is likely to result from therapy.

1. Tamoxifen Breast Cancer Prevention Trials

The use of tamoxifen to treat early breast cancer is associated with a decrease of approximately 50% in the rate of contralateral tumours.[8] This led to the initiation of a pilot trial of tamoxifen to prevent disease at the Royal Marsden Hospital, London, UK in 1986. The early results of this trial have been reported and led to the IBIS (International Breast Cancer Intervention Study) conducted in the UK, Australia, New Zealand and other European countries.[4,6,9] Two other prevention trials utilising tamoxifen have been completed: the NSABP P-1 (National Surgical Adjuvant Breast and Bowel Project P-1) study[5] and the Italian Tamoxifen Prevention Study.[3] The eligibility criteria for all four studies varied and, not surprisingly, so did the results. The NSABP P-1 and the IBIS-I studies demonstrated a reduction in the risk of invasive breast cancer in women randomised to tamoxifen compared with those taking placebo (table I). The Royal Marsden and the Italian trials did not demonstrate this benefit. However, a retrospective, unplanned subset analysis of the Italian study has identified a group of high-risk women (women taller than 160cm, with at least one functioning ovary, who had menarche at no older than age 13 years and no full-term pregnancy before the age of 24 years) who did benefit from tamoxifen chemoprevention.[10]

The largest study (NSABP P-1) enrolled patients at increased risk for breast cancer because of age (≥60 years) or a history of lobular carcinoma *in situ* (LCIS) or because of a 5-year predicted risk for breast cancer of at least 1.66% as calculated by a modified Gail model.[5] In its original form, the Gail model predicted the combined risk of invasive and non-invasive breast cancers for White women by evaluating variables including age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, pathological diagnosis of atypical hyperplasia and age at menarche. The model was modified to calculate the risk of invasive breast cancer only and to allow for race-specific determinations of this risk.

The majority of the 7152 women enrolled on the IBIS-I and the 2494 women enrolled on the Royal Marsden trial were eligible because of a family history of disease. Only 4% of patients in each arm of the IBIS-I had prior diagnoses of LCIS or atypical hyperplasia. Approximately one-fifth of those enrolled on each arm of the Royal Marsden trial had had a prior biopsy for benign breast disease (although the particular lesion was not reported). The Italian trial enrolled >5000 healthy women aged 35–70 years who had had a hysterectomy. These women were recruited via national advertising and through their gynaecologists. There was no formal estimation of an individual participant's personal risk of developing breast cancer and, in fact, many of the women may have had a reduced risk, as 48.3% of participants had had bilateral ovariectomies. The NSABP P-1 study excluded women who were currently taking hormone replacement therapy (HRT), whereas all three of the other studies allowed this therapy. It is clear that these studies enrolled women of differing degrees of risk of developing breast cancer and that the biological changes which conferred that risk differed significantly. It is likely that the benefit of tamoxifen chemoprevention seen in some of the studies but not others results from the ability of tamoxifen to modulate some but not all of these risk factors. The risk factors that are associated with the development of estrogen receptor (ER)-positive breast cancer do appear to be modulated by tamoxifen, while those associated with the development of ER-negative breast cancer are not. The overview analysis of the four tamoxifen (20 mg/day for at least 5 years) prevention trials revealed that tamoxifen reduced ER-positive breast cancers by 48% (95% CI 36, 58; $p < 0.0001$) but had no effect on ER-negative breast cancers (odds ratio [OR] 1.22; 95% CI 0.89, 1.67). The premalignant lesions of LCIS and atypical ductal hyperplasia (ADH) are ER positive in the majority of cases,[11,12] and tamoxifen is likely to modulate the breast cancer risk associated with these lesions. In fact, women with atypical hyperplasia and LCIS who received tamoxifen in the NSABP P-1 study experienced highly significant reductions in their relative risk of developing invasive carcinoma (86% for atypical hyperplasia and 56% for LCIS). However, patients with primary breast cancers that are ER negative do not benefit from tamoxifen chemoprevention to prevent a contralateral breast cancer.[8,13]

In addition to the decrease in the risk of invasive breast cancer noted in the meta-analysis,[7] the NSABP P-1 and the IBIS-I studies demonstrated a decrease in the risk of non-invasive breast cancer. Tamoxifen therapy was associated with a risk ratio (RR) for non-invasive breast cancer in the NSABP P-1 study of 0.5 (95% CI 0.33, 0.77; $p < 0.002$) and in the IBIS-I study of 0.31 (95% CI 0.12, 0.82; $p = 0.01$). Additionally, women receiving tamoxifen while participating in the NSABP P-1 had a 29% reduction in the risk of having a breast biopsy and a 28% reduced risk of being diagnosed with benign breast disease.[14] Women participating in the NSABP P-1 study also experienced fewer hip, spine and radius (Colles') fractures.

The Royal Marsden, IBIS-I, Italian and NSABP P-1 investigators have all performed subset analyses of their data to determine whether or not specific groups of women benefited from tamoxifen chemoprevention. The Royal Marsden trial demonstrated no benefit to any subgroup – even those identified by the Claus model to be at an increased risk of hereditary breast cancer.[4,9] The IBIS-I investigators performed a limited subset analysis, which demonstrated that women benefited from tamoxifen chemoprevention regardless of age (<50 and ≥50 years) and whether or not they used concomitant HRT.[6] The NSABP P-1 investigators performed a more extensive subset analysis and confirmed benefit for women aged ≥35 years (≤49, 50–59 or ≥60 years); all Gail model risk categories (1.67–2.00, 2.01–3.00, 3.01–5.00 or ≥5.01); regardless of whether or not first-degree relatives had breast cancer (0, 1, 2, ≥3); and regardless of whether or not they had a prior history of LCIS or ADH.[5] Some subgroups had a greater degree of benefit than others; for example, participants with a history of ADH had a greater reduction in risk with tamoxifen therapy (86%). The Italian investigators have recently reported a re-analysis of their data, stratifying

Table II. Impact of age on tamoxifen-related adverse events[5]

Adverse event	Risk ratio[a] (95% CI)		
	total	age ≤49 years	age ≥50 years
Endometrial carcinoma	2.53 (1.3, 4.97)	1.21 (0.41, 3.6)	4.01 (1.7, 10.9)
Stroke	1.59 (0.93, 2.77)	0.76 (0.11, 4.49)	1.75 (0.98, 3.2)
Transient ischaemic attack	0.76 (0.4, 1.44)	0.76 (0.11, 4.49)	0.76 (0.37, 1.53)
Pulmonary embolism	3.01 (1.15, 9.27)	2.03 (0.11, 119.62)	3.19 (1.12, 11.15)
Deep vein thrombosis	1.6 (0.91, 2.86)	1.39 (0.51, 3.99)	1.71 (0.85, 3.58)

a Tamoxifen versus placebo.

patients according to a retrospectively developed model of risk of developing an ER-positive breast cancer.[10] All *post hoc* subset analyses must be viewed cautiously; however, the results are consistent with those from the IBIS-I and NSABP P-1 studies. Specifically, patients who were identified to be at increased risk of developing ER-positive breast cancer benefited from tamoxifen chemoprevention. At a median follow-up of 81.2 months, the subgroup of participants (n = 702) treated with tamoxifen had a reduction in risk of breast cancer of 82% (RR 0.18; 95% CI 0.05, 0.62; p = 0.003).[10] Participants at a high risk of developing ER-positive breast cancer and who used HRT during the trial also benefited from tamoxifen chemoprevention compared with placebo (p = 0.009). None of the four prevention studies have shown a decrease in mortality from breast cancer. An overview of the four studies shows no effect of tamoxifen prevention on all-cause mortality.[7]

The potential benefits of tamoxifen chemoprevention must be weighed against the risk of a tamoxifen-related adverse event. Three of the four studies demonstrated an increased risk of endometrial carcinoma with tamoxifen therapy (eligibility for the Italian study included prior hysterectomy). All four studies demonstrate an increase in thromboembolic events in women taking tamoxifen; however, in the Italian study these were primarily superficial thromboses. The relative risks of these complications is consistent between the NSABP P-1 study and the overview despite the fact that NSABP P-1 participants were not taking HRT but participants in all three of the other studies were permitted to do so. The relative risk of endometrial cancer was 2.53 (95% CI 1.35, 4.97) for participants in the NSABP P-1 study and 2.4 (95% CI 1.5, 4) in the overview. Venous thromboembolic events were also increased in all studies with a relative risk of 1.9 (95% CI 1.4, 2.6; p < 0.0001) in the overview and 1.6 (95% CI 0.91, 2.86) in the NSABP P-1 study. Some of the thromboembolic events were serious vascular events such as stroke. The NSABP P-1 study has analysed the impact of age on the relative risk of a tamoxifen-related adverse event (table II). The relative risk of endometrial cancer, stroke, pulmonary embolism and deep vein thrombosis was significantly higher for participants who were ≥50 years of age at the time of study enrolment.[5] Women receiving tamoxifen who were aged ≤49 years at the time of study entry had a much lower relative risk of a tamoxifen-related adverse events. Their average annual rates of adverse events per 1000 women were 1.32 for invasive endometrial carcinoma (1.09 for placebo); 1.45 for stroke (0.92 for placebo); 0.69 for pulmonary embolism (0.23 for placebo); and 1.6 for deep vein thrombosis (1.34 for placebo).

2. Balancing the Risks and Benefits of Tamoxifen Chemoprevention for an Individual Woman

The first step in determining whether or not an individual woman is a candidate for tamoxifen chemoprevention therapy is assessing her risk of developing breast cancer. The second is to determine if that risk may be modulated by tamoxifen. It is important to acknowledge that although increased risk may arise from many factors, data regarding the ability of tamoxifen to modulate many of these risk factors are limited. For example, obesity is associated with a relative risk of developing breast cancer of 1.2,[15] therapeutic radiation for Hodgkin's disease

with a relative risk of 5.2[16] and a germline mutation in *BRCA1* with a markedly increased risk of developing disease.[17] It is unclear whether or not tamoxifen therapy can modulate these risk factors.

Women with a strong family history of breast and/or ovarian cancer frequently present for risk assessment. Participants in the NSABP P-1 study with first-degree relatives with breast cancer (mothers, sisters and/or daughters) did benefit from tamoxifen therapy, with a risk ratio of 0.53 compared with a risk ratio of 0.46 for women without a family history. However, it is unclear whether or not women who carry mutations in *BRCA1* and/or *BRCA2* will also experience a reduction in risk. Analysis of the mutation status of 288 of the 320 participants in NSABP P-1 who developed breast cancer as of 30 September 1999 revealed that only 19 of 288 (6.6%) carried inherited disease-predisposing mutations.[18] Of the 19 mutation-positive participants, eight had mutations in *BRCA1*; five received tamoxifen and three received placebo (RR 1.67; 95% CI 0.32, 10.7). Eleven participants had mutations in *BRCA2*; three received tamoxifen and eight received placebo (RR 0.38; 95% CI 0.06, 1.56). Analysis of small subsets must be interpreted with caution; however it should be noted that only one of the cancers that developed in *BRCA1* mutation-positive women was known to be ER positive, whereas six developing in *BRCA2* mutation-positive participants were known to be ER positive.

A matched case control study of tamoxifen and the risk of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers indicated that women who received tamoxifen therapy as treatment for their first breast cancer have a reduction in their risk of developing a contralateral cancer.[19] ER status for the tumours was available for only a few of the patients and it is possible that the majority of patients receiving tamoxifen had primary cancers that were ER positive. The impact of tamoxifen on the relative risk of disease may vary with the specific mutation involved. Women with mutations in *BRCA1* are more likely to develop ER-negative cancers, while those with *BRCA2* mutations are more likely to develop ER-positive cancers.[18] Tamoxifen has not been effective in preventing contralateral breast cancers in clinical trials of sporadic breast cancer when the first cancer was ER negative.[20,21] However, the biology of ER-negative cancers arising from mutations in the BRCA1 gene may differ from sporadic ER-negative cancers and they may respond differently to tamoxifen.

Women with a personal history of non-invasive breast cancer and benign breast disease often present for assessment of their risk of developing invasive breast cancer. Women with non-invasive breast cancer were not eligible for any of the tamoxifen chemoprevention trials and a decision regarding whether or not to offer these women tamoxifen therapy to decrease their risk of developing a contralateral breast cancer should be made based on the ER status of their first cancer.[22] A diagnosis of LCIS is an indication for tamoxifen chemoprevention. Among 826 women with a prior history of LCIS enrolled in the NSABP P-1 study tamoxifen reduced the relative risk of invasive breast cancer by 56% (RR 0.44; 95% CI 0.16, 1.06). These women are candidates for tamoxifen chemoprevention therapy regardless of their Gail model risk calculation. The NSABP P-1 study enrolled 1193 women with a prior history of ADH. Tamoxifen therapy reduced the relative risk of invasive breast cancer by 86% (RR 0.14; 95% CI 0.03, 0.47) in these women. A Gail model risk calculation should be performed for all women with ADH and they should be counselled about tamoxifen chemoprevention if their 5-year risk of developing disease exceeds 1.67%.

The Gail model was the tool used to establish eligibility for participation in the NSABP P-1 study for women <60 years of age and without a history of LCIS. The model is available as the US National Cancer Institute (NCI) 'Risk Disk' from the NCI's Publications Locator website.[23] The US FDA approved tamoxifen to reduce the risk of breast cancer for women at high risk in 1998.[24] 'High risk' was defined as women at least 35 years of age with a 5-year predicted risk of invasive breast cancer of >1.67%, as calculated by the Gail model risk assessment tool.

The Gail model is the most widely used risk assessment model in the US. The model was developed from data from the Breast Cancer Detection Demonstration Project and in its original form predicted risk of both invasive and non-invasive breast cancer for White women undergoing annual screening mammography.[25] It was modified for use in the NSABP P-1 study to project the absolute risk of developing invasive breast cancer only.[26] Both versions of the model have been validated,[27-30] and it performs well in predicting numbers of breast cancer cases in specific risk factor strata. However, it has modest discriminatory accuracy at the individual level.[30] The model has been adjusted to take into account the differences in incidence of breast cancer in Hispanic and African American women; however, it has not been validated in these populations and may be less informative in these women.[31]

The Gail model uses very limited family history (first-degree relatives only) and therefore is inappropriate for assessing risk in women with a strong family history. Risk for these women is better assessed with the Claus model[32] or with pedigree construction and assessment of the risk of an inherited susceptibility for breast cancer. Detailed descriptions of the use of modelling for the likelihood of a *BRCA1* or *BRCA2* mutation within a family or individual are reviewed by Domchek et al.[33] and Rubinstein et al.[34] Women estimated to have an increased risk of carrying a mutation should be referred for genetic counselling and development of a personalised risk reduction strategy. Tyrer et al.[35] have recently developed a model that incorporates both personal risk factors (age, reproductive history, etc.) and detailed family history information when calculating an individual's risk of developing breast cancer. This model has not been validated but may serve as a useful tool in both research and clinical settings. Investigators continue to work to develop improved models to better predict the development of ER-positive and ER-negative breast cancer. Such improvements will allow better selection of patients likely to benefit from tamoxifen preventive therapy.

Although the breast cancer risk associated with estrogen as a single agent is poorly defined,[36,37] the use of continuous, oral, combined estrogen/progestogen HRT for 24 months or longer increases a woman's risk of developing invasive breast cancer.[38] It is unclear whether or not this risk is reduced by tamoxifen chemoprevention. Subset analysis of the Italian study indicated that women who were retrospectively defined as being at high risk of developing an ER-positive cancer who used HRT (not defined) during the study did benefit from tamoxifen ($p = 0.009$).[10] Participants in the IBIS-I trial experienced benefit from tamoxifen regardless of their history of HRT use. However, the greatest benefit was seen in the subgroup that had used HRT before study participation (OR 0.43; 95% CI 0.2, 0.91). Benefit in those who used HRT during the trial and those who had never used HRT was nearly equivalent (OR 0.76 and 0.73, respectively).

After assessing a woman's risk of developing breast cancer and determining whether or not this risk is likely to be modulated by tamoxifen, it is time to consider whether this potential benefit might be outweighed by the risk of a tamoxifen-related adverse event. All four randomised trials and the meta-analysis found an increased incidence of venous thromboembolic events in women taking tamoxifen. Tamoxifen therapy is contraindicated for women with a prior history of deep vein thrombosis and is relatively contraindicated for women at high risk of this event. Women who are immobilised or have inherited clotting disorders should not be offered this therapy. Women considering tamoxifen therapy must be made aware that they are at increased risk of a vascular-related event (table II). Age influences this risk, with younger women having lesser risk than their older counterparts. Tamoxifen also increases the risk of developing endometrial hyperplasia, endometrial carcinoma and uterine sarcoma in a woman with an intact uterus. In the NSABP P-1 study, the rate of invasive endometrial carcinoma per 1000 women was 2.3 for those receiving tamoxifen and 0.91 for those receiving placebo. However, the risk was affected by age and those aged ≥50 years had a relative risk of 4.01 compared with a relative risk of 1.21 for women aged ≤49 years. In addition to these risks, women taking tamoxifen

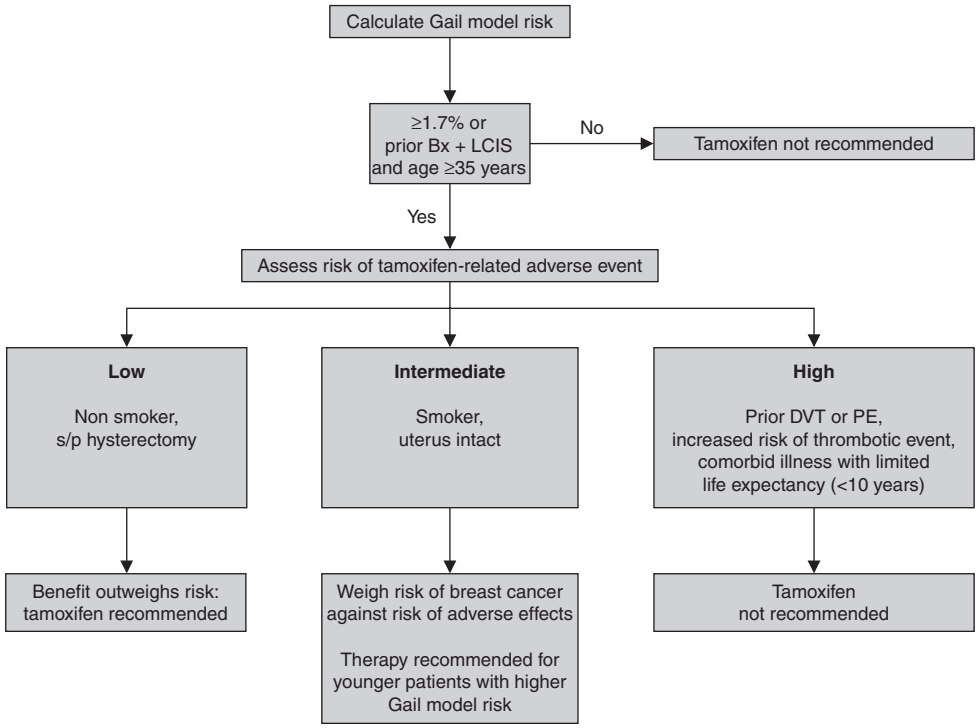

Fig. 1. Should a patient take tamoxifen chemoprevention? A decision tree. **Bx** = biopsy; **DVT** = deep vein thrombosis; **LCIS** = lobular carcinoma *in situ*; **PE** = pulmonary embolism; **s/p** = status post (i.e. have had a hysterectomy).

have an increased risk of developing cataracts and are more likely to experience hot flashes, vaginal discharge and sexual dysfunction.[39] However, careful assessment of health-related quality of life of participants in the NSABP P-1 study revealed that weight gain and depression were not increased in women receiving tamoxifen compared with those receiving placebo.

Race is also likely to influence the risk of a tamoxifen-related adverse event. However, the magnitude of the influence of race on the risk of stroke, pulmonary embolism and deep vein thrombosis in African American, Hispanic and Asian women is difficult to assess. In the NSABP P-1 study 96.4% of the participants were Caucasian and 1.7% were African American. All the other races combined comprised 2% of participants.

3. Reaching a Decision

Tamoxifen is the only drug approved thus far by the US FDA to lower the risk of developing breast cancer. The use of any drug to prevent a disease must be carefully considered. The potential benefits of the therapy must be weighed against the potential adverse events that may result (figure 1). A number of position papers and decision aids to help the counselling physician and the candidate for tamoxifen chemoprevention weighing the risks and benefits of therapy are available.[40-44] Although these documents provide guidance, the decision must be made in the context of an individual woman's overall health and risks in combination with an understanding of the various weights this individual will assign to each potential outcome that may result from therapy. Potential benefits and complications are not distributed equally among all women nor viewed with the same concern by all women. Al-

Table III. Level of Gail model risk associated with net health benefit with tamoxifen chemoprevention by race[44]

Age (y)	Caucasian		African American	
	no hysterectomy	hysterectomy	no hysterectomy	hysterectomy
<40	1.5	1.5	1.5	1.5
40–49	1.5	1.5	2.5	2
50–59	4	1.5	6.5	5.5
60–69	NA	3.5	NA	NA

NA = not available.

though some investigators[45] have given equal weight to the breast cancer prevented and the endometrial cancer caused by tamoxifen therapy when developing their decision aid, many women are likely to weigh these two events differently. The process of weighing the benefits and risks of tamoxifen for preventing breast cancer is hindered by the imprecise assessment of risk of developing disease and by the challenge of determining who is at greatest risk of a tamoxifen-related adverse events.

Gail et al.[44] have performed a sophisticated analysis of the potential risks and benefits of tamoxifen therapy among different populations and have developed an index estimating the net health outcome with therapy, which may serve as a guide. Age, race, absolute 5-year projected risk of invasive breast cancer and risk of endometrial carcinoma impact the net health index. Younger women have less risk of tamoxifen-related adverse events with equivalent potential of benefit. Therefore, these women are more likely to have a net health benefit from tamoxifen therapy in spite of being at the lowest levels of Gail model risk, even if they are at risk of developing endometrial complications (table III). Caucasian women are projected to experience a net health benefit at ages 40–49 years (even with intact uterus) and 50–59 years if they have had a hysterectomy. Because of the greater projected risk of tamoxifen-related thromboembolic events, African American women aged ≥40 years are estimated to experience a net health benefit only with higher Gail model risks (≥6.5 if aged 50–59 years and with intact uterus).

4. Alternatives to Standard-Dose Tamoxifen

4.1 Low-Dose Tamoxifen

The net health benefit with tamoxifen chemoprevention may be improved by better selection of patients who are likely to benefit from therapy and avoidance of use in those likely to experience an adverse event. The risk of endometrial carcinoma with tamoxifen use appears to be dose and time dependent.[46] The results of a neoadjuvant study of tamoxifen in women with breast cancer indicate that the antiproliferative effect of tamoxifen is maintained at lower doses.[47] These data have led to a multicentre, placebo-controlled, phase III trial examining the benefit of low-dose tamoxifen in healthy postmenopausal women taking HRT.[48] This study will be of particular interest as the withdrawal rate of women on the Italian Tamoxifen Prevention Study was lower for women who took estrogen replacement therapy at some point in the study than those who never took it (88% vs 75%, respectively, at 5 years).[49] It is possible that the combination of HRT and tamoxifen may decrease the risk of ER-positive breast cancer without increasing menopausal symptoms.[50] Preliminary evidence from the IBIS-I trial and the Italian study indicate that the combination of tamoxifen and HRT is not associated with a prohibitive increase in the risk of thromboembolic events.[51]

4.2 Selective Estrogen Receptor Modulators

The MORE (Multiple Outcomes of Raloxifene Evaluation) was a multicentre, randomised, double-blind trial designed to determine whether or not raloxifene therapy reduced the risk of osteoporotic

fracture in postmenopausal women with osteoporosis.[52] Follow-up at 4 years revealed that participants treated with raloxifene had fewer breast cancers than those receiving placebo.[53] These results have led the NSABP to initiate a second chemoprevention trial randomising participants to either tamoxifen or raloxifene. The study is accruing patients and results are anticipated in 2007.[54] Additional selective estrogen receptor modulators with improved bioavailability are being developed and include arzoxifene.[55]

4.3 Aromatase Inhibitors

The ATAC (Arimidex, Tamoxifen Alone or in Combination) trial compared adjuvant anastrozole with tamoxifen and the combination anastrozole and tamoxifen. Patients treated with anastrozole alone had fewer contralateral breast cancer events.[56] The potential benefit of anastrozole as a chemopreventative agent is being explored in IBIS-II.[7] This study has two strata. Stratum one will enrol women at risk of breast cancer to treatment with either anastrozole or placebo. Stratum two will enrol women with non-invasive breast cancer to treatment with either tamoxifen or anastrozole. The study began accruing patients in October 2003 and will determine if anastrozole is an effective chemopreventative agent. A comparison of the number of cancers that develop in patients in stratum one and stratum two will provide information regarding the relativity efficacy of tamoxifen and anastrozole in preventing breast cancer.

The NCI of Canada is assessing the impact of the aromatase inhibitor exemestane, with and without celecoxib, on the incidence of breast cancer in high-risk women.[57]

5. Conclusion

Tamoxifen is currently the only US FDA-approved medication for the chemoprevention of breast cancer and is likely to remain so for the next several years. Women aged ≥35 years with a 5-year risk of developing disease of ≥1.67% as determined by the Gail model should be informed of the potential benefit of tamoxifen chemoprevention. Therapy is associated with a 48% reduction in the risk of developing ER-positive breast cancer. The approval of tamoxifen for the chemoprevention of breast cancer ushers in a new era of research in breast cancer prevention. However, many women who are candidates for tamoxifen preventive therapy are reluctant to take this medication because of concerns about potential adverse effects.[58] Areas of intensive study include developing improved models of risk assessment for both ER-positive and ER-negative breast cancer, developing prevention therapies for ER-negative breast cancer and defining more effective and less toxic agents to prevent ER-positive breast cancer.

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Correspondence and offprints: Dr *Rita Kramer*, Breast Center, Baylor College of Medicine & the Methodist Hospital, Houston, TX 77030, USA.